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[Intervention Review]

SARS-CoV-2-neutralising monoclonal antibodies for treatment of COVID-19

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ABSTRACT

Background

Monoclonal antibodies (mAbs) are laboratory-produced molecules derived from the B cells of an infected host. They are being investigated as a potential therapy for coronavirus disease 2019 (COVID-19).

Objectives

To assess the effectiveness and safety of SARS-CoV-2-neutralising mAbs for treating patients with COVID-19, compared to an active comparator, placebo, or no intervention. To maintain the currency of the evidence, we will use a living systematic review approach.

A secondary objective is to track newly developed SARS-CoV-2-targeting mAbs from first tests in humans onwards.

Search methods

We searched MEDLINE, Embase, the Cochrane COVID-19 Study Register, and three other databases on 17 June 2021. We also checked references, searched citations, and contacted study authors to identify additional studies. Between submission and publication, we conducted a shortened randomised controlled trial (RCT)-only search on 30 July 2021.

Selection criteria

We included studies that evaluated SARS-CoV-2-neutralising mAbs, alone or combined, compared to an active comparator, placebo, or no intervention, to treat people with COVID-19. We excluded studies on prophylactic use of SARS-CoV-2-neutralising mAbs.

Data collection and analysis

Two authors independently assessed search results, extracted data, and assessed risk of bias using the Cochrane risk of bias tool (RoB2). Prioritised outcomes were all-cause mortality by days 30 and 60, clinical progression, quality of life, admission to hospital, adverse events (AEs), and serious adverse events (SAEs). We rated the certainty of evidence using GRADE.

Main results

We identified six RCTs that provided results from 17,495 participants with planned completion dates between July 2021 and December 2031. Target sample sizes varied from 1020 to 10,000 participants. Average age was 42 to 53 years across four studies of non-hospitalised participants, and 61 years in two studies of hospitalised participants.

Non-hospitalised individuals with COVID-19

Four studies evaluated single agents bamlanivimab (N = 465), sotrovimab (N = 868), regdanvimab (N = 307), and combinations of bamlanivimab/etesevimab (N = 1035), and casirivimab/imdevimab (N = 799). We did not identify data for mortality at 60 days or quality of life. Our certainty of the evidence is low for all outcomes due to too few events (very serious imprecision).

Bamlanivimab compared to placebo

No deaths occurred in the study by day 29. There were nine people admitted to hospital by day 29 out of 156 in the placebo group compared with one out of 101 in the group treated with 0.7 g bamlanivimab (risk ratio (RR) 0.17, 95% confidence interval (CI) 0.02 to 1.33), 2 from 107 in the group treated with 2.8 g (RR 0.32, 95% CI 0.07 to 1.47) and 2 from 101 in the group treated with 7.0 g (RR 0.34, 95% CI 0.08 to 1.56). Treatment with 0.7 g, 2.8 g and 7.0 g bamlanivimab may have similar rates of AEs as placebo (RR 0.99, 95% CI 0.66 to 1.50; RR 0.90, 95% CI 0.59 to 1.38; RR 0.81, 95% CI 0.52 to 1.27). The effect on SAEs is uncertain. Clinical progression/improvement of symptoms or development of severe symptoms were not reported.

Bamlanivimab/etesevimab compared to placebo

There were 10 deaths in the placebo group and none in bamlanivimab/etesevimab group by day 30 (RR 0.05, 95% CI 0.00 to 0.81). Bamlanivimab/etesevimab may decrease hospital admission by day 29 (RR 0.30, 95% CI 0.16 to 0.59), may result in a slight increase in any grade AEs (RR 1.15, 95% CI 0.83 to 1.59) and may increase SAEs (RR 1.40, 95% CI 0.45 to 4.37). Clinical progression/improvement of symptoms or development of severe symptoms were not reported.

Casirivimab/imdevimab compared to placebo

Casirivimab/imdevimab may reduce hospital admissions or death (2.4 g: RR 0.43, 95% CI 0.08 to 2.19; 8.0 g: RR 0.21, 95% CI 0.02 to 1.79). We are uncertain of the effect on grades 3-4 AEs (2.4 g: RR 0.76, 95% CI 0.17 to 3.37; 8.0 g: RR 0.50, 95% CI 0.09 to 2.73) and SAEs (2.4 g: RR 0.68, 95% CI 0.19 to 2.37; 8.0 g: RR 0.34, 95% CI 0.07 to 1.65). Mortality by day 30 and clinical progression/improvement of symptoms or development of severe symptoms were not reported.

Sotrovimab compared to placebo

We are uncertain whether sotrovimab has an effect on mortality (RR 0.33, 95% CI 0.01 to 8.18) and invasive mechanical ventilation (IMV) requirement or death (RR 0.14, 95% CI 0.01 to 2.76). Treatment with sotrovimab may reduce the number of participants with oxygen requirement (RR 0.11, 95 % CI 0.02 to 0.45), hospital admission or death by day 30 (RR 0.14, 95% CI 0.04 to 0.48), grades 3-4 AEs (RR 0.26, 95% CI 0.12 to 0.60), SAEs (RR 0.27, 95% CI 0.12 to 0.63) and may have little or no effect on any grade AEs (RR 0.87, 95% CI 0.66 to 1.16).

Regdanvimab compared to placebo

Treatment with either dose (40 or 80 mg/kg) compared with placebo may decrease hospital admissions or death (RR 0.45, 95% CI 0.14 to 1.42; RR 0.56, 95% CI 0.19 to 1.60, 206 participants), but may increase grades 3-4 AEs (RR 2.62, 95% CI 0.52 to 13.12; RR 2.00, 95% CI 0.37 to 10.70). 80 mg/kg may reduce any grade AEs (RR 0.79, 95% CI 0.52 to 1.22) but 40 mg/kg may have little to no effect (RR 0.96, 95% CI 0.64 to 1.43). There were too few events to allow meaningful judgment for the outcomes mortality by 30 days, IMV requirement, and SAEs.

Hospitalised individuals with COVID-19

Two studies evaluating bamlanivimab as a single agent (N = 314) and casirivimab/imdevimab as a combination therapy (N = 9785) were included.

Bamlanivimab compared to placebo

We are uncertain whether bamlanivimab has an effect on mortality by day 30 (RR 1.39, 95% CI 0.40 to 4.83) and SAEs by day 28 (RR 0.93, 95% CI 0.27 to 3.14). Bamlanivimab may have little to no effect on time to hospital discharge (HR 0.97, 95% CI 0.78 to 1.20) and mortality by day 90 (HR 1.09, 95% CI 0.49 to 2.43). The effect of bamlanivimab on the development of severe symptoms at day 5 (RR 1.17, 95% CI 0.75 to 1.85) is uncertain. Bamlanivimab may increase grades 3-4 AEs at day 28 (RR 1.27, 95% CI 0.81 to 1.98). We assessed the evidence as low certainty for all outcomes due to serious imprecision, and very low certainty for severe symptoms because of additional concerns about indirectness.

Casirivimab/imdevimab with usual care compared to usual care alone

Treatment with casirivimab/imdevimab compared to usual care probably has little or no effect on mortality by day 30 (RR 0.94, 95% CI 0.87 to 1.02), IMV requirement or death (RR 0.96, 95% CI 0.90 to 1.04), nor alive at hospital discharge by day 30 (RR 1.01, 95% CI 0.98 to 1.04). We assessed the evidence as moderate certainty due to study limitations (lack of blinding). AEs and SAEs were not reported.

Authors' conclusions

The evidence for each comparison is based on single studies. None of these measured quality of life. Our certainty in the evidence for all non-hospitalised individuals is low, and for hospitalised individuals is very low to moderate. We consider the current evidence insufficient to draw meaningful conclusions regarding treatment with SARS-CoV-2-neutralising mAbs.

Further studies and long-term data from the existing studies are needed to confirm or refute these initial findings, and to understand how the emergence of SARS-CoV-2 variants may impact the effectiveness of SARS-CoV-2-neutralising mAbs. Publication of the 36 ongoing studies may resolve uncertainties about the effectiveness and safety of SARS-CoV-2-neutralising mAbs for the treatment of COVID-19 and possible subgroup differences.

PLAIN LANGUAGE SUMMARY

Are laboratory-made, COVID-19-specific monoclonal antibodies an effective treatment for COVID-19?

Key messages

- We do not know whether antibodies (the body's natural defence against disease) made in a laboratory and all the same as one another (monoclonal) and designed to target COVID-19, are an effective treatment for COVID-19 because we assessed only six studies exploring different treatments in different types of patients.

- We identified 36 ongoing studies that will provide more evidence when completed.

- We will update this review regularly as more evidence becomes available.

What are 'monoclonal' antibodies?

Antibodies are made by the body as a defence against disease. However, they can also be produced in a laboratory from cells taken from people who have recovered from a disease.

Antibodies that are designed to target only one specific protein – in this case, a protein on the virus that causes COVID-19 – are 'monoclonal'. They attach to the COVID-19 virus and stop it from entering and replicating in human cells, which helps to fight the infection. Monoclonal antibodies have been used successfully to treat other viruses. They are thought to cause fewer unwanted effects than convalescent plasma, which contains a variety of different antibodies.

What did we want to find out?

We wanted to know if COVID-19 specific monoclonal antibodies are an effective treatment for COVID-19. We looked at whether they:

- reduced the number of deaths from any cause;

- improved symptoms or made them worse;

- increased admissions to hospital; and

- caused any serious or other unwanted effects.

What did we do?

We searched for studies that investigated one or more monoclonal antibodies to treat people with confirmed COVID-19 compared with placebo (sham treatment), another treatment or no treatment. Studies could take place anywhere globally and include participants of any age, gender or ethnicity, with mild, moderate or severe COVID-19.

We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and size.

What did we find?

We found six active studies including a total of 17,495 people. Four studies investigated non-hospitalised people with no symptoms or mild COVID-19. Two studies investigated hospitalised people with moderate to severe COVID-19. Studies took place across the world. Three studies were funded by pharmaceutical companies. The monoclonal antibodies they studied were bamlanivimab, etesevimab, casirivimab and imdevimab, sotrovimab, regdanvimab. We did not identify data for mortality at 60 days and quality of life.

Non-hospitalised people, with no symptoms or mild COVID-19 (four studies)

One study investigated different doses of bamlanivimab (465 people), compared to placebo.

We don't know whether bamlanivimab:

- increases or reduces the number of deaths because no participants died within 30 days of treatment;

- causes more or fewer serious unwanted effects because there were few events.

Bamlanivimab may reduce the number of admissions to hospital within 30 days of treatment compared to placebo.

- May cause slightly fewer unwanted effects than placebo.

- We did not find data for improved symptoms or worsened symptoms.

One study investigated a combination of bamlanivimab and etesevimab (1035 people), compared to placebo.

- Bamlanivimab and etesevimab may reduce the number of deaths and admissions to hospital.

- May cause slightly more unwanted effects.

- May cause more serious unwanted effects.

For treatment with bamlanivimab alone or in combination with etesevimab we did not find data for improved symptoms or worsened symptoms.

One study (phase 1/2 with 799 people) investigated different doses of casirivimab combined with imdevimab, compared to placebo.

- Casirivimab combined with imdevimab may reduce the number of hospital admissions or death.

- We don't know whether casirivimab and imdevimab causes more unwanted (grades 3 and 4) and serious unwanted effects than placebo because there were too few deaths to allow us to make a judgment.

- We did not find data for the number of people who died at day 30 and development of severe symptoms.

- We did not include results from phase 3 (5607 people) of this study, because of high risk of bias, as it was not clear which participants were included in the analysis.

One study (583 people) investigated sotrovimab, compared to placebo.

We don't know whether sotrovimab:

- increases or reduces the number of deaths and people requiring invasive mechanical ventilation or dying, because there were too few deaths to allow us to make a judgment.

- Sotrovimab may reduce the number of people requiring oxygen, unwanted (grades 3 to 4) and serious unwanted effects;

- may have little or no effect on unwanted effects (all grades).

Another study (327 people) investigated different doses of regdanvimab (40 mg/kg and 80 mg/kg), compared to placebo.

- Regdanvimab at either dose may reduce the number of admissions to hospital or death.

- May increase unwanted events (grades 3 to 4).

- Regdanvimab at a dose of 80 mg/kg may reduce unwanted effects (all grades) and 40 mg/kg may have little to no effect.

- We don't know whether regdanvimab increases or decreases the number of deaths, requirement for invasive mechanical ventilation, and serious unwanted effects, because there were too few events to allow us to make a judgment.

Hospitalised people with moderate to severe COVID-19 (2 studies)

One study (314 people) investigated bamlanivimab compared to placebo.

- We don't know whether bamlanivimab increases or decreases the number of deaths due to any cause up to 30 or 90 days after treatment because there were too few deaths to allow us to make a judgment (6 deaths with bamlanivimab and 4 deaths with placebo in 314 people).

- Bamlanivimab may slightly increase the development of severe COVID-19 symptoms five days after treatment and the number of people with unwanted effects.

- Bamlanivimab may have little to no effect on time until discharge from hospital.

- We don't know whether bamlanivimab causes serious unwanted effects by day 30 because the study was small and reported few serious unwanted effects.

Another study (9785 people) investigated casirivimab combined with imdevimab, compared to standard of care.

- Casirivimab combined with imdevimab has probably little to no effect on the number of deaths, requirement for invasive mechanical ventilation or death, and hospital discharge alive.

- We did not find data for unwanted and serious unwanted effects.

What are the limitations of the evidence?

Our confidence in the evidence is low because we found only six studies, and they did not report everything we were interested in, such as the number of deaths within 60 days and quality of life. We found 36 ongoing studies. When they are published, we will add their results to our review. These results are likely to change our conclusions and will also help us understand how new variants affect how well monoclonal antibodies work.

How up to date is this evidence?

The evidence is up to date to 17 June 2021.

Summary of findings 1. Bamlanivimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease)

Bamlanivimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease)

Patient or population: non-hospitalised individuals with COVID-19 **Setting:** outpatient **Intervention:** bamlanivimab **Comparison:** placebo

Outcomes	Dose	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty in the evidence (GRADE)	Comments
		Risk with placebo	Risk with SARS-CoV-2-specific mAb				
Mortality by day 30	Bamlanivimab 0.7 g	0 per 1000	**0 per 1000**	**Not estimable**	101 bamlanivimab/156 placebo (1 RCT)	⊕⊕⊖⊖ Low[a]	No events observed. We are uncertain whether 0.7 g bamlanivimab has any impact on mortality at up to day 30.
	Bamlanivimab 2.8 g	0 per 1000	**0 per 1000**	**Not estimable**	107 bamlanivimab/156 placebo (1 RCT)		No events observed. We are uncertain whether 2.8 g bamlanivimab has any impact on mortality at up to day 30.
	Bamlanivimab 7.0 g	0 per 1000	**0 per 1000**	**Not estimable**	101 bamlanivimab/156 placebo (1 RCT)		No events observed. We are uncertain whether 7.0 g bamlanivimab has any impact on mortality at up to day 30.
Mortality by day 60	Not reported	-	**-**	**-**	-	-	We did not identify any study reporting this outcome.
Clinical progression/improvement of symptoms	Not reported	-	**-**	**-**	-	-	We did not identify any study reporting this outcome.

Quality of life	Not measured	-	-	-	-	-	We did not identify any study reporting this outcome.
Admission to hospital by day 30	Bamlanivimab 0.7 g	58 per 1000	**10 per 1000** (1 to 77)	**RR 0.17** (0.02 to 1.33)	257 (1 RCT)	⊕⊖⊖⊖ Low[b]	Bamlanivimab 0.7 g may decrease hospital admission at day 30.
	Bamlanivimab 2.8 g	58 per 1000	**18 per 1000** (4 to 85)	**RR 0.32** (0.07 to 1.47)	263 (1 RCT)		Bamlanivimab 0.7 g may decrease hospital admission at day 30.
	Bamlanivimab 7.0 g	58 per 1000	**20 per 1000** (5 to 90)	**RR 0.34** (0.08 to 1.56)	257 (1 RCT)		Bamlanivimab 0.7 g may decrease hospital admission at day 30.
Adverse events: all grades	Bamlanivimab 0.7 g	269 per 1000	**267 per 1000 (178 to 404)**	**RR 0.99** (0.66 to 1.50)	257 (1 RCT)	⊕⊖⊖⊖ Low[b]	Bamlanivimab 0.7 g may have little to no effect on all-grade adverse events.
	Bamlanivimab 2.8 g	269 per 1000	**242 per 1000** (159 to 372)	**RR 0.90** (0.59 to 1.38)	263 (1RCT)		Bamlanivimab 2.8 g may have little to no effect on all-grade adverse events.
	Bamlanivimab 7.0 g	269 per 1000	**218 per 1000** (140 to 342)	**RR 0.81** (0.52 to 1.27)	257 (1 RCT)		Bamlanivimab 7.0 g may have little to no effect on all-grade adverse events.
Serious adverse events	Bamlanivimab 0.7 g	6 per 1000	**3 per 1000** (0 to 80)	**RR 0.51** (0.02 to 12.47)	257 (1 RCT)	⊕⊖⊖⊖ Low[b]	There were too few who experienced serious adverse events to determine whether bamlanivimab 0.7 g made a difference.
	Bamlanivimab 2.8 g	6 per 1000	**3 per 1000** (0 to 76)	**RR 0.48** (0.02 to 11.78)	263 (1 RCT)		There were too few who experienced serious adverse events to determine whether bamlanivimab 2.8 g made a difference.

	Bamlanivimab 7.0 g	6 per 1000	**3 per 1000** (0 to 80)	**RR 0.51** (0.02 to 12.47)	257 (1 RCT)	There were too few who experienced serious adverse events to determine whether bamlanivimab 7.0 g made a difference.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk on the comparison group and the **relative effect** of the intervention (and its 95% confidence interval).

CI: confidence interval; **mAb:** monoclonal antibody; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is the possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded two levels for very serious imprecision, no events observed, effect not estimable
[b]Downgraded two levels for very serious imprecision, because of small sample size, low number of events and/or wide confidence interval.

Summary of findings 2. Bamlanivimab/etesevimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease)

Bamlanivimab/etesevimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease)

Patient or population: non-hospitalised individuals with COVID-19 (asymptomatic and mild disease) **Setting**: outpatients **Intervention**: bamlanivimab/etesevimab **Comparison**: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with bamlanivimab/ etesevimab				
Mortality by day 30	19 per 1000	**1 per 1000** (0 to 15)	RR 0.05 (0.00 to 0.81)	1035 (1 RCT)	⊕⊕⊖⊖ Low[a]	Bamlanivimab/etesevimab may reduce all-cause mortality by day 30.

Mortality by day 60 - not reported	not reported		-	-	-	We did not identify any study reporting this outcome.
Clinical progression	not reported		-	-	-	We did not identify any study reporting this outcome.
Quality of life by day 30	not measured		-	-	-	We did not identify any study reporting this outcome.
Admission to hospital or death	70 per 1000	**21 per 1000** (11 to 41)	**RR 0.30** (0.16 to 0.59)	1035 (1 RCT)	⊕⊕⊖⊖ Low[a]	Bamlanivimab/ etesevimab may decrease the risk hospital admission by day 30.
Adverse events: all grades	116 per 1000	**133 per 1000** (96 to 184)	**RR 1.15** (0.83 to 1.59)	1035 (1 RCT)	⊕⊕⊖⊖ Low[b]	Bamlanivimab/ etesevimab may have little to no effect on the risk of all grade adverse events.
Serious adverse events	10 per 1000	**14 per 1000** (4 to 42)	**RR 1.40** (0.45 to 4.37)	1035 (1 RCT)	⊕⊕⊖⊖ Low[a]	Bamlanivimab/ etesevimab may increase the risk of serious adverse events.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is the possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_422966277463976837.

[a] Downgraded two levels for very serious imprecision due to low number of events and low sample size
[b] Downgraded two levels for very serious imprecision, because of small sample size

Summary of findings 3. Casirivimab/imdevimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease)

Casirivimab/imdevimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease)

Patient or population: non-hospitalised individuals with COVID-19 (asymptomatic and mild disease) **Setting**: outpatients **Intervention**: casirivimab/imdevimab **Comparison**: placebo

Outcomes	Dose	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Risk with placebo	Risk with casirivimab/imdevimab				
Mortality by day 30	not reported	-		-	-	-	Only one study which was excluded from analysis reported results on this outcome.
Mortality by day 60	not reported	-		-	-	-	We did not identify any study reporting this outcome.
Clinical progression: requirement of IMV (WHO 7, 8 or 9), 1.2g	not reported	-		-	-	-	Only one study which was excluded from analysis reported results on this outcome.
Quality of life	not measured	-		-	-	-	We did not identify any study reporting this outcome.
Admission to hospital or death	1.2g	-		-	-	-	
	2.4g	22 per 1000	**9 per 1000** (2 to 47)	**RR 0.43** (0.08 to 2.19)	446 (1 RCT)	⊕⊕⊖⊖ Low[a]	Casirivimab/imdevimab at 2.4 g or 8.0 g may reduce the occurrence of hospital admissions or death at day 30.
	8.0g	22 per 1000	**5 per 1000** (0 to 39)	**RR 0.21** (0.02 to 1.79)	450 (1 RCT)		
Adverse events: grade 3-4	1.2g	-		-	-	-	Only one study which was excluded from analysis reported results on this outcome.
	2.4g	15 per 1000	**12 per 1000** (3 to 51)	**RR 0.76** (0.17 to 3.37)	520 (1 RCT)	⊕⊕⊖⊖ Low[a]	There were too few who experienced am event to determine whether any dose of casirivimab/imdevimab made a difference
	8.0g	15 per 1000	**8 per 1000** (1 to 42)	**RR 0.50** (0.09 to 2.73)	522 (1 RCT)		

Adverse events: all grades	not reported	-		-	-	-	Only one study which was excluded from analysis reported results on this outcome.
Serious adverse events	1.2g	-		-	-	-	Only one study which was excluded from analysis reported results on this outcome.
	2.4g	23 per 1000	**16 per 1000** (4 to 54)	**RR 0.68** (0.19 to 2.37)	520 (1 RCT)	⨁◯◯◯ Low[a]	There were too few who experienced am event to determine whether any dose of casirivimab/imdevimab made a difference.
	8.0g	23 per 1000	**8 per 1000** (2 to 38)	**RR 0.34** (0.07 to 1.65)	522 (1 RCT)		

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is the possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded two levels due to very serious imprecision; low sample size and low number of events

Summary of findings 4. Sotrovimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease)

Sotrovimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease)

Patient or population: non-hospitalised individuals with COVID-19 (asymptomatic and mild disease) **Setting**: outpatients **Intervention**: sotrovimab **Comparison**: placebo

Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants** (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with sotrovimab				

Mortality by day 30	3 per 1000	**1 per 1000** (0 to 28)	**RR 0.33** (0.01 to 8.18)	583 (1 RCT)	⊕⊕⊖⊖ Low[a]	There were too few who experienced mortality to determine whether sotrovimab made a difference.
Mortality by day 60	not reported		-	-	-	We did not identify any study reporting this outcome.
Clinical progression: oxygen requirement (≥ 5 WHO scale)	65 per 1000	**7 per 1000** (1 to 29)	**RR 0.11** (0.02 to 0.45)	583 (1 RCT)	⊕⊕⊖⊖ Low[b]	Sotrovimab may reduce the number of participants with any oxygen requirement.
Clinical progression: IMV or death (≥ 7 WHO scale)	10 per 1000	**1 per 1000** (0 to 28)	**RR 0.14** (0.01 to 2.76)	583 (1 RCT)	⊕⊕⊖⊖ Low[a]	There were too few who experienced an event to determine whether sotrovimab made a difference.
Quality of life by day 30	not reported		-	-	-	We did not identify any study reporting this outcome.
Admission to hospital or death by day 30	72 per 1000	**10 per 1000** (3 to 35)	**RR 0.14** (0.04 to 0.48)	583 (1 RCT)	⊕⊕⊖⊖ Low[b]	Sotrovimab may reduce the occurrence of hospital admissions or death.
Adverse events: all grades	194 per 1000	**169 per 1000** (128 to 225)	**RR 0.87** (0.66 to 1.16)	868 (1 RCT)	⊕⊕⊖⊖ Low[b]	Sotrovimab may have little to no effect on the occurrence of all grade adverse events.
Adverse events: grades 3 and 4	62 per 1000	**16 per 1000** (7 to 37)	**RR 0.26** (0.12 to 0.60)	868 (1 RCT)	⊕⊕⊖⊖ Low[b]	Sotrovimab may reduce the occurrence of grade 3-4 adverse events.
Serious adverse events	59 per 1000	**16 per 1000** (7 to 37)	**RR 0.27** (0.12 to 0.63)	868 (1 RCT)	⊕⊕⊖⊖ Low[b]	Sotrovimab may reduce the occurrence of serious adverse events.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

**This study included a total of 868 participants. All were 868 participants randmoised were included in the safety set, but only 583 participants were analysed in the efficacy set.

CI: confidence interval; **RR:** risk ratio; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is the possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded two levels for very serious imprecision, because of low sample size, very low number of events and very wide confidence interval
[b] Downgraded two levels for very serious imprecision, because of low sample size and/or low number of events

Summary of findings 5. Regdanvimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease)

Regdanvimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease)

Patient or population: non-hospitalised individuals with COVID-19 (asymptomatic and mild disease) **Setting**: outpatient **Intervention**: regdanvimab **Comparison**: placebo

Outcomes		Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Risk with placebo	Risk with regdanvimab				
Mortality by day 30	Regdanvimab 40mg/kg CT-P59 80 mg/kg	0 per 1000	**0 per 1000** (0 to 0)	Not estimable	(1 RCT)	⨁⨁◯◯ Low[a]	No events observed. We are uncertain whether CT-P59 has any impact on mortality at up to day 30.
Mortality by day 60	not reported	-	-	-	-	-	-
Clinical progression: development of severe symptoms (≥ 7 WHO scale, IMV)	40 mg/kg	0 per 1000	**0 per 1000** (0 to 0)	Not estimable	(1 RCT)	⨁⨁◯◯ Low[a]	No events observed. We are uncertain whether 40 mg/kg regdanvimab has any impact on IMV requirement or death.
	80 mg/kg	0 per 1000	**0 per 1000** (0 to 0)	**RR 3.00** (0.12 to 72.80)	103 (1 study)	⨁⨁◯◯ Low[b]	There were too few who experienced IMV or death to determine whether CT-P59, 80 mg/kg made a difference.
Quality of life by day 30	not measured	-	-	-	-	-	

Admission to hospital or death by day 30	40 mg/kg	87 per 1000	**39 per 1000** (12 to 124)	**RR 0.45** (0.14 to 1.42)	204 (1 RCT)	⊕⊖⊖⊖ Low[b]	Regdanvimab, 40 mg/kg or 80 mg/kg may decrease hospital admission or death by day 30.
	80 mg/kg	87 per 1000	**49 per 1000** (17 to 140)	**RR 0.56** (0.19 to 1.60)	206 (1 RCT)		
Adverse events: all grades	40 mg/kg	309 per 1000	**297 per 1000** (198 to 442)	**RR 0.96** (0.64 to 1.43)	215 (1 RCT)	⊕⊖⊖⊖ Low[b]	Regdanvimab 40 mg/kg may have little to no effect on all grade adverse events.
	80 mg/kg	309 per 1000	**244 per 1000** (161 to 377)	**RR 0.79** (0.52 to 1.22)	220 (1 RCT)		Regdanvimab 80 mg/kg may reduce the occurrence of all grade adverse events.
Adverse events: grades 3 and 4	40 mg/kg	18 per 1000	**48 per 1000** (9 to 239)	**RR 2.62** (0.52 to 13.12)	215 (1 RCT)	⊕⊖⊖⊖ Low[b]	Regdanvimab 40 mg/kg or 80 mg/kg may increase the occurrence of grade 3 adverse events.
	80 mg/kg	18 per 1000	**36 per 1000** (7 to 195)	**RR 2.00** (0.37 to 10.70)	220 (1 RCT)		
Serious adverse events by day 30	not reported	0 per 1000	0 per 1000 (0 to 0)	not estimable	(1 RCT)	⊕⊖⊖⊖ Low[b]	We are uncertain whether regdanvimab, 40 mg/kg or 80 mg/kg has an effect on serious adverse events.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is the possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded two levels for very serious imprecision, because no events were observed, the sample size small and the effect not estimable
[b] Downgraded two levels for very serious imprecision, because few event(s) were observed and/or the sample size was small.

Summary of findings 6. Bamlanivimab compared to placebo in hospitalised individuals with COVID-19 (moderate to severe disease)

Bamlanivimab compared to placebo in hospitalised individuals with COVID-19 (moderate to severe disease)

Patient or population: hospitalised individuals with COVID-19 (moderate to severe disease) **Setting**: inpatient **Intervention**: bamlanivimab **Comparison**: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty in the evidence (GRADE)	Comments
	Risk with placebo	Risk with bamlanivimab				
Mortality by day 30	26 per 1000	**37 per 1000** (11 to 128)	**RR 1.39** (0.40 to 4.83)	314 (1 RCT)	⊕⊕⊖⊖ Low[a]	We are uncertain whether bamlanivimab has an effect on mortality at 28 days.
Mortality by day 90	73 per 1000	**79 per 1000** (36 to 168)	**HR 1.09** (0.49 to 2.43)	314 (1 RCT)	⊕⊕⊖⊖ Low[a]	Bamlanivimab may have little to no effect on mortality by day 90.
Clinical progression: need for NIV, IMV, ECMO, or renal replacement therapy at day 5 (group 5, 6 or 7) assessed with: 7-point scale, lower better	180 per 1000	**211 per 1000** (135 to 333)	**RR 1.17** (0.75 to 1.85)	311 (1 RCT)	⊕⊖⊖⊖ Very low[a,b]	Bamlanivimab may slightly increase the development of severe symptoms (assessed by the need for NIV, IMV, ECMO, or renal replacement therapy) at day 5.
Quality of life	not measured			-	-	We did not identify any study reporting this outcome.
Time to hospital discharge up to 26.10.2020, absolute effects for day 10	762 per 1000	**752 per 1000** (664 to 816)	**HR 0.97** (0.76 to 1.18)	314 (1 RCT)	⊕⊕⊖⊖ Low[a]	Bamlanivimab may have little to no impact on hospital discharge until data cut off (26 October 2020).
Adverse events: grades 3 and 4 by day 30	179 per 1000	**227 per 1000** (145 to 354)	**RR 1.27** (0.81 to 1.98)	314 (1 RCT)	⊕⊕⊖⊖ Low[a]	Bamlanivimab may slightly increase the risk of grade 3 and 4 adverse events.
Serious adverse events by day 30	33 per 1000	**31 per 1000** (9 to 104)	**RR 0.93** (0.27 to 3.14)	314 (1 RCT)	⊕⊕⊖⊖ Low[a]	We are uncertain whether bamlanivimab has an effect the occurrence of serious adverse events.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio; **HR:** hazard Ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is the possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_422871223304980961.

[a] Downgraded two levels for very serious imprecision, because of wide confidence interval, low sample size and/or low number of events, imbalances in baseline characteristics.
[a] Downgraded one level for serious indirectness, because the time frame of 5 days was short for assessing clinical status.

Summary of findings 7. Casirivimab/imdevimab compared to usual care alone in hospitalised individuals with COVID-19 (moderate to severe disease)

Casirivimab/imdevimab compared to usual care in hospitalised individuals with COVID-19 (moderate to severe disease)

Patient or population: hospitalised individuals with COVID-19 (moderate to severe disease) **Setting**: inpatient **Intervention**: casirivimab/imdevimab **Comparison**: usual care alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty in the evidence (GRADE)	Comments
	Risk with usual care alone	Risk with **casirivimab/imdevimab**				
Mortality by day 30	236 per 1000	**221 per 1000** (205 to 241)	**RR 0.94** (0.87 to 1.02)	9785 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	Casirivimab/imdevimab 8.0 g has probably little to no effect on mortality by day 30 in the overall cohort of hospitalised participants.
Mortality by day 60	not reported			-	-	We did not identify any study reporting this outcome.
Clinical progression: need for IMV or death (WHO ≥ 7)	248 per 1000	**238 per 1000** (223 to 258)	**RR 0.96** (0.90 to 1.04)	9198 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	Casirivimab/imdevimab 8.0 g has probably little to no effect on IMV requirement or death by day 30 in the overall cohort of hospitalised participants.

Quality of life	not measured		-	-	-	We did not identify any study reporting this outcome.
Hospital discharge alive by day 30	690 per 1000	**697 per 1000** (676 to 718)	**RR 1.01** (0.98 to 1.04)	9785 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	Casirivimab/imdevimab 8.0 g has probably little to no effect on discharge from hospital alive by day 30 in the overall cohort of hospitalised participants.
Adverse events: grades 3 and 4 by day 30	not reported		-	-	-	We did not identify any study reporting this outcome.
Serious adverse events by day 30	not reported		-	-	-	We did not identify any study reporting this outcome.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is the possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded one level due to serious risk of bias, the study was not blinded. Currently, there is no clearly defined standard of care for COVID-19, therefore, a lack of blinding can have resulted in differential treatments/timings of treatment between arms.

BACKGROUND

Description of the condition

The clinical syndrome novel coronavirus disease 2019 (COVID-19) is a rapidly spreading infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; WHO 2020a). Declared a pandemic on 11 March 2020, COVID-19 is unprecedented in comparison to previous coronavirus outbreaks, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), with 813 and 858 deaths, respectively (WHO 2007; WHO 2019). Despite intensive international efforts to contain its spread, it has resulted in more than 198 million confirmed cases and more than 4.2 million deaths worldwide up to 3 August 2021 (WHO 2020b), impacting severely on healthcare facilities, healthcare workers, and medical equipment resources.

Since 23 March 2020, weekly hospitalisation rates in the USA fluctuated between 3 and 17.2 per 100,000 population, with a recent peak increase at the end of December 2020 (CDC 2020). Risk for severe disease, hospitalisation and mortality is higher for individuals aged 65 years or older, smokers and individuals with certain underlying medical conditions, such as cancer, chronic kidney disease, chronic obstructive pulmonary disease (COPD), heart conditions, immunocompromised state, obesity, sickle cell disease or type 2 diabetes mellitus (Huang 2020; Liang 2020; WHO 2020a; Williamson 2020). COVID-19 case fatality ratios varied widely between countries and reporting periods, from 0.0% to more than 25% (Johns Hopkins 2021). However, these numbers may be misleading as they tend to overestimate the infection fatality ratio (the probability of dying for an infected individual) due to varying testing frequency, lag in reporting dates, and variations in case definitions, especially at the beginning of a pandemic where the main focus lies on severe cases (WHO 2020c). A recent estimate of the infection fatality ratio of SARS-CoV-2 based on seroprevalence data from the general population of a country ranged between 0.00% and 1.54% for 51 different locations (corrected median: 0.23%; Ioannidis 2020).

The median incubation time is estimated to be between five and six days, and 97.5% of symptomatic cases develop symptoms within 11.5 days of exposure (Lauer 2020). Signs and symptoms can include sore throat, cough, fever, headache, fatigue, and myalgia (muscle pain) or arthralgia (joint pain) (Struyf 2020). Other symptoms include shortness of breath, chills, nausea or vomiting, diarrhoea, nasal congestion, haemoptysis (coughing up blood), and conjunctival congestion (WHO 2020a). The proportion of infected people with mild disease is around 80% (Wu 2020). Of those, 20% may remain completely asymptomatic (Buitrago-Garcia 2020), 14% are affected by severe disease, and 5% experience critical disease with intensive care unit (ICU) admittance due to respiratory failure, septic shock, or multiple organ dysfunction (Wu 2020). Due to the extent of the pandemic and a current lack of potent medication and vaccines, targeted immunotherapies such as monoclonal antibodies (mAbs) raise hopes for combating the disease.

Description of the intervention

Monoclonal antibodies (mAbs) are laboratory-produced molecules derived from natural B cells of hosts who have experienced or been injected with the antigen of interest, to substitute antibodies that are able to mimic a person's own immune attack (Bayer 2019). While traditional serum therapy uses antibodies derived from more than one type of white cell (polyclonal), mAbs target only a single, predetermined epitope, thereby generally showing fewer adverse events, such as serum sickness and anaphylaxis (Marston 2018). More than 75 mAbs have already been licensed by the US Food and Drug Administration (FDA) for a spectrum of medical conditions, especially in oncology and immunology (Kaplon 2020; Lu 2020b).

The main principle of the production of monoclonal antibodies follows this sequence:

- isolation and identification of antibodies against the desired antigen;
- selection of the best candidate antibodies;
- mass production of these antibodies;
- and consequently, testing of these antibodies.

The first step, the method to create, isolate and identify potential antibodies, has evolved markedly over time. The first mAb, a mouse IgG2a antibody, was licensed in 1986 to prevent kidney transplant rejection by targeting CD3 on T-lymphocytes. Early mAbs were generated using a hybridoma technique, which involves the extraction of B-lymphocytes from the spleen of an immunised animal (e.g. a mouse), fusion with immortal myeloma cells and in vitro culturing of the cells (-omab; Bayer 2019; Liu 2014). Antii-mouse antibody reactions in patients, and advances in genetic engineering led to the development of chimeric mAbs. These use the same hybridoma technique but replace the constant region of the mouse antibodies with equivalent proteins from human antibodies (~ 65% human, identified by ending -ximab; Bayer 2019). In humanised mAbs, all regions except the complementary-determining regions (CDRs) that create contact with the antigen, are replaced with its human equivalents (~ 95% human, identified by the ending -zumab; Bayer 2019). Both latter strategies sometimes result in low antibody specificity. The most recent generation which aims at resolving this issue, called fully humanised or human mAbs (identified by the ending -umab), can be generated by two routes. The first route follows the hybridoma technique, but uses genetically-altered mice that carry human antibody genes (Bayer 2019). The second route, called phage display, involves the isolation of B-lymphocytes from human blood, obtaining the genetic information of the CDRs by polymerase chain reaction (PCR), and inserting it into bacteriophages that are used to infect *Escherichia coli*. The *E coli* generate a cell library that can be more easily screened for ideal candidate antibodies (Liu 2014).

Ideally, mAbs intended for clinical practice should be easily mass-produced, show high potency (high antigen binding activity), be stable (prolonged shelf-life), have a long half-life, and should not elicit a strong immune response (Marovich 2020). Immunogenicity varies by drug dosage, route of administration, possible contamination, structural features, and humanness of the mAbs, as well as by patient characteristics, such as age, genetic background, and related diseases (Lu 2020b). The strategy to target a single epitope can, depending on the specific target, be utilised both for halting disease progression and as temporary prophylaxis for groups with increased antigen exposure, such as healthcare workers, or those at increased risk of severe disease and mortality (Marston 2018). This may also interrupt the chain of infections. A mixture of mAbs, 'mAbs cocktails', may be more efficient for some antigens, so that they do not escape or mutate.

Although the majority of mAbs are licensed and used to treat chronic diseases, mAbs have also been used to treat infectious diseases, such as Zaire Ebola virus (Antibody Society 2020), respiratory syncytial virus, anthrax and *Clostridioides difficile*, which highlights the great potential of mAbs for the treatment of COVID-19 (Marovich 2020).

How the intervention might work

SARS-CoV-2 stems from the coronavirus family, characterised by a positive-sense, single-stranded RNA (ribonucleic acid; Lu 2020a). The spike proteins on its envelope, which give the virus its name, play a critical role in enabling it to enter a host cell by two mechanisms (Hoffmann 2020; Ou 2020). The human angiotensin-converting enzyme 2 (ACE2) receptor on the spike protein binds to ACE2 proteins that are found throughout the body, but with higher expression in respiratory epithelial cells, type I and II alveolar cells in the lungs, oral cavity, kidneys, testes and intestines (Tolouian 2020). This activates the S proteins' fusion machinery, which inserts into the cellular plasma membrane, brings the viral membrane into proximity and fuses them to create a portal to deposit the virus RNA genome into the host cell, where it starts replicating (Glaunsinger 2020; Tolouian 2020).

Although the exact cellular mechanisms are yet to be uncovered, it is hypothesized that the ACE2 protein plays additional roles in COVID-19 disease severity, especially lung injury. Excessive Inflammation (the so-called 'cytokine storm' seen in some cases), especially interleukin 1 and 6 (IL-1, IL-6), activates the kallikrein-kinin system, which in several steps produces des-Arg^9-BK (DABK). DABK is a ligand that binds to the bradykinin 1 receptor (B1R), responsible for controlling vascular permeability. Usually, ACE2 proteins play the role of guardians of B1R activity by counteracting DABK. Due to internalisation of ACE2 by SARS-CoV-2, they are unable to fulfill their role. In addition, inflammation increases the expression of B1Rs. Both overstimulation and overexpression of B1Rs may lead to increased plasma leakage, which in turn activates more plasma kallikrein–kinin, creating a loop to facilitate local angioedema in the lung, and is potentially responsible for acute respiratory distress syndrome (ARDS) (Van de Veerdonk 2020a; Van de Veerdonk 2020b; Buszko 2020).

Due to the importance of this pathway in viral replication and symptom severity, the focus of current research on SARS-CoV-2-neutralising monoclonal antibodies is on blocking the binding of SARS-CoV-2 to the ACE2 receptor on human cells by targeting the receptor-binding domain on the spike protein of the virus (Marovich 2020). The first COVID-19-specific mAb, bamlanivimab, has been tested in humans since June 2020 (Eli Lilly and Co 2020; NCT04427501). Interim results show a possible lower symptom burden and fewer hospitalisations, with a favourable safety profile in the mAbs group as compared with placebo (Chen 2020).

Studies have examined the effect of previously established immune-modulatory mAbs, such as: IL-6 and IL-1 receptor antagonists (tocilizumab, sarilumab; canakinumab, RPH-104; Catanzaro 2020), and kallikrein-targeting mAbs (e.g. lanadelumab), in controlling the cytokine storm. In this review, we focus on SARS-CoV-2-neutralising mAbs only. As of 10 November 2020, at least 120 SARS-COV-2-neutralising mAbs targeting the spike protein are in discovery, development or testing phases, and 16 are in clinical trial phases (Chinese Antibody Society 2020; Yang 2020). Many questions, besides their potential clinical effectiveness and most favourable timing of administration, remain to be addressed. For example: their adverse events, the duration of protection, and possible mutations of the virus that lead to antibody resistance (for example, cluster 5 linked to mink farming, with previously unseen mutations; WHO 2020d). Changes to the virus may mean the viruses are no longer neutralised or cleared by the mAb, and may instead lead to increased severity of the infection, termed 'antibody-dependent enhancement (ADE)' (Lee 2020).

Why it is important to do this review

The drastically increasing numbers of COVID-19 cases worldwide and the enduring scarcity of treatment options threatens to burden health systems and increase mortality. Many ongoing studies are investigating pharmacological treatment options, but up to now only a few options have shown an effect. With the exception of corticosteroids in people on ventilation (Lamontagne 2020; WHO 2020e) and remdesivir (Beigel 2020; NIH 2020), supportive care remains the only current treatment option, in addition to oxygen therapy in mild cases and invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) in severe cases (NIH 2020). Multiple vaccines against SARS-CoV-2 have been approved in several countries. For example: BNT162b2 by Pfizer-BioNTech, mRNA-1273 by Moderna and Janssen, COVID-19 Vaccine by Johnson&Johnson (FDA 2021a), AZD1222 by AstraZeneca (AstraZeneca 2020), CoronaVac by Sinovac (WHO 2021a). However, their distribution takes time and not everyone may be willing to be vaccinated. In addition, vaccines may not work equally well for everyone. Immunocompromised individuals, for example, may show a lower immune response to the vaccine (Monin-Aldama 2021) and once infected, may be unable to clear the virus, which can lead to long bouts of illness and forms a source for the emergence of new variants (Choi 2020; Kemp 2021). In unvaccinated nosocomial infections, passive immunisation with SARS-CoV-neutralising mAbs may be a possibility to prevent a severe disease course.

Since November 2020, the emergence of several specific variants that have evolved independently from one another has caused concerns (WHO 2020f). Variant B.1.1.7 (also known as 20I/501Y.V1 or VOC 202012/01, now called alpha) was first identified in the UK and spread rapidly throughout the UK, becoming the dominant variant (Volz 2020). It has now spread globally with 114 countries (Volz 2020). B.1.1.7 is associated with increased transmissibility, and early evidence suggests an increase in disease severity (Muik 2021; Tang 2020). Another variant, B.1.351 (also known as 20H/501Y.V2 and now called beta), was initially identified in South Africa. It may also be more transmissible, and has shown resistance to antibody neutralisation (Zhou 2021) and some vaccine resistance (Madhi 2021). Variant P.1 (now called gamma), first identified in Brazil, might reduce antibody neutralisation (Wang 2021). Early in vitro findings suggest that bamlanivimab may efficiently neutralise the lineage B.1.1.7. However, no neutralising effect could be detected against variant B.1.351 (Widera 2021). Variant B.1.617, first found in India and so far categorised by the WHO as a variant of interest, consists of double mutations on the spike protein of the virus. These mutations may decrease binding to mAbs and their neutralisation capability (Cherian 2021; WHO 2021b). Monoclonal antibody cocktails or broadly acting SARS-CoV-2 mAbs such as VIR-7831 (Starr 2021) may be developed to avoid virus escape.

The urgent need to evaluate therapies with a theoretical mechanism of action against SARS-CoV-2 persists due to the limited range of therapeutic options once infected, and the prevalence of individuals who may show an inhibited response to vaccines (e.g. when undergoing chemotherapy) . mAbs are one such option. We will conduct this systematic review as a living evidence synthesis to identify, track, evaluate and update information quickly on research efforts regarding SARS-CoV-2-neutralising mAbs. We will include information on SARS-CoV-2-neutralising mAbs in the early stages of clinical development, as well as providing information on the effectiveness and safety of these mAbs from randomised controlled trials (RCTs) to gain a complete picture of the field. Extensive work in the field of systematic reviews for interventions for COVID-19 has already been undertaken. This work has included immunomodulatory mAbs. There has been one Cochrane Review concerning interleukin-6 agonists (Ghosn 2021) and a non-Cochrane review that aimed to summarise all studies on immunotherapies (e.g. Mansourabadi 2020)).

Various relevant projects may feed into the current undertaking. A research initiative supported by the World Health Organization (WHO) and Cochrane is mapping and evaluating all RCTs for COVID-19, including studies on mAbs (WHO/Cochrane 2020). Another interesting resource is the COVID-19 antibody therapeutics tracker (Yang 2020). This is a collaboration between the Chinese Antibody Society and the Antibody Society that includes mAb studies in different phases (Antibody Society 2020; Chinese Antibody Society 2020). In addition, the Australian clinical guideline is continually being updated for emerging treatments and already includes recommendations on bamlanivimab and casirivimab plus imdevimab (National COVID-19 Clinical Evidence Taskforce 2020).

The current systematic review will fill gaps by identifying, describing, evaluating, and (if available RCTs are identified), meta-analysing all evidence for SARS-CoV-2-neutralising mAbs. It will provide a frequently updated summary of the evidence on mAb development.

OBJECTIVES

To assess the effectiveness and safety of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-neutralising monoclonal antibodies (mAbs) for treating patients with COVID-19 compared to an active comparator, placebo, or no intervention. To maintain the currency of the evidence, we will use a living systematic review approach.

A secondary objective is to track newly developed SARS-CoV-2-targeting mAbs from first tests in humans onwards.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) because this study design provides the best evidence for experimental therapies in highly-controlled therapeutic settings. For RCT data, we used the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a). We had planned to include non-standard RCT designs, such as cluster-randomised studies (methods as recommended in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021b)) and cross-over studies, but have not identified any. In cross-over studies, we would have only considered results from the first period before cross-over because COVID-19 is not a chronic condition, and its exact course and long-term effects are yet to be defined.

To track the development of specific mAbs targeting SARS-CoV-2, we included all prospectively registered studies, including non-randomised studies of interventions (NRSIs) on SARS-CoV-2-neutralising mAbs in humans. We excluded animal studies, pharmacokinetic studies, and in vitro studies.

We included the following formats if sufficient information was available on study design, characteristics of participants, interventions, and outcomes.

- Full-text publications.
- Preprint articles.
- Abstract publications.
- Results published in study registries.

We included preprints and conference abstracts to have a complete overview of the ongoing research activity, especially for tracking newly emerging SARS-CoV-2-neutralising antibodies. We did not apply any limitation with respect to the length of follow-up. We screened platform trials and we are continually following these because they may add new treatment arms.

Types of participants

For RCTs, we included participants with a confirmed diagnosis of COVID-19 (virus antigens or RNA detected). We did not exclude any studies based on age, gender, ethnicity, disease severity, or setting (in- or outpatients). We excluded studies that evaluate mAbs for treatment of other coronavirus diseases such as severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS), or other viral diseases, such as influenza. If studies enrolled populations with mixed viral diseases, we had planned to only include them if study authors provided subgroup data for COVID-19.

For tracking of emerging mAbs by listing non-randomised studies, we also accepted studies in healthy individuals, which are often used for safety assessments in order to gain a complete picture of the current developments.

Types of interventions

We included the following interventions.

- SARS-CoV-2-neutralising mAbs.
- 'Antibody cocktails' that include SARS-CoV-2-neutralising mAbs.

We included the following comparisons for studies with a control arm.

- Any mAb therapy compared with a control intervention, for example, drug treatments (including, but not limited to hydroxychloroquine, remdesivir), standard or hyperimmune immunoglobulin, convalescent plasma, or others. Co-interventions were allowed but must have been comparable between intervention groups.
- Any mAb therapy compared with no treatment or placebo. Co-interventions were allowed but must have been comparable between intervention groups.

We also included studies that compare several mAbs with each other and another treatment, placebo or no treatment, and we included studies that compare several doses of one type of mAb with another treatment, placebo or no treatment.

We excluded SARS-CoV-2-neutralising mAbs used for prevention of COVID-19 and we excluded mAbs that are not specifically designed to treat COVID-19 (such as nivolumab, tocilizumab, canakinumab, etc.).

Types of outcome measures

We evaluated core outcomes based on the Core Outcome Measures in Effectiveness Trials (COMET) Initiative for COVID-19 patients and additional outcomes (COMET 2020; Marshall 2020).

We stratified analyses by disease severity, thereby separating non-hospitalised (asymptomatic or mild disease) and hospitalised individuals (moderate to severe disease) with COVID-19 according to the WHO clinical progression scale (Marshall 2020; see Figure 1). At the later stage, reduction of viral replication may no longer be the main driver of the disease, instead, inflammation and coagulopathy may be more important (Marovich 2020).

Figure 1. ECMO: extracorporeal membrane oxygenation; FiO_2: fraction of inspired oxygen; NIV: non-invasive ventilation; pO_2: partial pressure of oxygen; RNA: ribonucleic acid; SpO_2: oxygen saturation [a]WHO Clinical Progression Scale from The Lancet Infectious diseases: Marshall 2020. Copyright © 2020 Elsevier Ltd. All rights reserved: reproduced with permission. [b]If hospitalised for isolation only, record status for ambulatory patient.

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy*	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥200	7
	Mechanical ventilation pO_2/FIO_2 <150 (SpO_2/FiO_2 <200) or vasopressors	8
	Mechanical ventilation pO_2/FiO_2 <150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

Timing of outcome measurement

In case of time-to-event analysis (e.g. for mortality, time to discharge from hospital, and time to improvement of symptoms), we included the outcome measure based on the longest follow-up time. We also collected information on outcomes from all other time points reported in the publications.

We included adverse events occurring during active treatment, as well as long-term adverse events. If sufficient data were available, we grouped the measurement time points of eligible outcomes. For example, we grouped adverse events and serious adverse events into those measured directly after treatment (up to seven days after treatment), medium-term outcomes (up to 15 days after treatment), and longer-term outcomes (more than 30 days after treatment).

Primary outcomes

Effectiveness of SARS-CoV-2-neutralising mAbs

- All-cause mortality at up to 30 days
- All-cause mortality at up to 60 days

- Clinical progression, improvement of symptoms, or development of severe symptoms according to the WHO scale
  - WHO Clinical Progression Scale (Marshall 2020), measured daily over the course of the study (Figure 1); or
  - assessed as individual items included in the Progression Scale (need for respiratory support, duration):
    - ☐ oxygen by mask or nasal prongs
    - ☐ oxygen by non-invasive ventilation or high-flow nasal cannula
    - ☐ intubation and mechanical ventilation
    - ☐ mechanical ventilation or vasopressors, high-flow oxygen
    - ☐ mechanical ventilation and vasopressors, dialysis or extracorporeal membrane oxygenation (ECMO)
- Quality of life, including fatigue, assessed with standardised scales, for example, WHOQOL-100, at up to seven days; up to 30 days, and longest follow-up available
- Admission to hospital or death for non-hospitalised and hospital discharge and alive for hospitalised participants

Safety outcomes

- Number of participants with adverse events (all grades, grades 1 to 2, grades 3 to 4)
- Number of participants with serious adverse events

Secondary outcomes

- Length of hospital stay (for those admitted to hospital)
- Admission to intensive care unit (ICU)
- Length of ICU stay
- Viral clearance, assessed with reverse transcription-polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to three, seven, and 15 days
- Time to sustained recovery (for hospitalised participants)
- Neurologic dysfunction (for hospitalised participants)
- Thromboembolic events
- Renal failure

Search methods for identification of studies

We carried out weekly searches for completed and ongoing studies in all languages to limit language bias. We conducted weekly checks for newly emerging mAbs and changing terminology regarding mAbs included in the search strategy. We adapted the strategy where necessary.

Electronic searches

For the identification of studies on the effectiveness and safety of SARS-CoV-2-neutralising mAbs, we designed search strategies in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2021). Information Specialist Ina Monsef developed the search strategy based on input by clinicians. It was reviewed by Information Specialist Carolyn Dorée. Due to the international urgency for research on therapies for COVID-19, we assumed that the abstracts of clinical studies would have been published in English. If the full-text publication was published in a language that lay outside the abilities of our team (English, German, Dutch, French, Italian, Malay, and Spanish), we planned to involve Cochrane TaskExchange to identify people who are able to translate (taskexchange.cochrane.org). We restricted the database search to records added since 1 January 2020, as the first studies on COVID-19 were registered on 23 January 2020 (Zhu 2020). We searched the following databases up to 17 June 2021.

- MEDLINE (via Ovid; 1 January 2020 to 17 June 2021; Appendix 1)
- Embase (via Ovid; 1 January 2020 to 17 June 2021; Appendix 2)
- Cochrane COVID-19 Study Register (covid-19.cochrane.org; inception to 17 June 2021; Appendix 3) including:
  - PubMed, daily updates
  - Embase.com, weekly updates
  - ClinicalTrials.gov (www.clinicaltrials.gov), daily updates
  - World Health Organization International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch), weekly updates
  - medRxiv (www.medrxiv.org), weekly updates
  - Cochrane Central Register of Controlled Trials (CENTRAL), monthly updates
- PubMed (for epublications ahead of print only; 1 January 2020 to 17 June 2021; Appendix 4)
- Epistemonikos COVID-19 L*VE Platform (app.iloveevidence.com/loves; inception to 17 June 2021; Appendix 5)
- World Health Organization COVID-19 Global literature on coronavirus disease (bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov; inception to 17 June 2021; Appendix 6)

To track ongoing research efforts and address the potential influence of publication bias on our conclusions, we searched relevant study registries to find ongoing and completed, but not yet published studies. If results were uploaded into the study registry that had not yet been published elsewhere, we integrated these data for the current review and will add or replace data in future updates of this review in case of publication.

To identify prospectively registered platform trials that may add a mAb arm during the course of the study (such as the RECOVERY trial (RECOVERY 2020) or the REMAP-CAP study(REMAP-CAP 2020)), we conducted a separate search with monthly updates in the Cochrane COVID-19 Study Register (Appendix 7). We listed the eligible studies in the section named Studies awaiting classification and regularly checked whether they had added additional treatment arms that include mAbs.

Between submission and publication, we conducted a shortened RCT-only search up to 30 July 2021 (Appendix 8).

Searching other resources

- We checked the reference lists of:
  - all identified studies;
  - relevant review articles; and
  - current treatment guidelines for further literature.
- We conducted forwards citation searching on the included studies via Google Scholar.
- We contacted experts in the field, drug manufacturers, and regulatory agencies in order to retrieve information on unpublished studies.

- We compared our results with results from projects that aim to track COVID-19 intervention research, such as:
  * www.covid-trials.org;
  * covid-nma.com/dataviz;
  * chineseantibody.org/covid-19-track.

Data collection and analysis

Selection of studies

Two review authors (NK, CH, KLC, ZK, ET, MP, NS) independently screened search results for eligibility by reading the abstracts using the Covidence software (Covidence). Following the living review approach, we screened any new citations retrieved by the weekly searches immediately. Abstracts that both review authors found eligible, or abstracts that they disagreed upon or rated as uncertain, were obtained as full-text publications for further discussion. Two review authors assessed the full-text articles of selected studies. If the two review authors were unable to reach consensus, we consulted all review authors who were involved in study selection to reach a final decision.

The search for platform trials was conducted every two months (from November 2020 to July 2021). To identify potential platform trials, two review authors (NK, NS, CH) independently screened the results in Endnote X9.

We documented the study selection process in a flow chart, as recommended in the PRISMA statement (Moher 2009), and showed the total numbers of retrieved references and the numbers of included and excluded studies. We listed all studies that we excluded after full-text assessment and the reasons for their exclusion in the Characteristics of excluded studies section.

Data extraction and management

We treated RCTs differently from non-RCTs. For RCTs, we conducted data extraction according to the guidelines proposed by Cochrane (Li 2020). Two review authors (NK, MP, CH) independently extracted data using a customised data extraction form developed in Microsoft Excel (Microsoft 2018). We resolved disagreements by discussion. If no agreement was obtained, we involved a third review author to resolve the disagreement.

We extracted the following information if reported.

- General information: author, title, source, publication date, country, language, duplicate publications.
- Study characteristics: study design, setting and dates, source of participants, inclusion/exclusion criteria, treatment cross-overs, compliance with assigned treatment, length of follow-up.
- Participant characteristics: age, gender, ethnicity, number of participants recruited/allocated/evaluated, additional diagnoses, the severity of disease, previous treatments, concurrent treatments, complementary medicine (e.g. quercetin, elderberry, zinc).
- Interventions: type of mAbs, the target of mAbs, dose, frequency, timing, duration and route of administration, setting (e.g. inpatient, ambulant), duration of follow-up.
- For RCT studies: control intervention, dose, frequency, timing, duration and route of administration, setting, duration of follow-up.
- Outcomes: as specified under Types of outcome measures.
- 'Risk of bias' assessment: study design, confounding, the definition of risk estimates, selection bias, attrition bias, detection bias, reporting bias.

We included non-RCTs for tracking of emerging mAbs from first-in-human studies onwards, without the aim to meta-analyse, and extracted characteristics as outlined in Table 1.

Assessment of risk of bias in included studies

We assessed the risk of bias in RCTs by using the Risk of Bias 2.0 (RoB 2) tool (Sterne 2019), for the effect of the assignment to the intervention (the intention-to-treat (ITT) effect). The outcomes that we assessed were those specified for inclusion in the summary of findings tables.

Two review authors (NK, CH, KLC, MP, ET, ZK, MN) independently assessed the risk of bias for each outcome. In case of discrepancies among judgments and inability to reach consensus, we consulted a third review author to reach a final decision. We assessed the following types of bias as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021c).

- Bias arising from the randomisation process
- Bias due to deviations from the intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

For cross-over studies, we had planned to use the RoB 2 tool, as outlined in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021b), because we would have only considered results from the first period before cross-over.

For cluster-RCTs, we had planned to add a domain to assess bias arising from the timing of identification and recruitment of participants in relation to the timing of randomisation as recommended in the RoB 2 guidance for cluster-randomised studies (Eldridge 2021) and in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021b).

To address these types of bias, we used the signalling questions recommended in RoB 2 to reach a judgment using the following options.

- 'Yes': if there is firm evidence that the question is fulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question).
- Probably yes': a judgment has been made that the question is fulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question).
- 'No': if there is firm evidence that the question is unfulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question).
- 'Probably no': a judgment has been made that the question is unfulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question).
- 'No information': if the study report does not provide sufficient information to allow any judgment.

We used the algorithms proposed by RoB 2 to assign each domain one of the following levels of bias.

- Low risk of bias.
- Some concerns.
- High risk of bias.

Subsequently, we derived an overall risk of bias rating for each prespecified outcome in each study in accordance with the following suggestions.

- 'Low risk of bias': we judge the study to be at low risk of bias for all domains for this result.
- 'Some concerns': we judge the study to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.
- 'High risk of bias': we judge the study to be at high risk of bias in at least one domain for the result or we judge the trial to have some concerns for multiple domains in a way that substantially lowers confidence in the results.

We used the RoB 2 Excel tool to implement RoB 2 (available from riskofbias.info) and stored and presented our detailed RoB 2 assessments as supplementary online material (available at: zenodo.org/record/4746642#.YJl0OLUzY2w).

Measures of treatment effect

For continuous outcomes, we planned to record the mean, standard deviation, and total number of participants in both treatment and control groups. Where continuous outcomes used the same scale, we performed analyses using the mean difference (MD) with 95% confidence intervals (CIs). For continuous outcomes measured with different scales, we had planned to perform analyses using the standardised mean difference (SMD). For interpreting SMDs, we would have re-expressed SMDs in the original units of a particular scale with the most clinical relevance and impact (e.g. clinical symptoms with the WHO Clinical Progression Scale (Marshall 2020)).

For dichotomous outcomes, we recorded the number of events and participants in both treatment and control groups to obtain the pooled risk ratio (RR) with a 95% CI (Deeks 2021). We had planned to use Peto odds ratio (OR) if the number of observed events was small (less than 5% of sample per group, Deeks 2021). However, because there was very little difference in the effect estimate whether RR or Peto OR was used, for consistency and interpretability we decided to report RRs.

If available, we extracted and reported hazard ratios (HRs) for time-to-event outcomes (e.g. time to death). If HRs were not available, we would have made every effort to estimate the HR as accurately as possible from available data using the methods proposed by Parmar and Tierney (Parmar 1998; Tierney 2007). If sufficient studies provided HRs, we would have used HRs rather than RRs or MDs in a meta-analysis, as they provide more information.

Unit of analysis issues

The aim of this review was to summarise studies that analyse data at the level of the individual. We would have accepted cluster-randomised studies for inclusion. We collated multiple reports of one study so that the study, and not the report, was the unit of analysis.

Studies with multiple treatment groups

As recommended in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a), for studies with multiple treatment groups of the same intervention (i.e. dose, route of administration), we evaluated whether study arms were sufficiently homogeneous to be combined. When arms could not be pooled, we compared each arm with the common comparator separately. For pairwise meta-analyses, we had planned to split the 'shared' group into two or more groups depending on the number of treatment arms and included two or more (reasonably independent) comparisons. For this purpose, for dichotomous outcomes, both the number of events and the total number of participants would have been divided, and for continuous outcomes, the total number of participants would have been divided with unchanged means and standard deviations (SDs).

Dealing with missing data

Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* suggests a number of potential sources for missing data, which we have taken into account: at study level, at outcome level, and at summary data level (Deeks 2021). At all levels, it is important to differentiate between data 'missing at random', which may often be unbiased, and 'not missing at random', which may bias the study and consequently, the review results.

We contacted three principal investigators from included RCTs (ACTIV-3; BLAZE-1 (phase 2); Weinreich (phase 1/2)) and requested data for our prioritised outcomes. We received two responses, from ACTIV-3 and Weinreich (phase 1/2) that they would be unable to provide the requested information, but both stated that a more complete outcome set will be reported in follow-up publications. The authors of BLAZE-1 (phase 2) did not respond. As no additional data were provided, we explicitly decided that data were missing at random.

Assessment of heterogeneity

We planned to assess the heterogeneity of treatment effects between studies using a Chi^2 test with a significance level at $P < 0.1$. We would have used the I^2 statistic (Higgins 2003), to quantify possible heterogeneity (I^2 statistic between 30% and 60% may signify moderate heterogeneity, I^2 statistic between 50% and 90% may signify substantial heterogeneity, and $I^2 > 75\%$ may signify considerable heterogeneity; Deeks 2021). If we considered heterogeneity to be substantial ($I^2 > 50\%$), we had planned to explore potential causes through sensitivity and subgroup analyses. If we could not find a reason for heterogeneity, we would not have performed a meta-analysis but had planned to comment on results from all studies and presented these in tables. As we did not perform meta-analyses, we could not assess heterogeneity.

Assessment of reporting biases

As mentioned above, we searched study registries to identify completed trials that have not been published elsewhere to determine publication bias.

We intended to explore potential publication bias by generating a funnel plot and statistically testing this by conducting a linear regression test for meta-analyses involving at least 10 studies (Page 2021). We would have considered $P < 0.1$ as significant for this test. As we identified fewer than 10 studies per comparison and did not

pool the data in meta-analysis, and we did not generate a funnel plot.

Data synthesis

If the clinical and methodological characteristics of individual studies had been sufficiently homogeneous, we would have pooled the data in meta-analysis. However, th studies originate from different convalescents who were infected in different countries (e.g. China, USA) and at different time points. Although most of the included mAbs target the spike protein of the virus, they all target different epitopes on the spike protein. One mAb, sotrovimab, was derived from a SARS patient. Therefore, the affinity and stability might be very different from monoclonal antibody to monoclonal antibody. Due to the possibility of antibody-dependent enhancement (Arvin 2020), which may be dose-dependent, we had decided at the beginning of the review process that for the current version, we would not pool different doses of mAbs. We may change this for future updates if doses seem to be sufficiently homogeneous. Based on these decisions, we reported results separately per substance and substance combination. We did not perform a meta-analysis, because we had only one study per comparison. We commented on the results narratively, with the results from all studies presented in forest plots to prepare for future updates. We used Review Manager Web (RevMan Web 2020) software to create forest plots (RevMan Web 2020). One review author entered the data into the software, and a second review author checked the data for accuracy.

If meta-analysis had been possible, we would have used the random-effects model for all analyses as we anticipated that true effects are related but are not the same for included studies. We planned to treat placebo and no treatment, which both usually include standard of care at different institutions and time points, as the same intervention. We would have performed analyses according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2021). We planned to analyse studies including different disease stages separately, grouping them into mild, moderate, severe, and critical. However, for this review, we decided to follow the classification of the WHO Progression Scale (Marshall 2020; Figure 1) and group into mild versus moderate and severe disease (outpatients with mild disease; and inpatients who are classified with moderate or severe disease according to the WHO Progression Scale). We would have assessed the effects of potential biases in sensitivity analyses (see Sensitivity analysis). For binary outcomes, we would have based our estimation on the between-study variance on the calculation performed using the Mantel-Haenszel method. We used the inverse variance method for continuous outcomes, outcomes that included data from cluster-RCTs, or outcomes where HRs were available. We planned to explore heterogeneity where the I^2 statistic was more than 50% with subgroup analyses. If we could not find a cause for the heterogeneity, we planned to comment on the results as a narrative with the results from all studies presented in tables, instead of performing a meta-analysis.

We presented non-randomised, prospectively registered studies narratively in table form (see Appendix 9).

Subgroup analysis and investigation of heterogeneity

To explore heterogeneity, we planned to perform subgroup analyses of the following characteristics. The limited number of RCTs that provided results and the variation of SARS-CoV-2-neutralising mAbs used across the studies prevented us from performing any pre-planned subgroup analyses.

- Age of participants (divided into applicable age groups, e.g. children; 18 to 65 years, 65 years and older).
- Pre-existing conditions (diabetes, respiratory disease, hypertension, immunosuppression).
- Timing of first dose administration since symptom onset (up to three days, four to seven days and more than seven days).
- Antibodies detected at baseline.

We had planned to use the tests for interaction to test for differences between subgroup results.

We could not perform subgroup analysis, because we identified only one study per comparison.

Sensitivity analysis

We had planned to perform sensitivity analysis of the following characteristics for our primary outcomes.

- 'Risk of bias' assessment components (studies with a low risk of bias or some concerns versus studies with a high risk of bias).
- Comparison of preprints of COVID-19 interventions versus peer-reviewed articles.
- Comparison of premature termination of studies with completed studies.

We could not perform sensitivity analysis, because we identified only one study per comparison.

Summary of findings and assessment of the certainty of the evidence

Summary of findings tables

We created summary of findings tables and evaluated GRADE for interventions evaluated in RCTs using the GRADEpro GDT software, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2021). We created a separate table per mAb type.

For time-to-event outcomes, we calculated absolute effects at specific time points, as recommended in the GRADE guidance 27 (Skoetz 2020).

According to Chapter 14 of the updated *Cochrane Handbook for Systematic Reviews of Interventions*, the “most critical and/or important health outcomes, both desirable and undesirable, limited to seven or fewer outcomes” should be included in the summary of findings table(s) (Schünemann 2021). We included outcomes prioritised according to the Core Outcome Set for intervention studies (COMET 2020) and patient-relevant outcomes.

Non-hospitalised individuals with COVID-19 and asymptomatic or mild disease

- All-cause mortality (up to 30 and 60 days)
- Clinical progression, improvement of symptoms, or development of severe symptoms according to the WHO Clinical Progression Scale (Marshall 2020)
- Quality of life, assessed with standardised scales (e.g. WHOQOL-100), at up to seven days, up to 30 days, and longest follow-up available

- Admission to hospital
- Adverse events (all grades, grades 1 to 2, grades 3 to 4)
- Serious adverse events

Hospitalised individuals with COVID-19 and moderate to severe disease

- All-cause mortality (up to 30 and 60 days)
- Clinical progression, improvement of symptoms or development of severe symptoms according to the WHO Clinical Progression Scale (Marshall 2020)
- Quality of life, assessed with standardised scales (e.g. WHOQOL-100) at up to seven days, up to 30 days, and longest follow-up available
- Hospital discharge
- Adverse events (all grades, grades 1 to 2, grades 3 to 4)
- Serious adverse events

Assessment of the certainty in the evidence

We used the GRADE approach to assess the certainty in the evidence for the outcomes listed in the previous section.

The GRADE approach uses five domains (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty in the body of evidence for each prioritised outcome. We followed the current GRADE guidance for these assessments in their entirety as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 14 (Schünemann 2021).

We used the overall 'Risk of bias' judgment, derived from the RoB 2 tool, to inform our decision on downgrading for risk of bias. We phrased the findings and certainty in the evidence as suggested in the informative statement guidance (Santesso 2020).

Methods for future updates

Living systematic review considerations

Our information specialist (IM) will provide us with new records each week, which two review authors will screen, extract, evaluate, and integrate following the guidance for Cochrane living systematic reviews (Cochrane LSR). We will run searches for platform trials monthly, and manually check platform trials that were previously identified and listed as 'studies awaiting classification' for additional treatment arms.

We will wait until the accumulating evidence changes one or more of the following components of the review before republishing the review.

- The findings of one or more prioritised outcomes.
- The credibility (e.g. GRADE rating) of one or more prioritised outcomes.
- New settings, populations, interventions, comparisons, or outcomes studied.

We will review the review scope and methods approximately monthly, or more frequently if appropriate, in light of potential changes in COVID-19 research (for example, when additional comparisons, interventions, subgroups or outcomes, or new review methods become available).

RESULTS

Description of studies

Results of the search

We searched all databases and screened the resulting records weekly up to 17 June 2021, and then undertook an RCT-only top-up search up to 30 July 2021. Based on newly developing SARS-CoV-2-specific mAbs, we have added terms to our search strategy; see Differences between protocol and review for the ongoing changes that are still continually being implemented. Our searches retrieved 14,408 records for the mAbs-specific searches. After removing duplicates, we screened 11,516 records based on their titles and abstracts. We excluded 11,327 records that did not meet the prespecified inclusion criteria. Of the remaining 189 records, we included 95 records (of which 28 are listed for tracking; see Appendix 9).

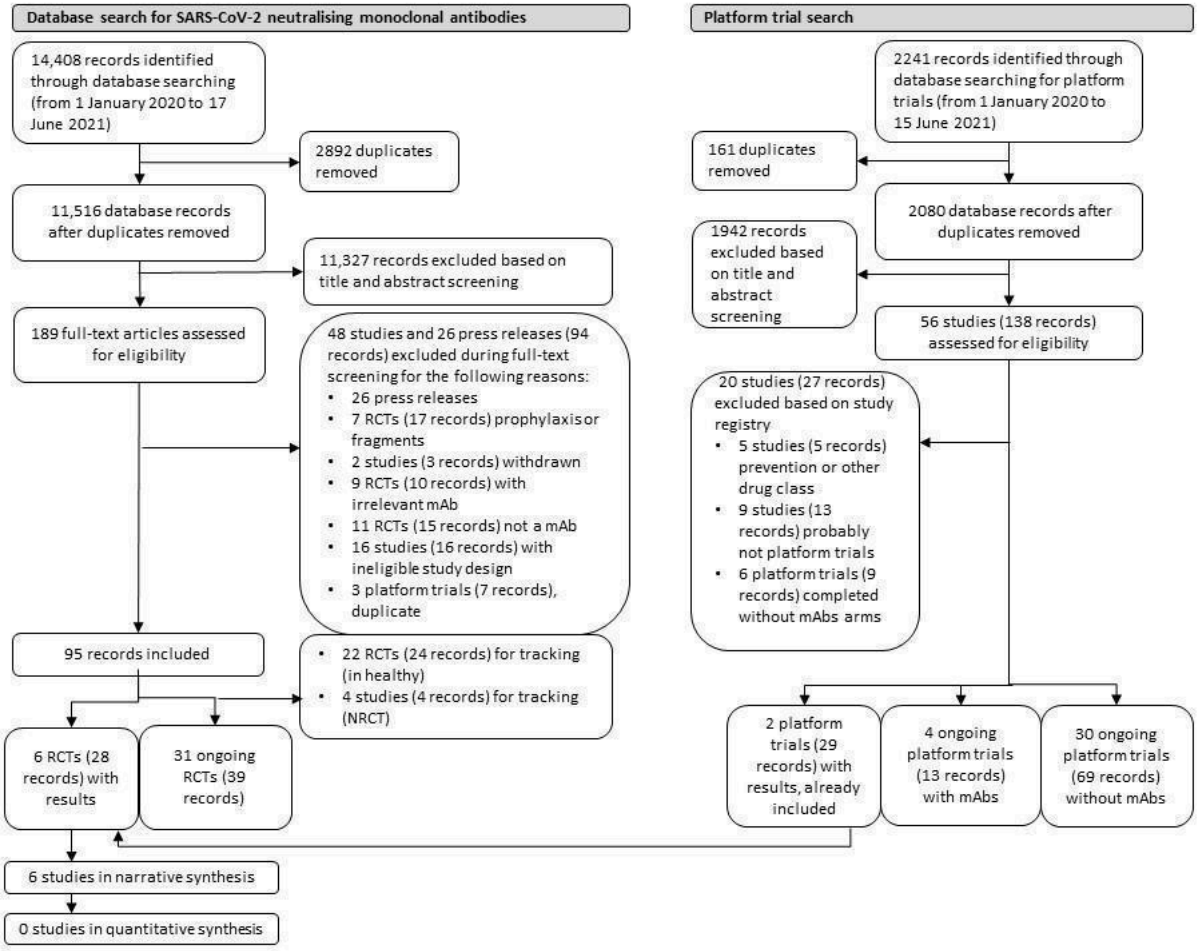
- 6 RCTs (in 28 records) are included in this review, of which three are published as preprint only and one as journal publication with additional data from two preprints.
- 31 RCTs (in 39 records) on 18 different mAbs or mAb combinations are currently ongoing.

Our platform trial search yielded 2241 records. After removing 161 duplicates, we screened 2080 during title and abstract screening and looked at 138 registry records in more detail. Of these, we excluded 20 studies (27 records). We categorised the remaining studies as follows:

- 2 platform trials (29 attached records) are included (already identified by mAbs-specific search), one of these has added new treatment arms and is thus also listed as an ongoing study;
- 4 platform trials (13 records) with at least one mAb as an experimental treatment are ongoing (already identified by mAbs-specific search);
- 30 platform trials (69 records) that may potentially add a mAb during the course of the study are ongoing.

The study flow diagram in Figure 2 illustrates the study selection process according to PRISMA guidelines (Moher 2009).

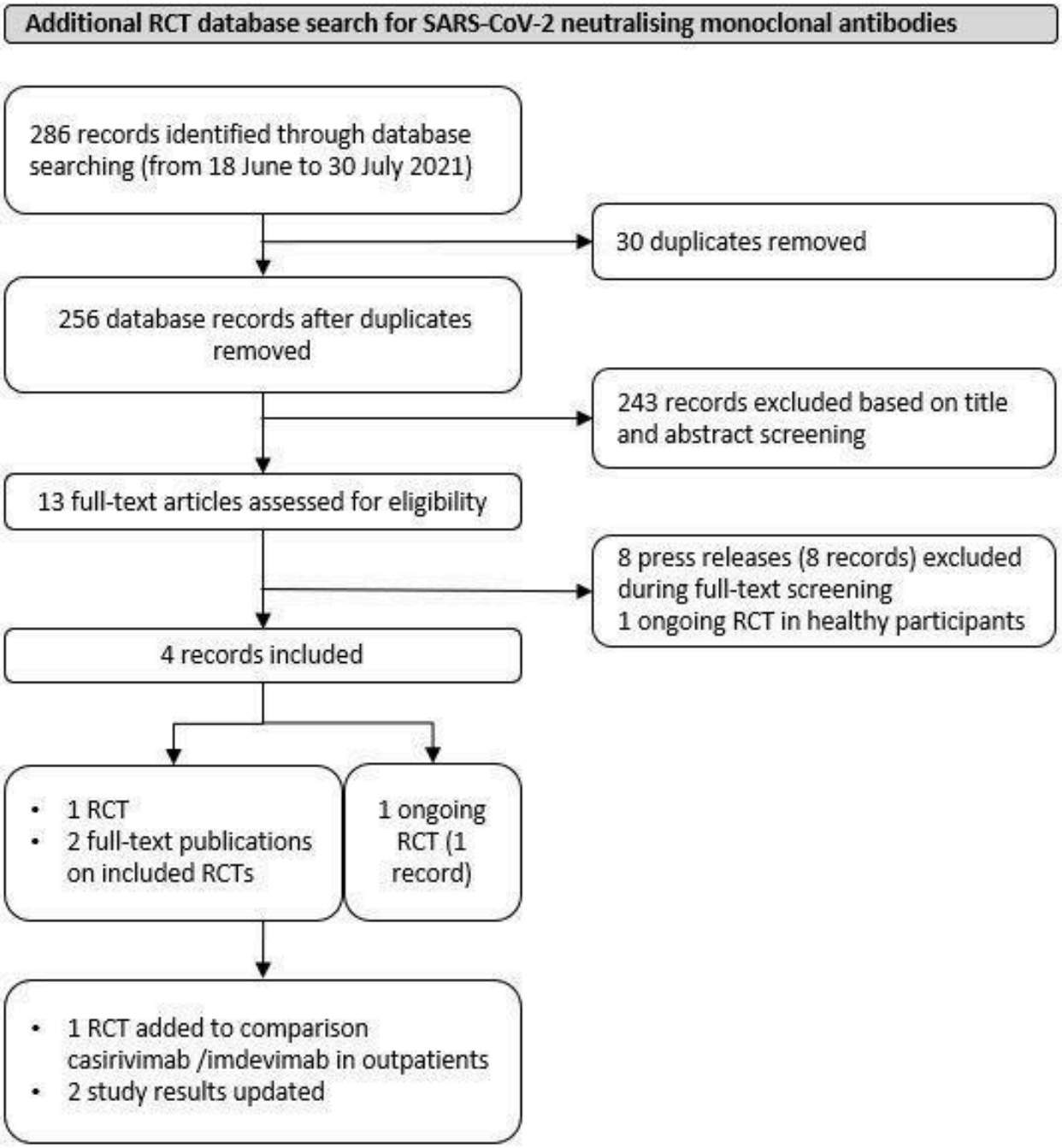
Figure 2. PRISMA flow diagram



Update search between submission and peer review

To keep our review as updated as possible, we conducted an additional search for RCTs in infected individuals only (18 June to 30 July 2021, search strategy: Appendix 8). From the 286 records, we assessed 13 full-text articles (Figure 3); of these, eight were press releases and one an ongoing RCT in healthy participants. We included the following four studies:

Figure 3. PRISMA flow diagram RCT search between 18 June and 30 July 2021



- one ongoing RCT (NCT04952805);
- one preprint from a not yet included study (O'Brien 2021);
- two publications with updated results (ACTIV-3; BLAZE-1 (phase 3)).

We integrated the data from the already included studies with updated results. Results from O'Brien 2021 will be integrated into the next version of this review, and we have listed the study under Characteristics of studies awaiting classification.

Included studies

Randomised controlled trials in individuals with COVID-19

Design and sample size

We included six randomised controlled trials (RCTs) according to our inclusion criteria, involving 17,495 randomised participants (ACTIV-3; BLAZE-1 (phase 2); COMET-ICE; Eom 2021; RECOVERY; Weinreich (phase 1/2); Weinreich (phase 3)). Three studies were published as preprint only (COMET-ICE; Eom 2021; RECOVERY), one study was published in three full-text publications, one conference

abstract (BLAZE-1 (phase 2); BLAZE-1 (phase 3)), another study was published as a journal article with additional data from one preprint (ACTIV-3), and one study was published as a journal article with additional data from two preprints (Weinreich (phase 1/2); Weinreich (phase 3)).

All six included RCTs are still active or ongoing due to different reasons, e.g. follow-up of participants (COMET-ICE), addition of study arms with mAbs (ACTIV-3; BLAZE-1 (phase 3); RECOVERY), or part 2 or 3 of the study recruiting (Eom 2021 (80 mg/kg), Weinreich (phase 3)). The estimated study completion dates ranged from July 2021 to December 2031. All but one study (RECOVERY), were blinded. BLAZE-1 (phase 2) and BLAZE-1 (phase 3) are part of a phase 2 to 3 study currently recruiting participants with completion planned in June 2022 with an estimated number of 3160 participants. Similarly, Eom 2021 is a two-part phase 2 to 3 study, currently recruiting participants into part 2 of the study with completion planned in September 2021 with 1020 participants. Results of a preplanned interim analysis of part 1 of the study were published in a preprint (Eom 2021). COMET-ICE was a phase 2 to 3 study with an estimated completion date in July 2021. Recruitment was stopped on 10 March 2021 due to profound efficacy after 1057 participants had been randomised. There were separate data cut-offs for efficacy and safety for the presented interim analysis. Weinreich (phase 1/2) and Weinreich (phase 3) was a continually enrolling phase 1 to 3 study currently recruiting new participants for phase 3. Phase 1 to 2 was completed and results were reported separately (Weinreich (phase 1/2)). Based on results from phase 1 to 2, the trial was amended in November 2020 and only participants with at least one risk factor for severe COVID-19 were included and no longer randomised to 8.0 g casirivimab and imdevimab. In February 2021, participants were no longer randomised to placebo. Weinreich (phase 3) comprised three cohorts (cohort 1: ≥ 18 years, cohort 2: < 18 years, cohort 3: pregnant at randomisation), but results were reported for cohort 1 only. Completion for phase 3 is planned for November 2021 with 6420 participants.

The studies ACTIV-3 and RECOVERY were platform trials with an adaptive design that allows adding and dropping experimental drugs during the course of the study. In ACTIV-3, the bamlanivimab arm was stopped after interim analysis for futility. This study has added additional SARS-CoV-2-neutralising mAb arms, which are further described in the section on ongoing studies. The estimated completion date is July 2022 with 10,000 participants. RECOVERY is an open-label study with a planned completion date in December 2031 and an estimated enrolment of 40,000 participants. So far it has only one SARS-CoV-2 specific mAb treatment arm. The factorial design allowed randomisation of a single participant into between zero and four treatment arms based on predefined groups of treatment (i.e., convalescent plasma and casirivimab/imdevimab were in the same group, therefore mutually exclusive). An overview of included studies can be found in Table 1. A more detailed description of the methods, eligibility criteria, interventions, and outcomes is provided in the Characteristics of included studies.

Setting and participants

All studies were multicentre trials. The RECOVERY study was conducted at different sites in the UK. The other studies were conducted at different global sites in the USA and Puerto Rico (this site was added after publication of the interim analysis; BLAZE-1 (phase 3)), the USA, Chile, Mexico, and Romania (Weinreich (phase 1/2); Weinreich (phase 3)), the USA, South Korea, Romania, Spain (Eom 2021), the USA, Canada, Brazil, Spain (COMET-ICE) and the USA, Denmark, and Singapore (ACTIV-3; sites in India, Poland, Spain, Switzerland, and the UK joined after publication of interim results).

In five studies, a confirmed SARS-CoV-2 infection was necessary for inclusion (ACTIV-3; BLAZE-1 (phase 2); COMET-ICE; Eom 2021; Weinreich (phase 1/2); Weinreich (phase 3)). RECOVERY included participants with confirmed or suspected SARS-CoV-2 infection. Positive polymerase chain reaction (PCR) rates at baseline ranged from 80% in Weinreich (phase 1/2) and ACTIV-3 to more than 93% in Eom 2021; Weinreich (phase 3) and RECOVERY. No concerning mutations were identified in viral RNA sequences from 255 participants in ACTIV-3. In six participants deletions in codon 69-70 were detected. Genomes in all but one person with alpha variant contained the B strain.

Four studies included non-hospitalised participants with clinical symptoms of mild disease according to the definition of the WHO Clinical Progression Scale (Figure 1; BLAZE-1 (phase 2); COMET-ICE; Eom 2021; Weinreich (phase 1/2); Weinreich (phase 3)). In BLAZE-1 (phase 2), the median age ranged from 39 to 46 years between the treatment groups, and 56.4% of participants were female. In the phase 3 part (BLAZE-1 (phase 3)), the mean age was 53.8 standard deviation ((SD) = 16.8), and 52% were female. In Eom 2021, the median age ranged from 51 to 52 years (interquartile range (IQR) 40 to 61 years), and 49.2% were female. In Weinreich (phase 1/2); Weinreich (phase 3) and COMET-ICE, the median age of the participants was 42 years (IQR 30 to 53 years), 50 years (IQR 38 to 59 years), and 53 years (IQR 18 to 96 years), and 52.9%, 51.3% and 54% of participants were female. Risk factors for severe COVID-19 progression were present in 60.5% in Weinreich (phase 1/2), 67% in BLAZE-1 (phase 2) and 99.7% in COMET-ICE. In Weinreich (phase 3) all participants had at least one risk factor for severe COVID-19 and in Eom 2021 73.44% had comorbidities at baseline.

Two studies included moderately to severely ill, hospitalised participants (ACTIV-3; RECOVERY). The median age of the participants in ACTIV-3 was 61 years (IQR 49 to 71) and 44% of participants were female. Differences between the intervention and control groups in terms of co-existing illnesses were observed in this study. More participants in the intervention group compared to the placebo group suffered from diabetes (33% versus 24%), renal impairment (15% versus 6%), and heart failure (7% versus 1%). At baseline, 27% did not require supplementary oxygen, 57% received oxygen (either < 4 litres/minute or ≥ 4 litres/minute), and 15% received oxygen by noninvasive ventilation (NIV) or high-flow device. No participants required invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) at baseline. In RECOVERY the median age of the participants was 61.9 years (IQR 14.4 to 14.6) and 37% were female. Fifty-three percent of the participants had previous diseases, including diabetes (26.3%), heart disease (21%), chronic lung disease (23%), tuberculosis (0.35%), HIV (0.47%), severe liver disease (1.42%) and severe kidney impairment (5.2%). At baseline, 6.6% of the participants did not receive oxygen, 61.3% received simple oxygen, 26.2% received oxygen by NIV and 6% received invasive mechanical ventilation (IMV).

Baseline serum antibody status was negative for about 70% of the participants in Weinreich (phase 3), 50% in Weinreich (phase 1/2), and 30% in RECOVERY. Eom 2021 reported that less than

6% of the participants were tested positive for immunoglobulin G (IgG) on day 1. In ACTIV-3, 50% of the participants were tested positive for neutralising antibodies (nAb) and 59% had detectable anti-nucleocapsid (N) antibodies.

Interventions

We included six RCTs (ACTIV-3; BLAZE-1 (phase 2); BLAZE-1 (phase 3); COMET-ICE; Eom 2021; RECOVERY; Weinreich (phase 1/2); Weinreich (phase 3)). These included 17,495 randomised participants: 486 participants were assigned to receive varying doses of bamlanivimab (0.7 g, 2.8 g, 7.0 g, ACTIV-3; BLAZE-1 (phase 2)), 632 participants were assigned to receive combination therapy of bamlanivimab and etesevimab (2.8 g each; BLAZE-1 (phase 2); BLAZE-1 (phase 3)), 3600 participants were assigned to receive a combination of casirivimab and imdevimab at different doses (1.2 g, 2.4 g, 8.0 g; Weinreich (phase 1/2); Weinreich (phase 3)), 430 participants were assigned to receive sotrovimab (COMET-ICE), and 216 participants were assigned to receive regdanvimab (0.04 g/kg or 0.08 mg/kg, Eom 2021). A total of 3150 control group participants were assigned to receive placebo infusions. In RECOVERY 4839 participants were allocated to receive a combination of casirivimab and imdevimab (8.0 g). Ninety percent of participants with completed follow-up at time of analysis received the combination and 4946 participants were allocated to receive standard of care. Less than 1% of participants with completed follow-up at time of analysis received a combination of casirivimab and imdevimab (8.0 g). All included substances target the spike protein of SARS-CoV-2.

BLAZE-1 (phase 2) randomised participants into five groups who received either bamlanivimab monotherapy at a dose of 0.7 g, 2.8 g, 7.0 g, combination therapy of bamlanivimab and etesevimab in equal doses of 2.8 g, or placebo IV. Additional arms with different doses of bamlanivimab/etesevimab have been added during the course of the study, but do not have published results yet. In BLAZE-1 (phase 3), participants were treated with a combination of bamlanivimab and etesevimab in equal doses of 2.8 g, or placebo IV. Concomitant treatment was not reported in any phase.

In COMET-ICE, participants were randomised to either 0.5 g sotrovimab (also known as VIR-7831) or single dose of placebo IV. Concomitant treatment was not reported.

Eom 2021 randomised participants into three groups who were treated with regdanvimab (also known as CT-P59) at a dose of 0.04 g/kg or 0.08 g/kg or a single dose of placebo IV. Concomitant medications were taken by more than 10% of the participants in the three study arms included analgesics, antibiotics, antithrombotic agents, agents acting on the renin-angiotensin system, beta-blocking agents, corticosteroids, cough and cold preparations, lipid-modifying agents and vitamins.

Weinreich (phase 1/2) randomised participants into three groups who were treated with a combination of casirivimab and imdevimab (manufactured under the trade name REGN-COV2) in equal doses, at a dose of 2.4 g or 8.0 g or a single dose of placebo IV. No concomitant treatment was reported. Similarly, in Weinreich (phase 3) participants were randomised to receive 1.2 g, 2.4 g or 8.0 g of casirivimab and imdevimab or placebo IV. Concomitant treatment was not reported.

In ACTIV-3, participants were randomised to either 7.0 g bamlanivimab or a single dose of placebo IV. Pre- and concomitant treatments in both study arms included remdesivir and when indicated, antibiotic, antifungal, antiviral, angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB), antiplatelet/anticoagulant, immune-modulating medication, or supplemental oxygen.

RECOVERY randomised participants into two groups to receive either a single dose casirivimab/imdevimab (8.0 g) or standard of care. Pre- and concomitant treatments in both study arms included corticosteroids, aspirin, colchicine, azithromycin, remdesivir, tocilizumab or sarilumab, hydroxychloroquine, lopinavir-ritonavir.

Funding and conflicts of interest

Three studies were funded by pharmaceutical companies (BLAZE-1 (phase 2); COMET-ICE; Eom 2021). Weinreich (phase 1/2) and Weinreich (phase 3) were supported by pharmaceutical companies and partly funded by public sources. In all four studies, the pharmaceutical company was involved in analysing and interpreting the data. Two studies were funded by public sources (ACTIV-3; RECOVERY), with donations of study medications by the manufacturing pharmaceutical companies. However, RECOVERY explicitly reported that the medication sponsor had no role in study conduct and publication of results. Except for the preprints of Weinreich (phase 1/2) and Weinreich (phase 3), all authors reported their conflicts of interest.

Outcomes

In BLAZE-1 (phase 2), the primary outcome was the change in SARS-CoV-2 viral load from baseline to day 11. Planned secondary outcomes were viral clearance at days 7, 11, 15, and 22 and time to SARS-CoV-2 clearance, symptom resolution and time to symptom resolution, symptom improvement and time to symptom improvement, COVID-19-related deterioration (hospitalisation, emergency room or death by days 29, 60 and 85), and change in symptom questionnaire score. Additional biocatalytic and pharmacokinetic/pharmacodynamic methods were conducted. Safety outcomes included treatment-emergent adverse events rated according to the Medical Dictionary for Regulatory Activities (MedDRA) and serious adverse events. The term "treatment-emergent adverse events" is used, which is defined as any "event that first occurred or worsened in severity after baseline", therefore we treated these as regular adverse events. The phase 3 publication reported the combined endpoint hospital admission or death as the primary outcome. Additional reported outcomes for bamlanivimab/etesevimab included: mortality, the combined endpoint hospitalisation, emergency department visit or death, change in viral load at day 7, time to sustained symptom resolution, reduction in viral load to days three and five, time to viral clearance, and adverse events.

In COMET-ICE, the primary endpoint was hospitalisation ≥ 24 hours or death due to any cause up to day 29. Secondary efficacy endpoints included: the composite endpoint emergency room visit, hospitalisation or death, all-cause mortality (at days 29, 60, 90), patient-reported outcomes (mean change in inFLUenza Patient-Reported Outcome score (FLU PRO Plus)), changes in viral load, progression to supplemental oxygen up to day 29, incidence and titres of serum anti-drug antibodies (ADA). Safety endpoints were adverse events (including adverse events of special interest) and serious adverse events. Patient-reported outcomes, change in viral load, and various time points for all-cause mortality and adverse events were not reported. Secondary and exploratory endpoints

were excluded from this interim analysis, because the study was still ongoing.

In Eom 2021, the primary efficacy endpoint of part 1 was time to negative conversion up to day 28, time to clinical recovery up to day 14. Secondary efficacy endpoints (assessed up to days 7, 14, 28) were the proportion of patients with negative seroconversion; proportion of patients with clinical symptoms requiring hospitalisation, oxygen, therapy, or mortality; proportion of patients requiring supplemental oxygen; intensive care unit (ICU) transfer; all-cause mortality; time to clinical recovery; duration of fever; hospital admission; need for IMV; patients requiring rescue therapy, time to National Early Warning Score 2 (NEWS2) of 0, scores of other known symptoms (vomiting, diarrhoea, loss of taste or smell), incidence of antibody-dependent enhancement, viral serology for SARS-CoV-2 antibody. Safety outcomes were reported as treatment-emergent adverse events (TEAEs; including TEAEs of special interest), treatment-emergent serious adverse events (TESAEs). The endpoints duration of fever, time to National Early Warning Score 2 (NEWS2) of 0, scores of other known symptoms (vomiting, diarrhoea, loss of taste or smell) were not reported in the preprint, and the outcome proportion of patients with negative seroconversion was not reported up to day 7.

In Weinreich (phase 1/2), for the reported phase 2 data, the primary virological endpoint was time-weighted average change in viral load from baseline through day 22, according to the statistical analysis plan; in the publication, this outcome was reported through day 7. Secondary endpoints were time to negative reverse transcription PCR (RT-qPCR) test on nasopharyngeal swabs, change in viral shedding at each visit through day 29, time-weighted average change from baseline in viral shedding (days 5, 7, 15, and 29), the percentage of participants with one or more and two or more medically attended visits through day 29, number of COVID-19-related medically attended visits by day 29, proportion of admissions to hospital, ICU admission, outpatient visits, percentage of participants requiring mechanical ventilation, days of hospitalisation due to COVID-19 by day 29, all-cause mortality, time to symptom onset and duration of symptoms. Only the primary virological endpoint, percentage of participants with one or more and two or more medically attended visits through day 29, number of COVID-19-related medically attended visits by day 29 and the proportion of admissions to hospital were reported in this final analysis of phase 1 to 2 in the form of a preprint. Safety outcomes were reported as TEAEs, adverse events of special interest and TESAEs. Weinreich (phase 3) reported for phase 3 the endpoints all-cause mortality by day 29 (for the doses 1.2g and 2.4 g), percentage of participants requiring mechanical ventilation (for the doses 1.2 g and 2.4 g), hospital admissions, days of hospitalisation due to COVID-19 by day 29 (for the doses 1.2 g and 2.4 g), admission to ICU (for the doses 1.2 g and 2.4 g), TEAEs all grades, TEAEs grades 3 to 4 and TESAEs.

In the ACTIV-3 study, the primary outcomes were time to sustained recovery up to 90 days, defined as hospital discharge and being alive and home for at least 14 days, and two outcomes (pulmonary and pulmonary plus outcome) measured on 7-level ordinal scales, adapted from the WHO. The pulmonary outcome was based on oxygen requirements and the pulmonary plus outcome was based on oxygen requirements in combination with organ dysfunction associated with the progression of the disease. The secondary outcomes were death from any cause, composite of sustained recovery and mortality through day 90, time to hospital discharge, days alive outside of acute care hospital, ordinal outcomes on days 14 and 28, change in National Early Warning (NEW) score through day 5, clinical organ failure, composite of death and clinical organ failure, and a composite of cardiovascular and thromboembolic events. The primary safety outcome was a composite outcome of death, serious adverse events, or grades 3 or 4 adverse events assessed through day five. Secondary outcomes included all-cause mortality through day 90 and a composite outcome considering time to sustained recovery and mortality through day 90. In addition, infusion-related reactions, serious adverse events or death, adverse events of any grade through day 7 and at days 14 and 28 were planned. All preplanned outcomes for this stage have been reported except days alive outside of acute care hospital and change in NEW score (reported as odds ratio (OR)).

In RECOVERY, outcomes were reported at day 28 after randomisation. The primary outcome was all-cause mortality. Secondary outcomes were time to hospital discharge, use of IMV or death. Subsidiary outcomes were use of ventilation, duration of IMV, use of renal dialysis or haemofiltration, thrombotic events. Safety outcomes included cause-specific mortality, major cardiac arrhythmia, major bleeding, early safety of antibody-based therapy and non-coronavirus infection. All preplanned outcomes, except non-coronavirus infection were reported in the preprint.

Ongoing randomised controlled trials testing SARS-CoV-2-specific mAbs

We identified 36 ongoing studies in addition to the included platform trial ACTIV-3 which have added new mAbs. These are listed in Appendix 10, more information on each study can be found in the Characteristics of ongoing studies. Of these RCTs, four are ongoing platform trials without results on mAbs yet (ACTIV-2; AGILE; DISCOVERY; OPTIMISE-C19) and 32 are standard RCTs (EUDRACT2020-003401-60; NCT04411628; NCT04426695; NCT04551898; NCT04584697; NCT04593641; NCT04627584; NCT04631666; NCT04631705; NCT04634409; NCT04644120; NCT04644185; NCT04649515; NCT04666441; NCT04674566; NCT04683328; NCT04709328; NCT04723394; NCT04734860; NCT04748588; NCT04770467; NCT04771351; NCT04779879; NCT04780321; NCT04787211; NCT04787211; NCT04796402; NCT04796402; NCT04805671; NCT04805671; NCT04822701; NCT04822701; NCT04840459; NCT04840459; NCT04900428; NCT04900428; NCT04913675; NCT04952805), which evaluated 23 different SARS-CoV-2-specific mAb types or mAb combinations (e.g., AZD7442, MAD0004J08, BRII-196/BRII-198, casirivimab/imdevimab, bamlanivimab/etesevimab, C135-LS/C144-LS). Most SARS-CoV-neutralising mAbs in humans have proceeded to phase 2 studies onwards.

Two of the ACTIV-3 arms, BRII-196/BRII-198, and sotrovimab, were closed with 343 and 344 randomised participants each for futility, and results have not yet been published (NIH 2021).

Ongoing platform trials

ACTIV-2 is being conducted in outpatients and has five active mAbs treatment arms (bamlanivimab, BRII-196/BRII-198, AZD7442 (IV or IM), C135-LS/C144-LS). The estimated study completion date is May 2023.

The studies ACTIV-3, AGILE, and DISCOVERY include hospitalised patients and randomise(d) into various mAb treatment

arms (ACTIV-3: AZD7442, bamlanivimab, BRII-196/BRII-198 and VIR-7831; AGILE: VIR-7832 and VIR-7831; DISCOVERY: AZD7442). In ACTIV-3, the bamlanivimab arm was stopped for futility after an interim analysis. We included the published results in this review. Randomisation to VIR-7831 and BRI196/BRII/198 has stopped, but participants are still being recruited for the AZD7442 arm. Results had not been published by the time of review writing. The estimated study completion date is July 2022. AGILE is expected to complete by April 2022. DISCOVERY is planned to complete in March 2023.

OPTIMISE-C19 includes any COVID-19 positive patient who is eligible for the examined mAbs under US Food and Drug Administration (FDA) emergency use authorization (EUA), which may change over time. Currently, the study randomises patients into bamlanivimab, bamlanivimab/etesevimab, or casirivimab/imdevimab treatment arms and is estimated to have completed by December 2022.

Studies awaiting classification: ongoing platform trials without SARS-CoV-2-specific mAbs

To facilitate rapid testing of emerging treatments, adaptive platform trials have become more frequent, because they allow more flexibility in adding new treatment arms and dropping futile treatment arms without registration of a new study. From our specific search for these studies, we have identified five ongoing platform trials with at least one SARS-CoV-2-specific mAb as a treatment arm (ACTIV-2; ACTIV-3; AGILE; DISCOVERY; OPTIMISE-C19), which are also listed above as included studies. We identified an additional 30 ongoing platform trials without any SARS-CoV-2-specific mAb treatment arms (ACCORD & ACCORD 2; ACOVACT; ACTIV-1 IM; ACTT-4; ANTICOV; ARCO-Home; BEAT COVID-19; BET-A (ACTIV-5); BET-B (ACTIV-5); CATALYST; CCAP; COLHEART-19; COPPS; CORIMUNO; COVID MED; DEFINE; EU SolidAct; I-SPY; NCT04359095; NCT04590586; PaTS-COVID; PRINCIPLE; PROTECT-Surg; REMAP-CAP; SOLIDARITY; SWISSPED-RECOVERY; TACTIC-E; TACTIC-R; TOGETHER-3; VIRCO). For regular tracking, we decided to list them under the Studies awaiting classification section.

Excluded studies

Tracking of SARS-CoV-2-specific mAbs under development

We excluded 27 studies (29 records) from our search on SARS-CoV-2-specific mAbs because they were conducted on healthy participants; however, we listed these studies for tracking (details in Appendix 9).

- 23 RCTs (25 records) were excluded because they are being done on healthy participants (Track: NCT04852978; Track: ChiCTR2100042150; Track: jRCT2071200117; Track: NCT04896541; Track: NCT04429529; Track: NCT04441918; Track: NCT04441931; Track: NCT04479631; Track: NCT04479644; Track: NCT04483375; Track: NCT04507256; Track: NCT04519437; Track: NCT04525079; Track: NCT04532294; Track: NCT04533048; Track: NCT04537910; Track: NCT04561076; Track: NCT04567810; Track: NCT04590430; Track: NCT04592549; Track: NCT04691180; Track: NCT04700163; Track: NCT04932850)
- 4 studies (4 records) are non-randomised studies (Track: NCT04617535; Track: NCT04701658; Track: NCT04603651; Track: NCT04656691)

Randomised controlled trials in healthy participants

The 23 RCTs on healthy participants examined 19 different mAbs or mAb combinations (ADM03820, anti-SARS-CoV-2 chicken egg IgY, AZD7442, bamlanivimab, BGB-DXP593, BRII-196, BRII-196/BRII-199, BRII-198, casirivimab/imdevimab, CT-P59, C144-LS/C-135-LS, etesevimab, HFB30132A, HLX70, JMB2002, MW33, SCTA01, TY027, MAD0004J08). Studies planned to include between 16 and 974 participants. All except ADM03820, anti-SARS-CoV-2 chicken egg IgY, HFB30132A, JMB2002, and HLX70 are also being investigated in infected individuals (Appendix 9).

Year of completion	Studies
2020	7 (Track: NCT04441918; Track: NCT04441931; Track: NCT04525079; Track: NCT04533048; Track: NCT04537910; Track: NCT04567810; Track: NCT04483375), of these, 5 show completed but without results
2021	11 (Track: ChiCTR2100042150 Track: NCT04429529; Track: NCT04479631; Track: NCT04479644; Track: NCT04507256; Track: NCT04519437; Track: NCT04532294; Track: NCT04561076; Track: NCT04590430; Track: NCT04592549; Track: NCT04691180)
2022	4 (Track: NCT04852978; Track: NCT04896541; Track: NCT04700163; Track: NCT04932850)

One study did not report a planned completion date.

Non-randomised studies

All four non-randomised studies are US-based prospective cohorts or expanded access studies that investigate single dose infusions (IV) of mAbs or mAb combinations in outpatients; three of these in participants with risk factors (Track: NCT04701658; Track: NCT04603651; Track: NCT04617535).

Track: NCT04701658 provides bamlanivimab (IV) and will compare the treatment with matched controls for their primary outcome hospitalisation or death by day 29. Completion is planned for June 2021 with 3000 participants. Track: NCT04603651 provides expanded access to bamlanivimab (IV), however, expanded access is no longer available according to clinicaltrials.gov. Track: NCT04656691 provided at-home infusions of bamlanivimab by registered nurses and examines the frequency of hospitalisations and safety in 4000 participants (study completed according to clinicaltrials.gov). Track: NCT04617535 provides expanded access

to casirivimab/imdevimab (IV), no further information regarding sample size or outcomes is reported.

Excluded studies

From the main search, we excluded 94 records (26 press releases and 48 studies) that did not match our inclusion criteria (Figure 2):

- 7 studies (17 records) investigated mAbs as prevention of SARS-CoV-2 infection (BLAZE-2; NCT04452318; NCT04625725; STORM CHASER; NCT04859517; NCT04894474) or mAb fragments (NCT04514302);
- 2 studies (3 records) were no longer available in the study registry (NCT04766671; NCT04454398);
- 20 studies (25 records) with irrelevant interventions (9 studies not SARS-CoV-2-specific mAb: EUDRACT2020-002713-17; FORCE; NCT04275245; NCT04341116; NCT04369469; NCT04415073; NCT04494724; NCT04516564; NCT04586153; 2 studies polyclonal Abs: NCT04453384; NCT04469179; 9 studies other interventions: COREG; COVERAGE; C-SMART; MAS-COVID; NCT04453384; NCT04494984; NCT04569786; NCT04574869; PANAMO);
- 16 studies (16 records) with ineligible study design (ChiCTR2000030012; Dhand 2021a; Dong 2021; Alam 2021; Bariola 2021; Beam 2021; Cohen 2021; Dale 2021; Dhand 2021b; Ganesh 2021; Karr 2021; Kutzler 2021; Rainwater-Lovett 2021; Shirk 2021; Webb 2021; Yang 2020);
- 3 studies (7 records) were duplicates;
- 26 press releases of included or ongoing studies.

From the platform trial search, we excluded 20 studies (27 records) for the following reasons (Figure 2):

- 5 platform trials (5 records) explored treatments for prevention of SARS-CoV-2 or other drug classes only (ACTIV-4; COVER HCW; CROWN CORONA; NCT04498273; PROFACT-01);
- 9 studies (13 records) did not plan to add treatment arms (AMMURAVID; ASCOT-ADAPT; COVERAGE; COVID_Aging; C-SMART; jRCT2031190264; NCT04629703; PO-COV-III-20; RESP301-002);
- 6 platform trials (in 9 records) were completed without having added a mAb (ACTT; ACTT-2; ACTT-3; EUCTR2020-001243-15-BE; NCT04354428; NCT04370262).

Risk of bias in included studies

Risk of bias in randomised controlled trials

We assessed methodological quality and risk of bias for each comparison and outcome of the six RCTs (ACTIV-3; BLAZE-1 (phase 2); COMET-ICE; Eom 2021; RECOVERY; Weinreich (phase 1/2); Weinreich (phase 3)) that provided outcomes relevant for this review using the Risk of Bias 2.0 (RoB 2) tool (Sterne 2019), recommended in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021c). Since there were separate publications as preprints on phases 1 to 2 (Weinreich (phase 1/2)) and phase 3 (Weinreich (phase 3)) for the Weinreich study, we assessed risk of bias separately for the relevant outcomes provided.

Please refer to the risk of bias table section after the 'Characteristics of studies' section for more detailed information on the risk of bias assessments for each outcome. The completed RoB 2 tool with responses to all assessed signalling questions is available online at: https://zenodo.org/record/5159915#.YQq7pYgzY2w.

Risk of bias in randomised controlled trials in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease)

Bamlanivimab compared with placebo in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease)

We judged the risk of bias for BLAZE-1 (phase 2), the only study assessing bamlanivimab (LY3819253, LY-CoV555) in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease), to be low across outcomes: all-cause mortality up to 30 days (see Risk of bias table for Analysis 1.1), admission to hospital or death (see Risk of bias table for Analysis 1.2), viral clearance at days 7 and 15 (see Risk of bias table for Analysis 1.3; Risk of bias table for Analysis 1.4), all grades of adverse events (see Risk of bias table for Analysis 1.5), and serious adverse events (see Risk of bias table for Analysis 1.6). We could not assess the risk of bias for all-cause mortality up to 60 days, clinical progression/improvement of symptoms or development of severe symptoms, length of hospital stay, admission to ICU and length of ICU stay, viral clearance at day 3, adverse events (grades 1 to 2, and grades 3 to 4), quality of life (up to7 days, 30 days and longest follow-up), renal failure and thromboembolic events, as BLAZE-1 (phase 2) did not report these outcomes.

Bamlanivimab/etesevimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease)

We judged the risk of bias for BLAZE-1 (phase 2), the only study assessing the combination of bamlanivimab and etesevimab in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease) to be high at the study level, and thus across the outcomes (all-cause mortality by day 30, hospital admission or death, viral clearance at days 7 and 15, all grades adverse events and serious adverse events) because the staggered start of treatment arms caused the bamlanivimab/etesevimab arm to be randomised later than the placebo arm due to adjustment of the allocation ratio. As the standard of care is evolving quickly, groups may not be comparable. We could not assess the risk of bias for all-cause mortality up to 60 days, clinical progression/improvement of symptoms or development of severe symptoms, length of hospital stay, admission to ICU and length of ICU stay, viral clearance at day 3, adverse events (grades 1 to 2, and grades 3 to 4), quality of life (up to seven days, 30 days and longest follow-up), renal failure and thromboembolic events, as BLAZE-1 (phase 2) did not report these outcomes. Due to the high risk of bias, reported outcomes were not included in the analysis but reported narratively instead.

For BLAZE-1 (phase 3), we judged the risk of bias to be low across the outcomes: all-cause mortality up to 30 days (see Risk of bias table for Analysis 2.1), admission to hospital or death (see Risk of bias table for Analysis 2.2), length of hospital stay, viral clearance at days 3, 7, and 15 (see Risk of bias table for Analysis 2.3; Risk of bias table for Analysis 2.4; Risk of bias table for Analysis 2.5), all grades adverse events (see Risk of bias table for Analysis 2.6) and serious adverse events (see Risk of bias table for Analysis 2.7). We could not assess the risk of bias for all-cause mortality up to 60 days, clinical progression or development of severe symptoms,

admission to ICU and length of ICU stay, viral clearance (at days 3, 7, and 15), adverse events (grades 1 to 2 and grades 3 to 4), quality of life (up to seven days, 30 days and longest follow-up), renal failure and thromboembolic events, as BLAZE-1 (phase 3) did not report these outcomes.

Casirivimab/imdevimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease)

We judged the risk of bias for Weinreich (phase 1/2) (preprint), the only study assessing the combination of casirivimab and imdevimab in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease) to be of low risk of bias across the outcomes grades 3 to 4 adverse events (see Risk of bias table for Analysis 3.2), and serious adverse events (see Risk of bias table for Analysis 3.3). For the outcome hospital admission or death (see Risk of bias table for Analysis 3.1) we judged the risk of bias to be of some concern because the statistical analysis plan and protocol were not provided with the preprint. We could not assess the risk of bias for: all-cause mortality at up to 30 and 60 days, clinical progression/improvement of symptoms, length of hospital stay, admission to ICU and length of ICU stay, clinical progression/improvement of symptoms or development of severe symptoms, viral clearance (at days 3, 7, 15) and adverse events (all grades and grades 1 to 2), quality of life (up to seven days, 30 days and longest follow-up), renal failure and thromboembolic events, as Weinreich (phase 1/2) did not report these outcomes.

For Weinreich (phase 3) (preprint), we judged the risk of bias to be high across the outcomes: mortality by day 30, clinical progression/improvement of symptoms, admission to hospital or death, length of hospital stay, admission to ICU, adverse events (all grades and grades 3 to 4) and serious adverse events, because participants without risk factors were excluded from analysis and it was unclear which participants were included in the analysis set. More participants were missing than the ones not receiving or discontinuing treatment. Furthermore, data for participants who received casirivimab/imdevimab at a dose of 8.0 g were not reported on all relevant outcomes. We could not assess the risk of bias for all-cause mortality at up 60 days, length of ICU stay, development of severe symptoms, viral clearance (at days 3,7 and 15) and adverse events grades 1 to 2, quality of life (up to day 7 days, 30 days and longest follow-up), renal failure and thromboembolic events, as Weinreich (phase 3) did not report these outcomes. Due to the high risk of bias, reported outcomes were not included in the analysis but reported narratively instead.

Sotrovimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease)

We judged the risk of bias for COMET-ICE, the only study assessing sotrovimab in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease) to be some concerns across the outcomes: all-cause mortality up to 30 days (see Risk of bias table for Analysis 4.1), development of severe symptoms according to WHO scale (see Risk of bias table for Analysis 4.2; Risk of bias table for Analysis 4.3), admission to hospital or death (see Risk of bias table for Analysis 4.4), admission to ICU (see Risk of bias table for Analysis 4.5) and for safety outcomes (adverse events (all grades and grades 3 to 4), and serious adverse events; see Risk of bias table for Analysis 4.6; Risk of bias table for Analysis 4.7; Risk of bias table for Analysis 4.8), because the trial was stopped preliminary and protocol or statistical analysis plan were not available. We could not assess the risk of bias for all-cause mortality up to 60 days, clinical progression/improvement of symptoms, length of hospital stay, length of ICU stay, viral clearance (at days 3, 7, 15), adverse events grades 1 to 2, quality of life (up to seven days, 30 days and longest follow-up), renal failure and thromboembolic events, as COMET-ICE did not report these outcomes.

Regdanvimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease)

We judged the risk of bias for Eom 2021, the only study assessing regdanvimab in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease) to be low across the outcomes: mortality up to 30 days (see Risk of bias table for Analysis 5.1), development of severe symptoms (see Risk of bias table for Analysis 5.2), admission to hospital or death (see Risk of bias table for Analysis 5.3), admission to ICU (see Risk of bias table for Analysis 5.4) and viral clearance at day 15 (see Risk of bias table for Analysis 5.5), and safety outcomes (adverse events all grades (see Risk of bias table for Analysis 5.6), adverse events grades 3 to 4 (see Risk of bias table for Analysis 5.7) and serious adverse events (see Risk of bias table for Analysis 5.8)). We could not assess the risk of bias for all-cause mortality up to 60 days, clinical progression/improvement of symptoms, length of hospital stay, length of ICU stay, viral clearance at days three and seven, adverse events grades 1 to 2, quality of life (up to seven days, 30 days and longest follow-up), renal failure and thromboembolic events, as Eom 2021 did not report these outcomes.

Risk of bias in randomised controlled trials in hospitalised individuals with COVID-19 (moderate to severe disease)

Bamlanivimab compared to placebo in hospitalised individuals with COVID-19 (moderate and severe disease)

Overall, we judged the risk of bias for ACTIV-3, the only study that assessed bamlanivimab in hospitalised individuals, to be low across outcomes: all-cause mortality by days 30 and 90 (see Risk of bias table for Analysis 6.1; Risk of bias table for Analysis 6.2), clinical progression/improvement of symptoms or development of severe symptoms (see Risk of bias table for Analysis 6.3; Risk of bias table for Analysis 6.4), hospital discharge (time-to-event and at day 5; see Risk of bias table for Analysis 6.5; Risk of bias table for Analysis 6.6), adverse events grades 3 to 4 (see Risk of bias table for Analysis 6.7), and serious adverse events by days 30 and 90 (see Risk of bias table for Analysis 6.8; Risk of bias table for Analysis 6.9), time to sustained recovery by day 90 (see Risk of bias table for Analysis 6.10), neurological dysfunction at day 28 (transient ischemic events see Risk of bias table for Analysis 6.11, acute delirium CVA see Risk of bias table for Analysis 6.12 and cerebrovascular event see Risk of bias table for Analysis 6.13), thromboembolic events (see Risk of bias table for Analysis 6.14) and renal dysfunction (see Risk of bias table for Analysis 6.15). We noted differences in the baseline characteristics of the participants between treatment groups, but we assumed that these differences are unlikely to indicate problems with the randomisation process. We could not assess the risk of bias for the outcome quality of life (up to 7 days, 30 days and longest follow-up), admission to ICU and length of ICU stay, viral clearance (at days three, seven, and 15), and adverse events (all grades and grades 1 to 2) as these were not reported in the study.

Casirivimab/imdevimab compared to placebo in hospitalised individuals with COVID-19 (moderate and severe disease)

We judged the risk of bias for RECOVERY, the only study assessing casirivimab/imdevimab in hospitalised individuals to be high across the outcomes: all-cause mortality up to 30 days (see Risk of bias table for Analysis 7.1), development of severe symptoms according to WHO scale (see Risk of bias table for Analysis 7.2), hospital discharge alive by day 30 (see Risk of bias table for Analysis 7.3), thromboembolic events (see Risk of bias table for Analysis 7.4) and renal dysfunction (need for dialysis) (see Risk of bias table for Analysis 7.5), because of the open-label design of the study control group participants may have received concomitant treatment more quickly. We could not assess the risk of bias for the outcomes: all-cause mortality at up to 60 days, clinical progression/improvement of symptoms, quality of life (up to seven days, 30 days, and longest follow-up), safety outcomes (adverse events (all grades, grades 1 to 2, grades 3 to 4) and serious adverse events), length of hospital stay, admission to ICU, length of ICU stay, viral clearance (at days 3, 7, 15), time to sustained recovery, and neurologic dysfunction, as RECOVERY did not report these outcomes.

Effects of interventions

See: **Summary of findings 1** Bamlanivimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease); **Summary of findings 2** Bamlanivimab/etesevimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease); **Summary of findings 3** Casirivimab/imdevimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease); **Summary of findings 4** Sotrovimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease); **Summary of findings 5** Regdanvimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease); **Summary of findings 6** Bamlanivimab compared to placebo in hospitalised individuals with COVID-19 (moderate to severe disease); **Summary of findings 7** Casirivimab/imdevimab compared to usual care alone in hospitalised individuals with COVID-19 (moderate to severe disease)

SARS-CoV-2-specific mAbs in non-hospitalised individuals with COVID-19 and asymptomatic or mild disease

Bamlanivimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease)

We present our certainty in the evidence for prioritised outcomes for the comparison bamlanivimab and placebo in non-hospitalised individuals in Summary of findings 1. We included only one study for this comparison, which did not report the outcomes mortality by day 60, clinical progression or development of severe symptoms, and quality of life (BLAZE-1 (phase 2)). Since all outcomes were evaluated separately for each treatment arm (0.7 g, 2.8 g, 7.0 g of bamlanivimab), we did not pool the data.

Primary outcomes

All-cause mortality (by days 30 and 60)

One RCT (BLAZE-1 (phase 2)) reported all-cause mortality at day 29 for 465 participants.

None of the participants died by day 29 (101 participants in dose 0.7 g arm, 107 participants in 2.8 g arm, 101 participants in 7.0 g arm and 156 participants in placebo arm; effect estimates not estimable, low-certainty evidence for all arms; Analysis 1.1). For each comparison, our main reason for downgrading was very serious imprecision due to no observed events in any of the groups. BLAZE-1 (phase 2) did not report all-cause mortality at up to 60 days.

Admission to hospital or death

Admission to hospital was reported for 465 participants at day 29 (BLAZE-1 (phase 2)). Data indicate that treatment with 0.7 g, 2.8 g or 7.0 g bamlanivimab may result in a decrease in admissions to hospital compared to treatment with placebo, with 10, 18 and 20 admissions per 1000 for the bamlanivimab groups as compared to 58 per 1000 in the placebo group (risk ratio (RR) 0.17, 95% confidence interval (CI) 0.02 to 1.33; RR 0.32, 95% CI 0.07 to 1.47; and RR 0.34, 95% CI 0.08 to 1.56, respectively; 1 RCT). For each comparison, our main reason for downgrading was very serious imprecision due to low sample size and low number of events.

Adverse events (all grades, grades 1 to 2, grades 3 to 4)

BLAZE-1 (phase 2) reported the number of participants with one or more adverse events, which first occurred or worsened in severity after baseline measurement, for 465 participants. Since the data were evaluated separately for each treatment arm (0.7 g, 2.8 g, and 7.0 g bamlanivimab), we did not pool the data.

Treatment with 0.7 g, 2.8 g or 7.0 g bamlanivimab may result in little to no difference in the occurrence of adverse events (267, 242 and 218 per 1000) compared to treatment with placebo (269 per 1000; RR 0.99, 95% CI 0.66 to 1.50; RR 0.90, 95% CI 0.59 to 1.38; and RR 0.81, 95% CI 0.52 to 1.27, respectively; 1 RCT, 257, 263 and 257 participants; low-certainty evidence; Analysis 1.5).

For each comparison, our main reason for downgrading was very serious imprecision due to low sample size, low number of events, and wide confidence intervals. Adverse events were coded according to MedDRA, the Medical Dictionary for Regulatory Activities, and were classified as mild, moderate and severe. Therefore, we could not summarise grades 1 to 2 and grades 3 to 4 adverse events.

Serious adverse events

BLAZE-1 (phase 2) assessed serious adverse events for 465 participants. Since the data were evaluated separately for each treatment arm that received different doses of bamlanivimab (0.7 g, 2.8 g, 7.0 g), we have not pooled the data.

There were too few participants who experienced serious adverse events to determine whether treatment with 0.7 g, 2.8 g or 7.0 g bamlanivimab has an effect on serious adverse events (3 per 1000 for all arms) compared to treatment with placebo (6 per 1000; RR 0.51, 95% CI 0.02 to 12.47; RR 0.48, 95% CI 0.02 to 11.78; and RR 0.51, 95% CI 0.02 to 12.47, respectively; 1 RCT; low-certainty evidence; Analysis 1.6). For each comparison, our main reason for downgrading was very serious imprecision due to low sample size, very low number of events, and very wide confidence intervals.

Additional outcomes

BLAZE-1 (phase 2) did not report length of hospital stay, admission to ICU, length of ICU stay, thromboembolic events, or renal failure.

Viral clearance (up to days 3, 7 and 15)

We defined viral clearance as a negative RT-PCR test after treatment and planned to include clearance up to three, seven and 15 days. BLAZE-1 (phase 2), defined viral clearance as two consecutive negative RT-PCR test results for SARS-CoV- 2. Since the data were evaluated separately for each treatment arm that received different doses of bamlanivimab (0.7 g, 2.8 g, 7.0 g), we did not pool the data.

- **Viral clearance up to day 3:** BLAZE-1 (phase 2) did not report viral clearance up to day 3.
- **Viral clearance up to day 7:** BLAZE-1 (phase 2) assessed viral clearance up to day 7 for 444 participants in total. Evidence suggests that treatment with 0.7 g, 2.8 g, or 7.0 g bamlanivimab may have little to no effect on viral clearance at days 7, with 10 out of 99 participants in the 0.7 g arm, 12 out of 101 participants in the 2.8 g arm, and 8 out of 99 participants in the 7.0 g arm achieving viral clearance compared to 16 out of 145 in the placebo arm (RR 0.92, 95% CI 0.43 to 1.93; RR 1.08, 95% CI 0.53 to 2.18; and RR 0.73, 95% CI 0.33 to 1.65, respectively; 1 RCT; Analysis 1.3). The evidence is uncertain due to the small sample size and wide confidence intervals.
- **Viral clearance up to day 15:** BLAZE-1 (phase 2) assessed viral clearance at day 15 for 414 participants. Evidence suggests that treatment with 0.7 g, 2.8 g, or 7.0 g bamlanivimab may have little to no effect on viral clearance at day 15, with 25 out of 91 participants in the 0.7 g arm, 30 out of 97 participants in the 2.8 g arm, and 25 out of 94 participants in the 7.0 g arm achieving viral clearance compared to 34 out of 132 in the placebo group (RR 1.07, 95% CI 0.69 to 1.66; RR 1.20, 95% CI 0.79 to 1.82; and RR 1.03, 95% CI 0.66 to 1.61, respectively; 1 RCT; Analysis 1.4). The evidence is uncertain due to the small sample size and wide confidence intervals.

Bamlanivimab/etesevimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease)

We present our certainty in the evidence for prioritised outcomes for bamlanivimab/etesevimab compared with placebo in non-hospitalised individuals in Summary of findings 2. This comparison was examined in a two-part study (BLAZE-1 (phase 2); BLAZE-1 (phase 3)), reported in two separate publications and one conference abstract. We decided to not include the phase 2 part of the study, because the start of treatment arms was staggered, and the allocation ratio was adjusted. This resulted in a late start of the bamlanivimab/etesevimab arm on 22 August 2021, while the placebo group was mainly enrolled up to 21 August 2021, with only 13 participants having been enrolled and analysed after this date. Therefore, we report on phase 2 narratively only. The outcomes mortality by day 60, clinical progression or development of severe symptoms and quality of life were not reported.

Primary outcomes

All-cause mortality (by days 30 and 60)

The phase 3 part reported data on 1035 participants. Bamlanivimab/etesevimab may reduce overall mortality by day 30 as compared with placebo (1 death per 1000 participants as compared to 19 per 1000 in the placebo group; RR 0.05, 95% CI 0.00 to 0.81; 1 RCT, 1035 participants; low-certainty evidence; Analysis 2.1). Our main reason for downgrading was very serious imprecision due to the low number of events. BLAZE-1 (phase 3) did not report all-cause mortality by day 60.

In BLAZE-1 (phase 2), no deaths occurred by day 29 (112 in bamlanivimab/etesevimab arm, 151 in placebo arm), mortality by day 60 was not reported.

Admission to hospital or death

BLAZE-1 (phase 3) reported the outcome admissions to hospital for 1035 participants by day 29. Treatment with bamlanivimab/etesevimab (21 per 1000) may result in a decrease in admissions to hospital by day 29 compared to treatment with placebo (70 per 1000; RR 0.30, 95% CI 0.16 to 0.59; 1 RCT, 1035 participants; low-certainty evidence; Analysis 2.2). Our main reason for downgrading was very serious imprecision due to low number of events.

In BLAZE-1 (phase 2), 1 out of 112 in the bamlanivimab/etesevimab and 9 out of 156 in the non-concurrent placebo arm were hospitalised.

Adverse events (all grades, grades 1 to 2, grades 3 to 4)

BLAZE-1 (phase 3) reported the number of participants with one or more adverse events, whichever first occurred or worsened in severity after baseline measurement for 1035 participants in this comparison.

Treatment with bamlanivimab/etesevimab may have little to no effect on the occurrence of adverse events (133 per 1000) compared to treatment with placebo (116 per 1000; RR 1.15, 95% CI 0.83 to 1.59; 1 RCT, 1035 participants; low-certainty evidence; Analysis 2.6). Our main reason for downgrading was very serious imprecision due to the low sample size. Adverse events were coded according to MedDRA, the Medical Dictionary for Regulatory Activities, and were classified as mild, moderate, and severe. Therefore, we could not summarise grades 1 to 2 and grades 3 to 4 adverse events.

In BLAZE-1 (phase 2), 12 out of 112 in the bamlanivimab/etesevimab arm and 42 out of 156 in the non-concurrent placebo arm experienced at least one adverse event.

Serious adverse events

BLAZE-1 (phase 3) assessed serious adverse events for 1035 participants. Treatment with bamlanivimab/etesevimab may increase the occurrence of serious adverse events (14 per 1000) as compared with placebo (10 per 1000; RR 1.40, 95% CI 0.45 to 4.37; 1 RCT, 1035 participants; low-certainty evidence; Analysis 2.7). Our main reason for downgrading was very serious imprecision due to the low number of events and wide confidence interval.

In BLAZE-1 (phase 2), 1 out of 112 participants in the bamlanivimab/etesevimab arm and 1 out of 156 in the placebo arm experienced an event.

Additional outcomes

BLAZE-1 (phase 3) did not report the additional outcomes admission to ICU, length of ICU stay, thromboembolic events, and renal failure.

Length of hospital stay

The mean duration of hospitalisation was 7.3 days (SD = 6.4 days; 11 participants) in the bamlanivimab/etesevimab arm and 11.2 days (SD = 10.1 days, 33 participants) in the placebo arm.

Viral clearance (up to days 3, 7, and 15)

The study defined viral clearance as two consecutive negative RT-PCR test results for SARS-CoV- 2.

BLAZE-1 (phase 3) reported a Kaplan-Meier graph including the number of events per day, which we used to calculate cumulative frequency of viral clearance. Evidence from BLAZE-1 (phase 3) suggests that more people may achieve viral clearance at days 3, 7, and 15 when treated with bamlanivimab/etesevimab compared with placebo (day 3: RR 2.12, 95% CI 1.16 to 3.86; day 7: RR 1.81, 95% CI 1.27 to 2.60; day 15: RR 1.34, 95% CI 1.07 to 1.67; 1 RCT, 968 participants).

In BLAZE-1 (phase 2), 14 out of 100 in the experimental group and 16 out of 145 in the placebo group achieved viral clearance at day 7, and 34 out of 98 in the experimental group compared to 34 out of 132 participants in the placebo arm achieved viral clearance.

Casirivimab/imdevimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease)

For the comparison casirivimab/imdevimab versus placebo in non-hospitalised individuals with COVID-19, we identified one phase 1/2/3 study with published results (Weinreich (phase 1/2); Weinreich (phase 3)) from phase 1/2 in one full-text and one preprint publication, and phase 3 in an additional preprint. The first part of the study randomised participants to either 2.4 g or 8.0 g treatment or placebo. In the course of phase 3 of the study on 14 November 2020, the treatment doses were amended, the 8 g arm was stopped and a 1.2 g arm was added. In addition, the eligibility was amended from participants with and without participants to participants with at least one risk factor for severe disease. For the first part of the study, we have considered the preprint with updated data, including 799 randomised participants. Of these, 665 were included in the modified full analysis set which included only participants who tested positive on central RT-qPCR.

Due to very serious risk of bias, we decided to not pool the data from phase 3 with the remaining data and report these narratively only. In particular, we could not follow the participant flow throughout the study; it was unclear whether the 1040 participants without risk factors were initially randomised and if so, why data were not reported. In addition, the origin of the number of participants in the placebo group of the safety set is not clearly documented, and results for the 8.0 g casirivimab/imdevimab arm are reported arbitrarily. Only data for cohort 1 were provided. The concurrent placebo groups vary but participants overlap with each other. Results based on phase 1 are presented in Summary of findings 3.

Primary outcomes

All-cause mortality (by days 30 and 60)

The phase 1/2 part of the study by Weinreich (phase 1/2) did not report all-cause mortality by days 30 or 60.

In the phase 3 part of the study, the number of events in all treatment arms (1.2 g, 2.4 g and 8.0 g) was very low and does not allow us to explore whether casirivimab/imdevimab may have an effect on all-cause mortality by day 29 when compared with placebo. In both the 1.2 g and 2.4 g treatment arms, one participant died out of 736 and 1355 participants, in the 8.0 g, no one died out of 625. The reported concurrent placebo groups varied, in the combined placebo group, 3 out of 1341 participants died.

Clinical progression or development of severe symptoms according to the WHO scale

The phase 1/2 part of the study did not report any data on clinical progression or development of severe symptoms that could be translated into an outcome based on the WHO progression scale, although IMV requirement was planned at the protocol stage.

The phase 3 part reported the number of participants that require IMV (WHO scale 7, 8, 9), which does not explicitly includes deaths, for the 1.2 g and 2.4 g casirivimab/imdevimab arms. The number of events was too low to explore the direction of the effect of casirivimab/imdevimab.

Clinical progression to IMV	Casirivimab/imdevimab		Placebo	
	Events	Participants analysed	Events	Participants analysed
1.2 g	1	736	2	748
2.4 g	1	1355	6	1341
8.0 g	NR	NR	NR	NR

In addition to the very serious bias, it is not explicitly mentioned whether the outcome includes death events and may therefore be prone to effect distortion in case people died before receiving IMV.

Admission to hospital or death

In the phase 1/2 part of the study, casirivimab/imdevimab at 2.4 g or 8.0 g may reduce the frequency of hospital admission or death compared with placebo (9 and 5 per 1000 compared to 22 per 1000 in the placebo group; 2.4 g: RR 0.43, 95% CI 0.08 to 2.19, 446 participants; 8.0 g: RR 0.21, 95% CI 0.02 to 1.79, 450 participants;

1 RCT; low-certainty evidence; Analysis 3.1). Our main reason for downgrading was the low sample size and low number of events.

The phase 3 part of the study reported the number of participants admitted to hospital or dead by day 29:

Hospital admission or death	Casirivimab/imdevimab		Placebo	
	Events	Participants analysed	Events	Participants analysed
1.2 g	7	736	24	748
2.4 g	18	1355	62	1341
8.0 g	13	625	38	593

Due to the very serious risk of bias, we are uncertain whether casirivimab/imdevimab has an effect on hospital admissions or death.

Adverse events

The phase 1/2 part of the study reported grades 3 to 4 adverse events only. There were too few events to determine whether casiribimab/imdevimab at 2.4 g or 8.0 g has an effect on the occurrence of grades 3 to 4 adverse events (12 and 8 per 1000 compared to 15 per 1000 for the placebo arm; 2.4 g: RR 0.76, 95% CI 0.17 to 3.37, 520 participants; 8.0 g: RR 0.50, 95% CI 0.09 to 2.73, 522 participants; 1 RCT; low-certainty evidence; Analysis 3.2). We graded down due to very serious imprecision, the sample size was small with a low number of events.

Part 3 of the study reported all grades adverse events and grades 3 to 4 adverse events separately:

Adverse events		Casirivimab/imdevimab		Placebo	
		Events	Participants analysed	Events	Participants analysed
All grades	1.2 g	59	827	189	1843
	2.4 g	142	1849		
	8.0 g	85	1012		
Grades 3 to 4	1.2 g	11	827	62	1843
	2.4 g	18	1849		
	8.0 g	15	1012		
Serious adverse events	1.2 g	9	827	74	1843
	2.4 g	24	1849		
	8.0 g	17	1012		

We are uncertain whether casiriviamb/imdevimab 1.2 g, 2.4 g or 8.0 g has an effect on adverse events or serious adverse events.

Serious adverse events

The number of events in phase 1/2 of the study was too small to determine whether any dose of casirivimab/imdevimab (2.4 g, 8.0 g) may have an effect on the occurrence of serious adverse events compared with placebo (16 and 8 per 1000 as compared to 23 per 1000; 2.4 g: RR 0.68, 95% CI 0.19 to 2.37, 520 participants; 8.0 g: RR 0.34, 95% CI 0.07 to 1.65; 1 RCT, 522 participants; low-certainty evidence; Analysis 3.3). We downgraded two levels for very serious imprecision; the sample size was low with a small number of events.

Serious adverse events reported in the phase 3 preprint publication are listed under adverse events.

Additional outcomes

For this comparison, the following outcomes were not reported in any of the preprints: length of ICU stay, viral clearance, frequency of thromboembolic events, and frequency of renal failure.

Length of hospital stay

The phase 3 portion of the trial reported on the length of hospital stay for dose 1.2 and 2.4 g as mean days and standard deviation, however, the number of participants who contributed to this outcome was very low (1.2 g: N = 7, concurrent placebo N = 24; 2.4 g: N =18, concurrent placebo N = 62). The data for 8.0 g are not reported. It is unclear whether patients who died were accounted for (i.e., earlier death means a shorter hospital stay).

Admission to ICU

The phase 3 part of the trial reported the number of participants admitted to the ICU. However, the number of events was too low to explore whether casirivimab/imdevimab has an effect on this outcome (1.2 g: 3 out of 736, 7 out of 749 in the concurrent placebo arm; 2.4 g: 6 out of 1355 as compared to 18 out of 1341 in the concurrent placebo arm). The results for the 8.0 g arm was not reported and it is unclear whether competing events (i.e. deaths) were accounted for.

Sotrovimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease)

We present our certainty in the evidence for prioritised outcomes for the comparison sotrovimab compared with placebo in non-hospitalised individuals in Summary of findings 4. The one eligible trial with results (COMET-ICE) for this comparison has been stopped for profound efficacy by the data monitoring committee on 10 March 2021 with 1057 participants enrolled. The preprint, uploaded on 28 May 2021, included participants up to 19 January 2021 for efficacy (583) and up to 17 February 2021 for safety (868) for preplanned interim analysis, the sets vary substantially in the number of participants analysed.

Primary outcomes

All-cause mortality (by days 30 and 60)

Only one participant in the placebo group had died by day 29 (291 participants in sotrovimab arm, 292 in placebo arm; 1 RCT, 583 participants; low-certainty evidence; Analysis 4.1), therefore, there were too few events to determine whether treatment with 0.5 g sotrovimab has an effect on mortality at 30 days. Our main reason for downgrading was very serious imprecision due to few events, which led to a very wide confidence interval. COMET-ICE did not report all-cause mortality at up to 60 days.

Clinical progression or development of severe symptoms according to the WHO scale

COMET-ICE reported provided information on several stages of severe or critical progression. Based on relevance, we decided to include two related endpoints that translate to development of severe symptoms based on the WHO progression scale, requirement of oxygen (≥ 5) and requirement of invasive mechanical ventilation (≥ 7), both including deaths.

Included in both analyses were 583 participants. Evidence suggests that sotrovimab may reduce the number of participants with oxygen requirement (WHO ≥ 5; 7 per 1000 participants) compared with placebo (65 per 1000; RR 0.11, 95% CI 0.02 to 0.45; 1 RCT, 583 participants; low-certainty evidence; Analysis 4.2). For the outcome IMV requirement or death, the number of events was too small to determine whether sotrovimab may have an effect (1 per 1000 as compared to 10 per 1000 in the placebo group; RR 14, 95% CI 0.01 to 2.76; 1 RCT, 583 participants; low-certainty evidence; Analysis 4.3). Our main reason for downgrading was the low sample size and low number of events.

Admission to hospital or death

Sotrovimab may reduce the number of hospital admissions or death (10 per 1000) compared to placebo (72 per 1000; RR 0.14, 95% CI 0.04 to 0.48; 1 RCT, 583 participants; low-certainty evidence; Analysis 4.4). Our main reason for grading down was the small sample size and low number of events.

Adverse events (all grades, grades 1 to 2, grades 3 to 4)

Evidence suggests that treatment with sotrovimab compared to placebo may have little to no effect on the occurrence of any grade adverse events (169 per 1000 as compared to 194 per 1000 with placebo; RR 0.87, 95% CI 0.66 to 1.16; 1 RCT, 868 participants; low-certainty evidence; Analysis 4.6). Occurrence of grades 3-4 adverse events may be reduced by treatment with sotrovimab compared to placebo (16 versus 62 per 1000 for sotrovimab and placebo, respectively; RR 0.26, 95% CI 0.12 to 0.60; 1 RCT, 868 participants; low-certainty evidence; Analysis 4.7). Grades 1 to 2 adverse events were not reported separately. We downgraded two levels due to the low sample size.

Serious adverse events

Treatment with sotrovimab may reduce the occurrence of serious adverse events compared to placebo (16 per 1000 compared to 59 per 1000 participants with placebo; RR 0.27, 95% CI 0.12 to 0.63; 1 RCT, 868 participants; low-certainty evidence; Analysis 4.8). We downgraded two levels due to very serious imprecision; the sample size was low with a small number of events.

Additional outcomes

For the comparison sotrovimab versus placebo in non-hospitalised individuals, we did not identify data for the outcomes length of hospital stay, length of ICU stay, viral clearance, thromboembolic events and renal failure.

Admission to ICU

The number of events is too low to determine whether treatment with sotrovimab reduces the number of participants admitted to ICU by day 29 (0 out of 291 in the sotrovimab group compared to 5 out of 292 in the sotrovimab group; RR 0.09, 95% CI 0.01 to 1.64; Analysis 4.5).

Regdanvimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease)

We present our certainty in the evidence for prioritised outcomes for the comparison regdanvimab compared with placebo in non-hospitalised individuals in Summary of findings 5. We included only one study (Eom 2021) which reported on part 1 of a two-part phase 2/3 study in form of a preprint. Mortality by day 60 and quality of

life were not measured or reported, serious adverse events were reported as treatment-emergent SAE; however, we considered this outcome as unreliable because no events were reported although hospitalisation events took place.

Primary outcomes

All-cause mortality (by day 30 and 60)

None of the participants had died by day 28 (101 in the CT-P59 40 mg/kg arm, 103 in the regdanvimab 80 mg/kg arm and 103 participants in placebo arm; effect estimate was not estimable; low-certainty evidence; Analysis 5.1). Our main reason for downgrading was very serious imprecision due to no observed events in any group.

Eom 2021 did not report all-cause mortality at up to 60 days.

Clinical progression or development of severe symptoms according to the WHO scale

The study reported the number of participants who had progressed to invasive mechanical ventilation or death, which translates into a WHO score of ≥ 7.

In the regdanvimab 40 mg/kg arm and placebo arm, no one required mechanical ventilation (among 101 participants in regdanvimab 40 mg/kg arm and 103 participants in placebo arm, effect not estimable; low-certainty evidence; Analysis 5.2). There were too few participants who experienced progress to invasive mechanical ventilation to determine whether treatment with CT-P59 80 mg/kg has an effect (1 in 103 in regdanvimab 80 mg arm, 0 in 103 in placebo arm; RR 3.00, 95% CI 0.12 to 72.89; 1 RCT, 206 participants; low-certainty evidence; Analysis 5.2).

For both comparisons, the main reason for downgrading was very serious imprecision due to very low number of events and resulting in very wide confidence intervals.

Admission to hospital or death by day 30

Treatment with either 40 mg/kg or 80 mg per kg regdanvimab may decrease the frequency of hospital admission or death by day 30 compared to placebo (39 or 49 per 1000 in the regdanvimab arms versus 87 per 1000 in the placebo arm; 40 mg/kg: RR 0.45, 95% CI 0.14 to 1.42; 1 RCT, 204 participants; 80 mg/kg: RR 0.56, 95% CI 0.19 to 1.60; 1 RCT, 206 participants; low-certainty evidence; Analysis 5.3). Our main reason for downgrading was very serious imprecision due to the small sample size and small number of events.

Adverse events (all grades, grades 1 to 2, grades 3 to 4)

Treatment with 40 mg/kg regdanvimab may have little to no effect on the occurrence of any grade adverse events compared with placebo (297 versus 309 per 1000 for regdanvimab and placebo, respectively; RR 0.96, 95% CI 0.64 to 1.43; 1 RCT, 215 participants; low-certainty evidence; Analysis 5.6). Treatment with 80 mg/kg regdanvimab may reduce the occurrence of any grade adverse events compared with placebo (244 versus 309 per 1000; RR 0.79, 95% CI 0.52 to 1.22; 1 RCT, 220 participants; low-certainty evidence). Our main reason for downgrading was the low sample size.

Treatment with either 40 mg/kg or 80 mg/kg regdanvimab may increase the occurrence of grade 3 adverse events compared to placebo, no grade 4 adverse events took place (48 and 36 per 1000 compared to 18 per 1000 in the placebo group; 40 mg/kg: RR 2.62, 95% CI 0.52 to 13.12; 1 RCT, 215 participants; 80 mg/kg: RR 2.00, 95% CI 0.37 to 10.70; 1 RCT, 220 participants; low-certainty evidence; Analysis 5.7). Our main reason for downgrading was the small sample size and low number of events.

Additional outcomes

The outcomes length of hospital stay, length of ICU stay, frequency of thromboembolic events, and frequency of renal failure were not available for this comparison.

Admission to ICU or death

None of the participants had been admitted to ICU by day 28 (101 in the CT-P59 40 mg/kg arm, 103 in the CT-P59 80 mg/kg arm and 103 participants in placebo arm; effect not estimable; Analysis 5.4).

Viral clearance (up to day 3, 7 and 15)

- **Viral clearance up to day 3 and 7:** not reported.
- **Viral clearance up to day 15:** Eom 2021 assessed viral clearance at day 15 for 309 participants. Evidence suggests that treatment with regdanvimab may have little to no effect on viral clearance at day 15, with 68 participants in each treatment arm, as compared to 62 out of 103 participants in the placebo arm achieving viral clearance (RR 1.12, 95% CI 0.91 to 1.38 for 40 mg/kg; RR 1.10, 95% CI 0.89 to 1.35 for 80 mg/kg, respectively; 1 RCT; Analysis 5.5).

SARS-CoV-2-specific mAbs in hospitalised individuals with COVID-19 (moderate to severe disease)

Bamlanivimab compared to placebo in individuals with COVID-19 (moderate to severe disease)

We present the certainty in the evidence for our prioritised outcomes for the comparison bamlanivimab versus placebo in hospitalised individuals with COVID-19 in Summary of findings 6. We included one study published as one full text and one preprint publication. The preprint with the final analysis reported the subgroups for seronegative and seropositive participants at baseline for mortality at 90 days, sustained recovery and serious adverse events. Quality of life was not reported.

Primary outcomes

All-cause mortality (by days 30 and 60)

One RCT reported all-cause mortality by days 28 and 90 for 314 participants (ACTIV-3).

We are uncertain whether bamlanivimab has an effect on all-cause mortality at 28 days (37 per 1000) when compared to treatment with placebo (26 per 1000; RR 1.39, 95% CI 0.40 to 4.83; 1 RCT, 314 participants; low-certainty evidence; Analysis 6.1). Our main reason for downgrading was very serious imprecision due to wide confidence interval, low sample size, and the low number of events.

The 90-day follow-up resulted in a hazard ratio (HR) of 1.09 (95% CI 0.49 to 2.43; 1 RCT, 314 participants; low-certainty evidence; Analysis 6.2), indicating that bamlanivimab may have little to no effect on mortality compared with placebo (79 per 1000 compared to 73 per 1000 with placebo). Our certainty in the evidence was low due to very serious imprecision; the sample size

was small, resulting in a low number of events and large confidence intervals.

The subgroup analysis of the primary study authors suggests that the effect may differ between seronegative and seropositive participants at baseline. In seronegative participants, 5.4% of participants with bamlanivimab as compared to 11.4% with placebo experienced an event (HR 0.46, 95% CI 0.14 to 1.48). In contrast, in the seropositive arm, 9.6% in the bamlanivimab arm as compared to 2.9% in the placebo arm experienced an event (HR 3.52, 95% CI 0.75 to 16.58).

Clinical progression or development of severe symptoms according to the WHO scale

ACTIV-3 reported the proportion of participants in each pulmonary clinical status category at day 5 for 311 participants per category. From this, we extracted severe symptoms based on the need for NIV, IMV, ECMO, or renal replacement therapy at day 5 (category 5 to 7 on the pulmonary-plus scale).

Bamlanivimab may result in a slight increase in severe symptoms at day 5 (211 per 1000) compared to placebo (180 per 1000; RR 1.17, 95% CI 0.75 to 1.85; 1 RCT, 311 participants; very low-certainty evidence; Analysis 6.3). Our main reason for downgrading was serious indirectness due to a short time frame of five days and serious imprecision due to wide confidence interval and low sample size, and for indirectness due to the short time frame of five days only.

We additionally extracted clinical status at day 5 by the need for intubation (which corresponds to category six at the pulmonary scale). From 161 participants treated with bamlanivimab, eight needed intubation, compared to five out of 150 participants in the control group. Treatment with bamlanivimab may result in a slight increase in the need for intubation at day 5 compared to placebo (RR 1.49, 95% CI 0.50 to 4.46; 1 RCT, 311 participants; Analysis 6.4).

Hospital discharge and alive

ACTIV-3 reported the HR for hospital discharge until data cut-off (26 October 2020) for 314 participants, stratified by disease severity and study site pharmacy and using the Fine and Gray method to correct for competing risks. Treatment with bamlanivimab may have little to no effect on time to hospital discharge (751 per 1000, based on control group risk at day 10) compared to treatment with placebo (762 per 1000; HR 0.97, 95% CI 0.78 to 1.20; 1 RCT, 314 participants; low-certainty evidence; Analysis 6.6). Our main reason for downgrading was serious imprecision due to the low sample size.

In addition to the HR, the study reported hospital discharge at day 5 for 314 participants. Evidence suggests there may be little to no difference between participants receiving bamlanivimab and placebo (RR 0.98, 95% CI 0.81 to 1.19; 1 RCT, 314 participants; Analysis 6.5).

Quality of life (at up to seven and 30 days, and longest follow-up, including fatigue)

We did not identify any study reporting this outcome.

Adverse events (all grades, grades 1 to 2, grades 3 to 4)

ACTIV-3 reported grades 3 to 4 adverse events at day 28 for 314 participants. Bamlanivimab may result in a slight increase of grades 3 to 4 adverse events (227 per 1000) compared to treatment with placebo (179 per 1000; RR 1.27, 95% CI 0.81 to 1.98; 1 RCT, 314 participants; low-certainty evidence; Analysis 6.7). Our main reason for downgrading was very serious imprecision due to wide confidence interval and low sample size. ACTIV-3 did not report adverse events of all grades and grades 1 to 2.

Serious adverse events

ACTIV-3 reported serious adverse events by day 28 for 314 participants. It is uncertain whether treatment with bamlanivimab has an effect on the occurrence of serious adverse events (31 per 1000) compared to treatment with placebo (33 per 1000); RR 0.93, 95% CI 0.27 to 3.14; 1 RCT, 314 participants; low-certainty evidence; Analysis 6.7). Our main reason for downgrading was very serious imprecision due to wide confidence interval, low sample size, and low number of events.

Treatment with bamlanivimab may reduce the occurrence of SAE by day 90 compared to placebo (9 out of 163 compared to 12 out of 151; RR 0.7, 95% CI 0.29 to 1.67). However, the number of events is low, resulting in a broad confidence interval. The effect may differ between seronegative and seropositive participants as reported in the primary publication; in the seronegative group, 5.4% of participants who received bamlanivimab experienced an SAE compared with 10.1% in the placebo arm (HR 0.51, 95% CI 0.15 to 1.70). In the seropositive group, 6% of those allocated to bamlanivimab experienced an SAE compared to 5.8% in the placebo arm (RR 1.1, 95% CI 0.3 to 4.11).

Additional outcomes

ACTIV-3 did not report results on length of hospital stay, admission to ICU, length of ICU stay, or viral clearance.

Time to sustained recovery

ACTIV-3 assessed time to sustained recovery up to day 90. Treatment with bamlanivimab may result in little to no difference in time to sustained recovery compared to treatment with placebo (HR 0.99, 95% CI 0.80 to 1.23; 1 RCT, 314 participants; Analysis 6.10). The evidence is uncertain due to the small sample size.

Neurological dysfunction

This outcome was reported by ACTIV-3 for 293 participants at day 28. Transient ischaemic events, acute delirium, and cerebrovascular events were reported separately. No transient ischaemic event occurred at day 28 in either group (RR not estimable; Analysis 6.11). Too few participants experienced acute delirium (4 out of 152 participants; RR 3.71, 95% CI 0.42 to 32.80) and cerebrovascular events (0 out of 152 participants; RR 0.31, 95% CI 0.01 to 7.53) to determine whether bamlanivimab has an effect compared to placebo (1 out of 141 participants; 1 RCT, 293 participants; Analysis 6.12; Analysis 6.13). The evidence is very uncertain due to the low number of events, small sample size and very wide confidence intervals.

Thromboembolic events

ACTIV-3 assessed thromboembolic events until data cut-off for 293 participants. Too few participants experienced thromboembolic events to determine whether bamlanivimab has an effect (3 out of 152 participants) compared with placebo (1 out of 141 participants; RR 2.78, 95% CI 0.29 to 26.44; 1 RCT, 293 participants; Analysis 6.14). The evidence is very uncertain due to the low number of events, small sample size, and very wide confidence intervals.

Renal failure

ACTIV-3 reported the need for dialysis at data cut-off for 293 participants. Too few participants experienced need for dialysis to determine whether bamlanivimab has an effect (2 out of 152 participants) compared with placebo (0 out of 141 participants; RR 4.64, 95% CI 0.22 to 95.83; 1 RCT, 293 participants; Analysis 6.15). The evidence is very uncertain due to the low number of events, small sample size, and very wide confidence intervals.

Casirivimab/imdevimab and usual care compared to usual care alone in hospitalised individuals with COVID-19 (moderate and severe disease)

The certainty in the evidence for our prioritised outcomes for the comparison casirivimab/imdevimab versus usual care in hospitalised individuals with COVID-19 can be found in Summary of findings 7. The one inlcuded study, published as a preprint with 9785 participants enrolled to either casirivimab/imdevimab or usual care, did not report mortality at 60 days, quality of life, adverse events and serious adverse events. This study reported a hierarchical analysis, testing participants who have not produced antibodies at baseline first, and upon significance testing all participants including seropositive and participants with unknown status, we will report on this subgroup for prioritised outcomes, taken over from the preprint, narratively as well (serostatus: negative, positive, unknown).

The outcomes mortality by day 60, quality of life, adverse events and serious adverse events were not planned to be reported.

Primary outcomes

All-cause mortality (by day 30 and 60)

Casirivimab/imdevimab has probably little to no effect on all-cause mortality by day 28 when compared with usual care (221 per 1000 participants died as compared to 236 per 1000 in the usual care group; RR 0.94, 95% CI 0.87 to 1.02; 1 RCT, 9785 participants; moderate-certainty evidence; Analysis 7.1). We downgraded one level due to serious risk of bias, which we rated as high based on the lack of blinding and a yet undefined standard of care, which may have led to differences in concomitant treatment (i.e. the timing of concomitant treatment).

The subgroup analysis of the primary study authors suggests that in seronegative participants, mortality was lower in the casirivimab/imdevimab arm with 24% mortality compared to 30% mortality in the usual care group (RR 0.80, 95% CI 0.70 to 0.91). Among participants who were seropositive or with unknown serostatus, there was no difference between the treatment groups (seropositive: 16% compared to 15%, RR 1.09, 95% CI 0.95 to 1.26; unknown: 24% compared to 24%, RR 0.98, 95% CI 0.78 to 1.22; for casirivimab/imdevimab versus placebo).

Clinical progression or development of severe symptoms according to the WHO scale

RECOVERY reported the number of participants who required invasive mechanical ventilation or death by day 28 for those who were not yet ventilated at baseline. Casirivimab/imdevimab has probably little to no effect on IMV requirement by day 28 compared to usual care in the complete enrolled sample (238 in the casirivimab/imdevimab arm compared to 248 per 1000 receiving usual care; RR 0.96, 95% CI 0.90 to 1.04; 1 RCT, 9198 participants; moderate-certainty evidence; Analysis 7.2). We downgraded one level due to serious risk of bias, which we rated as high based on the lack of blinding and a yet undefined standard of care, which may have led to differences in concomitant treatment (i.e., the timing of concomitant treatment).

Similar to the endpoint mortality, the subgroup analysis of the primary study authors suggests that for the seronegative group, the requirement of invasive mechanical ventilation was lower in the casirivimab/imdevimab arm than in the usual care arm (30% compared to 37%; RR 0.83, 95% CI 0.75 to 0.92). In the seropositive and unknown status groups, there was no difference between the treatment arms (seropositive: 19% compared to 17%, RR 1.10, 95% CI 0.97 to 1.24; unknown: 29% compared to 27%; RR 1.05, 95% CI 0.87 to 1.26).

Hospital discharge alive

In the complete randomised group, casirivimab/imdevimab has probably little to no effect on hospital charge alive by day 28 compared to placebo (697 compared to 690 per 1000; RR 1.01, 95% CI 0.98 to 1.04; 1 RCT, 9785 participants; moderate-certainty evidence; Analysis 7.3). We downgraded one level due to serious risk of bias, which we rated as high based on the lack of blinding and a yet undefined standard of care, which may have led to differences in concomitant treatment (i.e., the timing of concomitant treatment).

The subgroup analysis of the primary study authors suggests that in the seronegative group, more participants were discharged alive by day 28 compared to usual care (64% compared to 58%, RR 1.19, 95% CI 1.08 to 1.30), whereas there was no difference between the arms in the seronegative and unknown group (seropositive: 75% versus 77%, RR 0.94, 95% CI 0.88 to 1.00; unknown: 63% versus 64%, RR 0.96, 95% CI 0.83 to 1.10).

Additional outcomes

RECOVERY did not report results on our additional outcomes admission to ICU, length of ICU stay, viral clearance, and neurological dysfunction.

Length of hospital stay

Length of hospital stay was reported as median duration of hospitalisation. In the complete randomised sample, the median duration was 10 days in the casirivimab/imdevimab group compared to 10 days in the usual care group, it is unclear whether the reported interval was the range or the interquartile range.

Thromboembolic events

Treatment with casirivimab/imdevimab has probably little to no effect on thrombotic events compared with usual care in the complete randomised group; 249 out of 4839 experienced an event in the intervention arm; 248 out of 4946 experienced an

event under usual care (RR 1.03; 95% CI 0.86 to 1.22; 1 RCT, 9785 participants; Analysis 7.4).

Renal dysfunction

Treatment with casirivimab/imdevimab has probably little effect on the requirement of renal replacement therapy for those not on renal replacement therapy at baseline, with 203 out of 4783 in the casirivimab/imdevimab arm experiencing an event compared with 201 out of 4887 in the usual care arm (RR 1.03, 95% CI 0.85 to 1.25; 1 RCT, 9670 participants; Analysis 7.5).

DISCUSSION

Summary of main results

The aim of this review was to assess the effectiveness and safety of SARS-CoV-2-neutralising neutralising monoclonal antibodies (mAbs) for the treatment of COVID-19. We identified six randomised controlled trials (RCTs) (ACTIV-3; BLAZE-1 (phase 2); BLAZE-1 (phase 3); COMET-ICE; Eom 2021; RECOVERY; Weinreich (phase 1/2); Weinreich (phase 3)). Three studies were published as preprint only (COMET-ICE; Eom 2021; RECOVERY). Weinreich (phase 1/2) or as a journal publication with additional data from two preprints (Weinreich (phase 1/2); Weinreich (phase 3)).

Four studies included outpatients receiving either bamlanivimab or bamlanivimab in combination with etesevimab (BLAZE-1 (phase 2); BLAZE-1 (phase 3)), a combination of casirivimab and imdevimab (under the trade name REGN-COV2) (Weinreich (phase 1/2); Weinreich (phase 3)), regdanvimab (Eom 2021), or sotrovimab (COMET-ICE). Two studies included hospitalised participants treated with bamlanivimab (ACTIV-3) or a combination of casirivimab and imdevimab (RECOVERY).

All six included RCTs are active. However, most of them have stopped enrolment and participants are being followed-up. One study is continuing observation of the respective arm (COMET-ICE), two have added additional arms with different mAbs or doses (ACTIV-3, BLAZE-1 (phase 2)), and one continues with other treatments not relevant to this review (RECOVERY). BLAZE-1 (phase 2), part of a phase 2 to 3 study examining three doses of bamlanivimab and combination therapy with etesevimab, published interim results on 592 randomised participants. Additionally, results from phase 3 of this study were reported for 1035 participants who received bamlanivimab/etesevimab or placebo (BLAZE-1 (phase 3)). Regdanvimab at two different doses (0.04 g or 0.08g) compared to placebo was examined in Eom 2021, a two-part phase 2 to 3 study. Results of a preplanned interim anlysis of the first part of the study, including 327 participants, were reported in a preprint. COMET-ICE, another phase 2 to 3 study, examined sotrovimab compared to placebo and reported results of a preprint interim analysis on 583 participants. Recruitment was stopped on 10 March 2021 for benefit after 1057 participants had been randomised. There were separate data cut-offs for efficacy and safety. Weinreich (phase 1/2) published a final analysis of phase 1/2 on 799 participants who were assigned to casirivimab plus imdevimab (2.4g or 8.0g) or placebo and results from the ongoing phase 3 (Weinreich (phase 3)) where 5607 participants were randomised to receive the combination casirivimab plus imdevimab (at three different doses 1.2g, 2.4g, 8.0g) or placebo. Based on results from Weinreich (phase 1/2), the trial was amended in November 2020 and only participants with at least one risk factor for severe COVID-19 were included and no longer randomised to 8.0g casirivimab and imdevimab. In February 2021, participants were no longer randomised to placebo. ACTIV-3, a platform trial, stopped recruitment to the bamlanivimab arm for futility after preplanned interim analysis, including 314 patients. In RECOVERY, another platform trial, 9785 participants were randomised to receive either a combination of casirivimab and imdevimab or usual care.

Non-hospitalised individuals

Evidence suggests that the various doses of bamlanivimab may reduce admissions to hospital or death in outpatients (mild cases according to the previous World Health Organization (WHO) scale) compared to placebo, although the confidence intervals include both benefit and harm. Little to no effect may be seen on the occurrence of adverse events and viral clearance. The occurrence of serious adverse events was too rare to allow a judgment. All evidence should be interpreted with caution due to very serious imprecision; data are from one small study, event numbers are low and confidence intervals are wide.

For the mAb combination bamlanivimab and etesevimab compared to placebo in mild cases, evidence suggests a similar pattern to bamlanivimab. The combination may reduce admissions to hospital, but may have little to no effect on the occurrence of adverse events. We could not assess mortality in this study as there were no deaths, and the occurrence of serious adverse events was too rare to allow a judgment. Other preplanned outcomes for this review were not reported. Similar to the comparison for bamlanivimab alone in mild COVID-19, data are from one small study only, so evidence should be considered uncertain due to very serious imprecision.

Although a preprint with phase 3 data for the comparison between multiple doses of casirivimab and imdevimab to placebo was available, we base our summary on the part 1/2 preprint only due to several uncertainties regarding the included participants. Casirivimab/imdevimab may reduce hospital admissions, however, the confidence interval includes both benefits and harms. For the outcomes grades 3 to 4 adverse events and serious adverse events, there were too few events to allow a judgment. No other outcomes were reported in part 1/2 of the study. Evidence should be considered uncertain due to very serious imprecision.

Sotrovimab may reduce the number of participants with oxygen requirement, hospitalisations or death, the number of hospital admissions or death, and the occurrence of grades 3 to 4 and serious adverse events compared to placebo, although the confidence intervals include both benefit and harms. Events for the outcomes mortality and invasive mechanical ventilation (IMV) requirement or death were too rare to allow a judgment on the effect. Data for this comparison should be interpreted with caution as they originate from one small study with low number of events and wide confidence intervals.

Evidence suggests that regdanvimab at either 40 mg or 80 mg/kg may reduce hospital admissions, and the 80 mg/kg dose may reduce adverse events when compared with placebo, although the confidence interval includes both benefits and harms. In contrast, regdanvimab may increase grade 3 adverse events, however, the confidence intervals include both benefit and harm. It may have little to no effect on viral clearance at day 15. We could not assess mortality, IMV requirement or death, serious adverse events, and

admission to: intensive care unit (ICU), as no or few events took place. Due to the small sample size and low number of events, any evidence has to be interpreted with caution.

Hospitalised individuals

We are uncertain whether bamlanivimab has an effect on mortality and serious adverse events in hospitalised, moderate-to-severe COVID-19 cases, compared to placebo. It may increase grades 3 to 4 adverse events compared to placebo but seemed to have little to no effect on hospital discharge, non-invasive ventilation (NIV) or IMV requirement or death, and sustained recovery. The number of events for the outcomes neurological dysfunction, thromboembolic events and renal failure was too low to allow for judgment. Our certainty in the evidence is low due to very serious imprecision. Our certainty in the evidence for NIV or IMV requirement was further downgraded for indirectness due to the short time frame. The study authors reported results for 90-day mortality and serious adverse events (SAEs) that suggest a difference in effect between participants who were seronegative as compared to seropositive at baseline; for seronegative, the effect may be in favour of bamlanivimab, the opposite tendency was observed in seropositive participants.

Evidence for casirivimab/imdevimab suggests that the treatment at a dose of 8.0 g may have little to no effect on all-cause mortality, clinical progression to IMV or death, hospital discharge alive, thrombotic events, and renal replacement therapy requirement compared with usual care alone in the complete randomised cohort. We have moderate certainty in the evidence due to high risk of bias. In line with the subgroups from ACTIV-3, when looked at seronegative participants at baseline only, the study authors found an effect, while no effect was found for participants who already seroconverted or with unknown status.

Ongoing studies

Thirty-six RCTs examining 23 different SARS-CoV-2-specific mAbs or mAb combinations are currently ongoing or completed without published results. Of these, all except one are being explored in phase 2 studies onwards. We identified five additional mAbs that have not yet been tested in RCTs as part of our tracking of emerging mAbs.

Overall completeness and applicability of evidence

Completeness of the evidence

Completeness within our included studies varied. ACTIV-3 reported on all preplanned outcomes, and BLAZE-1 (phase 2) on all outcomes, but not in all preplanned formats. These outcomes are, unfortunately, not our complete set of preplanned outcomes. BLAZE-1 (phase 3); COMET-ICE; Eom 2021; RECOVERY and Weinreich (phase 3) reported up to eight preplanned outcomes, but Weinreich (phase 3) did not fully report these for all doses. Weinreich (phase 1/2) reported only three preplanned outcomes. We contacted study authors, but they could not provide us with additional data or did not reply. As some studies were published as interim analyses or preprints, we expect that more data will become available with the final analysis and in full publications.

Applicability of the evidence

Overall, the evidence included in this review represents two distinct populations: individuals with mild disease, and individuals with moderate-to-severe disease who are already hospitalised due to COVID-19. During the course of this review, the WHO progression scale has changed multiple times. Since the decision to use the scale in Figure 1, it was changed on 25 January 2021 to represent different cut-offs and categories: mild, moderate, severe and critical disease based on severity of pneumonia instead of hospitalisation (WHO 2021c). We will consider adopting the most recent scale in a future update of this review.

Four RCTs examined SARS-CoV-2-specific mAbs in outpatients with mild disease. The various treatment arms in the samples included between 63% to 100% of participants who have at least one risk factor for severe disease, which may be slightly overrepresented when compared to modelling estimates for the general population (Clark 2020). However, this subgroup would be in more urgent need for the prevention of serious adverse outcomes. This was reflected in the initial emergency use authorisation (EUA) that was provided by the US Food and Drug Administration (FDA) for the combination of casirivimab and imdevimab, bamlanivimab, and bamlanivimab with etesevimab. The EUA for bamlanivimab was revoked on 17 April 2021 per Eli Lilly's request for bamlanivimab alone due to an increase in virus variants that are resistant to bamlanivimab monotherapy (FDA 2021b).

The median time from symptom onset to randomisation ranged from two to six days (median five, range three to six days in BLAZE-1 (phase 2); four days, range 0 to 29 days in BLAZE-1 (phase 3); three days, rangetwo2 to four days in Eom 2021 and three days, range two to five days in Weinreich (phase 1/2)). We are unable to extrapolate the evidence from this time window to a longer period. It remains to be seen whether the time frame in the context of an RCT with predefined eligibility criteria (i.e. symptom onset within seven days of enrolment) can be transferred to a situation of possibly overwhelmed hospitals where space may be scarce for treatments that need intravenous infusions.

The platform trial that examined bamlanivimab in hospitalised, moderate-to-severe cases in the USA, Denmark and Singapore (ACTIV-3), had less restrictive eligibility criteria with a maximum of 12 days being allowed between symptom onset and treatment. However, the population that is considered to quote: "require admission to hospital for acute medical care" may vary depending on context. Despite this possible source of heterogeneity, in general, we would consider evidence from ACTIV-3 applicable to inpatients (moderate to severe disease). RECOVERY, which examined the combination casirivimab/imdevimab, allowed clinically suspected cases without a positive polymerase chain reaction(PCR) result to enter the study, but the number of non-confirmed cases was low (< 1% PCR-negative, ~ 2.3% unknown). The study did not limit inclusion based on time from symptom onset. However, time from symptom onset varied between the serostatus groups (seronegative: 7 days, 4 to 10; seropositive: 10 days, 7 to 13; unknown: 9 days, 6 to 13), underlining the assumption that SARS-CoV-2 specific mAbs may be more effective early in the course of the disease.

Over time, the virus has developed changes compared to the original strain. Some of these changes have led to increased resistance to viral neutralisation by antibody therapy (FDA 2021b;

Madhi 2021; Zhou 2021), which led to the retraction of the EUA for bamlanivimab monotherapy (FDA 2021b).

BLAZE-1 (phase 2) mentioned assessing viral strains at baseline, with only two out of the 613 included participants having detectable variants at baseline. The enrolment into the ACTIV-3 bamlanivimab arm stopped in October 2020, before the wider spread of variants, and reported. Therefore, results from these early studies probably apply mainly to the wild type variant. It is important to note that the beta, gamma, delta, and epsilon variants, which are currently more widespread, have shown resistance to bamlanivimab using pseudovirus and clinical viral isolate assays (Hoffmann 2021b; McCallum 2021; Planas 2021; Wang 2021b). Etesevimab has shown diminished activity against the alpha and epsilon variant but remained active against beta and delta (Planas 2021; McCallum 2021).

In the study on sotrovimab, virus variants were not assessed in participants. In vitro studies indicate that sotrovimab probably remains active against the alpha, beta, gamma (Cathcart 2021), and epsilon (McCallum 2021) variants. The study examining regdanvimab has not assessed the virus strains participants were infected with. In vitro, regdanvimab maintained potency against the gamma variant, but showed reduced binding to the beta and epsilon variants (Ryu 2021; McCallum 2021).

RECOVERY and Weinreich (phase 1/2)/Weinreich (phase 3) did not explicitly assess the variants that affected their participants. However, the dominant strain at the time of RECOVERY enrolment was the B1.1.7 (alpha) variant in the UK, which has not shown resistance to casirivimab/imdevimab (Wang 2021b). In general, imdevimab and the combination casirivimab/imdevimab has not shown diminished performance against alpha, beta, gamma, delta and epsilon variants (Hoffmann 2021a; Planas 2021; Copin 2021; McCallum 2021). Whereas, casirivimab alone was less active against the beta (Wang 2021b) and delta variants (Hoffmann 2021a).

Overall, combination therapies may be more applicable because of the broader spectrum of neutralisation and a smaller possibility of viral escape (Copin 2021).

Quality of the evidence

We judged the risk of bias to be low for two studies (ACTIV-3; Eom 2021), to be of some concerns for one study (COMET-ICE), and high for two studies (RECOVERY; Weinreich (phase 3)) for all reported outcomes. In BLAZE-1 (phase 2), we judged risk of bias to be of some concerns for the outcome hospital admission or death and for the other reported outcomes we judged risk of bias to be low. In Weinreich (phase 1/2) we judged risk of bias to be high for the outcomes hospital admission or death and adverse events grades 3 to 4, and for the other reported outcomes we judged risk of bias to be low. We excluded Weinreich (phase 3) from analysis due to the unclear participant flow diagram and potentially selected analyses.

All data included in the summary of findings tables resulted from analyses according to the intention-to-treat principle or modified intention-to-treat principle, as prespecified in the respective study protocol (exclusions if randomised by error, withdrawal before any study treatment or not positive on diagnostic reverse transcription polymerase chain reaction (RT-PCR)). However, we rated the certainty in the evidence as low or very low for each prioritised outcome in all studies except RECOVERY, due to serious imprecision based on low number of events, small sample size, and resulting wide 95% confidence intervals (for details, see summary of findings tables) with evidence per comparison resulting from one study only. We downgraded one outcome, development of severe symptoms (NIV, IMV or extracorporeal membrane oxygenation (ECMO)), because of serious indirectness, as we considered follow-up at day five as too short. For the results from RECOVERY, we rated down one level due to lack of blinding and the potential influence from participants or staff on additional treatment options, as usual care is constantly changing seen the rapid development of the pandemic.

Potential biases in the review process

The publication of preliminary results in form of press releases and preprints has become widespread during the COVID-19 pandemic. While we had decided to include and report on preprints, we have not tracked all possible sources of press releases because quality may be low and reports may lack detail regarding participants and outcomes, although some are indexed in Epistemonikos.

In addition to regular RCTs, we performed a search for ongoing platform trials, as they may add treatments during the course of the study. We are regularly checking these studies via the registry, any related trial websites we are aware of, and press releases that are indexed in Epistemonikos. Up to now, this has proved useful in identifying new treatment arms with SARS-CoV-2-specific mAbs in ACTIV-2, ACTIV-3, AGILE, RECOVERY, DISCOVERY, and OPTIMISE-C19. We will run these searches and check for additional treatment arms monthly. Interestingly, in addition to large-scale platform trials, flexible study designs such as combined phase 1/2/3 trials with preplanned interim analyses, the potential to change the treatment dose during the process, and the batch-wise recruitment of participants according to new cases have become common, posing a challenge on estimating the arrival of new studies and the decision on when to potentially update this review in the future.

Due to the novelty of SARS-CoV-2, numerous interventions are currently under development. To maintain the currency of our evidence and to follow the newly developed mAbs that enter clinical studies in humans, we adapted our search strategy each week, based on a monoclonal antibody tracker (Chinese Antibody Society 2020). Recently, this tracker has not identified any new SARS-CoV-2-specific mAbs. There may be two possible underlying reasons for this: 1) no mAbs have entered clinical trial phase, which is unlikely given the rapidly changing COVID-19-related treatment landscape, 2) updating the list may have been delayed or stopped. In the latter case, we may have missed studies that are identified only with a drug name that is currently unknown to us. However, we would count on the fact that clinical studies in an advanced phase and their publications would provide more keywords for identification by our search strategy. We, therefore, assume that we have identified and will identify important phase 2, 3, and 4 RCTs in individuals infected with SARS-CoV-2.

For feasibility reasons, we did an abbreviated search between submission and response to peer review. We included publications on already included studies, but listed one new study under Studies awaiting classification for integration into the next version of this review.

Before data extraction, we had decided not to pool different monoclonal antibodies/antibody cocktails due to the different

epitopes they are targeting, and not to pool different doses of the same mAb as they may produce varying levels of antibody-dependent enhancement. We acknowledge that combining across doses and substances may have provided insight into the class effect, however, this would limit its utility in clinical decision-making by combining substances that target different pathways and may be used in different settings due to varying prevalence of variants to which a mAb may have become resistant.

In contrast to the protocol, we changed some of our outcomes based on input from the German clinical guideline, and we faced difficulties obtaining a clear definition for outcomes covered by the WHO Progression Scale (Differences between protocol and review). Of note, most of our predefined outcomes are prone to competing events (i.e. death), therefore we have changed and replaced these where possible, and noted down where not reported. We do not think this has introduced bias, as we chose the outcomes based on clinical interest rather than the effect estimate.

Agreements and disagreements with other studies or reviews

We identified low-certainty evidence about the effects of bamlanivimab at doses of 0.7 g, 2.8 g, and 7.0 g, the combination of bamlanivimab and etesevimab, the of combination casirivimab and imdevimab, sotrovimab at a dose of 0.5 g, and regdanvimab at 40 mg/kg and 80 mg/kg compared to placebo in non-hospitalised individuals with asymptomatic or mild disease. Further, we identified low- to very low-certainty evidence that treatment with bamlanivimab in hospitalised individuals with moderate-to-severe disease is not effective for the treatment of COVID-19, when compared to placebo; and moderate-certainty evidence that casirivimab/imdeviman is not effective to treat COVID-19 when compared to usual care in the complete allocated cohort of a study.

The identified studies published as full texts and preprints are in line with the evidence used in the Australian clinical guideline (National COVID-19 Clinical Evidence Taskforce 2020). This guideline pooled the two studies that examined bamlanivimab, and did not consider the conference abstract on bamlanivimab/etesevimab. Another difference is that we decided to refrain from meta-analysing participants with mild versus moderate and severe disease, as working mechanisms are anticipated to differ between early administration and administration later during the course of the disease. The prioritised outcomes differed from this review, the guideline included clinical recovery for regdanvimab and withdrawals due to adverse events for casirivimab/imdevimab in non-hospitalised participants.

A difference in the mechanism between the granting of an emergency use authorization (EUA) and summaries in systematic reviews and recommendations by several national clinical guidance (e.g. Australia, Germany) should be noted. An EUA is possible only in the context of a declared emergency when no viable alternatives are available. It does not constitute the approval of a medical product but facilitates its availability when it is not yet approved or is approved for a different indication. This decision may be based on favourable interim or final analyses of an RCT and may be revoked once the justification of its issuance is no longer in place (FDA 2021c). In contrast, systematic reviews aim to synthesise all available evidence, usually from peer-reviewed journals only, thus targeting the inclusion of mature data (although for the current review, mainly interim analyses from preprint or full-text publications were available).

The efficacy and safety of SARS-CoV-2-neutralising mAbs are not yet well-characterised, with only a few studies having been published (BLAZE-1 (phase 2); COMET-ICE; Eom 2021; Weinreich (phase 1/2); ACTIV-3; RECOVERY). Additional data in the form of full-text publications are expected to be published soon, and several studies have completed recruitment, therefore new evidence will not be long in coming.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence for each comparison results from one study only, and we rated certainty in the evidence as low due to very serious imprecision for all comparisons except casirivimab/imdevimab versus usual care in hospitalised individuals (moderate certainty evidence). Therefore, the identified evidence is mostly insufficient to draw meaningful conclusions regarding treatment with any specific monoclonal antibody (mAb), and the disease stage in which mAbs should be used.

For non-hospitalised participants (asymptomatic or mild disease), we are uncertain about the effectiveness and safety of bamlanivimab, the combination of bamlanivimab/etesevimab, casirivimab/imdevimab, sotrovimab, and regdanvimab compared to placebo. Information on patient-relevant outcomes such as mortality, quality of life, and serious adverse events is either inconclusive or entirely lacking, although bamlanivimab alone and in combination with etesevimab, as well as casirivimab/imdevimab, sotrovimab, and regdanvimab may reduce the occurrence of hospital admission or death. Data on adverse events (AEs) vary for the substances, doses and even type of AE (all grades, grades 3-4, serious adverse events). For all comparisons, the 95% confidence interval includes both benefit and harm and our certainty in the evidence is low. We acknowledge that the true effect may substantially vary from the reported effects.

For hospitalised participants (moderate-to-severe disease), bamlanivimab may have little to no effect on efficacy outcomes when compared to placebo, but it may increase the occurrence of severe symptoms and grade 3 to 4 adverse events. Casirivimab/imdevimab has probably no effect on mortality, progression to invasive mechanical ventilation (IMV), and hospital discharge alive by day 30. Unfortunately, we are lacking important information on AE and SAE for this comparison. Subgroup analyses within the studies suggest that it could be worth examining the subgroup of participants who have not developed antibodies at baseline.

Implications for research

We did not conduct meta-analyses because studies were heterogeneous with regard to different mAbs used for treatment, setting, and inconsistently reported outcomes. Moreover, only one of the included studies reported all-cause mortality exceeding 60 days, and none reported quality of life. WHO Progression Scale outcomes are reported on various versions of the scale, at different time points and as different effect measures. This highlights the urgent need for adequately-powered randomised controlled trials (RCTs) with comparable study arms, as well as the assessment and

reporting of clinically relevant outcomes such as quality of life and long-term adverse events.

Future research will need to consider whether the emergence of SARS-CoV-2 variants impacts the effectiveness of SARS-CoV-2-neutralising mAbs. BLAZE-1 (phase 2) explored resistance to four variants for bamlanivimab and etesevimab, and further research will be required as variants emerge.

We identified 36 ongoing RCTs. Publication of these ongoing studies may resolve some uncertainties and allow a better judgment regarding the effectiveness and safety of SARS-CoV-2-neutralising mAbs for the treatment of COVID-19.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ACTIV-3

Study characteristics	
Methods	Drug name: bamlanivimab Trial design: randomised, adaptive, blinded, controlled, multicentre, phase 3 trial Type of publication: journal publication (English) NCT number: NCT04501978 (date of trial registration: 3 August 2020) • Ongoing: the study continues, however, the bamlanivimab arm was stopped for futility after interim analysis Number of participants in bamlanivimab comparison: • recruited: 326 • allocated: 326 • evaluated: 314 Estimated enrolment: 10,000 participants Estimated completion date: 22 July 2022*
Participants	Setting • Inpatient • Recruitment period: August to October 2020 • Multicentre: Denmark, Singapore, Spain, USA Eligibility criteria

ACTIV-3 *(Continued)*

- Inclusion criteria
  * Age ≥ 18 years
  * Informed consent by the patient or the patient's LAR
  * SARS-CoV-2 infection, documented by PCR or another NAT within 3 days prior to randomisation OR documented by NAT > 3 days prior to randomisation and progressive disease suggestive of ongoing SARS-CoV-2 infection per the responsible investigator
  * Duration of symptoms attributable to COVID-19 ≤ 12 days per the responsible investigator
  * Requiring admission for inpatient hospital acute medical care for clinical manifestation of COV-ID-19, per the responsible investigator, and not for purely public health or quarantine purposes
- Exclusion criteria
  * Prior receipt of any SARS-CoV-2 hIVIG, convalescent plasma from a person who had recovered from COVID-19 or SARS-CoV-2 nmAb at any time prior to hospitalisation
  * Not willing to abstain from participation in other COVID-19 treatment trials until after day 5
  * Any condition for which participation would not be in the best interest of the participant or that could limit protocol-specified assessments
  * Expected inability to participate in study procedures
  * WOCBP who are not already pregnant at study entry and who are unwilling to abstain from sexual intercourse with men or practice appropriate contraception through day 90 of the study
  * Men who are unwilling to abstain from sexual intercourse with women of child-bearing potential or who are unwilling to use barrier contraception through day 90 of the study
  * Presence at enrollment of any of the following (stage 1 only):
    ☐ stroke
    ☐ meningitis
    ☐ encephalitis
    ☐ myelitis
    ☐ myocardial infarction
    ☐ myocarditis
    ☐ pericarditis
    ☐ symptomatic congestive heart failure (NYHA class III-IV)
    ☐ arterial or deep venous thrombosis or pulmonary embolism
  * Current or imminent requirement for any of the following (stage 1 only):
    ☐ invasive mechanical ventilation
    ☐ ECMO
    ☐ mechanical circulatory support
    ☐ vasopressor therapy
    ☐ commencement of renal replacement therapy at this admission (i.e. not patients on chronic renal replacement therapy)

Participant characteristics:

- Age (median, IQR):
  * treatment: 63 (50-72)
  * control: 59 (48-71)
- Sex (female):
  * treatment: 66 (40%)
  * control: 71 (47%)
- Race or ethnic group:
  * white: treatment: 76 (47%); control: 71 (47%)
  * Hispanic: treatment: 41 (25%); control: 33 (22%)
  * black: treatment: 33 (20%); control: 34 (23%)
- Disease severity:
  * moderate to severe according to the WHO Clinical Progression Scale (NIV 15% of participants at randomisation)

ACTIV-3 *(Continued)*

- Co-morbidities:
  - obesity (BMI ≥ 30): treatment: 76 (47%); control: 71 (47%)
  - hypertension: treatment: 82 (50%); control: 72 (48%)
  - diabetes: treatment: 54 (33%); control: 36 (24%)
  - renal impairment: treatment: 24 (15%); control: 9 (6%)
  - asthma: treatment: 14 (9%); control: 14 (9%)
  - heart failure: treatment: 12 (7%); control: 1 (1%)
  - any: treatment: 117 (72%); control: 98 (65%)
- Pre-treatments:
  - remdesivir: treatment: 60 (37%); control: 66 (44%)
  - antibacterial agent: treatment: 54 (33%); control: 36 (24%)
  - glucocorticoid: treatment: 80 (49%); control: 74 (49%)
  - antiplatelet or anticoagulant agent: treatment: 106 (65%); control: 95 (63%)
  - ACE inhibitor or ARB: treatment: 41 (25%); control: 31 (21%)
  - NSAID: treatment: 17 (10%); control: 16 (11%)
- Concomitant treatments (prescribed at day 5):
  - antibiotics: treatment: 28 (17.5%); control: 20 (13.4%)
  - antifungals: treatment: 4 (2.5%); control: 2 (1.3%)
  - ACE inhibitor: treatment: 22 (13.8%); control: 16 (10.7%)
  - ARB: treatment: 15 (9.4%); control: 14 (9.4%)
  - antiplatelets/anticoagulants: treatment: 74 (46.3%); control: 61 (40.9%)
  - antiviral: treatment: 0 (0%); control: 0 (0%)
  - immune modulating medication: treatment: 67 (41.9%); control: 66 (44.3%)

Interventions	Intervention
	
	• Bamlanivimab
	  * Target: SARS-CoV-2 S protein
	  * Origin: derived from B lymphocytes of a convalescent naturally SARS-CoV-2-infected patient
	  * Dose: 7000 mg
	  * Frequency: single dose
	  * Route of administration: IV infusion
	
	Comparator
	
	• Placebo (0.9% sodium chloride solution), single-dose, IV infusion

Outcomes	Efficacy outcomes
	
	• All-cause mortality
	  * at up to 30 days: reported for day 28
	  * at up to 60 days: not planned, not reported
	• Development of severe symptoms according to WHO scale (≥ 6 on the WHO Clinical Progression Scale; for mild disease): reported for day 5
	• Length of hospital stay: not planned, not reported
	• Discharge from hospital: reported
	• Admission to ICU: not planned, not reported
	• Length of ICU stay: not planned, not reported
	• Quality of life, including fatigue: not planned, not reported
	• Viral clearance: not planned, not reported
	
	Safety outcomes
	
	• Number of participants with any grade AEs: planned, reported per category (could not be summarised)
	• Number of participants with grade 3 and grade 4 AEs: planned, reported
	• Number of participants with SAEs: reported

ACTIV-3 *(Continued)*

	Additional study outcomes • Time to sustained recovery
Notes	* Additional mAb arms: *VIR-7831* (administered by IV infusion, randomisation stopped); *BRII-196/BRII-198* (administered by IV infusion, randomisation stopped); *AZD7442* (600 mg AZD7442 (300 mg AZD8895 + 300 mg AZD1061, single-dose IV infusion) Developer: AbCellera, NIAID Vaccine Research Center, Eli Lilly and Company Funding: NIAID Conflicts of interest: AB: • NIH (NIAID); Medical Research Council, UK; TB: Novo Nordisk Foundation, Simonsen Foundation, GSK, Pfizer, Boehringer Ingelheim, Gilead Sciences, MSD, Lundbeck Foundation, Kai Hansen Foundation, SB: NIH, Hamilton, Faron, Sedana, Janssen, DoD, Oxford University, Brigham Young University; NYU, HC, RG & LJO: Gilead Sciences; DF: NIH, Cytovale; EG: NIAID, Gilead Sciences; AGe, BG, JN, SS: NIH; AGi: National Heart, Lung, and Blood Institute (NHLBI); TH: Basilea Pharmaceutica, Motif Bio, Genentech; MJ: Gilead Sciences, Regeneron; PK: Eli Lilly; MM: Roche-Genenrech, Novartis Pharmaceuticals, Citius Pharmaceuticals, Department of Defense, NIH/NHLBI, California Institute of Regenerative Medicine; RP: Gilead Sciences, MSD, ViiV Healthcare; US: NIH, Regeneron, Cytodyn; WS: NHLBI, Aerpio Pharmaceuticals; BTT: NHLBI, Bayer, Novartis, Thetis; JB, CB; MB; CC; VD; AGo; EHa; EHi; JUJ; ISJ; VK; KUK; HCL; BL; JL; NM; DM; TM; MP; AP; MPo; CR; MT; DW: nothing to disclose

BLAZE-1 (phase 2, 0.7g)

Study characteristics	
Methods	see BLAZE-1 (phase 2)
Participants	
Interventions	
Outcomes	
Notes	

BLAZE-1 (phase 2, 2.8g)

Study characteristics	
Methods	see BLAZE-1 (phase 2)
Participants	
Interventions	
Outcomes	
Notes	

BLAZE-1 (phase 2, 7.0g)

Study characteristics	
Methods	see BLAZE-1 (phase 2)
Participants	
Interventions	
Outcomes	
Notes	

BLAZE-1 (phase 2)

Study characteristics	

Methods	Drug name:
	• monotherapy: bamlanivimab
	• combination therapy: bamlanivimab and etesevimab
	Trial design: randomised, double-blind, placebo-controlled, multipart, phase 2/3, single-infusion study
	Type of publication: journal publication (English)
	NCT number: NCT04427501 (date of trial registration: 11 June 2020)
	• Ongoing: recruiting, updated 16 March 2021
	Number of participants:
	• recruited: 613
	• allocated: 592
	  * bamlanivimab monotherapy:
	  ☐ 700 mg: 104 participants
	  ☐ 2800 mg: 109 participants
	  ☐ 7000 mg: 104 participants
	  * combination therapy:
	  ☐ 2800 mg of bamlanivimab and 2800 mg of etesevimab: 114 participants
	  * placebo: 161 participants
	• received at least one dose: 573
	  * bamlanivimab monotherapy:
	  ☐ 700 mg: 101 participants
	  ☐ 2800 mg: 107 participants
	  ☐ 7000 mg: 101 participants
	  * combination therapy:
	  ☐ 2800 mg of bamlanivimab and 2800 mg of etesevimab: 112 participants (only 109 included in efficacy set)
	  * placebo: 152 participants
	Estimated enrolment: 3160 participants
	Estimated completion date: 31 May 2021

Participants	Setting

BLAZE-1 (phase 2) *(Continued)*

- Outpatient
- Recruitment period:
  * monotherapy 17 June-21 August 2020
  * combination therapy 22 August-3 September 2020
- multicentre (49 centres); USA

Eligibility criteria

- Inclusion criteria
  * ≥ 18 years of age at the time of randomisation
  * Currently not hospitalised
  * ≥ 1 mild or moderate COVID-19 symptoms:
    ☐ fever
    ☐ cough
    ☐ sore throat
    ☐ malaise
    ☐ headache
    ☐ muscle pain
    ☐ gastrointestinal symptoms
    ☐ shortness of breath with exertion
  * Sample collection for first positive SARS-CoV-2 viral infection determination ≤ 3 days prior to start of infusion
  * Men or non-pregnant women
  * Understand and agree to comply with planned study procedures
  * Agree to the collection of nasopharyngeal swabs and venous blood
  * Participant or LAR give signed informed consent
- Exclusion criteria
  * SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300, respiratory rate ≥ 30 per min, heart rate ≥ 125 per minute
  * Require mechanical ventilation or anticipated impending need for mechanical ventilation
  * Known allergies to any of the components used in the formulation of the interventions
  * Haemodynamic instability requiring use of pressors within 24 hours of randomisation
  * Suspected or proven serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking
  * Any co-morbidity requiring surgery within < 7 days, or that is considered life-threatening within 29 days
  * Any serious concomitant systemic disease, condition or disorder that, in the opinion of the investigator, should preclude participation in this study
  * History of a positive SARS-CoV-2 serology test
  * History of a positive SARS-CoV-2 test prior to the one serving as eligibility for this study
  * Received an investigational intervention for SARS-CoV-2 prophylaxis within 30 days before dosing
  * Received treatment with a SARS-CoV-2 specific mAb
  * History of convalescent COVID-19 plasma treatment
  * Participated in a previous SARS-CoV-2 vaccine study
  * Participated within the last 30 days in a clinical study involving an investigational intervention (if the previous investigational intervention has a long half-life, 5 half-lives or 30 days, whichever is longer, should have passed)
  * Concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
  * Pregnant or breastfeeding

Participant characteristics

BLAZE-1 (phase 2) *(Continued)*

- Age (median (IQR))
  - bamlanivimab monotherapy:
    - 700 mg: 39 (31-58)
    - 2800 mg: 45 (31-56)
    - 7000 mg: 46 (34-55)
  - combination therapy:
    - 2800 mg of bamlanivimab and 2800 mg of etesevimab: 44 (30-60)
  - Placebo: 46 (35-57)
- Sex (female):
  - bamlanivimab monotherapy:
    - 700 mg: 63 (62.4%)
    - 2800 mg: 51 (47.7%)
    - 7000 mg: 58 (57.4%)
  - combination therapy:
    - 2800 mg of bamlanivimab and 2800 mg of etesevimab: 58 (51.8%)
  - placebo: 85 (54.5%)
- Race or ethnic group (self-reported):
  - white:
    - bamlanivimab monotherapy: 700 mg: 90 (89.1%); 2800 mg: 90 (86.5%); 7000 mg: 89(89.0%)
    - combination therapy: 2800 mg of bamlanivimab and 2800 mg of etesevimab: 105 (94.6%)
    - placebo: 133 (88.1%)
  - black:
    - bamlanivimab monotherapy: 700 mg: 7 (6.9%); 2800 mg: 7 (6.7%); 7000 mg: 8 (8.0%)
    - combination therapy: 2800 mg of bamlanivimab and 2800 mg of etesevimab: 4 (3.6%)
    - placebo: 7 (4.6%)
  - Asian:
    - bamlanivimab monotherapy: 700 mg: 1 (1.0%); 2800 mg: 5 (4.8%); 7000 mg: 3 (3.0%)
    - combination therapy: 2800 mg of bamlanivimab and 2800 mg of etesevimab: 2 (1.8%)
    - placebo: 8 (5.3%)
  - Hispanic:
    - bamlanivimab monotherapy: 700 mg: 49 (48.5%); 2800 mg: 47 (43.9%); 7000 mg: 39 (38.6%)
    - combination therapy: 2800 mg of bamlanivimab and 2800 mg of etesevimab: 42 (37.5%)
    - placebo: 68 (43.6%)
- Disease severity: mild according to WHO Clinical Progression Scale (Figure 1)
- Co-morbidities:
  - BMI ≥ 30:
    - bamlanivimab monotherapy: 700 mg: 45/100 (45.0%); 2800 mg: 56/106 (52.8%); 7000 mg: 35/97 (36.1%)
    - combination therapy: 2800 mg of bamlanivimab and 2800 mg of etesevimab: 40/109 (36.7%)
    - placebo: 72/152 (47.4%)
- Pre-treatments: not reported
- Concomitant treatments: not reported

Interventions	Interventions

- Monotherapy: bamlanivimab or
- Combination therapy: bamlanivimab and etesevimab
  - Target: SARS-CoV-2 S protein
  - Origin: derived from B lymphocytes of a convalescent naturally SARS-CoV-2- infected patient
  - Dose:
    - bamlanivimab monotherapy: 700 mg/ 2800 mg/ 7000 mg
    - combination therapy of bamlanivimab and etesevimab: each 2800 mg
  - Frequency: single dose
  - Route of administration: intravenous infusion (IV)

BLAZE-1 (phase 2) *(Continued)*

	Comparator: • Placebo, single-dose, IV infusion

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: reported
	  * at up to 60 days: planned, not reported
	• Clinical progression/improvement of symptoms: planned as proportion of participants requiring mechanical ventilation; not reported
	• Admission to hospital (for outpatients only): reported as COVID-19-related deterioration (hospitalisation, emergency room visit, or death) by day 29
	• Length of hospital stay: planned, not reported
	• Admission to ICU: planned, not reported
	• Length of ICU stay: not planned, not reported
	• Quality of life: planned with Symptoms and Overall Clinical Status Participant Questionnaire at days 7, 11, 15, and 22, not reported
	• Viral clearance: reported at day 7, 11, 15 and 22
	Safety outcomes
	• Number of participants with any grade AEs: reported
	• Number of participants with grade 3 and grade 4 AEs: reported as treatment-emergent AEs, which was defined as AE emerging after first dose, coded according to the Medical Dictionary for Regulatory Activities (MedDRA)
	• Number of participants with SAEs: reported
	Additional study outcomes
	• Time to symptom resolution
	• Proportion of participants demonstrating symptom resolution via the symptom questionnaire on days 7, 11, 15, and 22
	• Change in symptom score (total of ratings) from baseline to days 7, 11, 15, and 22
	• Time to symptom improvement
	• Proportion of participants demonstrating symptom improvement via the symptom questionnaire on days 7, 11, 15, and 22
	• Time to SARS-CoV-2 clearance
	• SARS-CoV-2 viral load area under the response time curve (AUC) assessed through Day 29

Notes	Developer: • bamlanivimab: AbCellera, NIAID Vaccine Research Center, Eli Lilly and Company • etesevimab: Junshi Biosciences, Institute of Microbiology, Chinese Academy of Science (IMCAS), Eli Lilly and Company Funding: Eli Lilly and Company Conflicts of interest: • AA, PC, KC, MD, PK, AN, GO, DP, JS, AS, LS, DS, JV, TH, PE, RH, NK: Eli Lilly and Company; RG, JB: Eli Lilly and Company and Gilead Science; GH: Eli Lilly and Company, Gilead Sciences, Viiv, Janssen, Proteus, Bristol-Meyers-Squibb, Thera Technologies; PK: GlaxoSmithKline, Amgen, Thera Technologies, Merck, Gilead Sciences, Johnson & Johnson, Pfizer

BLAZE-1 (phase 3)

Study characteristics

Methods	Drug name:
	• combination therapy: bamlanivimab and etesevimab
	Trial design: randomised, double-blind, placebo-controlled, multipart, phase 2/3, single-infusion study
	Type of publication: journal publication (English)
	NCT number: NCT04427501 (date of trial registration: 11 June 2020)
	• Ongoing: recruiting, updated 26 July 2021
	Number of participants:
	• recruited: 1087
	• allocated: 1049 (14 were randomised, but did not receive infusion)
	  * combination therapy:
	  ☐ 2800 mg of bamlanivimab and 2800 mg of etesevimab: 518 participants
	  * placebo: 517 participants
	Estimated enrolment: 577 participants
	Estimated completion date: 24 June 2022

Participants	Setting • Outpatient • Recruitment period: * 3 September - 8 December 2020 • multicentre (49 centres); USA Eligibility criteria

BLAZE-1 (phase 3) *(Continued)*

- Inclusion criteria
  - not hospitalised
  - ≥ 18 years of age and satisfy at least one of the following at the time of screening
    - ☐ Are ≥ 65 years of age
    - ☐ Have a BMI ≥ 35
    - ☐ Have chronic kidney disease
    - ☐ Have type 1 or type 2 diabetes
    - ☐ Have immunosuppressive disease
    - ☐ Are currently receiving immunosuppressive treatment, or
    - ☐ Are ≥ 55 years of age AND have
    - ☐ cardiovascular disease, OR hypertension, OR chronic obstructive pulmonary disease (COPD)or otherchronic respiratory disease
    - ☐ Are 12-17 years of age (inclusive) AND satisfy at least one of the following at thetime of screening
    - ☐ Have a BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm
    - ☐ Have sickle cell disease
    - ☐ Have congenital or acquired heart disease
    - ☐ Have neurodevelopmental disorders, for example, cerebral palsy
    - ☐ Have a medical-related technological dependence, for example,tracheostomy, gastrostomy, or positive pressure ventilation (not relatedto COVID-19)
    - ☐ Have asthma or reactive airway or other chronic respiratory disease thatrequires daily medication for control
    - ☐ Have type 1 or type 2 diabetes
    - ☐ Have chronic kidney disease
    - ☐ Have immunosuppressive disease, or
    - ☐ Are currently receiving immunosuppressive treatment
- ≥ 1 mild or moderate COVID-19 symptoms:
  - fever
  - cough
  - sore throat
  - malaise
  - headache
  - muscle pain
  - gastrointestinal symptoms
  - shortness of breath with exertion
- Sample collection for first positive SARS-CoV-2 viral infection determination ≤ 3 days prior to start of infusion
- Men or non-pregnant women
- Understand and agree to comply with planned study procedures
- Agree to the collection of nasopharyngeal swabs and venous blood
- Participant or LAR give signed informed consent

BLAZE-1 (phase 3) *(Continued)*

- Exclusion criteria
  - SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300, respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute
  - Require mechanical ventilation or anticipated impending need for mechanical ventilation
  - Known allergies to any of the components used in the formulation of the interventions
  - Haemodynamic instability requiring use of pressors within 24 hours of randomisation
  - Suspected or proven serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking
  - Any co-morbidity requiring surgery within < 7 days, or that is considered life-threatening within 29 days
  - Any serious concomitant systemic disease, condition or disorder that, in the opinion of the investigator, should preclude participation in this study
  - History of a positive SARS-CoV-2 serology test
  - History of a positive SARS-CoV-2 test prior to the one serving as eligibility for this study
  - Received an investigational intervention for SARS-CoV-2 prophylaxis within 30 days before dosing
  - Received treatment with a SARS-CoV-2 specific mAb
  - History of convalescent COVID-19 plasma treatment
  - Participated in a previous SARS-CoV-2 vaccine study
  - Participated within the last 30 days in a clinical study involving an investigational intervention (if the previous investigational intervention has a long half-life, 5 half-lives or 30 days, whichever is longer, should have passed)
  - Concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
  - Pregnant or breastfeeding

Participant characteristics

- Age (median (SD))
  - combination therapy:
    - ☐ 2800 mg of bamlanivimab and 2800 mg of etesevimab: 54.3 (17.1)
  - Placebo: 53.3 (16.4)
- Sex (female):
  - combination therapy:
    - ☐ 2800 mg of bamlanivimab and 2800 mg of etesevimab: not reported
  - placebo: not reported
- Race or ethnic group (self-reported):
  - white:
    - ☐ combination therapy: 2800 mg of bamlanivimab and 2800 mg of etesevimab: 449/512 (87.7%)
    - ☐ placebo: 447/513 (87.1%)
  - black:
    - ☐ combination therapy: 2800 mg of bamlanivimab and 2800 mg of etesevimab: 44/512 (8.6%)
    - ☐ placebo: 39/513 (7.6%)
  - Asian:
    - ☐ combination therapy: 2800 mg of bamlanivimab and 2800 mg of etesevimab: 16/512 (3.1%)
    - ☐ placebo: 22/513 (4.3%)
  - Hispanic or Latin:
    - ☐ combination therapy: 2800 mg of bamlanivimab and 2800 mg of etesevimab: 149/517 (28.8%)
    - ☐ placebo: 155/516 (30.0%)
- Disease severity: mild according to WHO Clinical Progression Scale (Figure 1)

BLAZE-1 (phase 3) *(Continued)*

- Co-morbidities:
  - Chronic kidney disease:
    - ☐ combination therapy: 2800 mg of bamlanivimab and 2800 mg of etesevimab: 12 (2.3%)
    - ☐ placebo: 24 (4.6%)
  - Diabetes:
    - ☐ combination therapy: 2800 mg of bamlanivimab and 2800 mg of etesevimab: 151 (29.2%)
    - ☐ placebo: 134 (25.9%)
  - Immunosuppressive disease:
    - ☐ combination therapy: 2800 mg of bamlanivimab and 2800 mg of etesevimab: 7 (1.4%)
    - ☐ placebo: 9 (1.7%)
  - Immunosuppressive treatment:
    - ☐ combination therapy: 2800 mg of bamlanivimab and 2800 mg of etesevimab: 21 (4.1%)
    - ☐ placebo: 30 (5.8%)
- Pre-treatments: not reported
- Concomitant treatments: not reported

Interventions	Interventions
	
	• Combination therapy: bamlanivimab and etesevimab
	  * Target: SARS-CoV-2 S protein
	  * Origin: derived from B lymphocytes of a convalescent naturally SARS-CoV-2- infected patient
	  * Dose:
	  ☐ combination therapy of bamlanivimab and etesevimab: each 2800 mg
	  * Frequency: single dose
	  * Route of administration: intravenous infusion (IV)
	
	Comparator:
	
	• Placebo, single-dose, IV infusion

Outcomes	Efficacy outcomes
	
	• All-cause mortality
	  * at up to 30 days: reported
	  * at up to 60 days: planned, not reported
	• Clinical progression/improvement of symptoms: planned as proportion of participants requiring mechanical ventilation; not reported
	• Admission to hospital (for outpatients only): reported as COVID-19-related deterioration (hospitalisation, emergency room visit, or death) by day 29
	• Length of hospital stay: planned, reported as mean duration of hospitalisation
	• Admission to ICU: planned, not reported
	• Length of ICU stay: not planned, not reported
	• Quality of life: planned with Symptoms and Overall Clinical Status Participant Questionnaire at days 7, 11, 15, and 22, not reported
	• Viral clearance: reported as time to viral clearance
	
	Safety outcomes
	
	• Number of participants with any grade AEs: reported
	• Number of participants with grade 3 and grade 4 AEs: not planned, not reported
	• Number of participants with SAEs: reported
	
	Additional study outcomes
	
	• time to hospitalisation
	• time to symptom improvement up to Day 11
	• time to sustained symptom resolution up to Day 29

BLAZE-1 (phase 3) *(Continued)*

- proportion of participants with SARS-CoV-2 viral load greater than 5.27 on Day 7 (+2 days)
- change from baseline to Day 7 (±2 days) in viral load

Notes	Developer: • bamlanivimab: AbCellera, NIAID Vaccine Research Center, Eli Lilly and Company • etesevimab: Junshi Biosciences, Institute of Microbiology, Chinese Academy of Science (IMCAS), Eli Lilly and Company Funding: Eli Lilly and Company Conflicts of interest: • Eli Lilly and company: AA, PC, CC, KC, MD, PE, MD, BH, RH, TH, PK, BM, JM, AN, GO, DP, JS, AS, IS, LS, DS, JVN, • Eli Lilly, Astra Zeneca: NK • Eli Lilly, Pfizer, Johnson&Johnson, Merck, Gilead, Amgen: PK • Gilead, Viiv, Janssen, Proteus: GH • Gilead Sciences: RG • Eli Lilly, Novartis, ORIC Pharmaceutical, Tillotts Pharma, Genentech, Partner Therapeutics, Moderna, AzurRx, WebMD, Neoleukin Therapeutics: MD • Eli Lilly and Vitalink Pharmaceutical research, Moderna, GSK, Verona, Novartis, Nephron, Roche, Medicago, Exact, Boehringer Ingelheim: JB • nothing to disclose: MA, JC, CH, AI, RP

COMET-ICE

Study characteristics	
Methods	Drug name: sotrovimab (VIR-7831) Trial design: randomised, multicentre, double-blind, placebo-controlled, phase 2/3 study Type of publication: preprint (English) NCT number: COMET-ICE (date of trial registration: 10 September 2020) Ongoing: active, not recruiting, updated 7 May 2021 Number of participants: • screened: 795 patients (up to data cut-off on 19 January 2021) • allocated: 1057 up to 10 March 2021 • analysed: 583 patients (sotrovimab, 291; placebo, 292) Estimated enrolment: 1360 participants Estimated completion date: July 2021
Participants	Setting • Outpatient, 1 risk factor • Recruitment period: 27 August 2020 to 10 March 2021 • Multicentre (37 sites) in the USA, Brazil, Canada, Spain Eligibility criteria

COMET-ICE *(Continued)*

- Inclusion criteria
  - nonhospitalised patients with symptomatic COVID-19 and at least one risk factor for disease progression
  - ≥ 18 years and at high risk of progression of COVID-19 or ≥ 55 years old
  - Participants must have a positive SARS-CoV-2 test result and oxygen saturation ≥ 94% on room air and have COVID-19 symptoms and be ≤ 5 days from onset of symptoms
- Exclusion criteria
  - Currently hospitalised or judged by the investigator as likely to require hospitalisation in the next 24 hours
  - Symptoms consistent with severe COVID-19
  - Participants who, in the judgment of the investigator are likely to die in the next 7 days
  - Severely immunocompromised participants

Participant characteristics

- Age (median, range):
  - treatment: 53.0 (18-96)
  - control: 52.5 (18-88)
- Sex (male):
  - treatment: 135 (46%)
  - control: 131 (45%)
- Race or ethnic group:
  - white:
    - ☐ treatment: 254 (88%)
    - ☐ control: 252 (87%)
  - black/African American:
    - ☐ treatment: 16 (6%)
    - ☐ control: 22 (8%)
  - Asian:
    - ☐ treatment: 17 (6%)
    - ☐ control: 17 (6%)
  - American Indian or Alaska native:
    - ☐ treatment: 1 (<1%)
    - ☐ control: 0
  - Mixed race:
    - ☐ treatment: 2 (<1)
    - ☐ control: 0
- Hispanic ethnicity:
  - treatment: 190 (65%)
  - control: 178 (61%)
- Disease severity: mild according to WHO Clinical Progression Scale (Figure 1)
- Co-morbidities:
  - Obesity (63%), diabetes (23%), chronic kidney disease (< 1%, heart failure (< 1%), COPD (4%), asthma (16%)

Interventions	Intervention Sotrovimab (VIR-7831, GSK4182136) • Target: SARS-CoV-2 S protein • Origin: engineered mAb, its parental form is S309 (isolated from a SARS survivor) • Dose: 500 mg • Frequency: single dose • Route of administration: IV Comparator

COMET-ICE *(Continued)*

	• Placebo (sterile normal saline 0.9% NaCl), IV

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: 29-day mortality reported
	  * at up to 60 days: 60-day mortality planned, not yet reported
	• Clinical progression/improvement of symptoms: reported as proportion of patients who required supplemental oxygen
	• Development of severe symptoms according to WHO scale (≥ 6, for mild disease): reported as proportion of participants who progress to develop severe and/or critical respiratory COVID-19 as manifest by requirement for and method of supplemental oxygen at day 29
	• Admission to hospital: reported as proportion of participants with hospitalisation for acute management of illness > 24 hours or death
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to ICU: reported
	• Length of ICU stay: not planned
	• Quality of life, including fatigue, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days; up to 30 days, and longest follow-up: not planned
	• Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: planned, not yet reported
	• Thromboembolic events: not planned
	• Renal failure: not planned
	Safety outcomes
	• Number of participants with AEs (all grades, grade 1-2, grade 3-4): all AE and grade 3-4 AE reported
	• Number of participants with SAEs: reported
	Additional study outcomes
	• Occurrence of adverse events of special interest (AESI)
	• Severity and duration of participant-reported symptoms of COVID-19-related illness using the FLU-PRO patient-reported outcome instrument
	• Incidence and titres (if applicable) of serum ADA to VIR-7831
	• changes in viral load

Notes	Developer: Vir Biotechnology, Inc.; GlaxoSmithKline Funding: Vir Biotechnology, Inc.; GlaxoSmithKline Recruitment status: active, not recruiting Conflicts of Interest: • VIr Biotechnology: AG, YGR, EJ, MCC, JM, ES, JS, AF, AES • VIR Biotechnology, Pfizer, United Medical, Gilead Sciences, Merck Sharp & Dohme, GlaxoSmithKline: DRF • VIR Biotechnology and GlaxoSmithKline: HZ, CMH, JS, EM, EA, MA • GSK: NS, AP, PSP • VIR Biotechnology, GSK, Gilead Sciences: ALC • VIR biotechnology, Gilead Sciences, ViiV Healthcare: CB

Eom 2021

Study characteristics

Eom 2021 *(Continued)*

Methods	Drug name: regdanvimab (CT-P59) Trial design: randomised, parallel-group, placebo-controlled, quadruple-blinded, phase 2/3 study. Results are from part 1 of a two-part phase 2/3 study Type of publication: preprint publication (English) NCT number: NCT04602000 (date of trial registration: 26 October 2020) Ongoing: recruiting, updated 26 October 2020 Number of participants: • screened: 371 • randomised: 327 randomised • analysed ITTI: • CT-P59 40 mg/kg (n =101), CT-P59 80 mg/kg (n = 103), or placebo (n = 103). Estimated enrolment: 1020 participants Estimated completion date: September 2021

Participants	Setting
	
	• Outpatients
	• Recruitment period: between 7 October and 18 December 2020
	• Multicentre: South Korea, Romania, Spain and USA
	
	Eligibility criteria
	
	• Inclusion criteria
	  * Adult male or female patient, aged ≥ 18
	  * Diagnosed with SARS-CoV-2 infection at screening by using the sponsor-supplied rapid SARS-CoV-2 diagnostic test or RT-PCR
	  * Mild conditions meeting all of the following criteria:
	  ☐ SpO2 ≥ 94% on room air
	  ☐ not requiring supplemental oxygen
	• Exclusion criteria
	  * Patient with severe condition (previous or currently hospitalised, respiratory distress with respiratory rate ≥ 30 breaths/minute, requires supplemental oxygen, experienced shock, complicated with other organ failure, and ICU monitoring treatment is needed by investigator's discretion
	  * Prohibited treatments: drugs with actual or possible antiviral drugs and/or possible anti-SARS-CoV-2 activity; any SARS-CoV-2 hIVIG, convalescent plasma for the treatment of SARS-CoV-2 infection; any other investigational device or medical product including but not limited to mAbs (tocilizumab, sarilumab, etc.), fusion proteins, or biologics for the treatment of SARS-CoV-2; use of medications that are contraindicated with standard of care; SARS-CoV-2 vaccine)
	
	Participant characteristics
	
	• Age (median, IQR)
	  * CT-P59 40 mg/kg: 51.0 (42, 60)
	  * CT-P59 80 mg/kg: 51 (40, 60)
	  * Placebo: 52.0 (51, 61)
	• Sex (male):
	  * CT-P59 40 mg/kg: 59 (56.2%)
	  * CT-P59 80 mg/kg: 53.2%)
	  * Placebo: 48 (43.2%)

Eom 2021 *(Continued)*

- Race or ethnic group :
  - white:
    - ☐ CT-P59 40 mg/kg: 94 (89.5%)
    - ☐ CT-P59 80 mg/kg: 96 (86.5%)
    - ☐ Placebo: 96 (86.5%)
  - Asian:
    - ☐ CT-P59 40 mg/kg: 11 (10.5%)
    - ☐ CT-P59 80 mg/kg: 15 (13.5%
    - ☐ Placebo: 15 (13.5)%
- Disease severity: mild
- Co-morbidities, at least one, including cardiovascular disease, chronic respiratory disease, hypertension, diabetes mellitus, or pneumonia reported
  - CT-P59 40 mg/kg: 78 (74.3%)
  - CT-P59 80 mg/kg: 80 (72.1%)
- Pre-treatments: most pre-treatments excluded, see eligibility
- Concomitant treatments (≥ 1, including analgesics, antibacterials, anti-inflammatory and antithrombotic agents, antivirals, beta-blocking agents, etc., supplemental materian S1):
  - CT-P59 40 mg/kg: 90 (85.7%)
  - CT-P59 80 mg/kg: 92 (83.6 %)
  - Placebo: 97 (88.2%)

Interventions	Intervention • Regdanvimab (CT-P59) * Target: SARS-CoV-2 S protein (D614G) * Origin: not reported * Dose: 40 mg/kg and 80 mg/kg * Frequency: single infusion * Route of administration: IV infusion Comparator • Placebo (250 mL of 0.9% sodiumchloride, IV)
Outcomes	Efficacy outcomes • All-cause mortality * at up to 30 days: reported (day 28) * at up to 60 days: not planned • Clinical progression/development of severe symptoms * mechanical ventilation and vasopressors, dialysis or ECMO: reported as proportion of participants requiring mechanical ventilation due to SARS-CoV-2 infection, proportion of patients requiring supplemental oxygen due to SARS-CoV-2 infection up to day 14 and 28 • Admission to hospital: reported up to day 14 and 28 • Length of hospital stay (for those admitted to hospital): not planned • Admission to ICU: planned up to day 14 and 28, reported for one time point • Length of ICU stay: not planned • Quality of life: not planned • Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: reported as proportion of participants with negative conversion in nasopharyngeal swab specimen at day 14, 28, and survival analysis • Thromboembolic events: not planned • Renal failure: not planned Safety outcomes • Number of participants with AEs (all grades, grade 1-2, grade 3-4): reported as TEAE

Eom 2021 *(Continued)*

- Number of participants with SAEs: reported as TESAE, treatment-emergent serious adverse event.

Additional study outcomes

- Proportion of patients requiring additional prescription medication due to SARS-CoV-2 infection
- Time to clinical recovery
- Duration of fever (not reported)
- Proportion of participants reporting adverse events of special interest (infusion-related reactions, Hypersensitivity, and anaphylactic reactions)
- Incidence of Ab-dependent enhancement
- Proportion of participants with anti-drug Abs immunogenicity (not reported)
- Proportion of participants with anti-drug Abs SARS-CoV-2 infection-related signs and symptoms
- Viral shedding in nasopharyngeal swab specimen based on RT-qPCR and cell culture
- Genotype and phenotype of SARS-CoV-2 viral isolates
- Viral serology for SARS-CoV-2 antibody

Notes	Developer: Celltrion Funding: Celltrion Recruitment status: recruiting Other: 3 arms Conflicts of interest: • M.G.I.: research funding - AiCuris, Janssen, and Shire; consultant - Adagio, AlloVir, Celltrion, Cidara, Genentech, Roche, Janssen, Shionogi, and Viracor Eurofins; Data and Safety Monitoring Boards for Janssen, Merck, SAB Biotherapeutics, Sequiris, Takeda, and Vitaeris. • J.Y.K., Y.R.J., An.S.-C., O.S., Ad.S.-C., J.S.E.: investigators in COVID-19 clinical trials by Bukwang Pharm.Co., Ltd, Daewoong Pharmaceuticals, Enzychem Lifesciences, GC Pharma, Algernon Pharmaceuticals, Atea Pharmaceuticals, Diffusion Pharmaceuticals, or Regeneron Pharmaceuticals, outside the scope of the submitted work, and by Celltrion, Inc., within the scope of the submitted work. • S.J.L., S.H.K.: employees and shares in Celltrion, Inc. • I.C., J.H.S., S.G.L., M.R.K., D.R.C., and H.N.K. are employees of Celltrion, Inc. • L.-L.P., Y.-S.K., and S.H.C. declare no conflicts.

Eom 2021 (40 mg/kg)

Study characteristics	
Methods	see Eom 2021
Participants	
Interventions	
Outcomes	
Notes	

Eom 2021 (80 mg/kg)

Study characteristics	
Methods	See Eom 2021
Participants	
Interventions	
Outcomes	
Notes	

RECOVERY

Study characteristics	

Methods	Drug name: casirivimab/imdevimab
	
	Other drugs: lopinavir-ritonavir, corticosteroid, hydroxychloroquine, azithromycin, convalescent plasma, tocilizumab, immunoglobulin, aspirin, colchicine, baricitinib, anakinra, dimethyl fumarate
	
	Trial design: randomised, multicentre, factorial design, open-label platform trial
	
	Type of publication: preprint publication (English)
	
	NCT number: NCT04381936 (date of trial registration: 11 May 2020)
	
	Ongoing: recruiting, updated 5 May 2021
	
	Number of participants:
	
	• eligible: 11,464 participants
	• allocated:
	  * casirivimab/imdevimab 8 g (4g each): 4839 participants
	  * usual care: 4946 participants
	  * Primary efficacy analysis in seronegative participants:
	  ☐ REGEN-COV2: 1633 participants
	  ☐ usual care: 1520 participants
	
	Estimated enrolment: 40,000 participants
	
	Estimated completion date: December 2031

Participants	Setting
	
	• Hospitalised patients
	• Recruitment period: 18 September 2020 - 22 May 2021
	• Multicentre (127 hospitals), country: UK
	
	Eligibility criteria
	
	• Inclusion criteria:
	  * Hospitalised
	  * SARS-CoV-2 infection (clinically suspected or laboratory-confirmed)
	  * No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial

RECOVERY *(Continued)*

- Exclusion criteria
  - Received intravenous immunoglobulin treatment during the current admission
  - Children weighing < 40 kg or aged < 12 years

Participant characteristics

- Age (median (IQR))
  - casirivimab/imdevimab: 61.9 (14.6)
  - usual care: 61.9 (14.4)
- Sex (female):
  - casirivimab/imdevimab: 1806 (37%)
  - usual care: 1851 (37%)
- Race or ethnic group:
  - white:
    - ☐ casirivimab/imdevimab: 3768 (78%)
    - ☐ usual care: 3810 (77%)
  - black/Asian/minority ethnic:
    - ☐ casirivimab/imdevimab: 588 (12%)
    - ☐ usual care: 696 (14%)
- Disease severity: moderate to severe
- Co-morbidities:
  - any
    - ☐ casirivimab/imdevimab: 2557 (53%)
    - ☐ usual care: 2662 (54%)
  - diabetes
    - ☐ casirivimab/imdevimab: 1240 (26%)
    - ☐ usual care: 1337 (27%)
  - heart disease
    - ☐ casirivimab/imdevimab: 1038 (21%)
    - ☐ usual care: 1061 (21%)
  - chronic lung disease
    - ☐ casirivimab/imdevimab: 1085 (22%)
    - ☐ usual care: 1159 (23%)
  - HIV
    - ☐ casirivimab/imdevimab: 24 (<1%)
    - ☐ usual care: 22 (<1%)
  - severe liver disease
    - ☐ casirivimab/imdevimab: 69 (1%)
    - ☐ usual care: 70 (1%)
  - severe kidney impairment
    - ☐ casirivimab/imdevimab: 266 (5%)
    - ☐ usual care: 242 (5%)
- Pre-treatments:
  - corticosteroids
    - ☐ casirivimab/imdevimab: 4530 (94%)
    - ☐ usual care: 4639 (94%)
  - azithromycin
    - ☐ casirivimab/imdevimab: 124 (3%)
    - ☐ usual care: 124 (3%)
  - colchicine
    - ☐ casirivimab/imdevimab: 1085 (22%)
    - ☐ usual care: 1139 (23%)
  - aspirin
    - ☐ casirivimab/imdevimab: 1339 (28%)
    - ☐ usual care: 1389 (28%)

RECOVERY *(Continued)*

- Concomitant treatments:
  * corticosteroids
    ☐ casirivimab/imdevimab: 4152 (87%)
    ☐ usual care: 4341 (89%)
  * azithromycin
    ☐ casirivimab/imdevimab: 1204 (25%)
    ☐ usual care: 1220 (25%)
  * colchicine
    ☐ casirivimab/imdevimab: 1025 (21%)
    ☐ usual care: 1071 (22%)
  * aspirin
    ☐ casirivimab/imdevimab: 1670 (35%)
    ☐ usual care: 1727 (35%)
  * remdesivir
    ☐ casirivimab/imdevimab: 1152 (24%)
    ☐ usual care: 1205 (25%)
  * lopinavir-ritonavir
    ☐ casirivimab/imdevimab: 4 (< 1%)
    ☐ usual care: 2 (< 1%)
  * hydroxychloroquine
    ☐ casirivimab/imdevimab: 11 (< 1%)
    ☐ usual care: 9 (< 1%)
  * tocilizumab or sarilumab
    ☐ casirivimab/imdevimab: 666 (14%)
    ☐ usual care: 785 (16%)

Interventions	Intervention: casirivimab/imdevimab • Target: SARS-CoV-2 S protein • Origin: fully-human antibodies produced by the company's *VelocImmune* ® mice, which have been genetically modified to have a human immune system, as well as antibodies identified from humans who have recovered from COVID-19 • Dose: 8 g (casirivimab 4g and imdevimab 4g) in 250 mL 0.9% saline • Frequency: single-dose • Route of administration: intravenous (IV) infusion Comparator • Standard of care

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned, reported
	  * at up to 60 days: not planned, not reported
	• Clinical progression: planned and reported as composite endpoint of death or need for mechanical ventilation or ECMO; need for ventilation
	• Length of hospital stay: planned, reported (median duration)
	• Admission to ICU: not planned, not reported
	• Length of ICU stay: not planned, not reported
	• Quality of life, including fatigue: not planned, not reported
	• Viral clearance: not planned, not reported
	• Thromboembolic events: planned, reported
	• Renal failure: planned, reported (renal replacement therapy)
	Safety outcomes

RECOVERY *(Continued)*

	• Number of participants with adverse events (all grades, grade 1-2, grade 3-4): not planned, not reported • Number of participants with serious adverse events: reported selected outcomes including cause-specific mortality, major cardiac arrhythmia, and thrombotic and major bleeding events (only collected since 6 November 2021) Additional outcomes • use of invasive or non-invasive ventilation among patients not on any ventilation at randomisation • time to successful cessation of invasive mechanical ventilation (defined as cessation of invasive mechanical ventilation within, and survival to 28 days)
Notes	Funding: University of Oxford Recruitment status: recruiting Conflicts of interest: • DMW is an employee of Regeneron Pharmaceuticals and holds shares/share options in the company. All other authors have no conflict of interest or financial relationships relevant to the submitted work to disclose. No form of payment was given to anyone to produce the manuscript. The Nuffield Department of Population Health at the University of Oxford has a staff policy of not accepting honoraria or consultancy fees directly or indirectly from industry.

Weinreich (phase 1/2, 2.4 g)

Study characteristics	
Methods	See Weinreich (phase 1/2).
Participants	
Interventions	
Outcomes	
Notes	

Weinreich (phase 1/2, 8.0 g)

Study characteristics	
Methods	See Weinreich (phase 1/2).
Participants	
Interventions	
Outcomes	
Notes	

Weinreich (phase 1/2)

Study characteristics	

Methods	Drug name: casirivimab/imdevimab
	
	Trial design: randomised, double-blind, placebo-controlled, phase 1–3 clinical trial (continual enrolment); part 1-2 reported here
	
	Type of publication: journal publication for part 1, preprint for part 2 (English)
	
	NCT number: NCT04425629 (date of trial registration: 11 June 2020)
	
	• Ongoing: yes
	
	Number of participants:
	
	• screened: 926 (further data in Weinreich (phase 3); recruitment ongoing)
	• allocated: 799
	• evaluated: 437 participants in mFAS group 2 for primary analysis excluding previous publication, 665 participants mFAS since start of study (part 1 and 2), safety set all 780 participants who received at least one study dose
	  * 2.4 g: 215 mFAS, 258 safety
	  * 8.0 g: 219 mFAS, 260 safety
	  * placebo: 231 mFAS, 262 safety
	
	Estimated enrolment: 6420 participants
	
	Estimated completion date: November 2021

Participants	Setting
	
	• Outpatient
	• Recruitment period: 17 June-21 August 2020
	• Multicentre; USA, Chile, Mexico, Romania
	
	Eligibility criteria
	
	Inclusion criteria
	
	• Male or female ≥ 18 years of age (or country's legal age of adulthood) at randomisation
	• Laboratory-confirmed SARS-CoV-2 infection (positive RT-PCR test) ≤ 72 hours of randomisation
	• Experiencing > 1 of the following symptoms at randomisation
	  * fever
	  * cough
	  * shortness of breath
	• Experienced COVID-19 symptoms for < 7 days
	• Maintains O2 saturation ≥ 93% on room air
	• Willing and able to provide informed consent signed by study patient or LAR
	• Willing and able to comply with study procedures, including providing samples for viral shedding testing after discharge
	
	Exclusion criteria
	
	• Admitted to a hospital prior to randomisation, or hospitalised (inpatient) at randomisation due to COVID-19
	• Participated, or participating, in a clinical study evaluating COVID-19 convalescent plasma, mAbs against SARS-CoV-2, or IVIG within 3 months or < 5 half-lives of the investigational product (whichever is longer) prior to the screening visit; history of investigational or EUA-approved treatments (includes, but is not limited to: remdesivir, hydroxychloroquine, tocilizumab, sarilumab, and other immunomodulatory agents)
	• Requires IVIG for medical condition other than COVID-19

Weinreich (phase 1/2) *(Continued)*

- Known allergy or hypersensitivity to components of study drug
- Discharged, or is planned to be discharged, to a quarantine centre
- Pregnant or breastfeeding women
- Continued sexual activity in WOCBP or sexually active men who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 6 months after the last dose (combined hormonal contraception, intrauterine device, intrauterine hormone-releasing system, bilateral tubal ligation, vasectomised partner, and/or sexual abstinence)

Participant characteristics (FAS)

- Age (median, IQR):
  * 2.4 g: 42.0 (31.0 - 52.0)
  * 8.0 g: 42.0 (30.0 - 52.0)
  * placebo: 42.0 (32.0 - 53.0)
- Sex (male):
  * 2.4 g: 122 (45.9%)
  * 8.0 g: 120 (44.9%)
  * placebo: 50 (54%)
- Ethnicity (reported by participants):
  * Hispanic or Latino ethnicity
    - ☐ 2.4 g: 132 (49.6%)
    - ☐ 8.0 g: 134 (50.2%)
    - ☐ placebo: 137 (51.5%)
  * white
    - ☐ 2.4 g: 224 (84.2%)
    - ☐ 8.0 g: 230 (86.1%)
    - ☐ placebo: 227 (85.3%)
  * black or African American
    - ☐ 2.4 g: 27 (10.2%)
    - ☐ 8.0 g: 23 (8.6%)
    - ☐ placebo: 24 (9.0%)
  * Asian
    - ☐ 2.4 g: 6 (2.3%)
    - ☐ 8.0 g: 4 (1.5%)
    - ☐ placebo: 4 (1.5%)
  * American Indian or Alaska Native
    - ☐ 2.4 g: 1 (0.4%)
    - ☐ 8.0 g: 1 (0.4%)
    - ☐ placebo: 3 (1.1%)
  * unknown, not reported:
    - ☐ 2.4 g: 8 (3.0%)
    - ☐ 8.0 g: 9 (3.3%)
    - ☐ placebo: 8 (3.0%)

Disease severity:

- mild (according to WHO Clinical Progression Scale)

Co-morbidities:

- any risk factor for hospitalisation (including age ≥ 50, obesity, cardiovascular disease, chronic lung disease, chronic metabolic disease, chronic kidney disease, chronic liver disease, and immunocompromised)
  * 2.4 g: 165 (62.0%)
  * 8.0 g: 160 (59.9%)
  * placebo: 158 (59.4%)
- Pre-treatments: not reported

Weinreich (phase 1/2) *(Continued)*

- Concomitant treatments: not reported

Interventions	Intervention
	
	• Casirivimab/imdevimab
	  * Target: SARS-CoV-2 S protein
	  * Origin: derived from B lymphocytes of a convalescent naturally SARS-CoV-2- infected patient
	  * Dose: 2.4 g/ 8.0 g (1.2 g or 4 g each of casirivimab and imdevimab)
	  * Frequency: single dose
	  * Route of administration: IV infusion
	
	Comparator:
	
	• Placebo, single-dose, IV infusion

Outcomes	Efficacy outcomes
	
	• All-cause mortality
	  * at up to 30 days: planned, not reported
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: planned as progression to IMV, not reported
	• Admission to hospital or death: planned, reported
	• Length of hospital stay: planned, not reported
	• Admission to ICU: planned, not reported
	• Length of ICU stay: not planned
	• Quality of life: not planned
	• Viral clearance: test negativity mentioned under virology assessment, but not specifically as outcome
	
	Safety outcomes
	
	• Number of participants with any grade adverse events: AE planned to be categorised according to NCI-CTCAE v5.0, not reported
	• Number of participants with grade 3 and grade 4 AEs: planned, reported
	• Number of participants with SAEs: planned, reported
	
	Additional study outcomes
	
	• Viral shedding via nasal and serum samples from baseline up to day 29
	• Proportion of participants with ≥ 1 COVID-19-related medically attended visit through day 29
	• Proportion of participants with ≥ 2 COVID-19-related medically-attended visits through day 29
	• Total number of COVID-19-related medically-attended visits through day 29
	• Proportion of participants with ≥ 1 outpatient or telemedicine visit due to COVID-19 by day 29
	• Concentrations of REGN10933 and REGN10987 in serum and corresponding pharmacokinetic parameters
	• Immunogenicity as measured by anti-drug aBs to REGN10933 and REGN10987
	• Time to negative RT-qPCR in nasopharyngeal swabs with no subsequent positive RT-qPCR
	• Proportion of participants with ≥ 1 outpatient or telemedicine visit due to COVID-19 by day 29
	• Proportion of participants with infusion-related reactions (grade ≥ 2) through day 4
	• Proportion of participants with hypersensitivity reactions (grade ≥ 2) through day 29
	• Exploratory outcomes: self-reported symptoms using the Symptom Evolution of COVID-19 (SE-C19) instrument + PGIC + PGIS

Notes	Developer: Regeneron Pharmaceuticals Funding: Regeneron Pharmaceuticals Conflicts of interest:

Weinreich (phase 1/2) *(Continued)*

- journal publication:
  - AB, CK, NS, GY: BARDA, Regeneron pharmaceuticals, patents related to Anti-SARS-CoV-2-Spike Glycoprotein Antibodies
  - AS, RB, NB, AC, JD, AD, HG, JH, GH, RH, JI, WK, YK, BK, LP, AM, BM, TN, CP, CP, DR, SS, YS, KT, DW: BARDA, Regeneron Phamaceuticals
  - AH: BARDA, Regeneron Pharmaceuticals, Pfizer
  - AK: Gilead Sciences
  - MG, YS had nothing to disclose
- preprint (phase 1 to 2): not reported

Weinreich (phase 3)

Study characteristics

Methods	Drug name:
	• combination therapy: casirivimab/imdevimab
	Trial design: randomised, double-blind, placebo-controlled part 3 of a phase 1/2/3 study, initially 3 arms, reduced to two
	Type of publication: preprint (English)
	NCT number: NCT04425629 (date of trial registration: 11 June 2020)
	• Ongoing: recruiting, updated 20 May 2021
	Number of participants:
	• recruited: 6716
	• allocated with ≥ 1 risk factor: 4567
	  * combination therapy:
	  ☐ 1.2g: 838 participants
	  ☐ 2.4g: 1529 participants
	  ☐ 8.0g: 700 participants
	  * placebo: 2089 participants (748 for 1.2g; 1341 for 2.4g)
	Estimated enrolment: 6420 participants
	Estimated completion date: 26 November 2021

Participants	Setting • Outpatient • Recruitment period: 24 September 2020 -17 January 2021. • Multicentre; international (USA, Mexico, Chile, Romania) Inclusion criteria (Cohort 1) • ≥18 years of age • non-hospitaliSed, with a confirmed local SARS-CoV-2-positive diagnostic test result ≤72 hours and onset of any Covid-19 symptom, as determined by the investigator, ≤ 7 days before randomiSation. RandomiSation into the initial phase 3 portion was stratified by country and presence of risk factors for severe Covid-19. In the amended phase 3 portion, only patients with ≥1 risk factor for severe Covid-19 were eligible. For further details and exclusion criteria, see Weinreich (phase 1/2)

Weinreich (phase 3) *(Continued)*

Participant characteristics

- Age (median (IQR))
  - 1.2g: 48.5 (37. to 57.5)
  - 2.4g: 50.0 (39.0 to 60.0)
  - 8.0g: 51.0 (40.0 to 59.0)
  - Placebo: 48.5 (37.0 to 57.5), 48.5 (37.0 to 57.5), 50.0 (39.0 to 58.0)
- Sex (male):
  - 1.2g: 47.1%
  - 2.4g: 48.4%
  - 8.0g: 51.8%
  - Placebo: 47.1%, 47.2%, 47.4%
- Race or ethnic group (self-reported):
- white:
  - 1.2g: 80.0%
  - 2.4g: 85.7%
  - 8.0g: 85.4%
  - Placebo: 81.7%, 85.7%, 88.5%
- black:
  - 1.2g: 5.2%
  - 2.4g: 4.9%
  - 8.0g: 5.3%
  - Placebo: 5.1%, 4.9%, 4.7%
- Asian:
  - 1.2g: 5.2%
  - 2.4g: 3.8%
  - 8.0g: 4.2%
  - Placebo: 4.8%, 4.2%, 3.4%
- Hispanic:
  - 1.2g: 42.4%
  - 2.4g: 34.2%
  - 8.0g: 28.3%
  - Placebo: 39.4%, 35.1%, 29.7%
- Disease severity: mild according to WHO Clinical Progression Scale (Figure 1)

Weinreich (phase 3) *(Continued)*

- Co-morbidities:
  - obesity (BMI ≥ 30):
    - ☐ 1.2g: 55.7%
    - ☐ 2.4g: 58.1%
    - ☐ 8.0g: 61.4%
    - ☐ Placebo: 57.1%, 57.6%, 58.2%
  - cardiovascular disease:
    - ☐ 1.2g: 38.3%
    - ☐ 2.4g: 38.4%
    - ☐ 8.0g: 31.4%
    - ☐ Placebo: 35.3%
  - diabetes:
    - ☐ 1.2g: 12.8%
    - ☐ 2.4g: 14.9%
    - ☐ 8.0g: 15.5%
    - ☐ Placebo: 15.7%
  - immunosuppressed or on immunosuppressive medications:
    - ☐ 1.2g: 3.3%
    - ☐ 2.4g: 3.4%
    - ☐ 8.0g: 2.6%
    - ☐ Placebo: 2.5%
- Pre-treatments: not reported
- Concomitant treatments: not reported

Interventions	Interventions
	
	• casirivimab with imdevimab
	  * Target: SARS-CoV-2 S protein
	  * Origin: derived from B lymphocytes of a convalescent naturally SARS-CoV-2- infected patient
	  * Dose: 1.2g/ 2.4g/ 8.0g
	  * Frequency: single dose
	  * Route of administration: IV
	
	Comparator:
	
	• Placebo, single-dose, IV infusion

Outcomes	• All-cause mortality
	  * at up to 30 days: planned, reported
	  * at up to 60 days: planned, not reported
	• Clinical progression/improvement of symptoms: reported as proportion of participants requiring mechanical ventilation planned, reported
	• Admission to hospital (for outpatients only): planned, reported as proportion of patients with ≥1 Covid-19-related hospitalisation or all-cause death through day 29
	• Length of hospital stay (for those admitted to hospital): planned, reported as days of hospitalisation
	• Admission to ICU: planned, reported
	• Length of ICU stay: not planned, not reported
	• Quality of life: not planned, not reported
	• Viral clearance: not planned, not reported
	
	Safety outcomes
	
	• Number of participants with any grade AEs: not reported
	• Number of participants with grade 3 and grade 4 AEs: planned, reported as treatment-emergent AEs, which was defined as AE emerging after first dose, coded according to the Medical Dictionary for Regulatory Activities (MedDRA)

Weinreich (phase 3) *(Continued)*	• Number of participants with SAEs: reported as treatment-emergent SAEs Additional study outcomes: • Time to symptom resolution
Notes	Developer: Regeneron Pharmaceuticals Funding: Regeneron Pharmaceuticals Conflicts of interest: • Supported by Regeneron Pharmaceuticals, Inc. Certain aspects of this project have been funded in whole or in part with federal funds from the Department of Health and Human Services; Office of the Assistant Secretary for Preparedness and Response; Biomedical Advanced Research and Development Authority, under OT number: HHSO100201700020C.

aB: antibody; **ACE:** angiotensin-converting enzyme;**ADA:** Adenosine deaminase; **AE:** adverse event; **ARB:** angiotensin- receptor blocker; **AUC:** area under the curve; **BMI:** body mass index; **COPD:** chronic obstructive pulmonary disease; **ECMO:** extracorporeal membrane oxygenation; **EUA:** emergency use authorization; **ICU:** intensive care unit; **IV:** intravenous; **hIVIG:** human intravenous immunoglobulin;**IQR:** interquartile range;**ITTI:** intention-to-treat in PCR-positive participants; **LAR:** legally authorised representative; **mAb:** monoclonal antibody; **NaCl:** sodium chloride; **NCI-CTAE:** Common Terminology Criteria for Adverse Events; **NIAID:** National Institute of Allergy and Infectious Diseases; **NAT:** nucleic acid test; **NIAID:** National Institute of Allergy and Infectious Diseases;**NIH:** National Institutes of Health; **NIV:** noninvasive ventilation; **nmAb:** neutralising monoclonal antibody; **NSAID:** nonsteroidal anti-inflammatory drug; **NYHA:** New York Heart Association; **PaO2/FiO2:** ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; **PGIC:** Patient Global Impression of Change of symptoms associated with COVID-19; **PGIS:** Patient Global Impression of Severity of symptoms associated with COVID-19; **RT-PCR:** reverse transcription polymerase chain reaction; **RT-qPCR:** quantitative reverse transcription polymerase chain reaction; **SAE:** serious adverse event; **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2; **SpO2:** oxygen saturation; **TEAE:** treatment-emergent adverse event; **WHO:** World Health Organization; **WHOQOL-100:** World Health Organization quality-of-life scale; **WOCBP:** women of childbearing potential

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ACTIV-4	Platform trial on other drug class: anti-thrombotics
ACTT	Completed without adding relevant mAb
ACTT-2	Completed without adding relevant mAb
ACTT-3	Completed without adding relevant mAb
Alam 2021	Ineligible study design: retrospective
AMMURAVID	Does not add treatment arms
ASCOT-ADAPT	Does not add treatment arms
Bariola 2021	Ineligible study design: retrospective
Beam 2021	Ineligible study design: retrospective
BLAZE-2	SARS-CoV-2-specific mAb examined for prophylaxis
ChiCTR2000030012	Ineligible design: preclinical

Study	Reason for exclusion
Cohen 2021	Ineligible study design: retrospective
COREG	Ineligible intervention: other intervention
COVERAGE	Ineligible intervention: other intervention; does not add treatment arms
COVER HCW	Platform trial, but prophylaxis
COVID_Aging	Does not add treatment arms
CROWN CORONA	Platform trial, but on other treatment class (vaccines)
C-SMART	Ineligible intervention: other intervention; does not add treatment arms
Dale 2021	Ineligible study design: retrospective
Dhand 2021a	Ineligible study design: unclear design, probably retrospective
Dhand 2021b	Ineligible study design: retrospective
Dong 2021	Ineligible study design: unclear design, probably retrospective
EUCTR2020-001243-15-BE	Completed without adding relevant mAb
EUDRACT2020-002713-17	Ineligible intervention: mAb, not SARS-CoV-2-specific
FORCE	Ineligible intervention: mAb, not SARS-CoV-2-specific
Ganesh 2021	Ineligible study design: retrospective
jRCT2031190264	Does not add treatment arms
Karr 2021	Ineligible study design: retrospective
Kutzler 2021	Ineligible study design: retrospective
MAS-COVID	Ineligible intervention: other intervention
NCT04275245	Ineligible intervention: mAb, not SARS-CoV-2-specific
NCT04341116	Ineligible intervention: mAb, not SARS-CoV-2-specific
NCT04354428	Completed without adding relevant mAb
NCT04369469	Ineligible intervention: mAb, not SARS-CoV-2-specific
NCT04370262	Ineligible intervention: other intervention
NCT04415073	Ineligible intervention: mAb, not SARS-CoV-2-specific
NCT04452318	SARS-CoV-2-specific mAb examined for prophylaxis
NCT04453384	Ineligible intervention: polyclonal Ab
NCT04454398	Study withdrawn according to trial registry

Study	Reason for exclusion
NCT04469179	Ineligible intervention: polyclonal Ab
NCT04494724	Ineligible intervention: mAb, not SARS-CoV-2 specific
NCT04494984	Ineligible intervention: other intervention
NCT04497987	SARS-CoV-2 specific mAb for prophylaxis
NCT04498273	Platform trial, but for different drug class/prevention: thrombosis
NCT04514302	Ab fragment
NCT04516564	Ineligible intervention: mAb, not SARS-CoV-2-specific, healthy participants
NCT04569786	Ineligible intervention: other intervention
NCT04574869	Ineligible intervention: other intervention
NCT04586153	Ineligible intervention: mAb, not SARS-CoV-2-specific
NCT04625725	SARS-CoV-2-specific mAb examined for prophylaxis
NCT04629703	Does not add treatment arms
NCT04766671	Registry entry no longer available, study probably withdrawn
NCT04859517	SARS-CoV-2-specific mAb examined for prophylaxis
NCT04894474	SARS-CoV-2-specific mAb examined for prophylaxis
PANAMO	Ineligible intervention: other intervention
PO-COV-III-20	Does not add treatment arms
PROFACT-01	Platform trial, but non-presciption treatments
Rainwater-Lovett 2021	Ineligible study design: retrospective
RESP301-002	Does not add treatment arms
Shirk 2021	Ineligible study design: retrospective
STORM CHASER	SARS-CoV-2-specific mAb examined for prophylaxis
Track: ChiCTR2100042150	Included for tracking but excluded for analysis: healthy participants
Track: jRCT2071200117	Included for tracking but excluded for analysis: healthy participants
Track: NCT04429529	Included for tracking but excluded for analysis: healthy participants
Track: NCT04441918	Included for tracking but excluded for analysis: healthy participants
Track: NCT04441931	Included for tracking but excluded for analysis: healthy participants
Track: NCT04479631	Included for tracking but excluded for analysis: healthy participants

Study	Reason for exclusion
Track: NCT04479644	Included for tracking but excluded for analysis: healthy participants
Track: NCT04483375	Included for tracking but excluded for analysis: healthy participants
Track: NCT04507256	Included for tracking but excluded for analysis: healthy participants
Track: NCT04519437	Included for tracking but excluded for analysis: healthy participants
Track: NCT04525079	Included for tracking but excluded for analysis: healthy participants
Track: NCT04532294	Included for tracking but excluded for analysis: healthy participants
Track: NCT04533048	Included for tracking but excluded for analysis: healthy participants
Track: NCT04537910	Included for tracking but excluded for analysis: healthy participants
Track: NCT04561076	Included for tracking but excluded for analysis: healthy participants
Track: NCT04567810	Included for tracking but excluded for analysis: healthy participants
Track: NCT04590430	Included for tracking but excluded for analysis: healthy participants
Track: NCT04592549	Included for tracking but excluded for analysis: healthy participants
Track: NCT04603651	Included for tracking but excluded for analysis: non-randomised study design
Track: NCT04617535	Included for tracking but excluded for analysis: non-randomised study design
Track: NCT04656691	Included for tracking but excluded for analysis: non-randomised study design; previously NCT04639479
Track: NCT04691180	Included for tracking but excluded for analysis: healthy participants
Track: NCT04700163	included for tracking but excluded for analysis: healthy participants
Track: NCT04701658	Included for tracking but excluded for analysis: non-randomised study design
Track: NCT04852978	Track: mAbs in healthy volunteers
Track: NCT04896541	Included for tracking but excluded for analysis: healthy participants
Track: NCT04932850	Included for tracking but excluded for analysis: healthy participants
Webb 2021	Ineligible study design: retrospective
Yang 2020	Ineligible study design: preclinical

Ab: antibody; **mAb:** monoclonal antibody; **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2

Characteristics of studies awaiting classification *[ordered by study ID]*

ACCORD & ACCORD 2

Methods	Drug name: MEDI3506, bemcentinib, acalabrutinib, zilucoplan

ACCORD & ACCORD 2 *(Continued)*

	Trial design: controlled, randomised, open, parallel group, SOC control arm Identifiers: EUCTR 2020-001736-95 Target sample size: 1800 participants Planned completion date: 23 April 2021

Participants	Setting
	
	• inpatient
	• severity: all stages
	• multicentre, UK
	
	Eligibility criteria
	
	• Inclusion criteria
	  * Adults (≥ 18 years) with SARS-CoV-2 infection confirmed by laboratory tests and/or point of care tests (which may include results from a test that was performed prior to hospital admission if, in the opinion of the Investigator, it is relevant to ongoing COVID-19)
	  * Patients with symptoms and/or signs consistent with COVID-19, requiring treatment, a score of grade 3-5 on the 9-point ordinal scale
	  * Male patients must agree to use contraception
	  * Female patients are eligible to participate if not pregnant (see Appendix 5), not breastfeeding, and with effective contraception.
	  * Ability to provide informed consent signed by the study patient or LAR
	  * Antibiotic prophylaxis
	• Exclusion criteria
	  * Patients who have previously had a score of 6 or 7 on the 9-point ordinal scale
	  * Any patient whose interests are not best served by study participation, as determined by a senior attending clinician
	  * ALT/AST > 5 x ULN
	  * Known active infection with HIV or hepatitis B or C, stage 4 severe chronic kidney disease, active tuberculosis defined as requiring current treatment for tuberculosis
	  * Allergy to any study medication
	  * Experimental off-label usage of medicinal products as treatments for COVID-19 at the time of enrolment
	  * Patients participating in another clinical study of an investigational medicinal product, unless co-enrolment in the other study has been pre-approved by the Sponsor and Chief Investigator
	  * Inability to swallow capsules (administration via nasogastric tube is permitted in patients who become unable to swallow after starting the study drug)
	  * Patients with a permanent cardiac pacemaker implanted
	  * History of myocardial infarction within 3 months prior to the first dose, unstable angina, history of clinically significant dysrhythmias, or history of familial long QT. Patients with an implantable cardioverter-defibrillator device in place will be allowed to enrol
	  * Clinically significant hypokalaemia
	  * Therapeutic anticoagulation with vitamin K antagonists
	  * Previous bowel resection that would interfere with drug absorption
	  * Known history of myocardial infarction within 3 months prior to the first dose
	  * Known history of heart failure

Interventions	Intervention • Bemcentinib (oral use, 100 mg) • MEDI3506 (hIVIG G1 mAb 150 mg/mL) • Zilucoplan (subcutaneous use, 40 mg/mL) • Acalabrutinib (oral use, 100 mg)

ACCORD & ACCORD 2 *(Continued)*

	Comparator • Placebo, IV infusion

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: planned
	• Clinical progression: planned
	• Length of hospital stay: planned
	• Admission to ICU: not planned
	• Length of ICU stay: planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: planned
	Safety outcomes
	• Number of participants with grade 3 and grade 4 AEs: not planned
	• Number of participants with SAEs: planned
	Additional study outcomes
	• Time to sustained clinical improvement of at least 2 points (from randomisation) on a 9-point category ordinal scale, live discharge from the hospital, or considered fit for discharge (a score of 0, 1, or 2 on the ordinal scale), whichever comes first, by day 29 (this will also define the 'responder' for the response rate analyses)
	• Response rate (number and %) by treatment arm at days 2, 8, 15, 22, and 29
	• Time to live discharge from the hospital
	• Time from treatment start date to death
	• Clinical laboratory examinations, vital signs (blood pressure/heart rate/temperature/respiratory rate)
	• NEWS assessed daily while hospitalised and on days 15 and 29
	• Time to a NEWS2 of ≤ 2, maintained for at least 24 hours
	• Ranked trajectory over 29 days, with trajectory, ranked as defined in the protocol

Notes	Funding: University Hospital Southampton NHS Foundation Trust, UK There are various sub-protocols.

ACOVACT

Methods	Drug name: clazakizumab, lopinavir/ritonavir, pentaglobin, remdesivir, rivaroxaban, chloroquine or hydroxychloroquine (stopped), RAS blockade, asunercept Trial design: randomised, parallel, active-controlled, open-label platform trial, 3 main study arms and 3 substudies (the main study arms are exclusive, while patients from the main study arms may participate in one or more substudies) NCT number: NCT04351724 Target sample size: 500 participants Planned completion date: March 2022
Participants	Setting • Inpatient

ACOVACT *(Continued)*

- Severity: depending on the substudy (healthy controls up to severe disease)
- Multicentre, country: Austria

Eligibility criteria

- Inclusion criteria
  - Adults (≥ 18 years)
  - Laboratory-confirmed infection with SARS-CoV-2 ≤ 72 hours before randomisation
  - Hospitalisation due to SARS-CoV-2 infection except for substudy B, which may also include outpatients with COVID-19
  - Requirement of oxygen support (due to oxygen saturation < 94% on ambient air or > 3% drop in case of chronic obstructive lung disease)
  - Informed consent obtained, the patient understands and agrees to comply with the planned study procedures, except for substudy C: obtaining informed consent may be impossible due to the severe condition of the patient and may be waived
  - WOCBP: willingness to perform effective measures of contraception during the study.
- Exclusion criteria:
  - Moribund or estimated life expectancy < 1 month (e.g. terminal cancer, etc.)
  - Patient does not qualify for intensive care, based on local triage criteria
  - Pregnancy or breastfeeding
  - Severe liver dysfunction (e.g. ALT/AST > 5 times ULN)
  - Stage 4 chronic kidney disease or requiring dialysis (except for ritonavir/lopinavir)
  - Allergy or intolerances to any of the experimental substances, exclusion for the respective treatment arm
  - Anticipated discharge of hospital within 48 hours (for anti-viral treatment arms)
  - Known active HIV or viral hepatitis

Interventions	Intervention • Clazakizumab (single dose) • Lopinavir/ritonavir • Pentaglobin • Remdesivir • Rivaroxaban • Chloroquine or hydroxychloroquine (stopped) • RAS blockade • Asunercept • Candesartan Comparator • Thromboprophylaxis (according to local standard, most likely to be low molecular weight heparin) • Non-RAS blocked (active comparator, non-RAS blocking antihypertensive agents titrated to normotension, those with normal blood pressure may only be controlled without further treatment) • Best standard of care

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: planned
	• Clinical progression: planned
	• Length of hospital stay: planned
	• Admission to ICU: planned
	• Length of ICU stay: not planned

ACOVACT *(Continued)*

- Quality of life, including fatigue: not planned
- Viral clearance: planned

Safety outcomes

- Number of participants with grade 3 and grade 4 AEs: not planned
- Number of participants with SAEs: not planned

Additional study outcomes

- Drug-drug interactions with lopinavir/ritonavir
- Subgroup for obesity - mortality, duration of hospitalisation, ICU admission, new oxygen use
- Inflammatory parameters C-reactive protein, interleukin-6, procalcitonin, IgM concentrations, IgA concentrations, IgG concentrations
- Differential blood counts

Notes	Funding: Medical University of Vienna

ACTIV-1 IM

Methods	Drug name: infliximab, abatacept, remdesivir, cenicriviroc Trial design: randomised, parallel assignment, masking: triple (participant, investigator, outcome assessor) NCT number: NCT04593940 Target sample size: 2160 participants Planned completion date: September 2021

Participants	Setting
	
	• Inpatient
	• Multicentre, USA
	
	Eligibility criteria
	
	• Inclusion criteria
	  * Admitted to a hospital or awaiting admission in the ED with symptoms suggestive of COVID-19
	  * Participant (or LAR) provides informed consent prior to initiation of any study procedures
	  * Participant (or LAR) understands and agrees to comply with planned study procedures
	  * Male or non-pregnant female adults ≥ 18 years of age at time of enrolment
	  * Has laboratory-confirmed (within 14 days prior to enrolment) SARS-CoV-2 infection as determined by PCR or other commercial or public health assay in any specimen
	  * Ongoing illness of any duration, and at least one of the following:
	  ☐ radiographic infiltrates by imaging (chest X-ray, CT scan, etc.)
	  ☐ SpO2 ≤ 94% on room air
	  ☐ requiring supplemental oxygen
	  ☐ requiring mechanical ventilation or ECMO
	  * WOCBP must agree to either abstinence or use at least one primary form of contraception not including hormonal contraception from the time of screening through day 60
	  * Agrees to not participate in another intervention trial for the treatment of COVID-19 through day 60

ACTIV-1 IM *(Continued)*

- Exclusion criteria:
  * ALT or AST > 5 times the ULN
  * Estimated glomerular filtration rate (eGFR) < 30 mL/min (including patients receiving haemodialysis or hemofiltration)
  * Neutropenia (absolute neutrophil count < 1000 cells/µL) (< 1.0 x 103/µL or < 1.0 GI/L)
  * Lymphopenia (absolute lymphocyte count < 200 cells/µL) (< 0.20 x 103/µL or < 0.20 GI/L)
  * Pregnancy or breastfeeding
  * Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours
  * Known allergy to any study medication
  * Received cytotoxic or biologic treatments (such as anti-interleukin-1, anti-IL-6 (tocilizumab or sarilumab), IL-17, or T-cell- or B-cell-targeted therapies (e.g. rituximab), tyrosine kinase inhibitors including baricitinib, TNF inhibitors, or interferon within 4 weeks or 5 half-lives prior to screening
  * Suspected clinical diagnosis of current active tuberculosis (TB) or latent TB treated for < 4 weeks
  * Based on medical history and concomitant therapies that would suggest infection, suspected serious, active bacterial, fungal, viral (including, but not limited to, active HBV, HCV, or HIV/AIDS)
  * Live vaccine (that is, live attenuated) within 3 months before screening
  * Severe hepatic impairment (defined as liver cirrhosis Child stage C)
  * Current severe heart failure (NYHA III-IV)
  * In the investigator's judgment, the patient has any advanced organ dysfunction that would not make participation appropriate

Interventions	Intervention • Infliximab (single dose, IV infusion, 5 mg/kg) • Abatacept (single dose, IV infusion, 10 mg/kg) • Remdesivir (removed) • Cenicriviroc (loading dose: 450 mg (300 mg morning and 150 mg evening, day 2-29: 300 mg) Comparator • Placebo

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: not planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: planned
	• Length of hospital stay: planned as time to recovery
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	Safety outcomes
	• Number of participants with grade 3 and grade 4 AEs: planned
	• Number of participants with SAEs: planned
	Additional study outcomes
	• Number of participants with changes in abnormal WBC counts

ACTIV-1 IM *(Continued)*

Notes	Funding: National Center for Advancing Translational Science (NCATS) and Biomedical Advanced Research and Development Authority

ACTT-4

Methods	Drug name: baricitinib, dexamethasone, remdesivir Trial design: multicenter, adaptive, randomised blinded controlled trial Identifiers: NCT04640168 Target sample size: 1500 participants Planned completion date**:** June 2021

Participants	Setting
	
	• Inpatient
	• Multicentre: USA, Japan, Republic of Korea, Mexico, Singapore
	
	Eligibility criteria
	
	• Inclusion criteria
	  * Hospitalised with symptoms suggestive of COVID-19
	  * Participant (or LAR) provides informed consent prior to initiation of any study procedures and understands and agrees to comply with planned study procedures
	  * Male or non-pregnant female adult ≥ 18 years of age at time of enrolment
	  * Illness of any duration and has laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other commercial or public health assay (e.g. NAAT, antigen test) in any respiratory specimen or saliva ≤ 14 days prior to randomisation
	  * Within the 7 days prior to randomisation requiring new use of supplemental oxygen (or increased oxygen requirement if on chronic oxygen) and requires at the time of randomisation low- or high-flow oxygen devices or use of non-invasive mechanical ventilation (ordinal scale category 5 or 6)
	  * WOCBP must agree to either abstinence or use at least one primary form of contraception not including hormonal contraception from the time of screening through day 29
	  * Agrees not to participate in another blinded clinical trial (both pharmacologic and other types of interventions) for the treatment of COVID-19 through day 29

ACTT-4 *(Continued)*

- Exclusion criteria
  - Prior enrolment in ACTT-3 or ACTT-4
  - On invasive mechanical ventilation at the time of randomisation (ordinal scale category 7)
  - Anticipated discharge from the hospital or transfer to another hospital that is not a study site within 72 h of randomisation
  - Positive test for influenza virus during the current illness
  - Received ≥ 5 doses of remdesivir including the loading dose, outside of the study as treatment for COVID-19
  - Pregnancy or breastfeeding
  - Allergy to any study medication
  - Received convalescent plasma or IVIg for COVID-19, small molecule tyrosine kinase inhibitors, mAbs targeting cytokines, mAbs targeting T-cells or B-cells as treatment for COVID-19
  - Use of probenecid that cannot be discontinued at study enrolment
  - Received > 1 dose of dexamethasone ≥ 6 mg (or equivalent for other glucocorticoids) in the 7 days prior to time of randomisation
  - Received ≥ 20 mg/day of prednisone (or equivalent for other glucocorticoids) for ≥ 14 consecutive days in the 4 weeks prior to screening
  - Have diagnosis of current active or latent tuberculosis, if known, treated for < 4 weeks with appropriate therapy (by history only, no screening required)
  - Serious infection (besides COVID-19), immunosuppressive state, or immunosuppressive medications that in the opinion of the investigator could constitute a risk when taking baricitinib or dexamethasone
  - Live vaccine (that is, live attenuated) within 4 weeks before screening, or intend to receive a live vaccine (or live attenuated) during the study

Interventions	Intervention • Remdesivir • Baricitinib • Dexamethasone Comparator • Placebo

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: planned
	• Length of hospital stay: planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	Safety outcomes
	• Number of participants with grade 3 and grade 4 AEs: planned
	• Number of participants with SAEs: planned
	Additional study outcomes
	• Change from baseline in ALT, AST, C-reactive protein, creatinine, d-dimer concentration, glucose, haemoglobin, platelets, prothrombin time, total bilirubin, WBC count
	• Desirability of Outcome Ranking (DOOR)

ACTT-4 *(Continued)*

	• Time to recovery
Notes	Funding: NIAID

ANTICOV

Methods	Drug name: lopinavir plus ritonavir, hydroxychloroquine Trial design: randomised, adaptive platform trial, open-label study Identifiers: PACTR202006537901307 Target sample size: 3000 participants Planned completion date: December 2021

Participants	Setting
	
	• Outpatient
	• Multicentre, South Africa, Africa
	
	Eligibility criteria
	
	• Inclusion criteria
	  * Male or female patients
	  * Adults ≥ 18 years of age at the time of screening. Children > 12 years of age may be included if recommended by the DSMB after the first analysis
	  * COVID-19 confirmed by molecular biology for SARS-Cov-2 according to national guidelines, based on result within 24 hours prior to screening
	  * Viral syndrome with or without uncomplicated pneumonia, defined as SpO2 ≥ 94%
	  * Corrected QT interval (QTc - Fridericia) < 480 msec on ECG
	  * Signed written consent from the patient or LAR
	  * Accepting and having the ability to be reached by telephone throughout the study
	  * Having designated a contact person who can be contacted in case of emergency
	• Exclusion criteria:
	  * Abnormal physical examination findings
	  * Known glucose-6-phosphate dehydrogenase (G6PD) deficiency
	  * Feeling unwell for > 7 days prior to screening
	  * Severe cardiopathy or history of arrhythmia, renal or liver insufficiency
	  * History of congenital or acquired long QT-interval, family history of long QT arrythmia, cardiac disease such as heart failure, myocardial infarction, family history of sudden cardiac death, sudden cardiac death, bradycardia < 50 bpm
	  * Past history of retinopathy, such as spots or dark strings floating in the field of vision (floaters), blurred or fluctuating vision, impaired colour vision, dark or empty areas in vision
	  * History of severe skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis
	  * End-organ compromise requiring admission to a resuscitation or continuous care unit or short-term life-threatening comorbidity with life expectancy < 3 months
	  * Known pregnancy or breastfeeding, unless recommended by the Data and Safety Monitoring Board after the first interim analysis
	  * Prior treatment with lopinavir/ritonavir within 29 days prior to screening except if patients are receiving the same regimen as planned in this study
	  * Prior treatment with hydroxychloroquine within 29 days prior to screening or ongoing at screening
	  * Use of concomitant medications that are contraindicated

ANTICOV *(Continued)*

Interventions	Intervention • Lopinavir + ritonavir (opinavir 800 mg/ritonavir 200 mg; daily intake, oral) • Hydroxychloroquine (800 mg and 400 mg, daily-loading dose of 800 mg day 2-7: maintenance dose of 400 mg daily, oral) Comparator: • Paracetamol (dose: max 3g/day, oral route)

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned (up to 21 days)
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: not planned
	• Admission to hospital (for outpatients only): planned
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	Safety outcomes
	• Number of participants with grade 3 and grade 4 AEs: not planned
	• Number of participants with SAEs: planned
	Additional study outcomes
	• Disease-free status
	• Failure rate for each study arm

Notes	Funding: DNDi, Switzerland

ARCO-Home

Methods	Drug name: lopinavir, plaquenil, rezolsta, avigan Trial design: adaptive randomised trial Identifiers: EUCTR 2020-001528-32 Target sample size: 435 participants Planned completion date: 23 April 2021
Participants	Setting • Outpatient • Italy Eligibility criteria

ARCO-Home *(Continued)*

- Inclusion criteria
  - Participant (or LAR) provides written informed consent prior to initiation of any study procedures
  - Agrees to the collection of nasopharyngeal swabs and venous blood samples per protocol
  - Male or female adult ≥ 18 years of age at time of enrolment
  - Has laboratory-confirmed SARS-CoV-2 infection as determined by an approved molecular test (PCR) in Italy
  - Being symptomatic for < 5 days before starting therapy
  - Do not meet criteria for immediate hospitalisations (NEWS = 2)
- Exclusion criteria
  - Requires immediate hospitalisation or mechanical ventilation and/or supplemental oxygen therapy or have a NEWS = 2
  - Having already received any of the trial drug < 1 month before randomisation
  - Being concurrently involved in another trial for COVID-19
  - Pregnancy (based on home test)
  - HIV infection (based on patient's report)
  - Use of any antiretroviral medication
  - Hypersensitivity to any of the used in the experimental compound including excipients
  - Pacemaker or history or current evidence of clinically significant cardiac arrhythmia, active or clinically significant cardiac disease including congestive heart failure (NYHA Class III or higher)
  - Severe liver injury (Child-Pugh Class B or C)
  - Receiving drug that cannot be co-administered with any of the experimental compound (full list will be reported in the standard operative protocol to be developed in each of the five recruiting centres)
  - Autoimmune diseases receiving therapy at the time of randomisation
  - WOCBP and fertile men must agree to use at least one primary form of contraception for the duration of the study

Interventions	Intervention • Kaletra (oral use) • Plaquenil (oral use) • Rezolsta (oral use) • Avigan(oral use) Comparator • Other medicinal product(s), no placebo

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: not planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: not planned
	• Admission to hospital: planned as proportion of participants who do not need hospitalisation by day 14
	• Length of hospital stay (for those admitted to hospital): planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	Safety outcomes
	• Number of participants with grade 3 and grade 4 AEs: 3 planned, 4 not planned

ARCO-Home *(Continued)*

- Number of participants with SAEs: planned

Additional study outcomes

- Proportion of patients in each category at point N at time 0, 7, 14 and 28, by arm 9 (mean value of category at point N by arm at time 0, 7, 14 and 28)
- Mean variation of biomarker parameters from baseline to day 7, 14 and 28 after randomisation

Notes	Funding: Instituto Nazionale per le malattie infettive "Lazzaro Spallanzani"

BEAT COVID-19

Methods	Drug name: not further specified Trial design: Bayesian, adaptive, blinded, randomised platform trial Identifier: ACTRN12620000566932 Target sample size: 400 participants Planned completion date: 30 June 2023

Participants	Setting
	
	• Inpatient/outpatient: unclear
	• Severity: unclear
	• Australia
	
	Eligibility criteria
	
	• Inclusion criteria
	  * Adults with PCR-confirmed COVID-19 (regardless of symptom status) in 1 of 2 strata
	  * 1. Participants aged 50-64 years with any of the following listed comorbidities:
	  ☐ coronary (ischaemic) heart disease
	  ☐ hypertension
	  ☐ asthma
	  ☐ chronic obstructive pulmonary disease (COPD)
	  ☐ diabetes
	  ☐ previous stroke
	  ☐ active cancer
	  ☐ on immunosuppressive therapy: long-term oral steroids (equivalent to prednisone ≥ 20 mg daily) or other long-term immunosuppression.
	  * 2. Participants aged ≥ 65 years (regardless of comorbidity)
	  * Willing and able to comply with all study requirements, including treatment, timing or nature of required assessments.
	  * Documented informed consent, either written or e-consent
	• Exclusion criteria
	  * Hypoxaemia (SpO2 < 94% on room air)
	  * Resting HR > 110 bpm
	  * Systolic BP < 90 mmHg
	  * Pregnancy or lactation
	  * Presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule, including alcohol dependence or drug abuse
	  * If there are definite indications or contraindications to any of the study medications in the view of the doctor responsible for the care of the patient

BEAT COVID-19 *(Continued)*

Interventions	Intervention • Drugs (not further specified by now) Comparator • Not further specified

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: planned
	• Clinical progression/improvement of symptoms: planned
	• Admission to hospital (for outpatients only): not planned
	• Length of hospital stay (for those admitted to hospital): planned
	• Admission to ICU: planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: planned (using the Eq-5D)
	• Viral clearance: not planned
	Safety outcomes
	• Number of participants with grade 3 and grade 4 AEs: planned
	• Number of participants with SAEs: planned
	Additional study outcomes
	• Incidence of pneumonitis
	• Incidence of acute respiratory distress syndrome (ARDS)
	• Duration of fever
	• Composite endpoint of duration of key symptoms – cough, breathlessness, fatigue
	• General health status
	• Blood-based biomarkers: microRNA expression and serum proteins
	• Incidence of acute severe illness
	• Incidence of acute severe cardiorespiratory illness
	• Incidence of other COVID-19 related syndromes

Notes	Funding: NHMRC Clinical Trials Centre, University of Sydney

BET-A (ACTIV-5)

Methods	Drug name: remdesivir, risankizumab Trial design: multicentre, randomised, double-blinded trial NCT number: NCT04583956 Target sample size: 200 participants Planned completion date: December 2021
Participants	Setting • Inpatient/outpatient: inpatient • Multicentre, USA

BET-A (ACTIV-5) *(Continued)*

Eligibility criteria

- Inclusion criteria
  - Admitted to a hospital with symptoms suggestive of COVID-19 and requires ongoing medical care
  - Participant (or LAR) provides informed consent prior to initiation of any study procedures and understands and agrees to comply with planned study procedures
  - Male or non-pregnant female adult ≥ 18 years of age at time of enrolment
  - Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other commercial or public health assay in any specimen collected < 72 h prior to screening; OR PCR-positive in sample collected ≥ 72 h but < 14 days prior to screening AND non-improving or progressive disease suggestive of ongoing SARS-CoV-2 infection
  - Illness of any duration, and requiring, just prior to randomisation, supplemental oxygen (any flow), mechanical ventilation or ECMO (ordinal scale category 5, 6, or 7)
  - WOCBP must agree to either abstinence or use at least one acceptable method of contraception from the time of screening through 5 months post study IP dosing.
  - Agrees not to participate in another blinded clinical trial (both pharmacologic and other types of interventions) for the treatment of COVID-19 through day 29
- Exclusion criteria
  - ALT or AST > 5 times the ULN
  - Participants with a low glomerular filtration rate (eGFR)
  - Pregnancy or breastfeeding
  - Anticipated discharge from the hospital or transfer to another hospital that is not a study site within 72 h of enrolment
  - Allergy to any study medication
  - Received ≥ 5 doses of remdesivir prior to screening
  - Received ≥ 2 doses of > 60 mg of prednisone or equivalent in the 7 days prior to screening
  - Received small molecule tyrosine kinase inhibitors, including Janus kinase (JAK) inhibitors (e.g. baricitinib, ibrutinib, acalabrutinib, imatinib, gefitinib), in the 4 weeks prior to screening
  - Received mAbs targeting B-cells or cytokines, e.g. tumour necrosis factor (TNF) inhibitors, anti-IL-1 (e.g. anakinra, canakinumab), anti-IL-6 (e.g. tocilizumab, sarilumab, sitlukimab), or T-cells (e.g., abatacept)
  - Received granulocyte-macrophage colony-stimulating factor (GM-CSF) agents (e.g. sargramostim) within 2 months prior to screening
  - Received other immunosuppressants in the 4 weeks prior to screening
  - Received any live vaccine in the 4 weeks prior to screening
  - Known active tuberculosis, history of HIV, Hepatitis B (HBV) or untreated hepatitis C (HCV) infection, pulmonary alveolar proteinosis (PAP)
  - Has active malignancy, immunodeficiency, uncontrolled opportunistic infection, or uncontrolled cirrhosis
  - Positive test for influenza virus during the current illness
  - Previous participation in an ACTIV-5/BET trial

Interventions	Intervention • Remdesivir • Risankizumbab Comparator • Placebo, IV infusion

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days:

BET-A (ACTIV-5) *(Continued)*

- Clinical progression/improvement of symptoms: planned
- Admission to hospital (for outpatients only): not planned
- Length of hospital stay: planned
- Admission to ICU: not planned
- Length of ICU stay: not planned
- Quality of life, including fatigue: not planned
- Viral clearance: not planned

Safety outcomes

- Number of participants with grade 3 and grade 4 AEs: planned
- Number of participants with SAEs: planned

Additional study outcomes

- Clinical efficacy in adults hospitalised with COVID-19 according to clinical status on an 8-point ordinal scale
- Change from baseline in C-reactive protein (CRP) concentration, d-dimer concentration, ferritin concentration, fibrinogen concentration, troponin concentration, ALT, AST, creatinine, haemoglobin, international normalized ratio (INR), platelets, total bilirubin over time, WBC count
- Discontinuation or temporary suspension of study product administration
- Proportion of participants alive and without respiratory failure

Notes	Funding: NIAID

BET-B (ACTIV-5)

Methods	Drug name: remdesivir plus lenzilumab Trial design: randomised, parallel assignment, double-blind, multicentre platform trial NCT number: NCT04583969 Target sample size: 400 participants Planned completion date: 31 December 2021

Participants	Setting
	
	• Inpatient
	• Multicentre, USA
	
	Eligibility criteria
	
	• Inclusion criteria
	  * Admitted to a hospital with symptoms suggestive of COVID-19 and requires ongoing medical care
	  * Participant(or LAR) provides informed consent prior to initiation of any study procedures
	  * Participant(or LAR) understands and agrees to comply with planned study procedures
	  * Male or non-pregnant female adult ≥ 18 years of age at time of enrolment
	  * Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other commercial or public health assay in any specimen, collected < 72 hours prior to screening; OR in sample col-

BET-B (ACTIV-5) *(Continued)*

lected >/= 72 hours but < 14 days prior to screening AND non-improving or progressive disease suggestive of ongoing SARS-CoV-2 infection
    * Illness of any duration, and requiring, just prior to randomisation, supplemental oxygen (any flow), mechanical ventilation or ECMO (ordinal scale category 5, 6, or 7)
    * WOCBP must agree to either abstinence or use at least one acceptable method of contraception from the time of screening through 5 months post study intraperitoneal (IP) dosing
    * Agrees not to participate in another blinded clinical trial (both pharmacologic and other types of interventions) for the treatment of COVID-19 through day 29
- Exclusion criteria
    * ALT or AST > 5 times ULN
    * Pregnancy or breastfeeding
    * Anticipated discharge from the hospital or transfer to another hospital that is not a study site within 72 hours of enrolment
    * Allergy to any study medication
    * Received ≥ 5 doses of remdesivir prior to screening
    * Received ≥ 2 doses of > 60 mg of prednisone or equivalent in the 7 days prior to screening
    * Received small molecule tyrosine kinase inhibitors, including Janus kinase (JAK) inhibitors (e.g. baricitinib, ibrutinib, acalabrutinib, imatinib, gefitinib), in the 4 weeks prior to screening
    * Received mAbs targeting cytokines (e.g. tumour necrosis factor (TNF) inhibitors, anti-IL-1, e.g., anakinra, canakinumab, anti-IL-6 (e.g., tocilizumab, sarilumab, sitlukimab), or T-cells (e.g. abatacept) in the 4 weeks prior to screening
    * Received mAbs targeting B-cells in the 3 months prior to screening
    * Received granulocyte-macrophage colony-stimulating factor (GM-CSF) agents (e.g. sargramostim) within 2 months prior to screening
    * Received other immunosuppressants in the 4 weeks prior to screening
    * Received any live vaccine in the 4 weeks prior to screening
    * Known active tuberculosis, history of HIV, Hepatitis B (HBV) or untreated hepatitis C (HCV) infection, pulmonary alveolar proteinosis (PAP)
    * Has active malignancy, immunodeficiency, uncontrolled opportunistic infection, or uncontrolled cirrhosis
    * Has a medical condition that could, in the judgment of the investigator, limit the interpretation and generalisability of trial results
    * Positive test for influenza virus during the current illness
    * Previous participation in an ACTIV-5/BET trial

Interventions	Intervention Remdesivir plus lenzilumab Comparator • Remdesivir plus placebo, IV infusion

Outcomes	Efficacy outcomes
	
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: planned
	• Length of hospital stay: planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	
	Safety outcomes

BET-B (ACTIV-5) *(Continued)*

- Number of participants with grade 3 and grade 4 AEs: planned
- Number of participants with SAEs: planned

Additional study outcomes

- Clinical efficacy in adults hospitalised with COVID-19 according to clinical status on an 8-point ordinal scale
- Day of recovery
- Change from baseline in C-reactive protein (CRP) concentration, d-dimer concentration, ferritin concentration, fibrinogen concentration, troponin concentration, ALT, AST, creatinine, haemoglobin, international normalised ratio (INR), platelets, total bilirubin over time, WBC count
- Clinical efficacy, as assessed by time to recovery
- Discontinuation or temporary suspension of study product administration
- Subject 14-day mortality
- Proportion of participants alive and without respiratory failure

Notes	Funding: NIAID

CATALYST

Methods	Drug name: mylotarg, namilumab, remsima, infliximab Trial design: multicentre, randomised, placebo-controlled clinical trial Identifier: ISRCTN40580903 Target sample size: not known Planned completion date: May 2021

Participants	Setting
	• Inpatient
	• Multicentre, UK
	Eligibility criteria
	• Inclusion criteria
	  * Hospitalised adult (≥ 16 years) patients with a laboratory-confirmed diagnosis of SARS-CoV-2 pneumonia (confirmed by RT-PCR assay and chest X-ray)
	  * SaO2 of ≤ 94% while breathing ambient air PaO2:FiO2 ≤ 300 mg Hg (≤ 40 kPa)
	  * Arm 2: usual care + gemtuzumab ozogamicin) specific inclusion criteria (arm is currently not recruiting)
	  * The following criterion will apply until at least 3 patients have been allocated the IMP: intubated and requiring mechanical ventilation

CATALYST *(Continued)*

- Exclusion criteria
  - Patient or LAR refusal
  - Receiving palliative care with no active treatment
  - Known veno-occlusive disease
  - Chronic Obstructive Pulmonary Disease (known FEV1 < 50% predicted or ambulatory or long-term oxygen therapy)
  - Neutrophil count < 2 x 10^9/l or WBC count < 4.0 x 10^9/L
  - Current participation in another COVID-19 interventional trial
  - Known pregnancy or breastfeeding women
  - WOCBP who are unwilling to use effective contraception
  - Non-vasectomised men, sexually active with WOCBP, who are not willing to practise effective contraception
  - Known HIV or chronic hepatitis B or C infection
  - Known contraindications to any of the investigational medicinal products
  - Concurrent immunosuppression with biological agents or prednisone dose > 20 mg
  - History of haematopoietic stem cell transplant or solid organ transplant
  - Any other indication or medical history, that in the opinion of the local investigator means the patient is unsuitable for trial participation
  - Patients with tuberculosis or other severe infections
  - Patients with moderate or severe heart failure (NYHA class III/IV)

Interventions	Intervention • Mylotarg (IV use, 5 mg) • Namilumab (IV use, 20 to 150 mg/mL) • Remsima (IV use) • Infliximab (100 mg) Comparator • Placebo

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: not planned
	• Development of severe symptoms according to WHO scale (≥ 6 on the WHO Clinical Progression Scale; for mild disease): planned
	• Length of hospital stay: planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	Safety outcomes
	• Number of participants with grade 3 and grade 4 AEs: not planned
	• Number of participants with SAEs: planned
	Additional study outcomes
	• SpO2/FiO2
	• Routine laboratory measurement (baseline, days 1, 3, 7, and 14)
	• C-reactive protein (CRP)
	• Full blood count with neutrophil:lymphocyte ratios

CATALYST *(Continued)*

	• Ferritin, D-Dimer, lactate dehydrogenase and triglycerides
Notes	Funding: University of Birmingham

CCAP

Methods	Drug name: convalescent anti-SARS-CoV-2 plasma Trial design: multicentre, randomised, double-blinded, placebo-controlled trial NCT number: NCT04345289 Target sample size: 1100 participants Planned completion date: 15 June 2021

Participants	Setting
	
	• Inpatient
	• Multicentre, Denmark
	
	Eligibility criteria
	
	• Inclusion criteria
	  * ≥ 18 years of age
	  * Confirmed COVID-19 infection by presence of SARS-CoV-2 nucleic acid by PCR
	  * Evidence of pneumonia given by at least one of the following: SpO2 ≤ 93% on ambient air or PaO2/FiO2 < 300 mmHg/40 kPa or radiographic findings compatible with COVID-19 pneumonia
	  * For WOCBP: negative pregnancy test and willingness to use contraceptive (consistent with local regulations) during study period
	  * Signed Informed Consent Form by any patient capable of giving consent, or, when the patient is not capable of giving consent, by his or her LARs
	• Exclusion criteria
	  * In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 h, irrespective of the provision of treatment
	  * Participating in other drug clinical trials (participation in COVID-19 antiviral trials may be permitted if approved by sponsor)
	  * Pregnant or breastfeeding, positive pregnancy test in a pre-dose examination
	  * Any serious medical condition or abnormality of clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study

Interventions	Intervention • Convalescent plasma Comparator • Infusion placebo

Outcomes	Efficacy outcomes
	
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: planned
	• Clinical progression/improvement of symptoms: planned
	• Length of hospital stay: planned
	• Admission to ICU: not planned

CCAP *(Continued)*

- Length of ICU stay: planned
- Quality of life, including fatigue: not planned
- Viral clearance: not planned

Safety outcomes

- Number of participants with grade 3 and grade 4 adverse events: planned
- Number of participants with serious adverse events: planned

Additional study outcomes

- Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status
- Ventilator-free days
- Organ failure-free days

Notes	Funding: Thomas Benfield, Hvidovre University Hospital

COLHEART-19

Methods	Drug name: colchicine Trial design: randomised, open-label, controlled trial NCT number: NCT04355143 Target sample size: 150 participants Planned completion date: September 2021

Participants	Setting
	
	• Inpatient
	• Severity: unclear
	• USA
	
	Eligibility criteria
	
	• Inclusion criteria
	  * Confirmed COVID-19 infection by PCR
	  * Cardiac injury (elevated troponin level, elevated B-type natriuretic peptide (BNP) level, new ischaemic or arrhythmogenic changes on ECG/telemetry, new decrease in left ventricular ejection fraction (LVEF) or new pericardial effusion on ECG)
	  * Able to provide informed consent
	• Exclusion criteria
	  * Pregnancy, breastfeeding mothers, and WOCBP who are unable to use 2 forms of contraception
	  * Co-administration of CYPA3A4 and P-glycoprotein (P-gp) transport system inhibitors
	  * Concurrent use of strong CYP3A4 or P-gp inhibitors in patients with renal or hepatic impairment
	  * Severe haematological or neuromuscular disorders
	  * Severe renal impairmant with concomitant hepatic impairment

Interventions	Intervention • Colchicine Comparator

COLHEART-19 *(Continued)*

	• Placebo

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: planned
	• Clinical progression/improvement of symptoms: planned
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	Safety outcomes
	• Number of participants with grade 3 and grade 4 AEs: not planned
	• Number of participants with SAEs: not planned
	Additional study outcomes
	• Delta (peak minus baseline) troponin level
	• Delta (baseline to peak) brain natriuretic peptide (BNP) level
	• Change in left ventricular ejection fraction (LVEF) on ECG
	• Delta (peak minus baseline) C-Reactive protein (CRP) inflammatory biomarker level
	• Delta (peak minus baseline) D-Dimer inflammatory biomarker level
	• Re-hospitalisation at 90 days

Notes	Funding: University of California, Los Angeles

COPPS

Methods	Drug name: acebilustat, camostat Trial design: pragmatic, multi-arm, adaptive, phase 2, blinded, randomised, placebo-controlled platform trial Identifiers: NCT04662086 Target sample size: 240 participants Planned completion date: March 2022
Participants	Setting • Outpatient • USA Eligibility criteria

COPPS *(Continued)*

- Inclusion criteria
  - Outpatient setting
  - Age ≥ 18 years and ≤ 80 years at the time of the assessment
  - Able and willing to understand the study, adhere to all study procedures, and provide written informed consent
  - Initial diagnosis of COVID-19 disease as defined by an FDA-cleared molecular diagnostic assay positive for SARS-CoV-2 with no more than 72 hours from the initial swab used in the diagnosis to the time of commencing informed consent
  - At baseline, at least two symptoms should have moderate or higher severity score on the COVID Outpatient Symptom Scale (COSS)
  - Additional inclusion criteria may pertain to specific drugs as described in study-specific protocols
- Exclusion criteria
  - At screening, the participant needs to be admitted to the hospital or is being evaluated for potential admission
  - Previous use of drugs that may be active against COVID-19 in the eyes of the investigators
  - Participant has any abnormal laboratory test results at screening
  - Participantis using adrenocorticosteroids
  - Participant has a serious chronic disease (e.g. uncontrolled HIV, cancer requiring chemotherapy within the preceding 6 months, and/or moderate or severe hepatic insufficiency)
  - Has renal insufficiency requiring haemodialysis or continuous ambulatory peritoneal dialysis (CAPD)
  - Has liver impairment greater than Child Pugh A
  - History of alcohol or drug abuse in the previous 6 months, psychiatric disease that is not well controlled
  - Has taken another investigational drug within the past 30 days
  - Is deemed by the Investigator to be ineligible for any reason

Interventions	Intervention • Acebilustat (100 mg capsule administered orally once daily) • Camostat (200 mg tablet administered orally 4 times daily) Comparator • Placebo

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: planned
	• Admission to hospital: planned
	• Length of hospital stay: planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: planned
	Safety outcomes
	• Number of participants with grade 3 and grade 4 AEs: not planned
	• Number of participants with SAEs: not planned
	Additional study outcomes
	• Time from randomisation to sustained symptom resolution assessed over a 28-day period

COPPS *(Continued)*

- Time to first resolution
- Indicator participant has developed antibodies to SARS-CoV-2

Notes	Funding: Stanford University

CORIMUNO

Methods	Drug name: tocilizumab, and many more Trial design: randomised, controlled open-label trials; subprotocols are registered with separate NCT numbers NCT number: NCT04324047 NCT04331808 - tocilizumab (active, not recruiting) NCT04346797 - eculizumab (recruiting) NCT04324073 - sarilumab (active, not recruiting) NCT04341584 - anakinra (completed) NCT04343144 - nivolumab (not yet recruiting) NCT04345991 - plasma (recruiting) NCT04344782 - bevacizumab (not yet recruiting) NCT04344756 - tinzaparin or unfractionated heparin (not yet recruiting) Target sample size: 1000 participants Planned completion date: 31 December 2021

Participants	Setting
	
	• Outpatient
	• Multicentre, France
	
	Eligibility criteria
	
	• Inclusion criteria
	  * Laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or public health assay in any specimen < 72 hours and/or CT scan prior to randomisation
	  * Hospitalised patients
	  * Illness of any duration and severity (mild, moderate, severe, critical, see annexe 1), with symptoms (fever, cough, respiratory difficulties, shortness of breath), and at least one of the following:
	  ☐ radiographic infiltrates by imaging (CT scan)
	  ☐ clinical assessment (evidence of rales/crackles on exam or respiratory rate > 25/minutes)
	  ☐ SpO2 ≤ 94% on room air, SpO2≤97 % with O2 > 5L/minute
	  ☐ respiratory rate ≥ 30/minute
	  ☐ requiring mechanical ventilation
	  * With any comorbidities (such as acute kidney injury, cardiovascular condition, pulmonary disease, obesity, high BP, diabetes, chronic kidney diseases, haematological diseases, sickle cell diseases, autoimmune and auto-inflammatory, pregnant women, HIV infected, etc)
	  * Male or female adult ≥ 18 years of age at time of enrolment
	  * Participants must be able and willing to comply with study visits and procedures
	• Exclusion criteria
	  * Patients with any condition that the physician judges could be detrimental to the patient participating in this study; including any clinically important deviations from normal clinical laboratory values or concurrent medical conditions (active infection diseases such as severe bacterial infections, aspergillosis, tuberculosis, depending on the tested medication)
	  * Absence of health insurance

CORIMUNO *(Continued)*

	* Participant protected by law under guardianship or curatorship
Interventions	Intervention • Multiple, depending on subprotocol Comparator • Not further specified
Outcomes	Efficacy outcomes • All-cause mortality * at up to 30 days: not planned * at up to 60 days: not planned • Clinical progression/improvement of symptoms: planned • Admission to hospital: not planned • Length of hospital stay: not planned • Admission to ICU: not planned • Length of ICU stay: not planned • Quality of life, including fatigue: not planned • Viral clearance: not planned Safety outcomes • Number of participants with grade 3 and grade 4 AEs: not planned • Number of participants with SAEs: not planned Additional study outcomes: not planned
Notes	Funding: Assistance Publique - Hôpitaux de Paris

COVID MED

Methods	Drug name: losartan Trial design: randomised, double-blind, placebo-controlled trial Identifier: NCT04328012 Target sample size: 100 participants Planned completion date: 1 August 2021
Participants	Setting • Inpatient • Single centre, USA Eligibility criteria

COVID MED *(Continued)*

- Inclusion criteria
  - Hospitalised patient
  - Age ≥ 18 years
  - Able to ingest oral medication or be administered medication via gastric tube or equivalent
  - Laboratory confirmation of SARS-CoV-2 infection within 1 week prior to randomisation
  - Randomisation within 72 h of hospital admission
  - Negative pregnancy test for WOCBP
  - Patient or LAR able to provide informed consent
- Exclusion criteria
  - Allergy or intolerance to losartan or other ARBs
  - Already taking ACE or ARB (within 1 month)
  - Hypotension at time of enrolment (systolic BP < 100 mm Hg)
  - Hyperkalaemia (K ≥ 5.0 at time of screening or history of hyperkalaemia)
  - Severe renal dysfunction (estimated GFR < 30 mL/min at time of screening or history advanced renal disease)
  - Severe volume depletion or acute kidney injury (AKI) at time of enrolment
  - Known cirrhotic ascites
  - Known severe aortic or mitral valve stenosis, unstented renal artery stenosis
  - Co-administration with certain drugs due to CYP3A interactions if taken in < 24 hours
  - Severe hepatic insufficiency (LFTs > 5 times the ULN or known end-stage liver disease or cirrhosis)
  - Nausea/vomiting or aspiration risk precluding oral medications unless can be given by gastric tube
  - Pregnancy or breastfeeding
  - Absence of dependable contraception in WOCBP
  - Inability to obtain or declined informed consent

Interventions	Intervention • Losartan (25 mg daily for 14 days, oral) Comparator • Placebo (daily for 14 days)

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: not planned
	  * at up to 60 days: planned
	• Clinical progression/improvement of symptoms: planned
	• Length of hospital stay: planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	Safety outcomes
	• Number of participants with grade 3 and grade 4 AEs: not planned
	• Number of participants with SAEs: not planned
	Additional study outcomes
	• NIAID's COVID-19 Ordinal Severity Scale (NCOSS)

COVID MED *(Continued)*

Notes	Funding: Bassett Healthcare

DEFINE

Methods	Drug name: nafamostat mesilate, TD139 Trial design: randomised, single-blinded clinical trial NCT number: NCT04473053 Target sample size: 60 participants Planned completion date: 3 December 2021

Participants	Setting
	
	• Inpatient/outpatient: both
	• Single-centre
	
	Eligibility criteria
	
	• Inclusion criteria
	  * Provision of informed consent from the patient or representative
	  * Aged at least 16 years
	  * If WOCBP, the patient, and their partner(s), agree to use medically accepted double-barrier methods of contraception
	  * COVID-19 positive
	• Exclusion criteria
	  * Current or recent history of severe, progressive, and/or uncontrolled cardiac disease (NYHA class IV), uncontrolled renal disease (eGFR <30 mL/minute/1.73 m2), severe liver dysfunction (ALT/AST > 5 x ULN) or bone marrow failure (Hb < 80 g/L and ANC< 0.5 mm3 and platelet count < 50,000 uL), diabetes mellitus
	  * Women who are pregnant or breastfeeding
	  * Participation in another clinical trial of an investigational medicinal product (CTIMP)
	  * Known hypersensitivity to the study drug or excipients (e.g. lactose)
	  * Pre-existing or concomitant use of off-label treatments for COVID-19 that are not recognised as locally approved standard care
	  * Significant electrolyte disturbance (hyperkalaemia potassium > 5.0 mmol/L or hyponatraemia sodium < 120 mmol/L)
	  * Patient currently receiving potassium-sparing diuretics that cannot be reasonably withheld
	  * Patient currently receiving prophylactic or therapeutic anticoagulants or antiplatelet agents that cannot be reasonably withheld if randomised to nafamostat
	  * Patients (or their partners) planning on donating sperm/eggs during the trial period
	  * Ongoing dialysis
	  * History of serious liver disease (Child Pugh score > 10)
	  * Haemoglobin < 80 g/L
	  * Any known allergy to the study drug/excipients
	  * patient is unwilling or unable to comply with drug administration plan, laboratory tests or other study procedures

Interventions	Intervention • Nafamostat • TD139 Comparator

DEFINE *(Continued)*

	• Active: standard of care

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: not planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: planned
	• Admission to hospital (for outpatients only): not planned
	• Length of hospital stay: planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: planned
	Safety outcomes
	• Number of participants with grade 3 and grade 4 AEs: not planned
	• Number of participants with SAEs: planned
	Additional study outcomes
	• Physiological changes in the circulatory and respiratory system
	• Protein kinase of the proposed trial treatments in COVID-19 patients
	• Change in the expression of key coagulation biomarkers and key cytokines in the blood of COVID-19 patients during and after treatment period
	• To evaluate the improvement or deteroriation of patients
	• To evaluate the number of oxygen-free days
	• To evaluate SARS-CoV-2 viral load
	• To evaluate the use of renal dialysis or haemofiltration for each treatment arm
	• Recording the number of treatment-related adverse events

Notes	Funding: University of Edinburgh

EU SolidAct

Methods	Drug name: multiple drugs including baricitinib Trial design: randomized, multifactorial, adaptive platform trial NCT number: NCT04891133 Target sample size: 1900 participants Planned completion date: December 2025
Participants	Setting • Inpatient/outpatient: both • Multicentre Eligibility criteria

EU SolidAct *(Continued)*

- Inclusion criteria
  - GI1. ≥ 18 years of age
  - GI2. Laboratory-confirmed SARS-CoV-2 infection (new infection or reinfection) as determined by PCR not more than 9 days old.
  - GI3. Admitted to hospital
  - GI4. Informed consent by the participant or legally authorized representative
  - GI5A (SolidAct part A): moderate disease state defined as hospitalised patients without oxygen therapy or oxygen by mask or nasal prongs needed, or
  - GI5B (SolidAct part B): Severe/critical disease state defined as fulfilling at least one of the following criteria:
    - ☐ SpO2 < 90% on room air, or
    - ☐ SpO2 90% to 94% with a downwards trend and/or signs of respiratory distress*, or
    - ☐ Need of oxygen by NIV (CPAP, BIPAP), high flow or non-rebreather mask, or Need of mechanical ventilation/ECMO
    - ☐ *Persistently increased respiratory rate, use of accessory muscles, inability to complete full sentences. Clinical judgement must be applied to determine whether a low oxygen saturation is indicative of disease progression or severity or is habitual for a given patient (i.e., with underlying chronic lung disease).
- Additional inclusion criteria are given in the intervention-specific sub-protocols.
- Exclusion criteria
  - GE1. Anticipated transfer to another non-trial hospital within 72 hours

Interventions	Intervention • Multiple drugs, including Baricitinib Comparator • Placebo, active: standard of care

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: planned
	• Clinical progression/improvement of symptoms: planned
	• Development of severe symptoms according to WHO scale (≥ 6 on the WHO Clinical Progression Scale; for mild disease): not planned
	• Admission to hospital (for outpatients only): not planned
	• Length of hospital stay (for those admitted to hospital): planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: planned (at 90 days)
	• Viral clearance: planned
	Safety outcomes
	• Number of participants with grade 3 and grade 4 AEs: not planned
	• Number of participants with SAEs: planned
	Additional study outcomes
	1. Time from randomisation to recovery (shared secondary end point for part A and B)
	2. SpO2/FiO2-ratio at days 3, 5 and 8 (shared secondary end point for part A and B)
	3. Changes in C-reactive protein from baseline
	4. Changes in ferritin from baseline
	5. Changes in lactate dehydrogenase from baseline
	6. Changes in D-dimer from baseline

EU SolidAct *(Continued)*

	7. Changes in procalcitonin from baseline 8. Changes in neutrophils from baseline 9. Changes in lymphocytes from baseline 10. Changes in WBC count from baseline
Notes	Sponsors: Oslo University Hospital; Institut National de la Santé Et de la Recherche Médicale, France; Epidemiological and Clinical Research Information Network

I-SPY

Methods	Drug name: remdesivir, cenicriviroc, icatibant, razuprotafib, apremilast, pulmozyme, IC14, celecoxib Famotidine, narsoplimab, aviptadil acetate, cyclosporine Trial design: multicentre, randomised, open-label trial NCT number: NCT04488081 Target sample size: 1500 participants Planned completion date: November 2022

Participants	Setting
	
	• Inpatient
	• Multicentre, USA
	
	Eligibility criteria
	
	• Inclusion criteria
	  * Male or female, ≥ 18 years old
	  * Admitted to the hospital and placed on high-flow oxygen (greater than 6 L by nasal cannula or mask delivery system) or intubated for the treatment of (established or presumed) COVID-19
	  * Informed consent provided by the patient or LAR
	  * Confirmation of SARS-CoV-2 infection by PCR prior to randomisation
	• Exclusion criteria
	  * Pregnant or breastfeeding women
	  * History of allergic reactions attributed to compounds of similar chemical or biologic composition to study agent based on review of the medical record and patient history
	  * Comfort measures only
	  * Acute or chronic liver disease with a Child-Pugh score > 11
	  * Resident for > 6 months at a skilled nursing facility
	  * Estimated mortality > 50% over the next 6 months from underlying chronic conditions
	  * Time since requirement for high-flow oxygen or ventilation > 72 hours
	  * Anticipated transfer to another hospital which is not a study site within 72 hours

Interventions	Intervention • Cenicriviroc (CVC) [stopped] • Icatibant [stopped] • Razuprotafib [stopped] • Apremilast [stopped] • Pulmozyme plus remdesivir • IC14 plus remdesivir • Celecoxib and Famotidine plus remdesivir • Narsoplimab plus remdesivir

I-SPY *(Continued)*

	• Aviptadil plus remdesivir • Cyclosporine plus remdesivir Comparator • Remdesivir plus standard of care (200 mg loading dose on day 1, followed by 100 mg IV once daily maintenance doses for 4 or 9 days)

Outcomes	Efficacy outcomes
	
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: planned
	• Length of hospital stay: not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	
	Safety outcomes
	
	• Number of participants with grade 3 and grade 4 AEs: planned
	• Number of participants with SAEs: not planned
	
	Additional study outcomes
	
	• Identify agents that will result in substantial improvements to the clinical condition of participants with COVID-19

Notes	Funding: QuantumLeap Healthcare Collaborative

NCT04359095

Methods	Drug name: emtricitabine/tenofovir, colchicine pill, rosuvastatin Trial design: randomised, parallel-assignment, open-label trial Identifier: NCT04359095 Target sample size: 1200 participants Planned completion date: 31 May 2021

Participants	Setting
	
	• Inpatient
	• Multicentre, Colombia
	
	Eligibility criteria
	
	• Inclusion criteria
	  * Age ≥ 18 years
	  * Positive RT-PCR for COVID-19 or high suspicion of SARS COVID-19
	  * Requirement of in-hospital treatment, classified as either mild confirmed pneumonia and at least two risk factors (age ≥ 60 years, history of CD disease, DM, COPD, HT or cancer); or moderate pneumonia; or severe pneumonia; AND any one of further respiratory criteria

NCT04359095 *(Continued)*

- Exclusion criteria
  - Pregnancy
  - Known allergies to study drug
  - Hepatic cirrhosis (Child B or C) or hepatic abnormality manifested as ALT/AST 5 times above ULN
  - Glomerular filtration rate < 30 mL/minute/1.73 ^m2 by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula
  - Advanced or metastatic cancer
  - Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight questionnaire (FRAIL) score of fragility > 3

Interventions	Intervention • Emtricitabine + tenofovir • Colchicine + rosuvatatine • Emtricitabine/tenofobir + colchicine + rosuvastatin Comparator • Standard treatment

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: planned
	• Length of hospital stay: not planned
	• Admission to ICU: planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: planned
	Safety outcomes
	• Number of participants with grade 3 and grade 4 AEs: not planned
	• Number of participants with SAEs: not planned
	Additional study outcomes
	• Number of participants with treatment-related SAEs
	• Time to death
	• Number of participants with any AE related to treatment assessed by the NCORP Guidance for Collection of AEs related to COVID-19 Infection
	• Severe AEs

Notes	Funding: Universidad Nacional de Colombia

NCT04590586

Methods	Drug name: apremilast, lanadelumab, zilucoplan Trial design: phase 3, randomised, quadruple blind platform trial Identifiers: NCT04590586 Target sample size: 1400 participants

NCT04590586 *(Continued)*

	Planned completion date: August 2021

Participants	Setting
	• Inpatient
	• Multicentre
	Eligibility criteria
	• Inclusion criteria
	  * Adults (≥ 18 years of age) with active SARS-CoV-2 infection confirmed by laboratory tests and/or point-of-care tests.
	  * A score of Grade 2, 3, 4 or 5, as defined by an 8-point ordinal scale
	  * Male participants: must agree to use contraception during the treatment period and for at least 6 weeks after the last dose of study treatment and refrain from donating sperm during this period
	  * Female participants: not pregnant, not breastfeeding
	  * Ability to provide informed consent signed by the study participant or LAR
	  * Ability and willingness to participate in telephone/telemedicine follow-up visits if needed
	• Exclusion criteria
	  * Participant has any condition for which participation would not be in the best interest of the participant or that could prevent, limit, or confound the protocol-specified assessments
	  * Stage 4 severe chronic kidney disease or requiring dialysis
	  * Screening 12-lead ECG with a measurable QTc interval according to Fridericia correction (QTcF) ≥ 500 ms
	  * Anticipated transfer to another hospital that is not a study centre within 72 hours
	  * Participants who are currently pregnant or who are not willing to discontinue breastfeeding
	  * Participants participating in another clinical study of an investigational medicinal product or other unapproved (or investigational) treatment for COVID-19
	  * Active tuberculosis or a history of incompletely treated tuberculosis
	  * Active, uncontrolled systemic bacterial or fungal infection(s)

Interventions	Intervention • Apremilast (orally) • Lanadelumab (IV) • Zilucoplan (SC) injection in the abdomen, thigh, or upper arm Comparator • placebo for each substance

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: planned
	• Clinical progression/improvement of symptoms: planned
	• Length of hospital stay: planned
	• Admission to ICU: not planned
	• Length of ICU stay: planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	Safety outcomes
	• Number of participants with grade 3 and grade 4 AEs: planned

NCT04590586 *(Continued)*

	• Number of participants with SAEs: planned Additional study outcomes • Number of participants who achieve oxygen-free recovery at day 29 • Worst post-baseline score on the 8-point ordinal scale of clinical severity status • Number of participants who experience one or more treatment-emergent adverse events (TEAEs)
Notes	Funding: Amgen

O'Brien 2021

Methods	Drug name: casirivimab/imdevimab Trial design: randomised, double-blind, placebo-controlled, two-part phase 3 trial for prevention of SARS-CoV-2 infection among uninfected household contacts; here reported: PCR-positive cases (Part B) Type of publication: preprint (English) Identifiers: NCT04452318 Number of participants: • PCR-positive randomised: 314 • seronegative modified full analysis set (seronegative mFAS-B; asymptomatic, seronegative, confirmed positive): 204 • Safety set (including prevention study part):

Participants	Setting
	
	• Outpatient
	• Recruitment period: between July 13, 2020 and January 28, 2021 (contradictory to methods section)
	• Multicentre: 112 sites in the USA, Romania and Moldova
	
	Eligibility criteria
	
	• Inclusion criteria
	  * 18 years of age (irrespective of weight) and above at the signing of informed consent or adolescent participants ≥12 to < 18 years of age, or pediatric participants < 12 years of age at the signing of the assent (parent/guardian sign the informed consent)
	  * Asymptomatic household contact with exposure to an individual with a diagnosis of SARS-CoV-2 infection (index case); randomised within 96 hours of index case test sample
	  * Participant anticipates living in the same household with the index case until study day 29
	  * in good health based on medical history and physical examination at screening/baseline
	  * Willing and able to comply with study visits and study-related procedures/assessments
	  * Provide informed consent signed by study participant or legally acceptable representative

O'Brien 2021 *(Continued)*

- Exclusion criteria
  - History of prior positive SARS-CoV-2 RT-PCR test or positive SARS CoV-2 serology test at any time before the screening
  - Has lived with individuals who have had previous SARS-CoV-2 infection or currently lives with individuals who have SARS-CoV-2 infection; exception: index case
  - Active respiratory or non-respiratory symptoms consistent with Covid-19
  - History of respiratory illness with sign/symptoms of SARS-CoV-2 infection, in the opinion of the investigator, within the prior 6 months to screening
  - Nursing home resident
  - Any condition that may pose an additional risk to the participants by their participation; significant multiple/severe allergies; previous anaphylactic reaction
  - Current hospitalisation or was hospitalised (i.e, >24 hours) for any reason within 30 days of the screening visit
  - Treatment with another investigational agent in the last 30 days; SARS-CoV-2 vaccine; passive antibodies; hydroxychloroquine/chloroquine; remdesivir

Patient characteristics:

- Age (years, mean, SD):
  - treatment: 39.2 (17.7)
  - placebo: 42.5 (18.3)
- Sex (female):
  - treatment: 49.5%
  - placebo: 59.4%
- Race or ethnic group:
  - White: treatment: 78.2%; placebo: 90.6%
  - Black or African American: treatment: 6.9%; placebo: 3.8%
  - Asian: treatment: 8.9%; placebo: 2.8%
  - American Indian or Alaska Native: treatment: 1%; placebo: 0%
- Ethnicity Hispanic or Latino:
  - treatment: 33.5%
  - placebo: 35.8%
- Disease severity: mild
- Co-morbidities:
  - BMI > 30: treatment: 36.6%; placebo: 28.3%
  - chronic kidney disease: treatment: 2.0%, placebo: 2.9%
  - diabetes: treatment: 5%, placebo: 10.6%
  - immunosuppressive disease: treatment: 1%; placebo: 1%
- Pre-treatments: not reported
- Concomitant treatments: not reported

Interventions	Intervention
	
	• Casirivimab/imdevimab
	  * Target: SARS-CoV-2 S protein
	  * Origin: not reported
	  * Dose: 1200 mg
	  * Frequency: single-dose
	  * Route of administration: subcutaneous injection
	• Placebo

Outcomes	Outcomes Efficacy outcomes

O'Brien 2021 *(Continued)*

- All-cause mortality
  - at up to 30 days: not reported
  - at up to 60 days: not reported
- Clinical progression according to WHO scale: not reported
- Admission to hospital: reported
- Length of hospital stay: not reported
- Admission to ICU: not reported
- Length of ICU stay: not reported
- Quality of life, including fatigue: not reported
- Viral clearance: not reported

Safety outcomes

- Number of participants with AEs: reported as treatment-emergent adverse events; adverse events of special interest ≥ grade 3
- Number of participants with SAEs: planned

Additional study outcomes

- Proportion of participants who subsequently developed signs and symptoms of Covid-19 within 14 days of a positive RT-qPCR atbaseline or during the efficacy assessment period
- Number of weeks of symptomatic SARS-CoV-2 infection (broad-term)
- Number of weeks of high viral load (>4 $\log_{10}$ copies/ml) over 28 days
- Pharmacokinetics

Notes	Funding: jointly managed by Regeneron, the Covid-19 Prevention Network (CoVPN), and the National Institute of Allergy and Infectious Diseases (NIAID) Conflicts of interest: The study protocol was not published with the preprint publication.

PaTS-COVID

Methods	Drug name: ivermectin, aspirin Trial design: single-blind, randomised, clinical trial Identifiers: NCT04703608 Target sample size: 1200 participants Planned completion date: July 2022

Participants	Setting
	
	• Outpatient
	• Multicentre, Gambia
	
	Eligibility criteria
	
	• Inclusion criteria
	  * Cohort 1
	  ☐ Index case - individuals ≥ 5 years of age with confirmed COVID19 mild disease or moderate pneumonia defined as:
	  ☐ Mild disease - influenza-like illness, with any of the following symptoms: cough, fever, headache, sore throat, nasal congestion/runny nose, body pains (myalgia), fatigue

PaTS-COVID *(Continued)*

(malaise), diarrhoea, abdominal pain, anorexia, nausea or vomiting without evidence of pneumonia or hypoxia
- ☐ Moderate pneumonia - clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) with no need for supplemental oxygen (SpO2 ≥ 90% on room air or respiratory rate between 20 and 30 breaths/minute).
- ☐ Household contacts -individuals ≥ 5 years of age living in the same household with the index cases from cohort 1 will be offered to participate.

* Cohort 2
  - ☐ Individuals ≥ 12 years of age with suspected or confirmed COVID-19-associated severe pneumonia defined as signs of pneumonia (fever, cough, dyspnoea or fast breathing) plus one of: SpO2 < 90% on room air OR respiratory rate > 30 breaths/minute
  - ☐ Suspected COVID-19 disease is defined as clinically or radiologically suspected as determined by the most senior clinician available:

- Exclusion criteria
  * Pregnant women will be excluded from both Cohort 1 and Cohort 2.
  * Patients with allergies to the investigational products will be excluded
  * Cohort 1 (ivermectin): lactating mothers will be excluded
  * Cohort 2 (aspirin):
    - ☐ taking aspirin or other NSAIDs for any reason
    - ☐ any bleeding disorder (e.g. frequent nose bleeds, haemophilia)
    - ☐ active or recurrent peptic ulcer disease (defined as currently on triple therapy or had > 1 course of triple therapy in the past 12 months. Do not count symptoms of gastritis or on omeprazole as peptic ulcer disease)
    - ☐ Current active gastrointestinal haemorrhage
    - ☐ Severe liver disease or severe kidney disease (severe liver disease defined as cirrhosis with portal hypertension and history of variceal bleeding; severe kidney disease defined as stage 4/5 KD, eGFR < 30 mL/minute)
    - ☐ Gout
    - ☐ Suspected intra-cerebral haemorrhage
    - ☐ Diagnosed with a stroke on this admission

Interventions	Intervention • Ivermectin • Aspirin Comparator • Placebo

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: planned
	• Clinical progression/improvement of symptoms: not planned
	• Admission to hospital: not planned
	• Hospital discharge: planned
	• Length of hospital stay: not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: planned
	Safety outcomes
	• Number of participants with grade 3 and grade 4 AEs: not planned

PaTS-COVID *(Continued)*

- Number of participants with SAEs: not planned

Additional study outcomes

- Days from recruitment until clinical recovery
- Percentage of household members that get infected with SARS-CoV-2
- antibody measurements

Cohort 2:

- Hours of duration on oxygen supplementation
- Days from recruitment until clinical recovery
- Occurrence of clinical thrombotic and embolic events (myocardial infarction, pulmonary embolus, deep venous thrombosis, cerebrovascular accidents)
- Occurrence of clinical episodes of gastrointestinal bleeding
- Change in C-reactive protein and D-Dimer levels between baseline (enrolment) and day 3-5
- Persisting breathlessness at 28 days and 90 days after enrolment
- Self-reported health at 28 days and 90 days

Notes	Funding: London School of Hygiene and Tropical Medicine

PRINCIPLE

Methods	Drug name: hydroxychloroquine Trial design: parallel, cross-over, randomised trial (the trial will initially be two-arm, comparing usual care to usual care with hydroxychloroquine treatment) Identifiers: ISRCTN86534580 Target sample size: 3000 participants Planned completion date: April 2021

Participants	Setting
	
	• Outpatient
	
	Eligibility criteria
	
	• Inclusion criteria
	  * Participant is willing and able to give informed consent for participation in the study
	  * Participant is willing to comply with all trial procedures
	  * Onset of symptoms of possible COVID-19 in the community (continuous cough and/or high temperature) should be within 7 days of inclusion
	  * Patients aged ≥ 65 with or without comorbidity, and patients aged ≥ 50 years with the following listed comorbidities:
	  ☐ known weakened immune system due to serious illness or infection (e.g. chemotherapy)
	  ☐ known heart disease
	  ☐ known asthma or lung disease
	  ☐ known diabetes not treated with insulin
	  ☐ known mild hepatic impairment
	  ☐ known stroke or neurological problem

PRINCIPLE *(Continued)*

	• Exclusion criteria
	  * Patient currently admitted in hospital
	  * Almost recovered (generally much improved and symptoms now mild or almost absent)
	  * Patient already taking an intervention arm medication (hydroxychloroquine or azithromycin) or other macrolides or ketolides

Interventions	Intervention • Hydroxychloroquine sulphate Comparator • Placebo

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: not planned
	• Development of severe symptoms according to WHO scale (≥ 6 on the WHO Clinical Progression Scale; for mild disease): planned
	• Admission to hospital: planned
	• Length of hospital stay (for those admitted to hospital): planned
	• Admission to ICU: not planned
	• Length of ICU stay: planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	Safety outcomes
	• Number of participants with grade 3 and grade 4 adverse events: not planned
	• Number of participants with serious adverse events: planned
	Additional study outcomes
	• Time taken to self-reported recovery, defined as the first instance that a participant reports feeling recovered from possible COVID-19
	• Patient-reported illness severity
	• Duration of severe symptoms and symptom recurrence, measured by patient report on day recovered
	• Contacts with the health services, reported by patients and captured by reports of patients' medical records where the practice is a member of the RCGP RSC network
	• Consumption of antibiotics, measured using bi-weekly reports from participants' primary care medical records
	• Hospital assessment without admission, measured using patient report/carer report/medical record in primary care and hospital care
	• Negative effects on well-being
	• New infections in household

Notes	Funding: University of Oxford

PROTECT-Surg

Methods	Drug name: lopinavir-ritonavir, hydroxychloroquine Trial design: randomised, parallel, open-label, multicentre trial

PROTECT-Surg *(Continued)*

	Identifiers: NCT04386070 Target sample size: 6400 participants Planned completion date: May 2026

Participants	Setting
	
	• Inpatient
	• Multicentre: India, Ghana, Nigeria, South Africa, UK
	
	Eligibility criteria
	
	• Inclusion criteria
	  * Patients aged ≥ 16 years in the UK
	  * Planned to undergo any type of elective or emergency inpatient surgery requiring general or regional anaesthesia (such as vulnerable patients undergoing surgery for a fractured neck of femur)
	  * Asymptomatic of COVID-19, including patients with: those not tested, negative test results, positive test but no symptoms
	  * Informed patient consent
	• Exclusion criteria
	  * Procedures under local anaesthesia
	  * Symptomatic COVID-19 infection (by confirmed COVID-19 test or a clinical diagnosis); these patients will be eligible for the RECOVERY trial
	  * Existing regular preoperative treatment with trial drugs
	  * Known history of adverse reaction/contraindication to trial drugs
	  * Pregnancy (including caesarean section)
	  * Actively breastfeeding

Interventions	Intervention • Lopinavir-ritonavir • Hydroxychloroquine • Lopinavir-Ritonavir and Hydroxychloroquine Comparator • Control (normal practice; neither trial drug)

Outcomes	Efficacy outcomes
	
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: not planned
	• Length of hospital stay: planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	
	Safety outcomes
	
	• Number of participants with grade 3 and grade 4 AEs: not planned
	• Number of participants with SAEs: not planned
	
	Additional study outcomes

PROTECT-Surg *(Continued)*

- Pneumonia-free survival; ARDS-free survival; or death rate of pneumonia
- Rate of ARDs
- COVID-19 pulmonary complications
- Overall SARS-CoV-2 infected rate
- Pulmonary function

Notes	Funding: University of Birmingham

REMAP-CAP

Methods	Drug name: hydrocortisone, ceftriaxone, moxifloxacin or levofloxacin, piperacillin-tazobactam, ceftaroline, amoxicillin-clavulanate, macrolide, lopinavir/ritonavir, hydroxychloroquine, interferon-β1a, anakinra, tocilizumab, sarilumab, vitamin C, therapeutic anticoagulation, simvastatin, convalescent plasma, eritoran, apremilast, aspirin, clopidogrel, prasugrel, ticagrelor Trial design: randomised, embedded, open-label, multifactorial adaptive platform trial Identifiers: NCT02735707 Target sample size: 7100 participants Planned completion date: December 2023

Participants	Setting
	
	• Inpatient
	• Multicentre: USA, Australia, Belgium, Canada, Croatia, Germany, Hungary, Ireland, the Netherlands, New Zealand, Portugal, Romania, Spain, UK
	
	Eligibility criteria
	
	• Inclusion criteria
	  * Adult patient admitted to an ICU for severe CAP within 48 h of hospital admission with:
	  ☐ symptoms or signs or both that are consistent with lower respiratory tract infection AND
	  ☐ radiological evidence of new onset consolidation
	  * Up to 48 hours after ICU admission, receiving organ support with one or more of:
	  ☐ NIV or invasive ventilatory support;
	  ☐ receiving infusion of vasopressor or inotropes or both
	• Exclusion criteria
	  * Healthcare-associated pneumonia:
	  ☐ prior to this illness, is known to have been an inpatient in any healthcare facility within the last 30 days
	  ☐ resident of a nursing home or long-term care facility
	  * Death is deemed to be imminent and inevitable during the next 24 hours AND one or more of the patient, substitute decision maker or attending physician are not committed to full active treatment
	  * Previous participation in this study within the last 90 days

Interventions	Intervention • Hydrocortisone • Shock-dependent hydrocortisone • Ceftriaxone • Moxifloxacin or levofloxacin • Piperacillin-tazobactam • Ceftaroline

REMAP-CAP *(Continued)*

- Amoxicillin-clavulanate
- Macrolide administered for 3-5 days
- Macrolide administered for up to 14 days
- Oseltamivir
- Lopinavir/ritonavir
- Hydroxychloroquine
- Hydroxychloroquine + lopinavir/ritonavir
- Interferon-β1a
- Anakinra
- Fixed-duration higher-dose hydrocortisone
- Tocilizumab
- Sarilumab
- Vitamin C
- Therapeutic anticoagulation
- Simvastatin
- Convalescent plasma
- Protocolised mechanical ventilation strategy
- Eritoran
- Apremilast
- Aspirin
- Clopidogrel
- Prasugrel
- Ticagrelor

Comparator

- No intervention

Outcomes

Efficacy outcomes

- All-cause mortality
  - at up to 30 days: planned
  - at up to 60 days: planned
- Clinical progression/improvement of symptoms: not planned
- Length of hospital stay (for those admitted to hospital): planned
- Admission to ICU: not planned
- Length of ICU stay: planned
- Quality of life, including fatigue: planned
- Viral clearance: planned

Safety outcomes

- Number of participants with grade 3 and grade 4 AEs: not planned
- Number of participants with serious AEs: not planned

Additional study outcomes

- Destination at time of hospital discharge
- Readmission to the index ICU during the index hospitalisation
- ICU mortality
- Ventilator-free days
- Organ failure-free days
- World Health Organization 8-point ordinal scale outcome
- Occurrence of multi-resistant organism colonisation/infection
- Occurrence *Clostridium difficile*

REMAP-CAP *(Continued)*

- Occurrence of serious ventricular arrhythmia (including ventricular fibrillation) or sudden unexpected death
- Change from baseline influenza virus levels in upper and lower respiratory tract specimens
- Serial detection of SARS-CoV-2 in upper or lower respiratory tract specimens (using only specimens collected for routine clinical testing)

Notes	Sponsor: MJM Bonten

SOLIDARITY

Methods	Drug name: interferon beta-1a, remdesivir Trial design: multicentre, adaptive, randomised, open-label, controlled trial Identifiers: NCT04330690; NCT04575064; ISRCTN83971151; and more, one registration per country Target sample size: 2900 participants Planned completion date: 18 May 2022

Participants	Setting
	
	• Inpatient
	• Multicentre, worldwide
	
	Eligibility criteria
	
	• Inclusion criteria
	  * ≥ 18 years of age
	  * Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or public health assay in any specimen prior to randomisation
	  * Hospitalised at a participating centre
	• Exclusion criteria
	  * Anticipated transfer to another hospital, within 72 hours, which is not a study site
	  * Expected to not survive beyond 24 hours
	  * Known allergy to study medication or its components (non-medicinal ingredients)
	  * Receiving one of the study drugs at time of enrolment

Interventions	Intervention • Remidesivir • Interferon Comparator • Standard supportive care

Outcomes	Efficacy outcomes
	
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: planned
	• Clinical progression/improvement of symptoms: planned
	• Admission to hospital (for outpatients only): not planned
	• Length of hospital stay (for those admitted to hospital): planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned

SOLIDARITY *(Continued)*

- Quality of life, including fatigue: not planned
- Viral clearance: planned

Safety outcomes

- Number of participants with grade 3 and grade 4 AEs: planned
- Number of participants with SAEs: not planned

Additional study outcomes

- Oxygen-free days
- Duration of oxygen use
- Change in subject clinical status

Notes	Funding: Sunnybrook Health Sciences Centre

SWISSPED-RECOVERY

Methods	Drug name: methylprednisolone sodium succinate, Human normal immunoglobulin (IVIg) Trial design: randomised, open-label, controlled trial Identifiers: NCT04826588 Target sample size: 75 participants Planned completion date: April 2022

Participants	Setting
	• Inpatient
	• Switzerland
	Eligibility criteria
	• Inclusion criteria
	  * Hospitalised children (aged <18 years old)
	  * SARS-CoV-2 infection associated disease (clinically suspected or laboratory confirmed) with evidence of single or multi-organ dysfunction (called Pediatric Multisystem Inflammatory Syndrome temporally associated with COVID-19 [PIMS-TS]).
	  * No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial
	• Exclusion criteria
	  * Neonates/infants with a corrected gestational age of ≤ 44 weeks
	  * If the attending clinician believes that there is a specific contra-indication to one of the active drug treatment arms or that the patient should definitely be receiving one of the active drug treatment arms, then that arm will not be available for randomisation for that patient

Interventions	Intervention • Methylprednisolone sodium succinate • Human normal immunoglobulin (IVIg) Comparator • Standard of care
Outcomes	Efficacy outcomes

SWISSPED-RECOVERY *(Continued)*

- All-cause mortality
  - at up to 30 days: planned within 28 days
  - at up to 60 days: planned up to 6 months
- Clinical progression/improvement of symptoms: planned
- Length of hospital stay: planned
- Admission to ICU: not planned
- Length of ICU stay: not planned
- Quality of life, including fatigue: not planned
- Viral clearance: not planned

Safety outcomes

- Number of participants with grade 3 and grade 4 AEs: not planned
- Number of participants with SAEs: not planned

Additional study outcomes

- need for (and duration of) ventilation within 28 days and up to 6 months
- need for renal replacement therapy within 28 days and up to 6 months
- Number of patients who had thrombotic events within 28 days and up to 6 months
- Cardiac and neurological outcome (long-term impact) of Pediatric Multisystem Inflammatory Syndrome temporally associated with COVID-19 (PIMS-TS) after discharge
- Healthcare costs within 28 days

Notes	Funding: University Children's Hospital Basel

TACTIC-E

Methods	Drug name: EDP1815, dapagliflozin, ambrisentan Trial design: randomised, parallel-arm, open-label platform trial Identifiers: NCT04393246 Estimated enrolment: 1407 participants Planned completion date: 15 June 2021

Participants	Setting
	
	• Inpatient
	• UK
	
	Eligibility criteria
	
	• Inclusion criteria
	  * Age ≥ 18
	  * Have clinical picture strongly suggestive of COVID-19-related disease (with/without positive COVID-19 test) AND
	  ☐ risk count (as defined below) > 3 OR
	  ☐ risk count ≥ 3 if it includes radiographic severity score > 3
	  * Be considered an appropriate participant for intervention with immunomodulatory or other disease-modifying agents in the opinion of the investigator

TACTIC-E *(Continued)*

	• Exclusion criteria
	  * Inability to supply direct informed consent from patient or from next of kin or independent healthcare provider on behalf of patient
	  * Invasive mechanical ventilation at time of screening
	  * Contraindications to study drugs, including hypersensitivity to the active substances or any of the excipients
	  * Currently on any of the study investigational medicinal products, participation in an interventional clinical trial (observational studies allowed)
	  * Patient moribund at presentation or screening
	  * Pregnancy at screening, or unwilling to stop breastfeeding during treatment period
	  * Known severe hepatic impairment (with or without cirrhosis)
	  * Stage 4 severe chronic kidney disease or requiring dialysis (i.e. Cockcroft Gault estimated creatinine clearance < 30 mL/minute)
	  * Inability to swallow at screening visit
	  * Any medical history or clinically relevant abnormality that is deemed by the principal investigator and/or medical monitor to make the patient ineligible for inclusion because of a safety concern

Interventions	Intervention • EDP1815 • Dapagliflozin and ambrisentan Comparator • Standard of care

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: not planned
	• Clinical progression: planned
	• Length of hospital stay: not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	Safety outcomes
	• Number of participants with grade 3 and grade 4 AEs: not planned
	• Number of participants with SAEs: planned
	Additional study outcomes
	• Change in biomarkers thought to be associated with progression of COVID-19 compared to baseline: IL-6, ferritin, C-reactive protein (CRP), D-dimer, neutrophil/lymphocyte ratio, lactate dehydrogenase (LDH)
	• Time to Sp02 > 94% on room air
	• Time to clinical improvement

Notes	Funding: Cambridge University Hospitals NHS Foundation Trust

TACTIC-R

Methods	Drug name: ravulizumab, baricitinib Trial design: randomised, parallel arm, open-label platform trial Identifiers: NCT04390464 Target sample size: 1167 participants Planned completion date: May 2022

Participants	Setting
	
	• Inpatient
	• UK
	
	Eligibility criteria
	
	• Inclusion criteria
	  * Be aged ≥ 18
	  * Have clinical picture strongly suggestive of COVID-19-related (with/without positive COVID-19 test) and
	  ☐ risk count (as defined below) > 3 OR
	  ☐ ≥ 3 if risk count includes radiographic severity score > 3
	  * Be considered an appropriate subject for intervention with immunomodulatory in the opinion of the supervising clinician
	  * Be able to be maintained on venous thromboembolism prophylaxis or current maintenance therapy during inpatient dosing period, according to local guidelines
	  * Risk count: patients will be given a risk count equal to the cumulative points received for the following criteria (no = 0 points, yes = 1 point): male gender, age > 40 years, non-white ethnicity, diabetes, hypertension, neutrophils > 8.0 x 10 ^9/L, CRP > 40 mg/L, radiographic severity score > 3
	• Exclusion criteria
	  * Inability to supply direct informed consent or assent from next of kin or independent health-care provider on behalf of patient
	  * Mechanical ventilation at time of prior to dosing
	  * Contraindications to study drugs, including hypersensitivity to the active substances or any of the excipients
	  * Currently on any of the study investigational medicinal products
	  * Known unresolved *Neisseria meningitidis* infection
	  * Unwilling to be vaccinated against *N meningitidis* or receive prophylactic antibiotic cover until 2 weeks after vaccination
	  * Known active tuberculosis (no blood screening required), active hepatitis B or C (no blood screening required); active varicella zoster
	  * Concurrent participation in any interventional clinical trial including COVID-19-related disease trials (observational studies allowed)
	  * Patient moribund at presentation or screening
	  * Pregnancy at screening, unwillingness to adhere to breastfeeding advice in protocol
	  * Either ALT or AST > 5 times ULN
	  * Stage 4 severe chronic kidney disease or requiring dialysis (i.e. Cockcroft Gault estimated creatinine clearance < 30 mL/minute/1.73 m^2)
	  * Currently receiving probenecid or chronic IVIg treatment

Interventions	Intervention • Ravulizumab • Baricitinib Comparator

TACTIC-R *(Continued)*

	• Standard of care

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: planned
	• Length of hospital stay (for those admitted to hospital): planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: planned
	Safety outcomes
	• Number of participants with grade 3 and grade 4 AEs: not planned
	• Number of participants with SAEs: not planned
	Additional study outcomes
	• Time to Sp02 > 94% on room air
	• Proportion of participants with AEs of special interest in each treatment arm
	• Duration of oxygen therapy

Notes	Funding: Cambridge University Hospitals NHS Foundation Trust

TOGETHER-3

Methods	Drug name: lopinavir ritonavir, ascorbic acid Trial design: parallel, randomised, blinded trial Identifier: PACTR202007700757139 Target sample size: 420 participants Planned completion date: July 2021

Participants	Setting
	• Outpatient
	• Single-centre, South Africa
	Eligibility criteria
	• Inclusion criteria
	  * Men or women 18 to 80 years, inclusive, at the time of signing the informed consent
	  * Willing and able to provide informed consent
	  * Laboratory-confirmed SARS-CoV-2 infection, with test results within past 72 hours
	  * At increased risk of developing severe COVID-19 disease

TOGETHER-3 *(Continued)*

	• Exclusion criteria
	  * Known hypersensitivity to any of the study drugs
	  * Currently hospitalised
	  * Signs of respiratory distress prior to randomisation, including respiratory rate > 24 breath/minute and/or SpO2 < 93%
	  * Chronic kidney disease (stage IV or receiving dialysis)
	  * Known liver disease or cirrhosis
	  * Known personal or family history of long QT syndrome
	  * Taking chronic medications associated with prolonged QT and may induce Torsades de Pointes as per CredibleMeds.org, including certain antipsychotic medications or antidepressants (e.g. citalopram, venlafaxine, and bupropion) and unable to stop during the trial
	  * Baseline QTc interval of > 470 ms in men, and > 480 ms in women if indicated by the safety profile of the investigational product
	  * Potentially clinically significant pharmacokinetic and pharmacodynamic drug interactions as determined by the study clinical pharmacologist
	  * Currently participating in a clinical trial currently or within 30 days of randomisation

Interventions	Intervention • Lopinavir ritonavir Comparator • Ascorbic acid

Outcomes	Efficacy outcomes:
	• All-cause mortality
	  * at up to 30 days: not planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: not planned
	• Admission to hospital (for outpatients only): planned
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: planned
	Safety outcomes
	• Number of participants with grade 3 and grade 4 AEs: not planned
	• Number of participants with SAEs: planned
	Additional study outcomes
	• Lower respiratory tract infection, defined by SpO2 < 93% or decline from baseline of 6% in 2 measurements at least 2 hours apart

Notes	Funding: University of Washington

VIRCO

Methods	Drug name: favipiravir Trial design: adaptive, randomised, placebo-controlled, phase 2 trial Identifiers: NCT04445467

VIRCO *(Continued)*

	Target sample size: 190 participants Planned completion date: November 2020

Participants	Setting
	
	• Outpatient
	• Australia
	
	Eligibility criteria
	
	• Inclusion criteria
	  * Provision of informed consent by the participant or LAR
	  * Age ≥ 18 years
	  * Confirmed SARS-CoV-2 by nucleic acid testing in the past 5 days
	  * COVID-19-related symptom initiation within 5 days
	  * WOCBP must have a negative pregnancy test at screening. WOCBP and fertile male participants who are sexually active with a WOCBP must use highly effective methods of contraception throughout the study and for 1 week following the last dose of study treatment
	• Exclusion criteria
	  * Known allergy to the study medication
	  * On another antiviral for the treatment of COVID-19
	  * Pregnancy
	  * Patients with severe hepatic dysfunction equivalent to Grade C in the Child-Pugh classification
	  * Patients with renal impairment requiring dialysis
	  * Is deemed by the Investigator to be ineligible for any reason

Interventions	Intervention • Favipiravir Comparator • Placebo

Outcomes	Efficacy outcomes
	
	• All-cause mortality
	  * at up to 30 days: not planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: planned
	• Admission to hospital: not planned
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: planned
	
	Safety outcomes
	
	• Number of participants with grade 3 and grade 4 AEs: not planned
	• Number of participants with SAEs: planned
	
	Additional study outcomes
	
	• Time to viral clearance
	• Clinical symptoms
	• Biomarkers (lymphocyte count, C-reactive protein, Ferritin and lactate dehydrogenase)

VIRCO *(Continued)*

Notes	Funding: Bayside Health

Ab: antibody; **ACE:** angiotensis-converting enzyme; **AE:** adverse event; **ALT:** alanine aminotransferase;**ARB:** angiotensin receptor blocker; **ARDS:** acute respiratory distress syndrome; **AST:** aspartate aminotransferase; **AUC:** area under the curve; **BMI:** body mass index;**BP:** blood pressure; **bpm:** beats per minute: **CAP:** community-acquired pneumonia; **Child Pugh score:** clinical measures of liver disease; **Cmax:** maximum observed serum concentration; **CNS:** central nervous system; **COPD:** chronic obstructive pulmonary disease; **CT:** computed tomography; **DSMB:** Data Safety Monitoring Board;**ECG:** echocardiogram; **ECMO:** extracorporeal membrane oxygenation; **ED:** emergency department;**EQ-5D:** EuroQol 5 Dimensions; **FDA:** US Food and Drug Administration; **GFR:** glomrilar filtration rate; **IV:** intravenous; Hb: haemoglobin; **hIVIG:** human intravenous immunoglobulin;**HR:** heart rate; **ICU:** intensive care unit;**IV:** intravenous; **IVIg:** intravenous immunoglobulin **LAR:** legally authorised representative**;LFTs:** liver function tests; **mAb:** monoclonal antibody; **NAAT:** nucleic acid amplification test; **NEWS:** National Early Warning Score; **NIAID:** National Institute of Allergy and Infectious Diseases; **NIV:** noninvasive ventilation; **NP:** nasopharyngeal; **NSAID:** nonsteroidal anti-inflammatory drug; **NYHA:** New York Heart Association; **PaO2/FiO2:** ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; **PCR:** polymerase chain reaction;**RAS:** renin-angiotensin system; **RT-PCR:** reverse transcription-polymerase chain reaction; **SAE:** serious adverse event; **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2; **SC:** subcutaneous; **SpO2:** oxygen saturation;**TNF:** tumor necrosis factor;**ULN:** upper limit of normal; **WBC:** white blood cell; **WHOQOL:** World Health Organization quality of life scale; **SD:** standard deviation; **WOCBP:** women of childbearing potential

Characteristics of ongoing studies *[ordered by study ID]*

ACTIV-2

Study name	ACTIV-2: a study for outpatients with COVID-19
Methods	Drug name • Bamlanivimab • BRII-196/BRII-198 • AZD7442 (IV; IM) Other tested drugs: SNG001, camostat Trial design: multicentre, randomised, unblinded, adaptive platform trial Identifiers: NCT04518410 Target sample size: 2000 participants Planned completion date: May 2023
Participants	Setting • Outpatient • Recruitment period: August 2020 to May 2023 • Multicentre, country: USA, Puerto Rico Eligibility criteria

ACTIV-2 *(Continued)*

- Inclusion criteria:
  * Signed informed consent
  * Positive test for COVID-19 up to 7 days before participation in study
  * Able to begin study treatment no later than 10 days from self-reported onset of COVID-19 related symptom(s), and one or more of the following signs/symptoms within 48 hours of participating in the study:
    - ☐ fever or feeling feverish
    - ☐ cough
    - ☐ shortness of breath or difficulty breathing at rest or when active
    - ☐ sore throat
    - ☐ body pain or muscle pain/aches
    - ☐ fatigue
    - ☐ headache
    - ☐ chills
    - ☐ blocked nose/nasal congestion
    - ☐ runny nose
    - ☐ loss of taste or smell
    - ☐ nausea or vomiting
    - ☐ diarrhoea
    - ☐ temperature ≥ 38°C (100.4°F)
- Oxygen levels of ≥ 92% when resting (measured by study staff within 48 hours of participating in the study), unless participant is receiving long-term supplementary oxygen for an underlying lung condition
- Participant must agree not to participate in another clinical trial for the treatment of COVID-19 or SARS-CoV-2 during the study period until hospitalisation or 28 days after the start of the study, whichever occurs first.
- Exclusion criteria
  * History of, or current hospitalisation for COVID-19, current need for hospitalisation or immediate medical attention
  * Any use of the following medications up to 30 days before participating in the study:
    - ☐ hydroxychloroquine (except for long-term autoimmune diseases)
    - ☐ chloroquine and/or ivermectin (unless used for parasitic infection)
    - ☐ remdesivir, systemic and inhaled steroids (unless used for long-term conditions)
    - ☐ HIV protease inhibitors (unless used long-term for HIV infection)
  * Receipt of plasma from a person who recovered from COVID-19 any time before participating in the study
  * Receipt of a SARS-CoV-2 vaccine any time before participating in the study
  * Receipt of other investigational treatments for SARS-CoV-2 any time before participating in the study (not including drugs approved and taken for other conditions/diseases)
  * Receipt of systemic steroids (e.g. prednisone, dexamethasone) or inhaled steroids up to 30 days before participating in the study, unless this is a stable dose for a long-term condition
  * Known allergy/sensitivity or hypersensitivity to study drug or placebo
  * Any condition requiring surgery up to 7 days before participating in the study, or that is considered life-threatening up to 30 days before participating in the study
  * Other investigational drugs; protocol-defined inclusion/exclusion criteria may apply

Interventions	Intervention
	• LY3819253 (single dose IV infusion, phase 2 and 3 completed for this arm) • BRII-196 and BRII-198 (IV infusion, administered consecutively as single dose) • AZD7442 (single dose IV infusion, 300 mg AZD7442 (150 mg AZD8895 + 150 mg AZD1061) • AZD7442 (2 injections IM sequentially, 300 mg AZD8895 then 300 mg AZD1061) • Not relevant for this review: camostat mesilate (orally administered) • Not relevant for this review: SNG001 (inhalable)

ACTIV-2 *(Continued)*

	Comparator • Placebo (0.9% sodium chloride solution. Administered by IV infusion) • Placebo (0.9% sodium chloride Injection, United States Pharmacopeia. Administered IM as 2 separate injections)

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: planned
	• Clinical progression/improvement of symptoms: not planned
	• Development of severe symptoms according to WHO scale (≥ 6 on the WHO Clinical Progression Scale; for mild disease): not planned
	• Admission to hospital (for outpatients only): not planned
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	Safety outcomes
	• Number of participants with grade 3 and grade 4 AEs: planned, incidence of new AE ≥ grade 3
	• Number of participants with SAEs: not planned
	Additional study outcomes
	• Duration of targeted COVID-19 symptoms, symptom severity ranking and proportion of participants with ≥ 1 worsening symptom
	• Level of SARS-Cov-2 RNA at day 3, 7, 14 and 28
	• Time to self-report return to usual (pre-COVID-19) health
	• Oxygen saturation level
	• Incidence of new adverse events ≥ grade 2

Starting date	August 2020
Contact information	Study Chair: David Smith, MAS University of California, San Diego
Notes	Funding: NIAID Recruitment status: recruiting Other: platform trial, may add treatment arms

AGILE

Study name	AGILE
Methods	Drug name: VIR-7831 and VIR-7832 Other drugs: nomacopan, MK4482 Trial design: randomised, controlled, double-blind platform trial (open-label in phase 1) Identifiers: NCT04746183, EUDRACT 2020-001860-27

AGILE *(Continued)*

	Target sample size: 200 participants Planned completion date: December 2021

Participants	Setting
	
	• Inpatient
	• Recruitment period: July 2020 to November 2021
	• Multicentre, country: UK, South Africa
	
	Eligibility criteria
	
	• Inclusion criteria
	  * Adults (≥ 18 years) with laboratory-confirmed SARS-CoV-2 infection (PCR)
	  * Ability to provide informed consent signed by study patient or LAR
	  * WOCBP and male patients who are sexually active with WOCBP must agree to use a highly effective method of contraception from the first administration of trial treatment, throughout trial treatment and for the duration outlined in the candidate-specific trial protocol after the last dose of trial treatment
	  * Group A (severe disease)
	  ☐ patients with clinical status of Grades 5, 6, 7, 8, 9 as defined by the WHO Clinical Progression Scale
	  * Group B (mild-moderate disease)
	  ☐ ambulant or hospitalised patients with SpO2 > 94% radial artery
	• Exclusion criteria
	  * ALT and/or AST > 5 times ULN
	  * Stage 4 severe chronic kidney disease or requiring dialysis (i.e. estimated glomerular filtration rate < 30 mL/minute/1.73 m2)
	  * Pregnant or breastfeeding
	  * Anticipated transfer to another hospital that is not a study site within 72 hours
	  * Allergy to any study medication
	  * Patients taking other prohibited drugs within 30 days or 5 times the half-life (whichever is longer) of enrolment
	  * Patients participating in another clinical study
	  * Weight < 50 kg or > 100 kg

Interventions	Intervention: VIR-7831 and VIR-7832 Comparator • Placebo

Outcomes	Efficacy outcomes
	
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: planned
	• Development of severe symptoms according to WHO scale (≥ 6 on the WHO Clinical Progression Scale; for mild disease): planned
	• Admission to hospital (for outpatients only): not planned
	• Length of hospital stay (for those admitted to hospital): planned as time to discharge
	• Admission to ICU: planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: planned as time to negative PCR
	
	Safety outcomes

AGILE *(Continued)*

	• Number of participants with grade 3 and grade 4 AEs: planned • Number of participants with SAEs: planned Additional study outcomes • Actual versus planned candidate treatment received • NEWS assessed daily while hospitalised • Change in viral load over time • Biomarkers for response
Starting date	July 2020
Contact information	Helen E Reynolds, +44 (0)1517945553, AGILE%20(Early%20Phase%20Platform%20Trial%20for %20COVID-19)" type="EXTERNAL">livagile@liv.ac.uk
Notes	Funding: University of Liverpool, UK Recruitment status: recruiting

DISCOVERY

Study name	DISCOVERY
Methods	Drug name: AZD7442 Trial design: multicenter, adaptive, randomised trial NCT number: NCT04315948 Target sample size: 3100 participants Planned completion date: March 2023

Participants	Setting
	
	• Inpatient
	• Multicentre, France
	
	Eligibility criteria
	
	• Inclusion criteria
	  * Adult ≥ 18 years of age at time of enrolment
	  * Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or public health assay in any specimen < 72 hours prior to randomisation
	  * Hospitalised patients with illness of any duration, and at least one of the following:
	  ☐ clinical assessment (evidence of rales/crackles on exam) and SpO2 ≤ 94% on room air, or
	  ☐ acute respiratory failure requiring mechanical ventilation and/or supplemental oxygen
	  * WOCBP must agree to use contraception for the duration of the study

DISCOVERY *(Continued)*

	• Exclusion criteria
	  * Refusal to participate expressed by patient or LAR if they are present
	  * Spontaneous blood ALT/AST levels > 5 times the ULN
	  * Stage 4 severe chronic kidney disease or requiring dialysis (i.e. eGFR < 30 mL/minute)
	  * Pregnancy or breastfeeding
	  * Anticipated transfer to another hospital, which is not a study site within 72 hours
	  * Patients previously treated with one of the antivirals evaluated in the trial (i.e. remdesivir, interferon ß-1a, lopinavir/ritonavir, hydroxychloroquine) in the past 29 days
	  * Contraindication to any study medication including allergy

Interventions	Intervention • Remdesivir • Lopinavir/ritonavir • Hydroxychloroquine Comparator • Active: standard of care

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: planned
	• Clinical progression/improvement of symptoms: planned
	• Development of severe symptoms according to WHO scale (≥ 6 on the WHO Clinical Progression Scale; for mild disease): planned
	• Admission to hospital (for outpatients only): planned
	• Length of hospital stay (for those admitted to hospital): planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: planned
	Safety outcomes
	• Number of participants with grade 3 and grade 4 AEs: planned
	• Number of participants with SAEs: planned
	Additional study outcomes
	• The time to discharge or to a NEWS of ≤ 2 and maintained for 24 h, whichever occurs first
	• Number of oxygenation-free days in the first 28 days
	• Number of participants with a discontinuation or temporary suspension of study drugs (for any reason)
	• Changes from baseline in WBC count, haemoglobin, platelets, creatinine, blood electrolytes (including kalemia), prothrombine time, international normalised ratio (INR), glucose, total bilirubin, ALT, AST
	• Quantitative SARS-CoV-2 virus in nasopharyngeal sample
	• Quantitative SARS-CoV-2 virus in blood
	• Plasma concentration of lopinavir
	• Plasma concentration of hydroxychloroquine

Starting date	March 2020
Contact information	Florence Ader, Hospices Civils de Lyon

DISCOVERY *(Continued)*

Notes	Funding: Institut National de la Santé Et de la Recherche Médicale, France

EUDRACT2020-003401-60

Study name	EUDRACT2020-003401-60
Methods	Drug name: CT-P59 Trial design: randomised, controlled, parallel-group, double-blind study Identifiers: EUDRACT2020-003401-60 Target sample size: not reported Planned completion date: not reported
Participants	Setting • Inpatient • Recruitment period: not reported • Multicentre, Republic of Korea Eligibility criteria • Inclusion criteria * Age > 18 * Local laboratory confirmation of SARS-CoV-2 infection by RT-PCR from the upper or lower respiratory tract specimens no more than 4 days prior to the administration of the study drug * Onset of symptom no more than 10 days prior to the administration of the study drug * Patient with conditions meeting the following criteria, and currently hospitalised (or will be hospitalised prior to the administration of the study drug): ☐ 94% on room air and/or PaO2/FiO2 ratio = 300 mgHg, and ☐ Requiring supplemental oxygen * Patient with abnormal radiographic findings in lung suggestive of SARS-CoV-2 infection by investigator's discretion * Patient's weight is ≥ 99.9 kg * Patient and/or their LAR must be informed and given ample time and opportunity to read and/or understand the nature and purpose of this study including possible risks and side effects and must sign the informed consent form (ICF) before any study-specific procedures * Patient and their partner of childbearing potential must agree to use a highly effective method of contraception throughout the study (up to 6 months after the study drug administration) • Exclusion criteria * Patient needing ECMO, or invasive mechanical ventilation * Patient had a history of and/or concurrent use of medications including any therapy of following(s): ☐ Drugs with possible anti-SARS-CoV-2 activity or immunomodulators including but not limited to remdesivir, chloroquine, hydroxychloroquine, dexamethasone (alternative corticosteroids to dexamethasone), tocilizumab, sarilumab, and other immunomodulatory agents and HIV protease inhibitors for therapeutic purpose of SARS-CoV-2 infection prior to the study drug administration. ☐ Note: during the study, authorised drugs (or drugs approved for emergency use) against SARS-CoV-2 infection such as remdesivir or dexamethasone (alternative corticosteroids to dexamethasone), could be used by investigator's discretion considering the local practice where there is available supply

EUDRACT2020-003401-60 *(Continued)*

- ☐ Any SARS-CoV-2 hIVIG, convalescent plasma from a person who recovered from SARS-CoV-2 infection or SARS-CoV-2 mAb for the treatment of SARS-CoV-2 infection prior to the study drug administration
- ☐ Any other investigational device or medical product including but not limited to any monoclonal Ab, fusion proteins or biologics for the treatment of SARS-CoV-2 infection prior to the study drug administration
- ☐ Use of medications that are contraindicated with standard of care
- ☐ SARS-CoV-2 vaccine prior to the study drug administration

* Known allergy or hypersensitivity reaction to any mAb or to any components of study drug
* Patient has a history of and/or current disease or medical condition (active malignancy; severe liver disease (e.g. cirrhosis, or an ALT/AST level > 5 × ULN); renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73 m2) or receiving continuous renal replacement therapy, hemodialysis, peritoneal dialysis; any medical condition that would place the patient at an unreasonably increased risk through participation in this study; stroke or myocardial infarction, which is suspected to be related to SARS-CoV-2 infection after the onset of symptoms
* Documented current infection with HIV, hepatitis B or hepatitis C
* Patient who has received any other investigational device or medical product within 4 weeks prior to the study drug administration or 5 half-lives, whichever is longer
* patient currently abuses alcohol or drugs

Interventions	Intervention: CT-P59 • Target: SARS-CoV-2 S protein • Origin: not reported • Dose: • Frequency: single dose • Route of administration: IV infusion Comparator • Placebo, IV infusion

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: planned as change from baseline of the 8-point ordinal scale on day 7, 14 and 28 and proportion of new mechanical ventilation use on day 14 and 28
	• Length of hospital stay: planned as duration of hospitalisation in survivors up to day 28
	• Admission to ICU: planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	
	Safety outcomes
	• Number of participants with grade 3 and grade 4 AEs: not planned
	• Number of participants with SAEs: planned as AEs (including SAEs and AES), potential effects on the incidence of Ab-dependent enhancement, immunogenicity, vital signs, hypersensitivity monitoring, ECG findings, SARS-CoV-2 infection-related signs and symptoms, radiography (chest X-ray or chest CT), physical examination findings, clinical laboratory tests, pregnancy tests, and prior and concomitant medications
	
	Additional study outcomes
	• Mortality rate on day 14 and 90

EUDRACT2020-003401-60 *(Continued)*

	• Proportion of recovered participants on dayS 7, 14 and 28 • Clinical status by the 8-point ordinal scale on dayS 7, 14 and 28 • Time to improvement of at least 1 point from the status at baseline by 8-point ordinal scale up to day 28 • Number of days free of supplemental oxygen up to day 28 • Change from baseline of NEWS on day 7, 14 and 28
Starting date	23 November 2020
Contact information	Sung Hyun Kim; +82328505000; SungHyun.Kim@celltrion.com
Notes	Developer: Celltrion Inc. Funding: Celltrion Inc. Recruitment status: not reported

NCT04411628

Study name	NCT04411628
Methods	Drug name: bamlanivimab (LY3819253, LY-CoV555) Trial design: randomised, placebo-controlled, double-blind, sponsor-unblinded, single-ascending dose, phase 1 study NCT number: NCT04411628 (date of trial registration: 2 June 2020) Target sample size: 24 participants (actual enrolment) Completion date: 26 August 2020

Participants	Setting
	• Inpatient
	• Recruitment period: 30 October 2020- 26 August 2020
	• Multicentre, USA
	Eligibility criteria
	• Inclusion criteria
	  * 18 to75 years
	  * Hospitalised or in the process of being admitted to hospital and have an initial laboratory determination of current COVID-19 infection ≤ 72 h prior to randomisation
	  * Men or non-pregnant women
	  * Women of childbearing potential must agree to use at least one highly effective form of contraception for the entirety of the study
	  * Agree to the collection of nasopharyngeal swabs and venous blood

NCT04411628 *(Continued)*

	• Exclusion criteria
	  * Require mechanical ventilation or anticipated impending need for mechanical ventilation
	  * Received convalescent COVID-19 plasma treatment prior to enrolment
	  * Were resident in a nursing home or long-term care facility immediately prior to current hospitalisation
	  * Suspected or proven serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking the investigational product
	  * SpO2 < 88 % while breathing room air at rest at randomisation

Interventions	Intervention Bamlavinimab (LY3819253, LY-CoV555) • Target: SARS-CoV-2 S protein • Origin: derived from B lymphocytes of a convalescent naturally SARS-CoV-2-infected patient • Dose: not reported • Frequency: single dose • Route of administration: IV infusion Comparator • Placebo, IV infusion

Outcomes	Efficacy outcomes
	
	• All-cause mortality
	  * at up to 30 days: not planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: not planned
	• Length of hospital stay: not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	
	Safety outcomes
	
	• Number of participants with grade 3 and grade 4 AEs: planned
	• Number of participants with SAEs: planned
	
	Additional study outcomes
	
	• Pharmacokinetics: area under the concentration-time curve of bamlanivimab
	• Pharmacodynamics: change from baseline to day 29 in viral load

Starting date	28 May 2020
Contact information	Eli Lilly and Company, 1-877-CTLILLY (1-877-285-4559) or 1-317-615-4559
Notes	Developer: AbCellera, NIAID Vaccine Research Center, Eli Lilly and Company Funding: Eli Lilly and Company Recruitment status: completed

NCT04426695

Study name	NCT04426695
Methods	Drug name: casirivimab/imdevimab Trial design: randomised, parallel assignment, phase 1/phase 2/phase 3, quadruple masking NCT number: NCT04426695 (date of trial registration: 11 June 2020) Target sample size: 6900 participants Planned completion date: April 2021

Participants	Setting
	
	• Inpatient
	• Recruitment period: June 2020 to April 2021
	• Multicentre, country: USA, Brazil, Chile, Mexico, Romania, Republic of Moldova
	
	Eligibility criteria
	
	• Inclusion criteria
	  * Has SARS-CoV-2-positive antigen or molecular diagnostic test (by validated SARS-CoV-2 antigen, RT-PCR, or other molecular diagnostic assay) ≤ 72 hours prior to randomisation and no alternative explanation for current clinical condition. A historical record of positive result from test conducted ≤ 72 hours prior to randomisation is acceptable
	  * Symptoms consistent with COVID-19, as determined by investigator, with onset ≤ 10 days before randomisation
	  * Hospitalised for ≤ 72 hours with at least 1 of the following at randomisation; patients meeting more than one criterion will be categorised in the most severely affected category:
	  a. Cohort 1A: with COVID-19 symptoms but not requiring supplemental oxygen
	  b. Cohort 1: maintains SpO2 > 93% on low-flow oxygen as defined in the protocol
	  c. Cohort 2: high-intensity oxygen therapy without mechanical ventilation as defined in the protocol
	  d. Cohort 3: on mechanical ventilation
	• Exclusion criteria
	  * Phase 1 only: patients maintaining SpO2 > 94% on room air
	  * In the opinion of the investigator, unlikely to survive for > 48 hours from screening
	  * Receiving ECMO
	  * Has new-onset stroke or seizure disorder during hospitalisation
	  * Initiated on renal replacement therapy due to COVID-19

Interventions	Intervention REGN-CoV-2 (REGN10933 (casirivimab) + REGN10987 (imdevimab)) • Target: SARS-CoV-2 S protein • Origin: humanised mouse • Dose: not reported • Frequency: single dose • Route of administration: IV infusion Comparator: • Placebo, IV infusion
Outcomes	Efficacy outcomes

NCT04426695 *(Continued)*

- All-cause mortality
  - at up to 30 days: planned
  - at up to 60 days: planned
- Clinical progression/improvement of symptoms: mechanical ventilation and vasopressors, dialysis or ECMO: planned as Incidence required mechanical ventilation
- Length of hospital stay (for those admitted to hospital): planned
- Time to discharge: planned
- Admission to ICU: not planned
- Length of ICU stay: not planned
- Quality of life: not planned
- Viral clearance: planned
- Thromboembolic events: not planned
- Renal failure: not planned

Safety outcomes

- Number of participants with AEs (all grades, grade 1-2, grade 3-4): not planned
- Number of participants with SAEs: planned as treatment-emergent SAEs

Additional study outcomes

- Proportion of participants with infusion-related reactions
- Proportion of participants with hypersensitivity reactions
- Serum concentration of REGN10933 over time
- Serum concentration of REGN10987 over time
- Incidence of anti-drug Abs to REGN10933
- Incidence of anti-drug Abs to REGN10987

Starting date	11 June 2020
Contact information	Clinical Trials Administrator, 844-734-6643, NCT04426695,%20R10933-10987-COV-2066,%20Safety,%20Tolerability,%20and%20Efficacy%20of%20Anti-Spike%20(S)%20SARS-CoV-2%20Monoclonal%20Antibodies%20for%20Hospitalized%20Adult%20Patients%20With%20COVID-19" type="EXTERNAL">clinicaltrials@regeneron.com
Notes	Developer: Regeneron Pharmaceuticals Funding: Regeneron Pharmaceuticals Recruitment status: recruiting

NCT04551898

Study name	NCT04551898
Methods	Drug name: BGB-DXP593 Trial design: randomised, double-blind, placebo-controlled, phase 2 study NCT number: NCT04551898 (date of trial registration: 16 September 2020) Actual enrolment: 180 participants Actual completion date: January 2021
Participants	Setting

NCT04551898 *(Continued)*

- Probably outpatient
- Recruitment period: October-December 2020
- Multicentre, country: USA, Australia, Brazil, Mexico, South Africa

Eligibility criteria

- Inclusion criteria
  * Laboratory-confirmed SARS-CoV-2 infection (positive RT-PCR test or other authorised antigen testing methods) in any samples following local practice ≤ 72 hours prior to screening
  * Experienced COVID-19 symptoms for ≤ 7 days prior to treatment assignment, such as fever, cough, shortness of breath, sore throat, diarrhoea, vomiting, and dysgeusia
  * Agree to the collection of nasopharyngeal swabs, saliva, and venous blood
- Exclusion criteria
  * Severe COVID-19 having SpO2 ≤ 93 % on room air at sea level or PaO2/FiO2 < 300, respiratory rate ≥ 30/minute, heart rate ≥ 125/minute
  * Mechanical ventilation or anticipated impending need for mechanical ventilation
  * Known allergies to any of the components used in the formulation of the interventions
  * Have received an investigational intervention for SARS-CoV-2 prophylaxis within 30 days before dosing
  * Have received treatment with a SARS-CoV-2 specific monoclonal antibody

Interventions	Intervention BGB-DXP593 • Target: SARS-CoV-2 S protein • Origin: not reported • Dose: low/medium/high • Frequency: single dose • Route of administration: IV infusion Comparator: • Placebo, single dose, IV infusion

Outcomes	Efficacy outcomes
	
	• All-cause mortality
	  * at up to 30 days: 29 day mortality planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: not planned
	• Admission to hospital (for outpatients only): planned
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	• Thromboembolic events: not planned
	• Renal failure: not planned
	
	Safety outcomes
	
	• Number of participants with AEs (all grades, grade 1-2, grade 3-4): planned
	• Number of participants with AEs: planned
	
	Additional study outcomes

NCT04551898 *(Continued)*

	• Change from baseline to day 8 in SARS-CoV-2 viral shedding as measured by RT-qPCR in nasopharyngeal swab samples • Change from baseline to day 15 in SARS-CoV-2 viral shedding as measured by RT-qPCR in nasopharyngeal swab samples • Time to negative RT-qPCR in all tested samples with no subsequent positive RT-qPCR in any tested samples • Time-weighted average change in viral shedding as measured by RT-qPCR in nasopharyngeal swab samples • Time to resolution of all COVID-19-related symptoms
Starting date	30 October 2020
Contact information	BeiGene +1-877-828-5568, clinicaltrials@beigene.com
Notes	Developer: BeiGene Funding: BeiGene Recruitment status: completed Other: 4 arms, follow-up 85 days

NCT04584697

Study name	NCT04584697
Methods	Drug name: STI-2020 (COVI-AMG) Trial design: randomised, double-blind, placebo-controlled, phase 1/2 study NCT number: NCT04584697 (date of trial registration: 14 October 2020) Target sample size: 50 participants, actual enrolment: 0 participants Planned completion date: withdrawn, "Different study will be conducted"

Participants	Setting:
	• Outpatient
	• Recruitment period: December 2020-April 2021
	• Single vs multicentre: not reported, country: not reported
	Eligibility criteria
	• Inclusion criteria
	  * ≥ 18 years
	  * Must be COVID-19-positive by RT-PCR or an equivalent test, using an appropriate sample such as nasopharyngeal (NP), nasal, oropharyngeal (OP), or salivary) ≤ 72 hours prior to randomisation (a historical record of positive result from test conducted ≤ 72 hours prior to randomisation is acceptable if it can be documented)
	  * Asymptomatic or have mild symptoms but not requiring imminent (within 24hours) hospitalisation
	  * Willing and able to comply with all planned study procedures and be available for all study visits and follow-up as required by this protocol
	  * Participant or family member/caregiver must have provided written informed consent which includes signing the institutional review board approved consent form prior to participating in any study-related activity

NCT04584697 *(Continued)*

- Exclusion criteria
  - Documented infection other than COVID-19 that requires systemic treatment, and any other medical condition that in the investigator's opinion could interfere with the participant's safety or interfere with the assessments if enrolled in the study
  - Be pregnant or lactating and breastfeeding
  - Participated, or is participating, in a clinical research study evaluating COVID-19 convalescent plasma, mAbs against SARS-CoV-2, or IVIg within 3 months or < 5 half-lives of the investigational product (whichever is longer) prior to the screening visit

Interventions	Intervention STI-2020 (COVI-AMG) plus standard of care • Target: SARS-CoV-2 S protein • Origin: not reported • Dose: 40 mg/100 mg/200 mg • Frequency: single dose • Route of administration: injection Comparator • Placebo (diluent solution), single dose injection plus standard of care

Outcomes	Efficacy outcomes
	
	• All-cause mortality
	  * at up to 30 days: not planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: not planned
	• Admission to hospital (for outpatients only): not planned
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	• Thromboembolic events: not planned
	• Renal failure: not planned
	
	Safety outcomes
	
	• Number of participants with AEs (all grades, grade 1-2, grade 3-4): planned
	• Number of participants with SAEs: planned
	
	Additional study outcomes
	
	• Incidence of treatment-emergent AEs by type, frequency, severity, and causality (safety)
	• Incidence of dose-limiting toxicities (safety)
	• Incidence of clinically meaningful laboratory abnormalities (safety)
	• Viral load as assessed using plasma and salivary samples at various time points
	• Time from onset of COVID-19 symptoms to treatment
	• Presence and levels of anti-drug Abs directed to COVI-AMG
	• Cytokine levels post-treatment

Starting date	December 2020
Contact information	Mike Royal, MD, (858) 203-4100 ext 4146, mroyal@sorrentotherapeutics.com
Notes	Developer: Sorrento Therapeutics, Inc.

NCT04584697 *(Continued)*

	Funding: Sorrento Therapeutics, Inc. Recruitment status: not yet recruiting Other: withdrawn: "Different study will be conducted"

NCT04593641

Study name	NCT04593641
Methods	Drug name: regdanvimab (CT-P59) Trial design: randomised, double-blind, placebo-controlled, parallel group, single ascending dose, phase 1 study NCT number: NCT4593641 (date of trial registration: 20 October 2020) Actual enrolment: 18 participants Planned completion date: December 2020

Participants	Setting
	
	• Outpatient
	• Recruitment period: between September and December 2020
	• Multicentre, country: Republic of Korea
	
	Eligibility criteria
	
	• Inclusion criteria
	  * Adult male or female patient, aged between 18 to 60 years
	  * Patient with laboratory-confirmed SARS-CoV-2 infection by RT-PCR at screening
	  * Mild conditions meeting all of the following criteria:
	  ☐ oxygen saturation ≥ 94% on room air
	  ☐ not requiring supplemental oxygen
	  * Onset of symptoms is no more than 7 days prior to the study drug administration
	• Exclusion criteria
	  * Patient with severe condition meeting one of the following:
	  ☐ respiratory distress with respiratory rate ≥ 30 breaths/minute
	  ☐ requires supplemental oxygen
	  ☐ experienced shock
	  ☐ complicated with other organ failure, and ICU monitoring treatment is needed by investigator's discretion
	  ☐ Any other conditions suspected of being severe symptoms of SARS-CoV-2 infection, in the opinion of the investigator, including but not limited to radiographic findings in lung

Interventions	Intervention Regdanvimab (CT-P59) • Target: SARS-CoV-2 S protein • Origin: not reported • Dose: ascending dose, randomisation in 5:1 ratio • Frequency: single dose • Route of administration: intravenous infusion Comparator

NCT04593641 *(Continued)*

	• Placebo, single dose

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms:
	  * mechanical ventilation and vasopressors, dialysis or ECMO: planned as proportion of patients requiring supplemental oxygen, mechanical ventilation, clinical recovery up to day 28
	• Admission to hospital (for outpatients only): planned
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to ICU: planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: planned percentage of patients with positive/negative for qPCR and cell culture up to day 28
	• Thromboembolic events: not planned
	• Renal failure: not planned
	Safety outcomes
	• Number of participants with AEs (all grades, grade 1-2, grade 3-4): not planned
	• Number of participants with SAEs: not planned
	Additional study outcomes
	• Proportion of participants with treatment-emergent AEs of special interest (infusion-related reactions including hypersensitivity/anaphylactic reaction)
	• Proportion of participants with potential effects on the incidence of Antibody-Dependent Enhancement (ADE)
	• Duration (days) of viral shedding in nasopharyngeal swab specimens for qPCR and cell culture
	• Area under the concentration-time curve of viral titres for qPCR and cell culture
	• Actual results and change from baseline for viral shedding in nasopharyngeal swab specimens (titres) for qPCR and cell culture

Starting date	4 September 2020
Contact information	JooHee Lee, +82-32-850-5707, Celltrion
Notes	Developer: Celltrion Funding: Celltrion Recruitment status: active, not recruiting Other: 3 arms, alternative trial number: KCT0005896, EUDRACT-2020-003165-19

NCT04627584

Study name	NCT04627584
Methods	Drug name: MW33 Trial design: randomised, double-blind, placebo-controlled phase 2 study NCT number: NCT04627584 (date of trial registration: 13 November 2020)

NCT04627584 *(Continued)*

	Target sample size: 150 participants Planned completion date: September 2021

Participants	Setting
	
	• Outpatient
	• Recruitment period: between November 2020 and September 2021
	• Multicentre, country: China
	
	Eligibility criteria
	
	• Inclusion criteria
	  * Patients diagnosed with mild or moderate COVID-19 (as per the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial, 8th edition), China, or Clinical Management of COVID-19, WHO)
	  * At least one COVID-19 symptom, e.g. fever, cough, shortness of breath, sore throat, headache, muscle ache, and other respiratory or gastrointestinal symptoms, and has the symptom for ≤ 7 days prior to randomisation
	  * SARS-CoV-2 nasopharyngeal nucleic acid is tested to be positive (RT-PCR), IgM (-)/IgG (-) or IgM (+)/IgG (-) within 3 days before randomisation
	  * Male or female aged 18-80 years (including 18 and 80 years)
	  * Participants do not have a pregnancy plan, voluntarily take effective contraceptive measures during the screening period and the next 6 months, and have no sperm and egg donation plans, and voluntarily take non-pharmaceutical contraception measures during the trial period
	  * Participants voluntarily sign the informed consent form (ICF) based on sufficient knowledge of the nature, purpose, and procedures of the study, and shall be willing to comply with the study regulations
	• Exclusion criteria
	  * Diagnosed with severe or critical COVID-19 (as per the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial, 8th edition), China, or Clinical Management of COVID-19, WHO)
	  * Abnormal important organ function indicators
	  * Suspected or diagnosed with serious bacterial, fungal, viral, or other infection (except SARS-CoV-2 infection). In the opinion of the investigator, the conditions will prevent a participant from completing the study or impact interpretation of the study results
	  * Currently suffering from serious systemic diseases or mental disorders, and ineligible to participate in the study judged by the investigator
	  * A history of severe trauma, fracture, or surgery within 4 weeks prior to screening, or possibility of requiring a major surgery during the study
	  * Participated in clinical trials of SARS-CoV-2 vaccine or SARS-CoV-2 mAb, received or receiving convalescent plasma from patients recovered from COVID-19
	  * Prior or current use of antiviral drugs for treatment of COVID-19, including remdesivir, tocilizumab, interferon, ribavirin, abidol, lopinavir, and ritonavir, etc
	  * Currently enrolled into clinical studies with other drugs or devices; the time to start of this study from the end of previous participation in other drug clinical studies is < 30 days, or within 5 half-lives, or within the biological effect period of the drug (whichever is longer)
	  * Known to be allergic to any component of the investigational product; or those who have a history of allergies and judged by the investigator to be ineligible for enrolment
	  * Women who are pregnant or lactating
	  * Any conditions that are not suitable for enrolment judged by the investigator

Interventions	Intervention MW33 • Target: SARS-CoV-2 S protein • Origin: fully human

NCT04627584 *(Continued)*

	• Dose: 1200 mg/2400 mg • Frequency: not reported • Route of administration: injection Comparator • Placebo, injection

Outcomes	Efficacy outcomes
	
	• All-cause mortality
	  * at up to 30 days: not planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: not planned
	• Development of severe symptoms according to WHO scale (≥ 6 on the WHO Clinical Progression Scale; for mild disease): not planned
	• Admission to hospital (for outpatients only): not planned
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	• Thromboembolic events: not planned
	• Renal failure: not planned
	
	Safety outcomes
	
	• Number of participants with AEs (all grades, grade 1-2, grade 3-4): not planned
	• Number of participants with SAEs: not planned
	
	Additional study outcomes
	
	• Viral load in nasopharyngeal swabs from baseline to day 7

Starting date	December 2020
Contact information	Bei Zhao, +86-18817773189, beizhao@mabwell.com Song Lu, 15216868129, song.lu@mabwell.com
Notes	Developer: Mabwell (Shanghai) Bioscience Co., Ltd. Funding: Mabwell (Shanghai) Bioscience Co., Ltd. Recruitment status: recruiting Other: 3 arms

NCT04631666

Study name	NCT04631666
Methods	Drug name: DZIF-10c (BI 767551) Trial design: randomised, sequential assignment, phase 1/2a study NCT number: NCT04631666 (date of trial registration: 17 November 2020)

NCT04631666 *(Continued)*

	Estimated enrolment: 57 participants Planned completion date: July 2021

Participants	Setting
	
	• Outpatient
	• Recruitment period: between November 2020 and June 2021
	• Single centre, country: Germany
	
	Eligibility criteria
	
	• Inclusion criteria
	  * Groups 1A-1C
	  ☐ Age 18-65
	  ☐ SARS-CoV-2-RNA-negative in naso- or oropharyngeal swab obtained within 72 hours before study drug administration by qRT-PCR
	  ☐ Non-reactivity of serum antibodies (IgG, and IgA and/or IgM when tested) against SARS-CoV-2 by serological assay
	  * Groups 2C-2D
	  ☐ Age 18-70
	  ☐ SARS-CoV-2-RNA-positive in naso- or oropharyngeal swab obtained within 72 hours before study drug administration by qRT-PCR
	  ☐ Non-reactivity of serum antibodies (IgM and IgG or IgA and IgG) against SARS-CoV- 2 by serological assay
	  ☐ Disease severity 1-3 as defined by WHO R&D Blueprint Ordinal Scale (18 February 2020)

NCT04631666 *(Continued)*

- Exclusion criteria
  * Known hypersensitivity to any constituent of the investigational medicinal product
  * Hepatitis B infection indicated by detectable HBsAg (Hepatitis B surface antigen) in blood
  * Detectable Abs against hepatitis C virus in blood unless active hepatitis C is ruled out by negative HCV-RNA
  * HIV infection indicated by detectable HIV antigen and/or HIV antibodies in blood
  * Blood laboratory parameter abnormalities as listed below
    ☐ neutrophil count ≤ 1000 cells/µL
    ☐ haemoglobin ≤ 10 g/dL
    ☐ platelet count ≤ 100,000 cells/µL
    ☐ ALT ≥ 2.0 x ULN
    ☐ AST ≥ 2.0 x ULN
    ☐ Total bilirubin ≥ 1.5 ULN
    ☐ estimated glomerular filtration rate < 60 mL/minute/1.73 m2
  * Pregnancy or lactation
  * Any vaccination within 14 days prior to DZIF-10c administration
  * Receipt of any SARS-CoV-2 vaccine or SARS-CoV-2 mAb in the past
  * Diagnosis of bronchial asthma or history of bronchial hyperresponsiveness
  * Any chronic or clinically significant medical condition that in the opinion of investigator would jeopardise the safety or rights of the volunteer
  * History of systemic corticosteroids, immunosuppressive anti-cancer, or other medications considered significant by the trial physician within the last 6 months (a single administration of systemic corticosteroids within ≤ 6 months and ≥ 4 weeks of enrolment is acceptable)
  * Participation in another clinical trial of an investigational medicinal product within the past 12 weeks or expected participation during this study
  * Any kind of dependency on the principal investigator or employment by the sponsor or principal investigator
  * Legally incapacitated individuals, individuals held in an institution by legal or official order
  * If engaging in sexual activity that could result in pregnancy, inability or unwillingness to comply with the requirements for highly effective contraception

Interventions	Intervention
	
	DZIF-10c (BI 767551)
	
	• Target: SARS-CoV-2 S protein
	• Origin: not reported
	• Dose:
	  * Group 1A (n = 3-6): 2.5 mg/kg of DZIF-10c
	  * Group 1B (n = 3-6): 10 mg/kg of DZIF-10c
	  * Group 1C (n = 6): 40 mg/kg of DZIF-10c
	  * Group 2C (n = 3-6): 40 mg/kg infusion or maximum tolerated dose of DZIF-10c
	• Frequency: single dose
	• Route of administration: IV infusion
	
	Comparator
	
	• Placebo, sterile normal saline (NaCl 0.9%), IV infusion

Outcomes	Efficacy outcomes
	
	• All-cause mortality
	  * at up to 30 days: not planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: not planned

NCT04631666 *(Continued)*

- Development of severe symptoms according to WHO scale (≥ 6 on the WHO Clinical Progression Scale; for mild disease): not planned
- Admission to hospital (for outpatients only): planned
- Length of hospital stay (for those admitted to hospital): not planned
- Admission to ICU: not planned
- Length of ICU stay: not planned
- Quality of life, including fatigue: not planned
- Viral clearance: not planned
- Thromboembolic events: not reported
- Renal failure: not reported

Safety outcomes

- Number of participants with AEs (all grades, grade 1-2, grade 3-4): not planned
- Number of participants with SAEs: not planned

Additional study outcomes

- Incidence of treatment-emergent AEs
- Incidence of reactogenicity AEs
- Frequency of participants with Abs and magnitude of Abs targeting DZIF-10c
- Viral shedding determined by
  * qRT-PCR in nasopharyngeal swabs
  * qRT-PCR in oropharyngeal swabs
  * isolation of Infectious virus
- Viral replication determined by subgenomic SARS-CoV-2 mRNA
- Duration of COVID-19 symptoms
- Activity and frequency of SARS-CoV-2-reactive immune responses

Starting date	December 2020
Contact information	Florian Klein, 0221 478 85801 ext 0049, florian.klein@uk-koeln.de Henning Gruell, 0221 47896973 ext 0049, henning.gruell@uk-koeln.de
Notes	Developer: University of Cologne, University Marburg and Boehringer Ingelheim Funding: University of Cologne, The Clinical Trials Centre Cologne, Boehringer Ingelheim Recruitment status: recruiting

NCT04631705

Study name	NCT04631705
Methods	Drug name: DZIF-10c (BI 767551) Trial design: randomised, sequential assignment, phase 1/2a study NCT number: NCT04631705 (date of trial registration: 17 November 2020) Target sample size: 78 participants Planned completion date: July 2021
Participants	Setting

NCT04631705 *(Continued)*

- Outpatient
- Recruitment period: November 2020 to June 2021
- Single centre, country: Germany

Eligibility criteria

- Inclusion criteria
  * Groups 1A-1C
    - ☐ Age 18-65
    - ☐ SARS-CoV-2-RNA-negative in naso- or oropharyngeal swab obtained within 72 hours before study drug administration by qRT-PCR
  * Groups 2C-2D
    - ☐ Age 18-70
    - ☐ SARS-CoV-2-RNA-positive in naso- or oropharyngeal swab obtained within 72 hours before study drug administration by qRT-PCR
    - ☐ Non-reactivity of serum Abs (IgM and IgG or IgA and IgG) against SARS-CoV- 2 by serological assay
    - ☐ Disease severity 1-3 as defined by WHO R&D Blueprint Ordinal Scale (18 February 2020)
- Exclusion criteria
  * Known hypersensitivity to any constituent of the investigational medicinal product
  * Hepatitis B infection indicated by detectable HBsAg (Hepatitis B surface antigen) in blood, Abs against hepatitis C virus in blood unless active hepatitis C is ruled out by negative HCV-RNA, HIV infection
  * Blood laboratory parameter abnormalities
  * History of systemic corticosteroids, immunosuppressive anti-cancer, or other medications considered significant by the trial physician within the last 6 months (a single administration of systemic corticosteroids within ≤ 6 months and ≥ 4 weeks of enrolment is acceptable)
  * Participation in another clinical trial of an investigational medicinal product within the past 12 weeks or expected participation during this study
  * Any kind of dependency on the principal investigator or employment by the sponsor or principal investigator, legally incapacitated individuals, individuals held in an institution by legal or official order
  * If engaging in sexual activity that could result in pregnancy, inability or unwillingness to comply with the requirements for highly effective contraception, pregnancy or lactation
  * Any vaccination within 14 days prior to DZIF-10c administration, receipt of any SARS-CoV-2 vaccine or SARS-CoV-2 mAb in the past
  * Diagnosis of bronchial asthma or history of bronchial hyperresponsiveness
  * Any chronic or clinically significant medical condition that in the opinion of investigator would jeopardise the safety or rights of the volunteer

Interventions	Intervention: • Target: SARS-CoV-2 S protein • Origin: not reported • Dose: * Group 1A (n = 3-6): 2.5 mg/kg of DZIF-10c * Group 1B (n =3 -6): 10 mg/kg of DZIF-10c * Group 1C (n =6): 40 mg/kg of DZIF-10c * Group 2C (n = 3-6): 40 mg/kg of DZIF-10c (if Group 1C completed without dose-limiting toxicities) • Frequency: single dose • Route of administration: inhalation (orally) Comparator • Placebo, sterile normal saline (NaCl 0.9%), inhalation (orally)

NCT04631705 *(Continued)*

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: not planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: not planned
	• Admission to hospital (for outpatients only): planned
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	• Thromboembolic events: not planned
	• Renal failure: not planned
	Safety outcomes
	• Number of participants with AEs (all grades, grade 1-2, grade 3-4): not planned
	• Number of participants with SAEs: planned
	Additional study outcomes
	• Incidence of treatment-emergent AEs
	• Incidence of reactogenicity AEs
	• Frequency of participants with Abs and magnitude of Abs targeting DZIF-10c
	• Viral shedding determined by qRT-PCR in nasopharyngeal swabs
	• Viral shedding determined by qRT-PCR in oropharyngeal swabs
	• Viral shedding determined by the isolation of infectious virus
	• Viral replication determined by subgenomic SARS-CoV-2 mRNA
	• Duration of COVID-19 symptoms
	• Activity and frequency of SARS-CoV-2-reactive immune responses

Starting date	December 2020
Contact information	Florian Klein, +49-221-478-96973, florian.klein@uk-koeln.de Henning Gruell, +49-221-478-85801, henning.gruell@uk-koeln.de
Notes	Developer: University of Cologne, University Marburg and Boehringer Ingelheim Funding: University of Cologne, The Clinical Trials Centre Cologne, Boehringer Ingelheim Recruitment status: not yet recruiting Other: registry entry outcomes changed between November 2020 and March 2021

NCT04634409

Study name	BLAZE-4
Methods	Drug name: • Monotherapy: bamlanivimab • Combination therapy: bamlanivimab and etesevimab or sotrovimab Trial design: randomised, double-blind, placebo-controlled, phase 2 study

NCT04634409 *(Continued)*

NCT number: NCT04634409 (date of trial registration: 18 November 2020)

Target sample size: 700 participants

Planned completion date: June 2021

Participants	Setting
	• Outpatient
	• Recruitment period: 29 October 2020-31 December 2020
	• Multicentre, country: USA, Puerto Rico
	
	Eligibility criteria
	• Inclusion criteria
	  * Currently not hospitalised
	  * ≥ 1 mild or moderate COVID-19 symptoms: fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, or shortness of breath with exertion
	  * Must have sample taken for test confirming viral infection no more than 3 days prior to starting the drug infusion
	  * Men or non-pregnant women who agree to contraceptive requirements
	  * Understand and agree to comply with planned study procedures
	  * Agree to the collection of nasopharyngeal swabs and venous blood
	  * The participant or LAR give signed informed consent
	• Exclusion criteria
	  * BMI ≥ 35
	  * SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300, respiratory rate ≥ 30/minute, heart rate ≥ 125/minute
	  * Require mechanical ventilation or anticipated impending need for mechanical ventilation
	  * Have known allergies to any of the components used in the formulation of the interventions
	  * Have haemodynamic instability requiring use of pressors within 24 hours of randomisation
	  * Suspected or proven serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking intervention
	  * Have any co-morbidity requiring surgery within < 7 days, or that is considered life-threatening within 29 days
	  * Have any serious concomitant systemic disease, condition, or disorder that, in the opinion of the investigator, should preclude participation in this study
	  * Have a history of a positive SARS-CoV-2 test prior to the one serving as eligibility for this study
	  * Have received an investigational intervention for SARS-CoV-2 prophylaxis within 30 days before dosing
	  * Have received treatment with a SARS-CoV-2-specific mAb or convalescent COVID-19 plasma
	  * Have participated in a previous SARS-CoV-2 vaccine study or have received a SARS-CoV-2 vaccine, or have participated, within the last 30 days, in a clinical study involving an investigational intervention. If the previous investigational intervention has a long half-life, 5 half-lives or 30 days, whichever is longer, should have passed
	  * Concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
	  * Pregnant or breastfeeding
	  * Investigator site personnel directly affiliated with this study

Interventions	Intervention • Monotherapy: bamlanivimab (LY-CoV555, LY3819253) • Combination therapy: bamlanivimab (LY-CoV555, LY3819253) and etesevimab (LY-CoV016, LY3832479) or VIR-7831 • Target: SARS-CoV-2 S protein • Origin: derived from B lymphocytes of a convalescent naturally SARS-CoV-2- infected patient

NCT04634409 *(Continued)*

- Doses: not reported
- Frequency: not reported
- Route of administration: IV infusion

Comparator

- Placebo, IV infusion

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: mechanical ventilation and vasopressors, dialysis or ECMO: planned as percentage of participants demonstrating symptom improvement
	• Admission to hospital (for outpatients only): planned
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	• Thromboembolic events: not planned
	• Renal failure: not planned
	Safety outcomes
	• Number of participants with AEs: not planned
	• Number of participants with SAEs (all grades, grade 1-2, grade 3-4): not planned
	Additional study outcomes
	• Percentage of participants with SARS-CoV-2 viral load > 5.27
	• Change from baseline to day 7 in SARS-CoV-2 viral load
	• Percentage of participants demonstrating symptom resolution
	• Percentage of participants who experience COVID-related hospitalisation, COVID-19-related emergency room visit, or death

Starting date	29 October 2020
Contact information	Eli Lilly and Company, 1-877-CTLILLY (1-877-285-4559) or 1-317-615-4559, ClinicalTrials.gov@lilly.com
Notes	Developer • Bamlanivimab: AbCellera, National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center, Eli Lilly and Company • Etesevimab: Junshi Biosciences, Institute of Microbiology, Chinese Academy of Science (IMCAS), Eli Lilly and Company • Sotrovimab: GSK and Vir Biotechnology Funding: Eli Lilly and Company Recruitment status: recruiting Other: 4 arms

NCT04644120

Study name	NCT04644120
Methods	Drug name: ABBV-47D11 and ABBV-2B04 Trial design: randomised, sequential assignment, double-blind, placebo-controlled, phase 1 study NCT number: NCT04644120 (date of trial registration: 25 November 2020) Estimated enrolment: 54 participants Planned completion date: 5 September 2021

Participants	Setting
	
	• Inpatient, moderate disease
	• Recruitment period: November 2020-May 2021
	• Multicentre, countries: USA, Hungary, Israel, the Netherlands, Puerto Rico
	
	Eligibility criteria
	
	• Inclusion criteria
	  * Confirmed SARS-CoV-2 infection based on initial nucleic acid testing from respiratory swab, saliva, or other bodily fluid within 72 hours prior to randomisation
	  * Must have ≥ 1 symptom associated with COVID-19 with an onset of ≤ 8 days prior to randomisation and evidence of lower respiratory tract infection by clinical assessment or imaging
	  * Hospitalised or plans for hospital admission due to COVID-19 at the time of randomisation
	• Exclusion criteria
	  * SpO2 < 88% on room air at rest for 5 minutes OR PaO2/FiO2 ≤ 200 mmHg at randomisation
	  * Requiring high-flow oxygen therapy/non-invasive or invasive mechanical ventilation/ECMO or anticipated impending need for high-flow oxygen therapy/non-invasive or invasive mechanical ventilation/ECMO
	  * Prior treatment with a SARS-CoV-2-specific mAb or convalescent COVID-19 plasma

Interventions	Intervention • Target: SARS-CoV-2 S protein • Origin: discovered from the H2L2 Harbour Mice platform • Dose: 3 doses (A, B, C), not further specified • Frequency: single dose • Route of administration: IV infusion Comparator • Placebo, IV infusion

Outcomes	Efficacy outcomes
	
	• All-cause mortality
	  * at up to 30 days: not planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: not planned
	• Length of hospital stay: not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: planned
	• Thromboembolic events: not planned
	• Renal failure: not planned

NCT04644120 *(Continued)*

	Safety outcomes • Number of participants with AEs (all grades, grade 1-2, grade 3-4): planned • Number of participants with SAEs: not planned Additional study outcomes • Number of participants with study-drug-related grade 3 or higher infusion-related reactions • Time to negative SARS-CoV-2 by RT-PCR • Peak serum concentration of ABBV-47D11 • Time to peak serum concentration of ABBV-47D11 • Area under the serum concentration-time curve from day 1 (0 h) to day 29 (672 h) (AUC0-672h) of ABBV-47D11 • Terminal phase elimination half-Life (t1/2) of ABBV-47D11 • AUC from time 0 to infinity (AUCinf) of ABBV-47D11 • Detection of anti-drug Abs • Detection of neutralising anti-drug Abs • AUC for change from baseline (day 1) in SARS-CoV-2 ribose nucleic acid (RNA) RT-PCR
Starting date	10 December 2020
Contact information	ABBVIE Call Center, 844-663-3742, abbvieclinicaltrials@abbvie.com
Notes	Developer: AbbVie Funding: AbbVie Recruitment status: recruiting

NCT04644185

Study name	NCT04644185
Methods	Drug name: SCTA01 Trial design: randomised, adaptive, double-blinded, placebo-controlled phase 2/3 trial NCT number: NCT04644185 (date of trial registration: 25 November 2020) Target sample size: 795 participants Planned completion date: October 2021

Participants	Setting
	• Inpatient
	• Recruitment period: February 2021 to May 2021
	• Multicentre, countries: Argentina, Brazil, Chile, Colombia, Mexico, Peru
	Eligibility criteria
	• Inclusion criteria
	  * Hospitalised patients with severe COVID-19 (5 points on NIH 8-point ordinal scale)
	  * Male or female adults ≥ 18 years of age at time of enrolment
	  * Biological samples (not limited to any specific type) collected within 72 hours before randomisation is laboratory-confirmed as SARS-CoV-2 infection (PCR or antigen-based diagnostic tests)
	  * ≤ 10 days since symptoms of COVID-19 onset

NCT04644185 *(Continued)*

- Exclusion criteria
  - Patients who need NIV or high-flow oxygen (i.e. 6 points on the 8-point ordinal scale)
  - Patients with critical COVID-19
  - Patients with severe COVID-19 who received convalescent plasma or COVID-19 vaccine, or anti-SARS-CoV-2 spike (S) protein-targeted therapy
  - ALT/AST 5 times higher than ULN
  - Estimated glomerular filtration rate (eGFR) < 30 mL/min or on dialysis

Interventions	Intervention SCTA01 plus best supportive care • Target: SARS-CoV-2 S protein • Origin: not reported • Dose: 2 doses (low, high), not further specified • Frequency: not reported • Route of administration: not reported Comparator • Placebo plus best supportive care

Outcomes	Efficacy outcomes
	
	• All-cause mortality
	  * at up to 30 days: not planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: not planned
	• Length of hospital stay (for those admitted to hospital): not planned
	• Time to discharge: not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	• Thromboembolic events: not planned
	• Renal failure: not planned
	
	Safety outcomes
	
	• Number of participants with AEs (all grades, grades 1-2, grades 3-4): not planned
	• Number of participants with SAEs: planned
	
	Additional study outcomes
	
	• Time to clinical improvement (TTCI) (Phase II and III)
	• Change from baseline in viral shedding as measured by RT-qPCR (Phase II and III)
	• AUC 0-t (Phase II)
	• Clearance (CL)(Phase II)
	• Immunogenicity as measured by anti-drug Abs (Phase II, III)

Starting date	Estimated start date: 10 February 2021
Contact information	Ji Qi, +86-10-5862 8288 ext 9360, ji_qi@sinocelltech.com
Notes	Developer: Sinocelltech Ltd. Funding: Sinocelltech Ltd.

NCT04644185 *(Continued)*

	Recruitment status: not yet recruiting

NCT04649515

Study name	NCT04649515
Methods	Drug name: TY027 Trial design: randomised, placebo-controlled, double-blind, single-dose, multi-site, phase 3 study NCT number: NCT04649515 (date of trial registration: 2 December 2020) Target sample size: 1305 participants Planned completion date: December 2021
Participants	Setting • Inpatient • Recruitment period: between December 2020 and August 2021 • Multicentre, country: Singapore Eligibility criteria • Inclusion criteria * Symptomatic and RT-PCR confirmed COVID-19 within 6 days from symptom onset * Has any one of the following factors associated with disease progression: ☐ elevated lactate dehydrogenase (LDH) ☐ elevated C reactive protein (CRP) ☐ lymphocyte count below normal limit ☐ age ≥ 40 ☐ history of well-controlled diabetes, hypertension, chronic obstructive lung disease or ischaemic heart diseases ☐ stable chronic renal disease ☐ history of asthma * Disease outcome score of 6, 7, or 8 based on the COVID Scale * Willing to comply with the requirements of the study protocol and attend scheduled study visits * Can give written informed consent approved by the Ethical Review Board governing the site • Exclusion criteria * Aged < 21 years old * Woman who is pregnant or breast-feeding * With the following conditions, but not limited to: ☐ known or suspected congenital or acquired immunodeficiency; or receipt of immunomodulation therapy such as anti-cancer chemotherapy or radiation therapy; or long-term systemic corticosteroid therapy defined as prednisone or equivalent for > 2 consecutive weeks within the past 3 months ☐ Child-Pugh Class C chronic liver disease ☐ Renal insufficiency with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2 calculated by the CKD-EPI formula ☐ Suspected or confirmed active bacterial, fungal or mycobacterial infection * History of any allergic reaction to mAbs * Currently enrolled in another COVID-19 investigational drug study * Previously enrolled in a COVID-19 investigational vaccine study

NCT04649515 *(Continued)*

	* Any medical condition, which in the opinion of the Investigator, will compromise the safety of the patient
Interventions	Intervention TY027 • Target: SARS-CoV-2 S protein • Origin: fully engineered human IgG • Dose: 1.500 mg/2.000 mg • Frequency: single dose • Route of administration: IV infusion Comparator • Placebo, 0.9% saline, single dose, IV infusion

Outcomes	Efficacy outcomes
	
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: planned
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: planned
	• Thromboembolic events: not planned
	• Renal failure: not planned
	
	Safety outcomes
	
	• Number of participants with AEs (all grades, grade 1-2, grade 3-4): planned
	• Number of participants with SAEs: planned
	
	Additional study outcomes
	
	• Proportion of participants in categories 4, 3, 2 and 1 of the COVID scale
	• Number of days COVID-19 patients require supplemental oxygen, high-flow oxygen, non-invasive and invasive mechanical ventilation (if applicable)
	• Proportion of COVID-19 patients with a minimum of 0.5 log time-weighted viral load reduction from saliva samples, via sub-genomic qRT-PCR

Starting date	December 2020
Contact information	Justin Ng, +65 69046055, justin@tychanltd.com Anjali Baglody, +65 69046055, anjalib@tychanltd.com
Notes	Developer: Tychan Pte Ltd. Funding: Tychan Pte Ltd. Recruitment status: recruiting

NCT04666441

Study name	NCT04666441
Methods	Drug name: casirivimab/imdevimab Trial design: randomised, parallel assignment, quadruple-blinded, phase 2 study NCT number: NCT04666441 (date of trial registration: 14 December 2020) Target sample size: 1,400 participants; actual enrolment: 1164 Planned completion date: August 2021

Participants	Setting
	
	• Outpatient
	• Recruitment period: December 2020 to March 2021
	• Multicentre, country: USA
	
	Eligibility criteria
	
	• Inclusion criteria
	  * SARS-CoV-2-positive antigen or molecular diagnostic test ≤ 72 hours prior to randomisation, as defined by the protocol
	  * Low-risk symptomatic patient: has symptoms consistent with COVID-19 (as determined by the investigator) with onset ≤ 7 days before randomisation, and meets all of the following 8 criteria:
	  ☐ age ≤ 50
	  ☐ no obesity, with obesity defined as BMI ≥ 30 kg/m2
	  ☐ does not have cardiovascular disease or hypertension
	  ☐ does not have chronic lung disease or asthma
	  ☐ does not have type 1 or type 2 diabetes mellitus
	  ☐ does not have chronic kidney disease, with or without dialysis
	  ☐ does not have chronic liver disease
	  ☐ is not pregnant
	  * Asymptomatic patient: has had no symptoms consistent with COVID-19 (as determined by the investigator) occurring at any time < 2 months prior to randomisation
	  * Maintains O2 saturation ≥ 93% on room air
	• Exclusion criteria
	  * Admitted to a hospital for COVID-19 prior to randomisation, or is hospitalised (inpatient) for any reason at randomisation
	  * Known positive SARS-CoV-2 serologic test
	  * Positive SARS-CoV-2 antigen or molecular diagnostic test from a sample collected > 72 hours prior to randomisation
	  * Is immunosuppressed, based on investigator's assessment
	  * Has received or has participated, or is participating, in a clinical research study evaluating COVID-19 convalescent plasma, mAbs against SARS-CoV-2, or IVIg within 3 months or within 5 half-lives of the investigational product (whichever is longer) prior to the screening visit
	  * Prior, current, or planned future use of any of the following treatments: systemic corticosteroids (any indication), or COVID-19 treatments (authorised, approved, or investigational), any authorised, approved, or investigational vaccine for COVID-19
	  * Has known active infection with influenza or other non-SARS-CoV-2 respiratory pathogens, confirmed by a diagnostic test
	• Other protocol-defined inclusion/exclusion criteria apply

Interventions	Intervention REGN-CoV-2 (REGN10933 (casirivimab) + REGN10987 (imdevimab)) • Target: SARS-CoV-2 S protein

NCT04666441 *(Continued)*

- Origin: humanised mouse
- Dose: 4 doses (1, 2, 3, 4) not further specified
- Frequency: single dose
- Route of administration:
  - doses 1/ 2/ 3/4 IV infusion
  - doses 1/2 subcutaneous (s.c.)

Comparator

- Placebo, single-dose, intravenous infusion
- Placebo, single-dose, subcutaneous

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: not planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: not planned
	• Development of severe symptoms according to WHO scale (≥ 6 on the WHO Clinical Progression Scale; for mild disease): not planned
	• Admission to hospital (for outpatients only): not planned
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	• Thromboembolic events: not planned
	• Renal failure: not planned
	Safety outcomes
	• Number of participants with AEs (all grades, grade 1-2, grade 3-4): not planned
	• Number of participants with SAEs: not planned
	Additional study outcomes
	• Time-weighted average daily change from baseline in viral load (log 10 copies/mL)
	• Proportion of participants with high viral load, viral loads below the limit of detection, and viral loads below the lower limit of quantitation
	• Time-weighted average daily change from baseline in cycle threshold (Ct) as measured by RT-qPCR in NP samples
	• Time-weighted average daily change from baseline in Ct from day 1 to day 5, as measured by RT-qPCR in NP samples
	• Change from baseline in Ct as measured by RT-qPCR in NP samples
	• Change from baseline in viral load as measured by RT-qPCR in NP samples
	• Proportion of participants with treatment-emergent SAEs
	• Proportion of participants with infusion-related reactions (grade ≥ 2)
	• Proportion of participants with injection-site reactions (grade ≥ 2)
	• Proportion of participants with hypersensitivity reactions (grade ≥ 2)
	• Concentrations of REGN10933 in serum
	• Concentrations of REGN10987 in serum

Starting date	15 December 2020
Contact information	Clinical Trials Administrator, 844-734-6643, clinicaltrials@regeneron.com

NCT04666441 *(Continued)*

Notes	Developer: Regeneron Pharmaceuticals Funding: Regeneron Pharmaceuticals Recruitment status: active, not recruiting Other: • 4 arms IV infusion (doses 1/ 2/ 3/4) • 2 arms subcutaneous (doses 1/ 2)

NCT04674566

Study name	NCT04674566
Methods	Drug name: COR-101 Trial design: randomised, double-blind, placebo-controlled, parallel-group, multi-centre, first-in-human, phase Ib/II study NCT number: NCT04674566 (date of trial registration: 19 December 2020) Target sample size: 45 participants Planned completion date: June 2021

Participants	Setting
	
	• Inpatient
	• Recruitment period: January 2021-April 2021
	• Multicentre, country: not reported
	
	Eligibility criteria
	
	• Inclusion criteria
	  * Hospitalised for COVID-19 illness for ≤ 72 hours
	  * Positive SARS-CoV-2 test by standard RT-PCR assay or equivalent test
	  * Presence of moderate to severe clinical signs indicative of moderate or severe illness with COVID-19 prior to study treatment
	• Exclusion criteria
	  * Diagnosis of asymptomatic COVID-19, mild COVID-19, or critical COVID-19
	  * In the opinion of the investigator, is not likely to survive for > 48 hours beyond day 1
	  * New onset stroke or seizure disorder during hospitalisation and prior to day 1
	  * History of relevant CNS pathology or current relevant CNS pathology

Interventions	Intervention COR-101 • Target: SARS-CoV-2 S protein • Origin: fully human mAb • Dose: 4 doses (low dose, mid dose 1, mid dose 2, high dose) not further specified • Frequency: single dose • Route of administration: IV infusion Comparator

NCT04674566 *(Continued)*

	• Placebo, single dose, IV infusion

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned as proportion of participants who are not alive or have respiratory failure through day 28
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms:
	  * mechanical ventilation and vasopressors, dialysis or ECMO: planned as proportion of participants who are not alive or have respiratory failure through day 28
	• Development of severe symptoms according to WHO scale (≥ 6 on the WHO Clinical Progression Scale; for mild disease): not planned
	• Admission to hospital (for outpatients only): not applicable
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: planned as time to negative RT-PCR for SARS-CoV-2
	• Thromboembolic events: not planned
	• Renal failure: not planned
	Safety outcomes
	• Number of participants with AEs (all grades, grade 1-2, grade 3-4): not planned
	• Number of participants with SAEs: planned
	Additional study outcomes
	• Proportion of participants with treatment-emergent AEs
	• Proportion of participants with AEs of special interest
	• Change of viral load of SARS-CoV-2 from baseline, as measured from nasopharyngeal swab samples by qRT-PCR
	• Maximum serum concentration of COR-101 and time to maximum serum concentration, clearance for COR101, mean residence time
	• Percentage of participants with detectable neutralising antibodies to COR-101

Starting date	April 2021
Contact information	Corat Therapeutics Gmbh
Notes	Developer: Corat Therapeutics Gmbh Funding: Corat Therapeutics Gmbh Recruitment status: not yet recruiting

NCT04683328

Study name	MASP3
Methods	Drug name: SCTA01 Trial design: randomised, adaptive, double-blinded, placebo-controlled, multicentre phase 2/3 study

NCT04683328 *(Continued)*

NCT number: NCT04683328 (date of trial registration: 24 December 2020)

Target sample size: 560 participants

Planned completion date: 25 November 2021

Participants	Setting
	• Inpatient
	• Recruitment period: February 2021 to May 2021
	• Multicentre, country: USA
	Eligibility criteria
	• Inclusion criteria
	  * Male and female of ≥ 18 years at time of enrolment
	  * Participant (or LAR) is able and willing to provide written or verbal informed consent, which includes compliance with study requirements and restrictions listed in the consent form
	  * Female participants must agree to use an approved highly effective birth control (BC) method (< 1% failure rate per year) throughout the study (until completion of the day 85 follow-up visit), unless documented to have a reproductive status of non-childbearing potential or is post-menopausal
	  * Hospitalised participants with severe COVID-19 (6-8 point on WHO 10-Point Ordinal Scale):
	  ☐ point 6: oxygen by NIV or high-flow
	  ☐ point 7: intubation and mechanical ventilation, pO2/FiO2 ≥ 150 mmHg or SpO2/FiO2 ≥ 200 mmHg
	  ☐ point 8: mechanical ventilation pO2/FiO2 < 150 mmHg (or SpO2/FiO2 < 200 mmHg) or vasopressors
	  * Biological samples (not limited to any specific type) collected within 72 hours (allow retesting for potential participants who tested positive beyond 72 hours) before randomisation is laboratory-confirmed as SARS-CoV-2 infection (PCR, etc.)
	  * ≤ 14 days since the onset of COVID-19 symptoms
	• Exclusion criteria
	  * Participant has been intubated for > 72 hours (in the event of extubation and re-intubation, the calculation for the number of hours theparticipant has been intubated begins at the first intubation)
	  * Require or anticipated need for ECMO, suspected or proven septic shock or shock
	  * ALT/AST > 5 times higher than the ULN
	  * Severe chronic respiratory disease (e.g. known chronic obstructive pulmonary disease (COPD), pulmonary arterial hypertension (PAH), idiopathic pulmonary fibrosis (IPF), interstitial lung disease (ILD)) requiring supplemental oxygen therapy or mechanical ventilation pre-hospitalisation (e.g. prior to COVID-19 diagnosis)
	  * Use of prohibited medications
	  * Participants with severe COVID-19 who received convalescent plasma or COVID-19 vaccine, or anti-spike (S) SARS-CoV-2 therapy
	  * Moribund condition in the opinion of the clinical team

Interventions	Intervention SCTA01 plus best supportive care • Target: SARS-CoV-2 S protein • Origin: not reported • Dose: not reported • Frequency: single dose • Route of administration: IV infusion Comparator

NCT04683328 *(Continued)*

	• Placebo plus best supportive care

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: planned
	• Clinical progression/improvement of symptoms: planned as time to improvement of two categories on WHO 10-point ordinal scale from baseline at day 29
	• Length of hospital stay (for those admitted to hospital): planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	• Thromboembolic events: not planned
	• Renal failure: not planned
	Safety outcomes
	• Number of participants with AEs (all grades, grades 1-2, grades 3-4): not planned
	• Number of participants with SAEs: planned
	Additional study outcomes
	• Time to discontinue mechanical ventilation at day 29
	• Time to discontinue supplemental oxygen at day 29
	• Change from baseline in viral shedding as measured by RT-qPCR
	• Anti-drug Ab

Starting date	25 February 2021
Contact information	Ji Qi, +86-10-5862 8288 ext. 9360, ji_qi@sinocelltech.com
Notes	Developer: Sinocelltech Ltd. Funding: Sinocelltech Ltd. Recruitment status: not yet recruiting

NCT04709328

Study name	MAOP3
Methods	Drug name: SCTA01 Trial design: randomised, adaptive, double-blinded, placebo-controlled, multicentre, phase 2/3 study NCT number: NCT04709328 Target sample size: 690 participants Planned completion date: March 2022
Participants	Setting • Outpatient

NCT04709328 *(Continued)*

- Recruitment period: March 2021-January 2022
- Multicentre, country: USA

Eligibility criteria

- Inclusion criteria
  * Male or non-pregnant female adults, ≥ 18 years old of age at the time of randomisation
  * Participants should have at least one of COVID-19 risk factor
  * Participants should have at least 2 COVID-19-related symptoms
  * Has symptoms consistent with COVID-19 as determined by the investigator with onset ≤ 7 days before randomisation
  * First positive SARS-CoV-2 viral infection tested (PCR or antigen-based diagnostic tests) in samples collected ≤ 3 days prior to start of the infusion
  * Participants are currently not hospitalised
  * Participant (or LAR) has signed the consent form before any clinical activity related to SCTA01 trial
  * WOCBP must agree to use effective contraceptive methods during the study period
  * Participants should not participate in other clinical studies related to COVID-19 or SARS-CoV-2 infection
- Exclusion criteria
  * Known allergies to any of the components used in the formulation of the SCTA01/placebo
  * History of severe anaphylaxis, such as severe anaphylactic reaction, urticaria, and angioedema
  * SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300, respiratory rate ≥ 30/minute, heart rate ≥ 125/minute (FDA)
  * Require mechanical ventilation or anticipated impending need for mechanical ventilation
  * Suspected or proven serious bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking part in this study
  * Any serious concomitant systemic disease, condition, or disorder that, in the opinion of the investigator, should preclude participation in this study
  * Any co-morbidity requiring surgery within < 29 days, or that is considered life-threatening within 29 days
  * History of previous SARS-CoV-2 infection
  * Received convalescent plasma, COVID-19 vaccine, or anti-SARS-CoV-2 spike(S) protein-targeted therapy, or have participated in a clinical study involving an investigational intervention within past 30 days or 5-half lives of investigational product, whichever is longer
  * Have received an investigational intervention for SARS-CoV-2 prophylaxis within 30 days before dosing
  * Pregnant or lactating women
  * Anticipated hospitalisation or transfer to another medical site which is not a study site within 72 hours
  * Participants unable to follow the protocol during the study
  * Participants deemed inappropriate for enrolment by the investigator due to other factors

Interventions	Intervention SCTA01 plus standard of care • Target: SARS-CoV-2 S protein • Origin: not reported • Dose: 3 doses (low/middle/high), not further specified • Frequency: not reported • Route of administration: IV infusion Comparator • Placebo, IV infusion

NCT04709328 *(Continued)*

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms:
	  * WHO Clinical Progression Scale measured daily over the course of the study
	  * assessed as individual items included in the Progression Scale (need for respiratory support, duration)
	  ☐ oxygen by mask or nasal prongs
	  ☐ oxygen by NIV or high-flow nasal cannula
	  ☐ intubation and mechanical ventilation
	  ☐ mechanical ventilation or vasopressors, high-flow oxygen
	  ☐ mechanical ventilation and vasopressors, dialysis or ECMO: planned
	• Admission to hospital (for outpatients only): planned
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to ICU: planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: planned for 8 and 15 days
	• Thromboembolic events: not planned
	• Renal failure: not planned
	
	Safety outcomes
	• Number of participants with AEs (all grades, grades 1-2, grades 3-4): planned
	• Number of participants with SAEs: planned
	
	Additional study outcomes
	• Time to sustained resolution of all COVID-19-related symptoms
	• Time to symptom improvement
	• Proportion of participants with ≥ 1, ≥ 2 COVID-19-related hospitalisation
	• Proportion of participants who experienced COVID-19-related emergency room (ER) visit, with ≥ 1 ER visit due to COVID-19, or with ≥ 2 ER visits due to COVID-19 through day 29
	• Change from baseline (day 1) to day 8 or day 15 in SARS-CoV-2 viral shedding as measured by RT-qPCR in NP or OP samples
	• Discontinuation or temporary suspension of infusions (for any reason)
	• Number and proportion of participants with ADE
	• Mean concentration-time profiles of SCTA01
	• Incidence and titres (if applicable) of anti-drug Abs to SCTA01

Starting date	March 2021
Contact information	Qiang Guo, 86-10-5862 8288, NCT04709328,%20SCTA01-A301,%20To%20Evaluate%20SCTA01%20Treatment%20of%20High-risk%20Outpatients%20With%20COVID-19" type="EXTERNAL">qiang_guo@sinocelltech.com
Notes	Developer: Sinocelltech Ltd. Funding: Sinocelltech Ltd. Recruitment status: Not yet recruiting

NCT04723394

Study name	NCT04723394
Methods	Drug name: AZD7442 (AZD8895/tixagevimab + AZD1061/cilgavimab) Trial design: randomised, double-blind, placebo-controlled, multicenter, phase 3 study NCT number: NCT04723394 (date of trial registration: 5 January 2021) Target sample size: 1700 participants Planned completion date: May 2022
Participants	Setting • Outpatient • Recruitment period: January 2021-June 2021 • Multicentre, country: UK, USA, Germany, Hungary, Mexico Eligibility criteria • Inclusion criteria * Documented laboratory-confirmed SARS-CoV-2 infection, as determined by a molecular test (antigen or nucleic acid) from any respiratory tract specimen (e.g. oropharyngeal, NP, or nasal swab, or saliva) collected ≤ 3 days prior to day 1 * WHO Clinical Progression Scale score > 0 and < 4 * Participant must be dosed with IM injection no more than 7 days from self-reported onset of COVID-19-related symptoms (mild to moderate COVID-19) or measured fever, defined as the self-reported date of first reported sign/symptom * ≥ 1 of the following signs/symptoms must be present within 24 hours prior to day 1: cough, sore throat, shortness of breath or difficulty breathing at rest or with activity, body pain or muscle pain/aches, fatigue, headache, chills, nasal obstruction or congestion, nasal discharge, nausea or vomiting, diarrhoea, new loss of taste or smell * SpO2 ≥ 92% obtained at rest by study staff within 24 hours prior to day 1 (unless participant regularly receives chronic supplementary oxygen for an underlying lung condition) * Participant agrees not to participate in another clinical trial for the treatment of COVID-19 or SARS-CoV-2 during the study period until reaching hospitalisation or 28 days after entry into the study (whichever is earliest) * ≥ 18 years of age, provide informed consent, ability to comply with study requirements/procedure • Exclusion criteria * History or current hospitalisation for COVID-19 * Need for hospitalisation/immediate medical attention in a clinic/emergency room service * Previous adverse reaction to any mAbs or known allergy to components of the IM injection or placebo * Receipt of any investigational or licensed vaccine for prevention of COVID-19 at any time prior to entry into this study * Requirement or anticipated impending need for mechanical ventilation * Any significant disease, disorder, or finding that may increase risk that might affect his/her ability to participate in this study * Received convalescent COVID-19 plasma treatment any time prior to entry into this study * Pregnant or breastfeeding women * Receipt of any study drug in the previous 90 days or 5 half-lives (whichever is longer), or expected receipt of study drug during the study follow-up period, or concurrent participation in another interventional study
Interventions	Intervention AZD7442 (AZD8895/tixagevimab + AZD1061/cilgavimab)

NCT04723394 *(Continued)*

- Target: SARS-CoV-2 S protein
- Origin: not reported
- Dose: 600 mg
- Frequency: single dose
- Route of administration: 2 separate IM injections

Comparator

- Placebo, single dose

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms:
	  * WHO Clinical Progression Scale measured daily over the course of the study
	  * Assessed as individual items included in the Progression Scale (need for respiratory support, duration)
	  ☐ oxygen by mask or nasal prongs
	  ☐ oxygen by NIV or high-flow nasal cannula
	  ☐ intubation and mechanical ventilation
	  ☐ mechanical ventilation or vasopressors, high-flow oxygen
	  ☐ mechanical ventilation and vasopressors, dialysis or ECMO: planned
	• Admission to hospital: planned as a composite of either death from any cause or hospitalisation for COVID-19 complications or sequelae during the 168-day post-dose period (day 1 to day 169)
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to CU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: planned from baseline of SARS-CoV-2 RNA from nasal swabs through day 29
	• Thromboembolic events: not planned
	• Renal failure: not planned
	Safety outcomes
	• Number of participants with AEs (all grades, grade 1-2, grade 3-4): not planned
	• Number of participants with SAEs: not planned
	Additional study outcomes
	• Level of SARS-CoV-2 RNA from nasal swabs through day 29
	• Change from baseline of SARS-CoV-2 RNA from nasal swabs through day 29
	• Time to return to usual (pre-COVID-19) health through day 29
	• Duration of fever through day 29
	• Incidence of ADA to AZD7442 in serum over time

Starting date	22 January 2021
Contact information	AstraZeneca Clinical Study Information Center, 1-877-240-9479, NCT04723394, information.center@astrazeneca.com
Notes	Developer: AstraZeneca Funding: AstraZeneca Recruitment status: not yet recruiting

NCT04734860

Study name	NCT04734860
Methods	Drug name: STI-2020 (COVI-AMG) Trial design: randomised, double-blind, placebo-controlled, multicentre, phase 2 study NCT number: NCT04734860 (date of trial registration: 2 February 2021) Target sample size: 500 participants Planned completion date: November 2021

Participants	Setting
	• Outpatient
	• Recruitment period: March 2021-September 2021
	• Multicentre, country: not reported
	Eligibility criteria
	• Inclusion criteria
	  * Positive for COVID-19 by an approved antigen test
	  * Mild symptoms consistent with a COVID-19 viral infection
	  * Willing and able to comply with all planned study procedures and be available for all study visits and follow-up as required by the protocol
	  * Willing to follow contraception guidelines
	• Exclusion criteria
	  * Evidence of moderate COVID-19 per FDA severity categorisation
	  * Pregnant or lactating and breastfeeding or planning on either during the study
	  * Has a documented infection other than COVID-19
	  * Has received a COVID-19 vaccine
	  * Has participated, or is participating, in a clinical research study evaluating COVID-19 convalescent plasma, mAbs against SARS-CoV-2, or IVIg within 3 months or less than 5 half-lives of the investigational product (whichever is longer) prior to the screening visit

Interventions	Intervention STI-2020 (COVI-AMG) • Target: SARS-CoV-2 S protein • Origin: fully human • Dose: 40 mg/100 mg/200 mg • Frequency: single dose • Route of administration: injection Comparator • Placebo, diluent solution, single dose, injection

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: not planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: not planned
	• Development of severe symptoms according to WHO scale (≥ 6 on the WHO Clinical Progression Scale; for mild disease): not planned

NCT04734860 *(Continued)*

- Admission to hospital (for outpatients only): planned as proportion of participants who remained out of the hospital or emergency room through days 29, 43 and 70
- Length of hospital stay (for those admitted to hospital): not planned
- Admission to ICU: not planned
- Length of ICU stay: not planned
- Quality of life, including fatigue: probably planned as proportion of subjects who have 50%, 70%, and 90% reduction in PRO instrument score
- Viral clearance: not planned
- Thromboembolic events: not planned
- Renal failure: not planned

Safety outcomes:

- Number of participants with adverse events (all grades, grade 1-2, grade 3-4): not planned
- Number of participants with serious adverse events: not planned

Additional study outcomes:

- Viral load reduction from baseline to days 8, 15, 29, 43, and 70
- Time to resolution of fever

Starting date	March 2021
Contact information	Mike Royal, (858) 203-4100 ext 4146; NCT04734860,%20AMG-COV-201,%20Study%20to%20Evaluate%20a%20Single%20Dose%20of%20STI-2020%20(COVI-AMG%E2%84%A2)%20in%20Adults%20With%20Mild%20COVID-19%20Symptoms" type="EXTERNAL">mroyal@sorrentotherapeutics.com
Notes	Developer: Sorrento Therapeutics, Inc. Funding: Sorrento Therapeutics, Inc. Recruitment status: Not yet recruiting

NCT04748588

Study name	NCT04748588
Methods	Drug name: bamlanivimab (LY3819253, LY-CoV555) Trial design: randomised, open-label, controlled, phase 4 study NCT number: NCT04748588 (date of trial registration: 10 February 2021) Target sample size: 648 participants Planned completion date: March 2023
Participants	Setting • Inpatient, COVID-19 as nosocomial infection acquired in hospital • Recruitment period: February 2021 to January 2023 • Multicentre, country: Canada Eligibility criteria

NCT04748588 *(Continued)*

- Inclusion criteria
  - ≥ 18 years
  - Laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or public health assay, in any specimen prior to randomisation
  - Admitted to a participating centre
  - Is nosocomially acquired infection, as defined by ALL of:
    - ☐ COVID-19 diagnosis being made on admission day 3 or later;
    - ☐ Admitted for a reason other than COVID-19;
    - ☐ Within 5 days of COVID-19 diagnosis based on test collection date or initial development of symptoms, whichever was earliest
- Exclusion criteria
  - Plan for palliation within 24 hours
  - Known allergy to study medication or its components (non-medicinal ingredients)
  - Ordinal scale ≥ 6
  - Admitted to facility for non-medical reasons including primary psychiatric diagnosis or labour and delivery
  - Pregnancy or breastfeeding
  - Weight < 40 kg

Interventions	Intervention Bamlanivimab (LY3819253, LY-CoV555) • Target: SARS-CoV-2 S protein • Origin: derived from B lymphocytes of a convalescent naturally SARS-CoV-2-infected patient • Dose: 700 mg • Frequency: single dose • Route of administration: IV infusion Comparator • No intervention: standard of care

Outcomes	Efficacy outcomes
	
	• All-cause mortality
	  * at up to 30 days: not planned
	  * at up to 60 days: planned as in-hospital death
	• Clinical progression/improvement of symptoms: not planned
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to ICU: planned as the need for new intensive care admission
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	• Thromboembolic events: not planned
	• Renal failure: not planned
	
	Safety outcomes
	
	• Number of participants with AEs (all grades, grade 1-2, grade 3-4): not planned
	• Number of participants with SAEs: not planned
	
	Additional study outcomes
	
	• Need for new oxygen administration

Starting date	1 February 2021

NCT04748588 *(Continued)*

Contact information	Alain Tremblay, 4032103866, atrembla@ucalgary.ca Wendy Sligl, 780 492 8311, wsligl@ualberta.ca
Notes	Developer: Eli Lilly and Company Funding: University of Calgary; Sunnybrook Research Institute Recruitment status: not yet recruiting

NCT04770467

Study name	NCT04770467
Methods	Drug name: BRII-196 and BRII-198 Trial design: randomised, single-blinded, placebo-controlled, phase 2 study NCT number: NCT04770467 (date of trial registration: 25 February 2021) Target sample size: 56 participants Planned completion date: October 2022

Participants	Setting
	• Inpatient/outpatient: not reported
	• Recruitment period: February 2021-October 2022
	• Single- vs multicentre: single centre, country: China
	Eligibility criteria
	• Inclusion criteria
	  * Participant ≥ 18 years, signing informed consent
	  * SARS-CoV-2 infection by PCR ≤ 7 days
	  * ≥ 1 COVID-19-related symptoms or measured fever present within 48 hours prior to study entry (participants with mild-moderate COVID-19)
	• Exclusion criteria
	  * Recurring COVID-19 patients
	  * Participants with any unstable conditions, a history of significant hypersensitivity, or known allergy to components of the investigational agent
	  * Receipt of convalescent COVID-19 plasma, SARS-CoV-2 mAb treatment, SARS-CoV-2 vaccine, or other investigational treatments prior to study entry

Interventions	Intervention BRII-196 and BRII-198 • Target: SARS-CoV-2 S protein • Origin: not reported • Dose: not reported • Frequency: not reported • Route of administration: IV infusion Comparator: • Placebo, IV infusion

NCT04770467 *(Continued)*

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: not planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: not planned
	• Development of severe symptoms according to WHO scale (≥ 6 on the WHO Clinical Progression Scale; for mild disease): planned as proportion of participants who have mild-moderate COVID-19 and develop severe COVID-19 after randomisation
	• Admission to hospital (for outpatients only): not planned
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	• Thromboembolic events: not planned
	• Renal failure: not planned
	Safety outcomes
	• Number of participants with AEs (all grades, grades 1-2, grades 3-4): not planned
	• Number of participants with SAEs: planned
	Additional study outcomes
	• Change from pre-dose baseline in RBC count
	• Change from pre-dose baseline in WBC count
	• Change from pre-dose baseline in platelets count
	• Change from pre-dose baseline in haemoglobin result
	• Change from pre-dose baseline in creatine kinase result
	• Change from pre-dose baseline in ALT result
	• Time-weighted average changes in SARS-CoV-2 RNA levels in nasopharyngeal swabs from baseline to day 8
	• Duration of COVID-19-related symptoms through day 29 among participants with mild-moderate COVID-19

Starting date	March 2021
Contact information	Lili Chen, +86 10 6299 8808, lili.chen@briibio.com
Notes	Developer: Brii Biosciences, Inc. Funding: Brii Biosciences, Inc. Recruitment status: not yet recruiting Other: 2 cohorts (mild-to-moderate and severe)

NCT04771351

Study name	NCT04771351
Methods	Drug name: STI-2020 (COVI-AMG) Trial design: randomised, double-blinded, placebo-controlled, phase 2 study

NCT04771351 *(Continued)*

	NCT number: NCT04771351 (date of trial registration: 25 February 2021) Target sample size: 280 participants Planned completion date: September 2021

Participants	Setting
	
	• Inpatient
	• Recruitment period: between March 2021 and July 2021
	• Single vs multicentre: not reported, country: not reported
	
	Eligibility criteria:
	
	• Inclusion criteria
	  * Positive for COVID-19 by an approved antigen test
	  * Progressive disease suggestive of ongoing COVID-19 infection
	  * Requires hospitalisation for acute medical care
	  * Provides written informed consent
	  * Willing to follow contraception guidelines during the study
	• Exclusion criteria
	  * Requires high-flow oxygen supplementation
	  * Current or imminent respiratory failure
	  * Has rapidly progressing symptoms that in the investigator's opinion are likely to progress to needing high-flow oxygen or to respiratory failure within 24 to 48 hours
	  * Any condition which, in the investigator's opinion, would not be in the person's best interest or could prevent, limit, or confound the protocol-specified assessments
	  * Has participated, or is participating in, a clinical research study evaluating COVID-19 convalescent plasma, mAbs against SARS-CoV-2, or IV immunoglobulin within 3 months or < 5 half-lives of the investigational product (whichever is longer)
	  * Pregnant or lactating and breastfeeding, or planning on either during the study
	  * Unable to comply with planned study procedures and be available for all follow-up visits

Interventions	Intervention STI-2020 (COVI-AMG) • Target: SARS-CoV-2 S protein • Origin: not reported • Dose: 100 mg/200 mg • Frequency: single dose • Route of administration: injection Comparator • Placebo, diluent solution, injection

Outcomes	Efficacy outcomes
	
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: planned as proportion of participants with clinical improvement defined as ≤ 2 on the Ordinal Scale of Clinical Improvement at day 15 and day 29
	• Time to discharge: not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned

NCT04771351 *(Continued)*

- Viral clearance: not planned
- Thromboembolic events: not planned
- Renal failure: not planned

Safety outcomes

- Number of participants with AEs: not planned
- Number of participants with SAEs: not planned

Additional study outcomes

- Proportion of participants who are alive and free of respiratory failure at day 29
- Viral load reduction
- Time to sustained clinical improvement

Starting date	March 2021
Contact information	Mike Royal, (858) 203-4100 ext 4146, mroyal@sorrentotherapeutics.com
Notes	Developer: Sorrento Therapeutics, Inc. Funding: Sorrento Therapeutics, Inc. Recruitment status: not yet recruiting

NCT04779879

Study name	COMET-PEAK
Methods	Drug name: Sotrovimab (VIR-7831; Generation 1 and 2) Trial design: randomised, double-blinded, parallel group, multicentre, phase 2 study (part A double-blind, part B and C open-label) NCT number: NCT04779879 (date of trial registration: 3 March 2021) Estimated enrollment: 340 participants Planned completion date: April 2023

Participants	Setting
	• Outpatient
	• Recruitment period: February 2021-April 2021
	• Multicentre, country: USA
	Eligibility criteria
	• Inclusion criteria
	  * Participant must be aged ≥ 18 years at the time of obtaining informed consent
	  * Participants who have a positive SARS-CoV-2 test result ≤ 7 days prior to enrolment and oxygen saturation ≥ 94% on room air and have COVID-19 symptoms ≤ 7 days from onset of symptoms

NCT04779879 *(Continued)*

	• Exclusion criteria
	  * Currently hospitalised or judged by the investigator as likely to require hospitalisation in the next 24 hours
	  * Symptoms consistent with severe COVID-19
	  * Participants who, in the judgment of the investigator, are likely to die in the next 7 days
	  * Severely immunocompromised participants

Interventions	Intervention VIR-7831 (Generation 2) • Target: SARS-CoV-2 S protein • Origin: not reported • Dose: not reported • Frequency: not reported • Route of administration: IV infusion, IM injection Comparator: • VIR-7831 (Generation 1), IV infusion

Outcomes	Efficacy outcomes
	
	• All-cause mortality
	  * at up to 30 days: not planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: possibly planned as disease progression events
	• Development of severe symptoms according to WHO scale (≥ 6 on the WHO Clinical Progression Scale; for mild disease): not planned
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	• Thromboembolic events: not planned
	• Renal failure: not planned
	
	Safety outcomes
	
	• Number of participants with AEs (all grades, grade 1-2, grade 3-4): planned
	• Number of participants with SAEs: planned
	
	Additional study outcomes
	
	• Occurrence of adverse events of special interest (AESIs)
	• Occurrence of clinically significant abnormalities on 12-lead ECG readings

Starting date	18 February 2021
Contact information	Study Inquiry, 415-654-5281, clinicaltrials@vir.bio
Notes	Developer: Vir Biotechnology, Inc. Funding: Vir Biotechnology, Inc.; GlaxoSmithKline Recruitment status: recruiting

NCT04780321

Study name	NCT04780321
Methods	Drug name: Etesevimab (JS016) Trial design: randomised, double-blinded, placebo-controlled, phase 1b/2 study NCT number: NCT04780321 (date of trial registration: 3 March 2021) Target sample size: 90 participants Planned completion date: 30 June 2021

Participants	Setting
	• Outpatient
	• Recruitment period: October 2020-March 2021
	• Multicentre, country: China
	Eligibility criteria
	• Inclusion criteria
	  * Age 18-65 years (inclusive), men or women
	  * SARS-CoV-2 detected in the diagnostic specimen (nasopharyngeal swab)
	  * High homology of viral gene sequencing with the known SARS-CoV-2
	  * Mild/moderate illness COVID-19 or SARS-CoV-2 asymptomatic infection
	  * Within 7 days from the onset time of symptoms to randomisation or within 5 days from the first time of SARS-CoV-2-positive test to randomisation with required viral load
	  * No plan of pregnancy and being willing to use effective contraceptive measures
	  * Signed the informed consent form, sufficiently understanding of the content
	• Exclusion criteria
	  * Positive IgM/IgG against SARS-CoV-2 prior to randomisation
	  * Severe or critical illness
	  * Uncontrolled hypertension, cardiovascular/cerebrovascular diseases, lung diseases
	  * Type 1 diabetes, or newly diagnosed or poorly controlled type 2 diabetes
	  * Liver and kidney dysfunction, immune or inflammatory diseases, infections, surgery, tumours and other major diseases
	  * History of SARS-CoV-2 vaccination or participation in clinical trial with neutralising Ab against SARS-CoV-2
	  * Use of therapeutic biologics within 3 months prior to screening, or within the elimination period (5 half-lives) of such drugs as the day of dosing
	  * Has participated in any other interventional clinical study involving a study drug within 3 months prior to screening, or within the elimination period (5 half-lives) of the study drug as the day of dosing
	  * Platelets and haemoglobin test results during screening period are abnormal and have clinical significance
	  * Anaphylaxis, urine drug screening, alcohol dependence, lactation during pregnancy, blood loss, and others

Interventions	Intervention Etesevimab • Target: SARS-CoV-2 S protein • Origin: not reported • Dose: 25 mg/kg; 50 mg/kg; 100 mg/kg • Frequency: single dose • Route of administration: IV infusion

NCT04780321 *(Continued)*

	Comparator • Placebo, single-dose, IV infusion

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: not planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: not planned
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: planned as proportions of participants with negative conversion in viral nucleic acid test 7 days and 14 days after administration
	• Thromboembolic events: not planned
	• Renal failure: not planned
	Safety outcomes
	• Number of participants with AEs (all grades, grade 1-2, grade 3-4): not planned
	• Number of participants with SAEs: planned
	Additional study outcomes
	• Time to negative conversion in viral nucleic acid test (by RT-PCR) for diagnostic samples
	• Any AE, SAE occurring during the clinical study, and abnormality of 12-lead ECGs will be observed for all the participants
	• Viral load change from baseline
	• Pulmonary CT changes during the study period

Starting date	30 October 2020
Contact information	Jingjing Sheng, 17317890616, NCT04780321,%20JS016-002-Ib/II,%20JS016%20(Anti-SARS-CoV-2%20Monoclonal%20Antibody)With%20Mild%20and%20Moderate%20COVID-19%20or%20SARS-CoV-2%20Asymptomatic%20Infection%20Subects" type="EXTERNAL">jingjing_sheng@junshipharma.com
Notes	Developer: Shanghai Junshi Bioscience Co., Ltd. Funding: Shanghai Junshi Bioscience Co., Ltd. Recruitment status: recruiting

NCT04787211

Study name	NCT04787211
Methods	Drug name: BRII-196 and BRII-198 Trial design: randomised, placebo-controlled, single-blinded, single-dose, phase 2 study NCT number: NCT04787211 (date of trial registration: 8 March 2021) Target sample size: 24 participants (estimated enrollment)

NCT04787211 *(Continued)*

	Estimated completion date: December 2021

Participants	Setting
	• Outpatient
	• Recruitment period: March 2021 - December 2021
	• China
	Eligibility criteria
	• Inclusion Criteria:
	  * Participant ≥ 18 years who signed the informed consent
	  * SARS-CoV-2 infection by PCR ≤ 7 days
	  * One or more of COVID-19 related symptoms or measured fever present within 48 hours prior to study entry (participants with mild-moderate COVID-19)
	• Exclusion Criteria:
	  * Recurring COVID-19 patients
	  * Participants with any unstable conditions, a history of significant hypersensitivity, or known allergy to components of the investigational agent
	  * Receipt of convalescent COVID-19 plasma, SARS-CoV-2 mAb treatment, SARS-CoV-2 vaccine, or other investigational treatments prior to study entry

Interventions	Intervention BRII-196 and BRII-198 • Target: SARS-CoV-2 S protein • Origin: derived from convalesced COVID-19 patients • Dose: not reported • Frequency: single dose • Route of administration: IV infusion • 2 arms: drug administered to adult subject with severe COVID-19 and to adult participants with mild-moderate COVID-19 Comparator: • Placebo, IV infusion

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: not planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: not planned
	• Length of hospital stay (for those admitted to hospital): not planned
	• Time to discharge: not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	Safety outcomes
	• Number of participants with AEs (all grades, grades 1-2, grades 3-4): planned
	• Number of participants with SAEs: planned
	Additional study outcomes

NCT04787211 *(Continued)*

	• Time-weighted average changes in SARS-CoV-2 RNA levels in nasopharyngeal swabs from baseline to Day 8 • Change from pre-dose baseline in red blood cell count, white blood cell count, platelets count, haemoglobin result, creatine kinase result, alanine aminotransferase (ALT) result • Duration of SARS-CoV-2 related symptoms through day 29 among subjects with mild-moderate COVID-19 • Proportion of participants who have mild-moderate COVID-19 and develop severe COVID-19 after randomisation • Pharmacokinetics of BRII-196 and BRII-198: maximum serum concentration observed up to day 85
Starting date	March 2021
Contact information	Lili Chen +86 10 6299 8808 lili.chen@briibio.com
Notes	Developer: Brii Biosciences Limited Funding: Brii Biosciences Limited Recruitment status: not yet recruiting Other: 3 arms

NCT04796402

Study name	NCT04796402
Methods	Drug name: Bamlanivimab (LY-CoV555) Trial design: randomised, open-label, phase 4 study NCT number: NCT04796402 (date of trial registration: 12 March 2021) Target sample size: 576 participants (estimated enrollment) Estimated completion date: 31 December 2021
Participants	Setting • Outpatient • Recruitment period: 11 March 2021 - probably 30 June 2021 • Canada Eligibility criteria • Inclusion criteria * > 65 years at the time of SARS-CoV2 test * Age 55-64 at the time of SARS-CoV2 test and one or more disease characteristics: ☐ Not hospitalised ☐ Sample collection for first SARS-CoV2 test positive within 3 days prior to consent ☐ One or more mild COVID-19 symptoms and within 10 days from onset * Residents of Britisch Columbia, who understand and agree to planned study procedures and provide informed consent by telephone

NCT04796402 *(Continued)*

- Exclusion criteria
  - Medical conditions including:
    - ☐ Allergies to any of the components used in the formulation of the bamlanivimab
    - ☐ Hospitalisation or expected to need hospitalisation in the next 24 hours at the time of recruitment for COVID-19
    - ☐ Suspected or proven infection other than COVID-19 that could pose a risk to study inclusion
    - ☐ Any serious disease, condition or disorder that in the opinion of the clinicians should preclude participation
    - ☐ Require oxygen therapy due to COVID-19
    - ☐ Require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity
  - Weighs < 40 kg
  - History of vaccination against SARS-CoV2 or previous SARS-CoV2 infection
  - History of convalescent plasma or IVIG therapy within 3 months of first SARS-CoV2 viral determination positive
  - History of participation in any clinical study involving an investigational intervention within 30 days or 5 half-lives of the previous intervention, whichever is longer
  - Unable to achieve informed consent for any reason
  - Known Pregnancy or actively breast-feeding

Interventions	Intervention Bamlanivimab • Target: SARS-CoV-2 S protein • Origin: derived from B lymphocytes of a convalescent naturally SARS-CoV-2-infected patient • Dose: 700 mg /20 mL • Frequency: over at least one hour once daily • Route of administration: IV infusion Comparator: • Standard of Care (includes primary care and specialists care as indicated by the patient's primary care provider)

Outcomes	Efficacy outcomes
	
	• All-cause mortality
	  * at up to 30 days: planned as up to 28 days
	  * at up to 60 days: planned as 3 and 6 months post-treatment
	• Clinical progression/improvement of symptoms: not planned
	• Admission to hospital (for outpatients only): planned as any incidence of admission to hospital for > 24 hours in the 28 days following first positive test for SARS-CoV2
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: planned as assessment with medical outcomes study: 20-Item Short Form Survey Instrument (SF-20) up to 6 months post-treatment
	• Viral clearance: not planned
	
	Safety outcomes
	
	• Number of participants with AEs (all grades, grade 1-2, grade 3-4): not planned
	• Number of participants with SAEs: not planned
	
	Additional study outcomes
	
	• Hospitalisation by age and comorbidities up to 6 months

NCT04796402 *(Continued)*

	• Incidence and types of adverse reactions including anaphylaxis up to 6 months • Recruitment rate up to 8 weeks from day of first patient recruited to day of last patient recruited • Type and frequenca of viral variants in patients receiving bamlanivimab up to 8 weeks from day of first patient recruited to day of last patient recruited
Starting date	17 March 2021
Contact information	Fraser Health Authority Fraser Health Region, British Columbia, Canada B-Epic Study +1 236 332 9517 b-epicstudy@fraserhealth.ca
Notes	Developer: Fraser Health Funding: Fraser Health Recruitment status: recruiting

NCT04805671

Study name	NCT04805671
Methods	Drug name: ADG20 Trial design: randomised, double-blind, placebo-controlled, single-dose, phase 2/3 study NCT number: NCT04805671 (date of trial registration: 18 March 2021) Target sample size: 1084 participants (estimated enrollment) Estimated completion date: February 2023

Participants	Setting
	• Outpatient
	• Recruitment period: July 2021 - probably February 2023
	• Country: not provided
	Eligibility criteria
	• Inclusion criteria
	  * ≥ 18 years
	  * Has had SARS-CoV-2 positive antigen, RT-PCR, or other locally approved molecular diagnostic assay obtained within 5 days prior to randomisation
	  * Has had symptoms consistent with COVID-19 with onset 5 days before randomisation
	  * Has one or more COVID-19-related signs or symptoms on the day of randomisation
	  * Is > 55 years of age or is age of 18-54 years with one or more preexisting medical conditions that place the participant at high risk of progression of COVID-19

NCT04805671 *(Continued)*

	• Exclusion criteria
	  * Is currently hospitalised or in the opinion of the investigator, anticipated to require hospitalisation within 48 hours of randomisation
	  * Has severe COVID-19 or is on supplemental oxygen
	  * Has a history of a positive SARS-CoV-2 antibody serology test
	  * Has participated, within the last 30 days, in a clinical study involving an investigational intervention
	  * Has received a SARS-CoV-2 vaccine, monoclonal antibody, or plasma from a person who recovered from COVID-19 any time prior to participation in the study

Interventions	Intervention ADG20 • Target: SARS-CoV-2 S protein • Origin: not reported • Dose: not reported • Frequency: single dose on Day 1 • Route of administration: IM injection Comparator: • Placebo, single dose of normal saline, IM injection

Outcomes	Efficacy outcomes
	
	• All-cause mortality
	  * at up to 30 days: planned up to 29 days
	  * at up to 60 days: planned as day 60 and day 90
	• Clinical progression/improvement of symptoms: not planned
	• Admission to hospital (for outpatients only): planned up to 29 days
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: planned up to days 5, 7, 11, 14, 21, 29
	
	Safety outcomes
	
	• Number of participants with AEs (all grades, grades 1-2, grades 3-4): planned up to day 29
	• Number of participants with SAEs: not planned
	
	Additional study outcomes
	
	• Incidence of solicited injection site reaction through day 4
	• Time to sustained recovery defined as sustained improvement or resolution of COVID-19 symptoms through day 29
	• Change from baseline in SARS-CoV-2 viral load (log10 copies/mL) and duration of SARS-CoV-2 shedding assessed by RT-qPCR from saliva samples
	• Incidence of treatment emergent adverse events for 14 months
	• Pharmacokinetics of ADG20: assessment of PK parameters and incidence of anti-drug antibody (ADA)

Starting date	Estimated study start date: July 2021
Contact information	+1 781-819-0080 ClinicalTrials@adagiotx.com

NCT04805671 *(Continued)*

Notes	Developer: Adagio Therapeutics, Inc. Funding: Adagio Therapeutics, Inc. Recruitment status: not yet recruiting

NCT04822701

Study name	NCT04822701
Methods	Drug name: BI 767551 IV, BI 767551 inhalation Trial design: randomised, double-blind, placebo-controlled, phase 2/3 study (two phases) • Phase II: randomised, double-blind, placebo controlled, parallel group design comparing different doses and modes of administration of BI 767551 to placebo • Phase III: randomised, double-blind, placebo-controlled, parallel group design comparing BI 767551 to placebo NCT number: NCT04822701 (date of trial registration: 30 March 2021) Target sample size: 1500 participants (estimated enrollment) Estimated completion date: 30 June 2022

Participants	Setting
	
	• Outpatient
	• Recruitment period: not yet reported (currently recruiting)
	• Countries: Belgium, Netherlands, Portugal, Spain,USA (40 study locations)
	
	Eligibility criteria
	
	• Inclusion criteria
	  * ≥ 18 years old
	  * Signed written informed consent in accordance with International Council on Harmonisation - Good Clinical Practice (ICH-GCP) and local legislation prior to admission to the trial
	  * Documentation of laboratory-confirmed SARS-CoV-2 infection, as determined by a molecular test (antigen or nucleic acid) from any respiratory tract specimen (nasopharyngeal (NP) or nasal swab or saliva) collected no more than 72 hours prior to start of treatment
	  * Patients experienced mild to moderate Coronavirus Disease 2019 (COVID-19)-related symptoms or measured fever for no more than 5 days prior to start of treatment
	  * One or more of the following signs/symptoms present on day of start of treatment: fever, feeling feverish, fatigue, cough, shortness of breath at rest or during activity, sore throat, body pain or muscle pain/ aches, chills, headache, nasal obstruction or congestion, loss of smell or taste, nausea, diarrhea, vomiting, or dysgeusia
	  * WOCBP and men able to father a child must be ready and able to use highly effective methods of birth control that result in a low failure rate of less than 1% per year when used consistently and correctly

NCT04822701 *(Continued)*

- Exclusion criteria
  * Body weight > 40 kg
  * Severe or critical COVID-19 including at least one of
    - ☐ Oxygen saturation (SpO2) ≤ 93 % on room air or on their usual level of oxygen supplementation in case of chronic oxygen use
    - ☐ Ratio of arterial oxygen partial pressure (PaO2 in millimeters of mercury) to fractional inspired oxygen (FiO2) < 300 (in case arterial blood sample was taken)
    - ☐ History of hospitalization for COVID-19
    - ☐ Current or imminent need for hospitalization or immediate medical attention in the clinical opinion of the site investigator. Does not include patients hospitalized for isolation only
  * Receipt of intravenous immunoglobulin within 12 weeks prior to visit 2
  * Receipt of COVID-19 convalescent plasma treatment at any time prior to visit 2
  * Receipt of any SARS-CoV-2 monoclonal antibody treatment or SARS-CoV-2 vaccine at any time prior to visit 2
  * Receipt of an investigational product for COVID-19 within 5 half-lives prior to visit 2
  * Receipt of systemic steroids (e.g. prednisone, dexamethasone) within 4 weeks prior to visit 2 unless used for chronic condition further exclusion criteria apply
  * Exclusion criteria for phase 3 only:
    - ☐ previous enrolment in this trial
    - ☐ Patients participating in phase 2 are not eligible for phase 3
    - ☐ Re-screening is allowed once, for repeat of Quantitative Reverse Transcription Polymerase chain reaction (RT-qPCR) or antigen SARS-CoV-2 test, if required. The test method used for initial screening (RT-qPCR or antigen) should be used for re-screening

Interventions	Intervention BI 767551 • Target: SARS-CoV-2 S protein • Origin: derived from convalescent naturally SARS-CoV-2-infected patient • Dose: not reported • Frequency: single dose • Route of administration: IV infusion and inhalation Comparator: • Placebo IV infusion • Placebo inhalation

Outcomes	Efficacy outcomes
	
	• All-cause mortality
	  * at up to 30 days: planned as up to 29 days
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: planned as time to either an improvement of two points on the 11-point WHO Clinical Progression Scale or a score of 0 on the Clinical Progression Scale, whichever comes first over 29 days
	• Admission to hospital (for outpatients only): planned up to 29 days
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: planned as loss of detection of SARS-CoV-2 RNA by site collected NP swab at Day 4, 8, 15, 22 and 29

NCT04822701 *(Continued)*

	Safety outcomes • Number of participants with AEs (all grades, grade 1-2, grade 3-4): not planned • Number of participants with SAEs: not planned Additional study outcomes • Time-weighted change from baseline in viral shedding over 8 days in site collected NP swabs by RT-qPCR, defined as a change from baseline in log10 viral load • Hypoxia up to day 29
Starting date	21 April 2021
Contact information	Boehringer Ingelheim 1-800-243-0127 clintriage.rdg@boehringer-ingelheim.com
Notes	Developer: Boehringer Ingelheim Funding: Boehringer Ingelheim Recruitment status: recruiting

NCT04840459

Study name	NCT04840459
Methods	Drug name: Bamlanivimab and Casirivimab + Imdevimab Trial design: non-randomised, open-label, phase 2 study NCT number: NCT04840459 (date of trial registration: 12 April 2021) Target sample size: 1000 participants (estimated enrolment) Estimated completion date: 31 January 2022
Participants	Setting • Outpatient • Recruitment period: 8 April 2021 - probably 31 December 2021 • USA (Texas) Eligibility criteria

NCT04840459 *(Continued)*

- Inclusion criteria
  - Adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing
  - ≥ 12 years old and weighing at least 40 kg
  - are at "high risk" for progressing to severe COVID-19 and/or hospitalization and "high risk" defined as patients with one of the following:
    - ☐ Have a BMI > 35
    - ☐ Have chronic kidney disease
    - ☐ Have diabetes
    - ☐ Have immunosuppressive disease
    - ☐ Are currently receiving immunosuppressive treatment
    - ☐ > 65 years of age
    - ☐ > 55 years of age and have: cardiovascular disease or hypertension or chronic obstructive pulmonary disease/other chronic respiratory disease
    - ☐ 12 - 17 years of age and have BMI > 85th percentile for their age and gender based on CDC growth charts, or sickle cell disease or congenital/acquired heart disease or neurodevelopmental disorders or a medical-related technological dependence or asthma that requires daily medication for control
- Exclusion criteria
  - < 12 years old
  - Do not meet criteria to be classified as "high risk"

Interventions	Intervention Bamlanivimab • Target: SARS-CoV-2 S protein • Origin: derived from B lymphocytes of a convalescent naturally SARS-CoV-2-infected patient • Dose: 700 mg for adults and pediatric patients ≥ 12 years of age and weighing at least 40 kg • Frequency: single dose over 60 minutes • Route of administration: IV injection Casirivimab + Imdevimab • Target: SARS-CoV-2 S protein • Origin: derived from B lymphocytes of a convalescent naturally SARS-CoV-2-infected patient • Dose: 10 mL of casirivimab and 10 mL of imdevimab diluted together in the infusion bag containing 0.9% sodium chloride • Frequency: single dose • Route of administration: IV injection

Outcomes	Efficacy outcomes
	
	• All-cause mortality
	  * at up to 30 days: not planned
	  * at up to 60 days: not planned
	• Clinical progression/improvement of symptoms: not planned
	• Admission to hospital (for outpatients only): planned up to six weeks
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	
	Safety outcomes
	
	• Number of participants with AEs (all grades, grade 1-2, grade 3-4): not planned
	• Number of participants with SAEs: not planned

NCT04840459 *(Continued)*

	Additional study outcomes • Number of patients with mild to moderate COVID-19 who are at high risk for progressing to severe COVID-19 and/or hospitalization for 2 weeks • Rate of recovery after monoclonal antibody therapy up to 6 weeks
Starting date	20 November 2020
Contact information	Sohail Rao, MD +1 9563622387 s.rao@dhr-rgv.com Monica Betancourt-Garcia, MD +1 956-3623223. m.betancourt@dhr-rgv.com
Notes	Developer: Sohail Rao, DHR Health Institute for Research and Development Funding: Sohail Rao Recruitment status: recruiting

NCT04900428

Study name	NCT04900428
Methods	Drug name: STI-2099 (COVI-DROPS) Trial design: randomised, double-blind, placebo-controlled, phase 2 study NCT number: NCT04900428 (date of trial registration: 25 May 2021) Target sample size: 350 participants (estimated enrolment) Estimated completion date: March 2022

Participants	Setting
	• Outpatient
	• Recruitment period: July 2021 - probably March 2022
	• Countries: UK
	Eligibility criteria
	• Inclusion criteria
	  * ≥ 18 years old
	  * Positive for COVID-19 with any locally approved RT-PCR within 7 days of planned treatment
	  * Have no COVID-19 symptoms (asymptomatic) or mild illness/symptoms
	  * Must be willing and able to comply with all planned study procedures and be available for all in-person and telephonic study visits and follow-up as required per protocol
	  * Participant must have provided written informed consent
	  * Willing to follow contraception guidelines

NCT04900428 *(Continued)*

- Exclusion criteria
  * Moderate or severe illness/symptoms or rapidly progressive symptoms which are likely to progress such that a hospitalisation is imminent (within 24 to 48 hours)
  * Any medical condition that, in the Investigator's opinion, could adversely impact subject safety or key objectives of the study, including any intranasal pathology, or clinically significant laboratory abnormalities, or active clinical disease process
  * Documented acute infection other than COVID-19
  * Pregnant or lactating women who are breast feeding or planning to during the study
  * Has participated, or is participating, in a clinical research study evaluating COVID-19 convalescent plasma, mAbs against SARS-CoV-2, or intravenous immunoglobulin (IVIG) within 3 months or less than 5 half-lives of the investigational product (whichever is longer) prior to the screening visit

Interventions	Intervention STI-2099 (COVI-DROPS) • Target: SARS-CoV-2 S protein • Origin: not reported • Dose: 10 mg or 20 mg • Frequency: single dose • Route of administration: intranasally Comparator: • Placebo, 1ml diluent solution, intranasally

Outcomes	Efficacy outcomes
	
	• All-cause mortality
	  * at up to 30 days: not planned planned
	  * at up to 60 days: not planned
	• Development of severe symptoms according to WHO scale (≥ 6 on the WHO Clinical Progression Scale; for mild disease): planned as change in WHO Clinical Progression Scale score up to day 8 and from day 9-29
	• Admission to hospital: planned as the number of COVID-19-related urgent medically attended visits, emergency department assessments or hospitalisations through day 29
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	
	Safety outcomes
	
	• Number of participants with AEs (all grades, grade 1-2, grade 3-4): planned up to day 29
	• Number of participants with SAEs: not planned
	
	Additional study outcomes
	
	• Viral load change from baseline to day 8 and day 29 based on RT-PCR determined COVID-19 viral titres (Log-10 copies/mL) from NP swabs
	• Proportion of subjects alive and free of hospitalization > 24h duration for acute COVID-19 illness management through day 29
	• Change in patient-reported COVID-19 symptoms as assessed using the Patient Reported Outcome Instrument for Capture of COVID-19-Related Symptoms (score of 0-50, with lower score meaning better outcome)

NCT04900428 *(Continued)*

Starting date	July 2021
Contact information	Mike Royal, MD (858) 203-4100 ext 4146 mroyal@sorrentotherapeutics.com
Notes	Developer: Sorrento Therapeutics, Inc. Funding: Sorrento Therapeutics, Inc. Recruitment status: not yet recruiting

NCT04913675

Study name	NCT04913675
Methods	Drug name: Sotrovimab (VIR-7831) Trial design: randomised, open-label, phase 3 study NCT number: NCT04913675 (date of trial registration: 4 June 2021) Target sample size: 1020 participants (estimated enrollment) Estimated completion date: 29 November 2022

Participants	Setting
	• Outpatient
	• Recruitment period: June 2021 - probably November 2022
	• Multi-centre
	Eligibility criteria
	• Inclusion criteria
	  * Participant must be ≥ 12 years old at time of consent and at high risk of progression of COVID-19 or ≥ 55 years old
	  * Participants must have a positive SARS-CoV-2 test result and oxygen saturation ≥ 94% on room air and have COVID-19 symptoms and be ≤ 7 days from onset of symptoms
	• Exclusion criteria
	  * Currently hospitalised or judged by the investigator as likely to require hospitalisation in the next 24 hours
	  * Symptoms consistent with severe COVID-19
	  * Participants who, in the judgement of the investigator are likely to die in the next 7 days
	  * Known hypersensitivity to any constituent present in the investigational product

Interventions	Intervention: Sotrovimab (VIR-7831)
	• Target: SARS-CoV-2 S protein
	• Origin: engineered mAb, its parental form is S309 (isolated from a SARS survivor)
	• Dose:
	  * Arm 1: 500 mg IV
	  * Arm 2: 500 mg IM
	  * Arm 3: 250 mg IM
	• Frequency: single dose
	• Route of administration:
	  * Arm 1: IV infusion
	  * Arm 2 and 3: IM injection

NCT04913675 *(Continued)*

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: not planned
	  * at up to 60 days: not planned
	• Development of severe symptoms according to WHO scale (≥ 6 on the WHO Clinical Progression Scale; for mild disease): planned as proportion of participants who progress to develop severe and/or critical COVID-19 as manifest by requirement for and method of supplemental oxygen
	• Admission to hospital (for outpatients only): not planned
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance: not planned
	Safety outcomes
	• Number of participants with AEs (all grades, grade 1-2, grade 3-4): planned up to 24 weeks
	• Number of participants with SAEs: planned up to 24 weeks
	Additional study outcomes
	• Proportion of participants who have progression of COVID-19 up to day 29
	• Proportion of participants with a persistently high SARS-CoV-2 viral load at day 8 by qRT-PCR
	• Change from baseline in viral load by qRT-PCR
	• Pharmacokinetics of VIR-7831: assessment of PK parameters and incidence and titers of anti-drug antibody (ADA), occurrence of adverse events of special interest (AESI)

Starting date	9 June 2021
Contact information	not provided
Notes	Developer: Vir Biotechnology, Inc., GlaxoSmithKline Funding: Vir Biotechnology, Inc. Recruitment status: not yet recruiting

NCT04952805

Study name	NCT04952805
Methods	Drug name: MAD0004J08 Trial design: randomised, placebo-controlled, doubleb-lind, multicentre, seamless adaptive, phase 2-3 study NCT number: NCT04952805 (date of trial registration: 7 July 2021) Target sample size: 800 participants (estimated enrollment) Estimated completion date: 31 August 2022
Participants	Setting • Outpatient • Recruitment period: June 2021 - March 2022

NCT04952805 *(Continued)*

- Multi-centre, country: Italy,

Eligibility criteria

- Inclusion criteria
  * Signed written informed consent taken before any study procedure from any patient capable of giving consent, or, when the patient is incapable of doing so, by his or her legal/authorised representative.
  * Age ≥18 years. At least 30% of participants will be ≥ 65 years old.
  * First nasopharyngeal swab testing positive for SARS-CoV-2 by RT-PCR taken no more than 3 days before randomisation (Visit 1). Results of "rapid" semi-quantitative tests are not acceptable.
  * Asymptomatic to moderately symptomatic outpatients with no need for immediate hospitalszation: grade 1, or grade 2 or grade 3 of Clinical Severity Scale.
  * No childbearing potential (post-menopause, surgically-induced, or pharmacologically-induced sterility) or, if of childbearing potential, negative urinary pregnancy test (women) and commitment to use at least 2 forms of contraception for at least 168 days from administration of study drug (men and women).
- Exclusion criteria
  * Severe or critical COVID-19: grade 4 or grade 5 of clinical severity scale.
  * Current hospitalisation and/or hospitalisation or emergency room visit in the past 14 days.
  * Need for immediate hospitalisation for any reason in the investigator's opinion.
  * Severe liver disease as determined by values of ALT and/or AST >5x upper limit of normal (ULN) and/or history of liver cirrhosis.
  * Severe renal disease as determined by estimated creatinine clearance (CcCl) <30 mL/min or serum creatinine >2 mg/dL (>176.8 µmol/L) or ongoing renal dialysis.
  * Absolute neutrophil count (ANC) < 1000/µL.
  * Demyelinating and connective tissue disease.
  * Active tuberculosis or suspected active bacterial, fungal, viral, or other infection (besides COVID- 19).
  * Any condition that in the Investigator's opinion may be negatively affected by the study treatments and/or study procedures.
  * Any condition, including psychiatric disorders, alcohol, or substance abuse, which in the Investigator's opinion may interfere with completion of the study procedures.
  * Any condition with life expectancy <6 months in the Investigator's opinion.
  * Ongoing or planned pregnancy.
  * Ongoing breast feeding.
  * History of life-threatening event in the 1 month before Visit 1.
  * History of surgery in the 1 month before Visit 1.
  * History of treatment with blood components in the 6 months before Visit 1.
  * History of cancer treated with chemotherapy in the 6 months before Visit 1.
  * History of solid organ transplant at any time before Visit 1.
  * History of severe and/or serious allergic reaction to monoclonal antibodies or any component of MAD0004J08, including anaphylaxis at any time before Visit 1.
  * Treatment with an investigational drug or vaccine within 5 half-lives or 30 days (whichever is longer) of randomisation.
  * Treatment at any time with monoclonal antibodies bamlanivimab, bamlanivimab + etesevimab combination, and casiribimab + imdevimab combination.

Interventions	Intervention MAD0004J08 • Target: SARS-CoV-2 S protein • Origin: not reported

NCT04952805 *(Continued)*

- Dose:
  - Stage I:
    - ☐ Arm 1: 400 mg IM
    - ☐ Arm 2: 100 mg IM
  - Stage II
    - ☐ Arm 1: dose level selected in Stage I
- Frequency: single dose
- Route of administration: IM

Comparator:

- Placebo, 2.5mL 2R vial, IM

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned from baseline up to day 168
	  * at up to 60 days: planned from baseline up to day 168
	• Development of severe symptoms according to WHO scale (≥ 6 on the WHO Clinical Progression Scale; for mild disease): planned as hospitalised participants requiring supplemental oxygen therapy
	• Admission to hospital (for outpatients only): planned
	• Length of hospital stay (for those admitted to hospital): planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue: not planned
	• Viral clearance; planned at days 7, 28, 168
	Safety outcomes
	• Number of participants with AEs (all grades, grade 1-2, grade 3-4): planned as severe (grade 3) unsolicited AEs and/or serious unsolicited AEs (SAEs)
	• Number of participants with SAEs: planned as severe (Grade 3) unsolicited AEs and/or serious unsolicited AEs (SAEs)
	Additional study outcomes
	• Time to SARS-CoV-2 clearance in the URT
	• Unsolicited AEs, including clinically relevant laboratory and ECG abnormalities
	• Solicited local AEs at the injection site
	• Number of participants who develop ADA
	• SARS-CoV-2 viral load in nasopharyngeal swab
	• SPO2% and lowest SpO2 % post-baseline
	• SpO2 % < 94%
	• Area under the curve (AUC) of COVID-19 total symptom score (range: 0-24)
	• Participants with increased dose home oxygen therapy
	• Cumulative time of hospitalised oxygen therapy in days
	• MAD0004J08 serum concentration

Starting date	6 June 2021
Contact information	Pierpaola Borgonovo 003903626331 info.studiclinici@opis.it
Notes	Developer: AchilleS Vaccines Srl Siena, Toscana Life Sciences Sviluppo s.r.l.

NCT04952805 *(Continued)*

	Funding: Toscana Life Sciences Sviluppo s.r.l. Recruitment status: recruiting

OPTIMISE-C19

Study name	OPTIMISE-C19
Methods	Drug name: Bamlanivimab, Regeneron Casirivimab + Imdevimab, Bamlanivimab + Etesevimab Trial design: randomised, open-label, adaptive platform trial NCT number: NCT04790786 (date of trial registration: March 2021) Target sample size: 5000 participants (estimated enrollment) Estimated completion date: December 2022

Participants	Setting
	
	• Outpatient
	• Recruitment period: March 2021 to February 2022
	• Single-centre
	
	Eligibility criteria
	
	• Inclusion criteria
	  * COVID-19 positive patients
	  * Eligible for mAB under FDA EUA
	• Exclusion criteria
	  * Death is deemed to be imminent or inevitable
	  * Previous participation in this REMAP within the last 90 days

Interventions	Intervention Bamlanivimab • Target: SARS-CoV-2 S protein • Origin: derived from B lymphocytes of a convalescent naturally SARS-CoV-2- infected patient • Dose: 700 mg • Frequency: single dose • Route of administration: intravenously Casirivimab + Imdevimab • Target: SARS-CoV-2 S protein • Origin: derived from B lymphocytes of a convalescent naturally SARS-CoV-2- infected patient • Dose: 1200 mg for each drug (2400 mg total) • Frequency: single dose • Route of administration: intravenously Bamlanivimab + Etesevimab • Target: SARS-CoV-2 S protein • Origin: derived from B lymphocytes of a convalescent naturally SARS-CoV-2- infected patient • Dose: not reported • Frequency: single dose

OPTIMISE-C19 *(Continued)*

	• Route of administration: intravenously

Outcomes	Efficacy outcomes
	• All-cause mortality
	  * at up to 30 days: planned
	  * at up to 60 days: planned
	• Clinical progression/improvement of symptoms: not planned
	• Development of severe symptoms according to WHO scale (≥ 6 on the WHO Clinical Progression Scale; for mild disease): not planned
	• Admission to hospital (for outpatients only): not planned
	• Length of hospital stay (for those admitted to hospital): not planned
	• Admission to ICU: not planned
	• Length of ICU stay: not planned
	• Quality of life, including fatigue, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days; up to 30 days, and longest follow-up available: not planned
	• Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: planned as nasophyngeal viral loads at day 28
	Safety outcomes
	• Number of participants with AEs (all grades, grade 1-2, grade 3-4): not planned
	• Number of participants with SAEs: not planned
	Additional study outcomes
	• Alive and free from hospitalisation through day 28
	• Organ-support free days at day 28
	• SARS-CoV-2 plasma viral loads through day 28
	• SARS-CoV-2 antibody titers
	• SARS-CoV-2 antibody neutralisation
	• SARS-CoV-2 immune responses
	• Detection of SARS-CoV-2 variants through next-generation sequencing
	• Duration of SAR-CoV-2 infectivity
	• Non-culture surrogates for SARS-CoV-2 infectivity through day 28, 90
	• Duration of SAR-CoV-2 infectivity through day 90

Starting date	March 10, 2021
Contact information	Contact: David T Huang, MD, MPH(412) 647-6818huangdt@upmc.eduContact: Kelsey Linstrum, MS203-947-6013linstrumk@upmc.edu
Notes	Funding: David T. Huang, MD, MPH Collaborators: University of Pittsburgh Medical CenterBerry Consultants Recruitment status: recruiting

Ab: antibody; **ACE:** angiotensis-converting enzyme; **AE:** adverse event; **ALT:** alanine aminotransferase;**ARB:** angiotensin receptor blocker; **ARDS:** acute respiratory distress syndrome; **AST:** aspartate aminotransferase; **AUC:** area under the curve; **BMI:** body mass index;**BP:** blood pressure; **CAP:** community-acquired pneumonia; **Cmax:** maximum observed serum concentration; **CNS:** central nervous system; **COVID-19:** coronavirus disease 2019; **CT:** computed tomography; **ECG:** electrocardiogram; **ECMO:** extracorporeal membrane oxygenation; **ED:** emergency department;**eGFR:** estimated glomerular filtration rate; **FDA:** US Food and Drug Administration; **hIVIG:** human intravenous immunoglobulin;**HR:** heart rate; **ICU:** intensive care unit;**IM:** intramuscular(ly); **IV:** intravenous; **IVIg:** intravenous immunoglobulin; **kg:** kilogram; **LAR:** legally authorised representative; **mAb:** monoclonal antibody; **mg:** milligram; **mL:** millilitre; **NEWS:** National Early Warning

Score; **NIAID:** National Institute of Allergy and Infectious Diseases; **NIV:** noninvasive ventilation; **NP:** nasopharyngeal; **NSAID:** nonsteroidal anti-inflammatory drug; **NYHA:** New York Heart Association; **OP:** oropharyngeal; **PaO2/FiO2:** ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; **PCR:** polymerase chain reaction; **PRO:** patient-reported outcomes; **RBC:** red blood cell; **RNA:** ribonucleic acid; **RT-PCR:** reverse transcription-polymerase chain reaction; **RT-qPCR:** quantitative reverse transcription-polymerase chain reaction; **SAE:** serious adverse event; **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2; **SC:** subcutaneous; **SpO2:** oxygen saturation;**ULN:** upper limit of normal; **WBC:** white blood cell; **WHOQOL:** World Health Organization quality of life scale; **WOCBP:** women of childbearing potential

RISK OF BIAS

Legend: ✓ Low risk of bias ✗ High risk of bias ~ Some concerns

Risk of bias for analysis 1.1 Mortality by day 30

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
BLAZE-1 (phase 2, 0.7g)	✓	✓	✓	✓	✓	✓
BLAZE-1 (phase 2, 2.8g)	✓	✓	✓	✓	✓	✓
BLAZE-1 (phase 2, 7.0g)	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.2 Admission to hospital or death

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
BLAZE-1 (phase 2, 0.7g)	✓	✓	✓	✓	✓	✓
BLAZE-1 (phase 2, 2.8g)	✓	✓	✓	✓	✓	✓
BLAZE-1 (phase 2, 7.0g)	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.3 Viral clearance at day 7

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
BLAZE-1 (phase 2, 0.7g)	✓	✓	✓	✓	✓	✓
BLAZE-1 (phase 2, 2.8g)	✓	✓	✓	✓	✓	✓
BLAZE-1 (phase 2, 7.0g)	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.4 Viral clearance at day 15

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
BLAZE-1 (phase 2, 0.7g)	✓	✓	✓	✓	✓	✓
BLAZE-1 (phase 2, 2.8g)	✓	✓	✓	✓	✓	✓
BLAZE-1 (phase 2, 7.0g)	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.5 Adverse events: all grades

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
BLAZE-1 (phase 2, 0.7g)	✓	✓	✓	✓	✓	✓
BLAZE-1 (phase 2, 2.8g)	✓	✓	✓	✓	✓	✓
BLAZE-1 (phase 2, 7.0g)	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.6 Serious adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
BLAZE-1 (phase 2, 0.7g)	✓	✓	✓	✓	✓	✓
BLAZE-1 (phase 2, 2.8g)	✓	✓	✓	✓	✓	✓
BLAZE-1 (phase 2, 7.0g)	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.1 Mortality by day 30

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
BLAZE-1 (phase 3)	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.2 Admission to hospital or death

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
BLAZE-1 (phase 3)	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.3 Viral clearance at day 3

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
BLAZE-1 (phase 3)	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.4 Viral clearance at day 7

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
BLAZE-1 (phase 3)	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.5 Viral clearance at day 15

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
BLAZE-1 (phase 3)	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.6 Adverse events: all grades

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
BLAZE-1 (phase 3)	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.7 Serious adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
BLAZE-1 (phase 3)	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.1 Admission to hospital or death

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Weinreich (phase 1/2, 2.4 g)	✓	✓	✓	✓	~	~
Weinreich (phase 1/2, 8.0 g)	✓	✓	✓	✓	~	~

Risk of bias for analysis 3.2 Adverse events: grade 3 and 4

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Weinreich (phase 1/2, 2.4 g)	✓	✓	✓	~	✓	~
Weinreich (phase 1/2, 8.0 g)	✓	✓	✓	~	✓	~

Risk of bias for analysis 3.3 Serious adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Weinreich (phase 1/2, 2.4 g)	✓	✓	✓	✓	✓	✓
Weinreich (phase 1/2, 8.0 g)	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 4.1 Mortality by day 30

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
COMET-ICE	✓	✓	✓	✓	~	~

Risk of bias for analysis 4.2 Development of severe symptoms according to WHO scale (≥ 5, incl. death)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
COMET-ICE	✓	✓	✓	✓	~	~

Risk of bias for analysis 4.3 Development of severe symptoms according to WHO scale (≥ score 7, IMV, incl. death)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
COMET-ICE	✓	✓	✓	✓	~	~

Risk of bias for analysis 4.4 Admission to hospital or death

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
COMET-ICE	✓	✓	✓	✓	~	~

Risk of bias for analysis 4.5 Admission to ICU by day 29

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
COMET-ICE	✓	✓	✓	✓	~	~

Risk of bias for analysis 4.6 Adverse events: all grades

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
COMET-ICE	✓	✓	✓	✓	~	~

Risk of bias for analysis 4.7 Adverse events: grade 3 and 4

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
COMET-ICE	✓	✓	✓	✓	~	~

Risk of bias for analysis 4.8 Serious adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
COMET-ICE	✓	✓	✓	✓	~	~

Risk of bias for analysis 5.1 Mortality by day 30

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Eom 2021 (40 mg/kg)	✓	✓	✓	✓	✓	✓
Eom 2021 (80 mg/kg)	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 5.2 Development of severe symptoms according to WHO scale (≥ score 7, IMV, incl. death)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Eom 2021 (40 mg/kg)	✓	✓	✓	✓	✓	✓
Eom 2021 (80 mg/kg)	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 5.3 Admission to hospital or death by day 30

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Eom 2021 (40 mg/kg)	✓	✓	✓	✓	✓	✓
Eom 2021 (80 mg/kg)	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 5.4 Admission to ICU by day 30

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Eom 2021 (40 mg/kg)	✓	✓	✓	✓	✓	✓
Eom 2021 (80 mg/kg)	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 5.5 Viral clearance at day 15

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Eom 2021 (40 mg/kg)	✓	✓	✓	✓	✓	✓
Eom 2021 (80 mg/kg)	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 5.6 Adverse events: all grades

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Eom 2021 (40 mg/kg)	✓	✓	✓	✓	✓	✓
Eom 2021 (80 mg/kg)	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 5.7 Adverse events: grade 3 and 4

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Eom 2021 (40 mg/kg)	✓	✓	✓	✓	✓	✓
Eom 2021 (80 mg/kg)	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 5.8 Serious adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Eom 2021 (40 mg/kg)	✓	✓	✓	✓	✓	✓
Eom 2021 (80 mg/kg)	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 6.1 Mortality by day 30

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
ACTIV-3	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 6.2 Mortality by day 90

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
ACTIV-3	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 6.3 Development of severe symptoms: need for NIV, IMV, ECMO, or renal replacement therapy at day 5 (group 5, 6 or 7)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
ACTIV-3	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 6.4 Development of severe symptoms: clinical status at day 5, intubation (group 6 at pulmonary scale)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
ACTIV-3	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 6.5 Hospital discharge up to 26 October 2020

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
ACTIV-3	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 6.6 Hospital discharge: at day 5

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
ACTIV-3	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 6.7 Adverse events: grade 3 and 4 by day 30

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
ACTIV-3	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 6.8 Serious adverse events by day 30

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
ACTIV-3	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 6.9 Serious adverse events (90 day follow-up)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
ACTIV-3	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 6.10 Sustained recovery (90 day follow-up)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
ACTIV-3	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 6.11 Neurological dysfunction by day 30: transient ischemic events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
ACTIV-3	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 6.12 Neurological dysfunction by day 30: acute delirium CVA

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
ACTIV-3	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 6.13 Neurological dysfunction by day 30: cerebrovascular event

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
ACTIV-3	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 6.14 Thromboembolic events by day 30

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
ACTIV-3	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 6.15 Renal dysfunction (or need for dialysis) by day 30

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
ACTIV-3	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 7.1 Mortality by day 30

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
RECOVERY	✓	✗	✓	✓	✓	✗

Risk of bias for analysis 7.2 Development of severe symptoms: requirement for IMV or death by day 28 (WHO ≥ 7)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
RECOVERY	✓	✗	✓	✓	✓	✗

Risk of bias for analysis 7.3 Hospital discharge alive by day 30

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
RECOVERY	✓	✗	✓	✓	✓	✗

Risk of bias for analysis 7.4 Thromboembolic events by day 30

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
RECOVERY	✓	✗	✓	✓	✓	✗

Risk of bias for analysis 7.5 Renal dysfunction (or need for dialysis) by day 30

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
RECOVERY	✓	✗	✓	✓	✓	✗

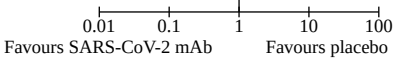
DATA AND ANALYSES

Comparison 1. Bamlanivimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Mortality by day 30	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.2 Admission to hospital or death	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.3 Viral clearance at day 7	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.4 Viral clearance at day 15	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.5 Adverse events: all grades	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.6 Serious adverse events	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Bamlanivimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 1: Mortality by day 30

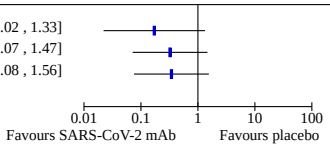
Study or Subgroup	Bamlanivimab Events	Bamlanivimab Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
BLAZE-1 (phase 2, 0.7g)	0	101	0	156	Not estimable		+ + + + + +
BLAZE-1 (phase 2, 2.8g)	0	107	0	156	Not estimable		+ + + + + +
BLAZE-1 (phase 2, 7.0g)	0	101	0	156	Not estimable		+ + + + + +



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.2. Comparison 1: Bamlanivimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 2: Admission to hospital or death

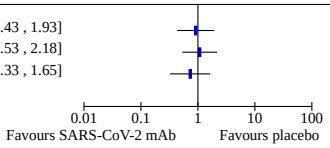
Study or Subgroup	Bamlanivimab or bamlanivimab with etesevimab Events	Bamlanivimab or bamlanivimab with etesevimab Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
BLAZE-1 (phase 2, 0.7g)	1	101	9	156	0.17 [0.02 , 1.33]		+ + + + + +
BLAZE-1 (phase 2, 2.8g)	2	107	9	156	0.32 [0.07 , 1.47]		+ + + + + +
BLAZE-1 (phase 2, 7.0g)	2	101	9	156	0.34 [0.08 , 1.56]		+ + + + + +



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.3. Comparison 1: Bamlanivimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 3: Viral clearance at day 7

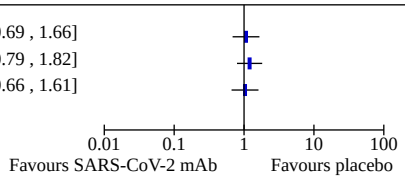
Study or Subgroup	Bamlanivimab or bamlanivimab with etesevimab Events	Bamlanivimab or bamlanivimab with etesevimab Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
BLAZE-1 (phase 2, 0.7g)	10	99	16	145	0.92 [0.43 , 1.93]		+ + + + + +
BLAZE-1 (phase 2, 2.8g)	12	101	16	145	1.08 [0.53 , 2.18]		+ + + + + +
BLAZE-1 (phase 2, 7.0g)	8	99	16	145	0.73 [0.33 , 1.65]		+ + + + + +

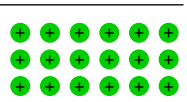


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.4. Comparison 1: Bamlanivimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 4: Viral clearance at day 15

Study or Subgroup	Bamlanivimab Events	Bamlanivimab Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
BLAZE-1 (phase 2, 0.7g)	25	91	34	132	1.07 [0.69 , 1.66]
BLAZE-1 (phase 2, 2.8g)	30	97	34	132	1.20 [0.79 , 1.82]
BLAZE-1 (phase 2, 7.0g)	25	94	34	132	1.03 [0.66 , 1.61]

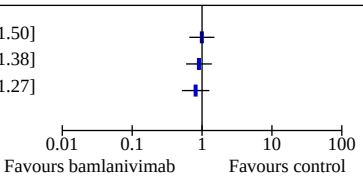


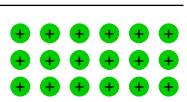


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.5. Comparison 1: Bamlanivimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 5: Adverse events: all grades

Study or Subgroup	Bamlanivimab Events	Bamlanivimab Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
BLAZE-1 (phase 2, 0.7g)	27	101	42	156	0.99 [0.66 , 1.50]
BLAZE-1 (phase 2, 2.8g)	26	107	42	156	0.90 [0.59 , 1.38]
BLAZE-1 (phase 2, 7.0g)	22	101	42	156	0.81 [0.52 , 1.27]

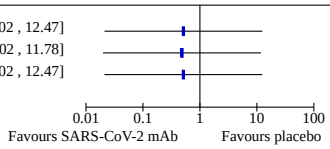


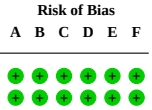


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.6. Comparison 1: Bamlanivimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 6: Serious adverse events

Study or Subgroup	Bamlanivimab or bamlanivimab with etesevimab Events	Bamlanivimab or bamlanivimab with etesevimab Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
BLAZE-1 (phase 2, 0.7g)	0	101	1	156	0.51 [0.02 , 12.47]
BLAZE-1 (phase 2, 2.8g)	0	107	1	156	0.48 [0.02 , 11.78]
BLAZE-1 (phase 2, 7.0g)	0	101	1	156	0.51 [0.02 , 12.47]



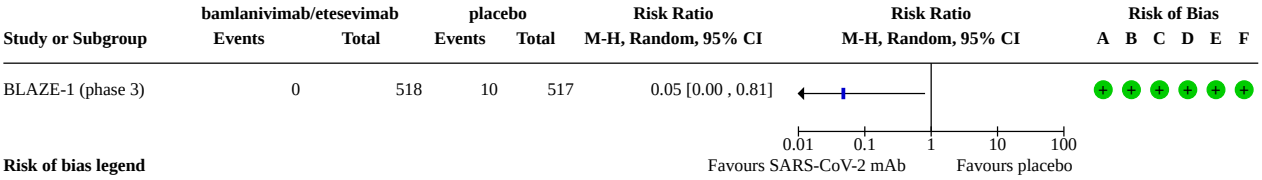


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 2. Bamlanivimab/etesevimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease)

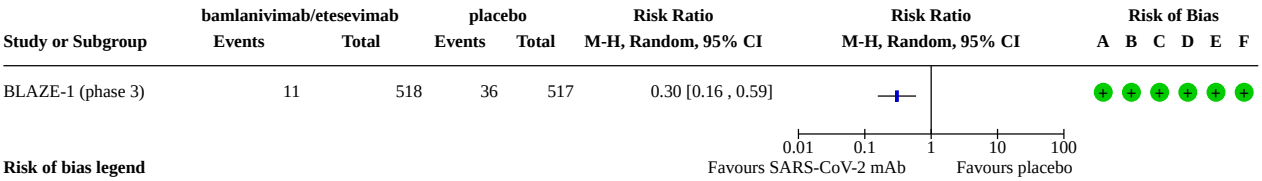
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Mortality by day 30	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.2 Admission to hospital or death	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.3 Viral clearance at day 3	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.4 Viral clearance at day 7	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.5 Viral clearance at day 15	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.6 Adverse events: all grades	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.7 Serious adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: Bamlanivimab/etesevimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 1: Mortality by day 30



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

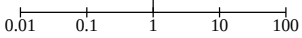
Analysis 2.2. Comparison 2: Bamlanivimab/etesevimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 2: Admission to hospital or death



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.3. Comparison 2: Bamlanivimab/etesevimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 3: Viral clearance at day 3

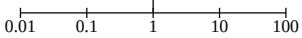
Study or Subgroup	bamlanivimab/etesevimab Events	Total	placebo Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
BLAZE-1 (phase 3)	32	486	15	482	2.12 [1.16 , 3.86]		+ + + + + +



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.4. Comparison 2: Bamlanivimab/etesevimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 4: Viral clearance at day 7

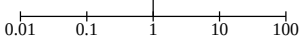
Study or Subgroup	bamlanivimab/etesevimab Events	Total	placebo Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
BLAZE-1 (phase 3)	75	486	41	482	1.81 [1.27 , 2.60]		+ + + + + +



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.5. Comparison 2: Bamlanivimab/etesevimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 5: Viral clearance at day 15

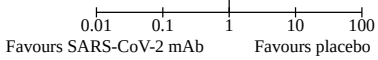
Study or Subgroup	bamlanivimab/etesevimab Events	Total	placebo Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
BLAZE-1 (phase 3)	136	486	101	482	1.34 [1.07 , 1.67]		+ + + + + +



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.6. Comparison 2: Bamlanivimab/etesevimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 6: Adverse events: all grades

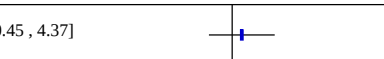
Study or Subgroup	bamlanivimab/etesevimab Events	Total	placebo Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
BLAZE-1 (phase 3)	69	518	60	517	1.15 [0.83 , 1.59]		+ + + + + +



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.7. Comparison 2: Bamlanivimab/etesevimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 7: Serious adverse events

Study or Subgroup	bamlanivimab/etesevimab Events	Total	placebo Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
BLAZE-1 (phase 3)	7	518	5	517	1.40 [0.45 , 4.37]		+ + + + + +



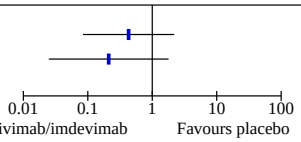
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 3. Casirivimab/imdevimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Admission to hospital or death	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.2 Adverse events: grade 3 and 4	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.3 Serious adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3: Casirivimab/imdevimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 1: Admission to hospital or death

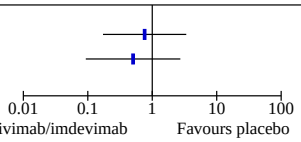
Study or Subgroup	casirivimab/imdevimab Events	Total	placebo Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Weinreich (phase 1/2, 2.4 g)	2	215	5	231	0.43 [0.08 , 2.19]		+ + + + ? ?
Weinreich (phase 1/2, 8.0 g)	1	219	5	231	0.21 [0.02 , 1.79]		+ + + + ? ?



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.2. Comparison 3: Casirivimab/imdevimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 2: Adverse events: grade 3 and 4

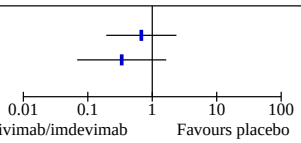
Study or Subgroup	casirivimab/imdevimab Events	Total	placebo Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Weinreich (phase 1/2, 2.4 g)	3	258	4	262	0.76 [0.17 , 3.37]		+ + + ? + ?
Weinreich (phase 1/2, 8.0 g)	2	260	4	262	0.50 [0.09 , 2.73]		+ + + ? + ?



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.3. Comparison 3: Casirivimab/imdevimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 3: Serious adverse events

Study or Subgroup	casirivimab/imdevimab Events	Total	placebo Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Weinreich (phase 1/2, 2.4 g)	4	258	6	262	0.68 [0.19 , 2.37]		+ + + + + +
Weinreich (phase 1/2, 8.0 g)	2	260	6	262	0.34 [0.07 , 1.65]		+ + + + + +



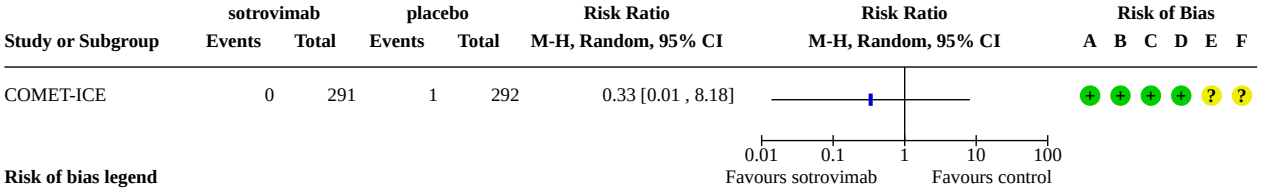
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 4. Sotrovimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Mortality by day 30	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 Development of severe symptoms according to WHO scale (≥ 5, incl. death)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.3 Development of severe symptoms according to WHO scale (≥ score 7, IMV, incl. death)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.4 Admission to hospital or death	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.5 Admission to ICU by day 29	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.6 Adverse events: all grades	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.7 Adverse events: grade 3 and 4	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.8 Serious adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

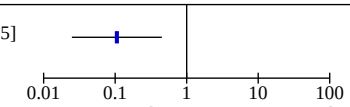
Analysis 4.1. Comparison 4: Sotrovimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 1: Mortality by day 30



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.2. Comparison 4: Sotrovimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 2: Development of severe symptoms according to WHO scale (≥ 5, incl. death)

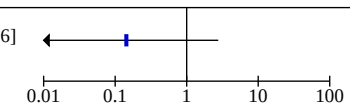
Study or Subgroup	sotrovimab Events	sotrovimab Total	placebo Events	placebo Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
COMET-ICE	2	291	19	292	0.11 [0.02 , 0.45]		+	+	+	+	?	?



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.3. Comparison 4: Sotrovimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 3: Development of severe symptoms according to WHO scale (≥ score 7, IMV, incl. death)

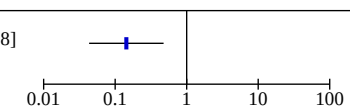
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
COMET-ICE	0	291	3	292	0.14 [0.01 , 2.76]		+	+	+	+	?	?



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.4. Comparison 4: Sotrovimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 4: Admission to hospital or death

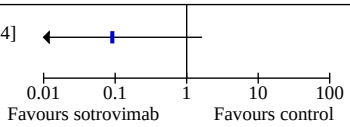
Study or Subgroup	sotrovimab Events	sotrovimab Total	placebo Events	placebo Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
COMET-ICE	3	291	21	292	0.14 [0.04 , 0.48]		+	+	+	+	?	?



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.5. Comparison 4: Sotrovimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 5: Admission to ICU by day 29

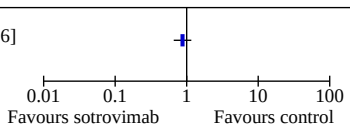
Study or Subgroup	sotrovimab Events	sotrovimab Total	placebo Events	placebo Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
COMET-ICE	0	291	5	292	0.09 [0.01 , 1.64]		+	+	+	+	?	?



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.6. Comparison 4: Sotrovimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 6: Adverse events: all grades

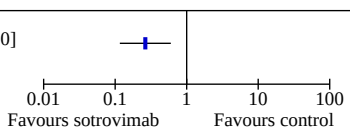
Study or Subgroup	sotrovimab Events	sotrovimab Total	placebo Events	placebo Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
COMET-ICE	73	430	85	438	0.87 [0.66 , 1.16]		+	+	+	+	?	?



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

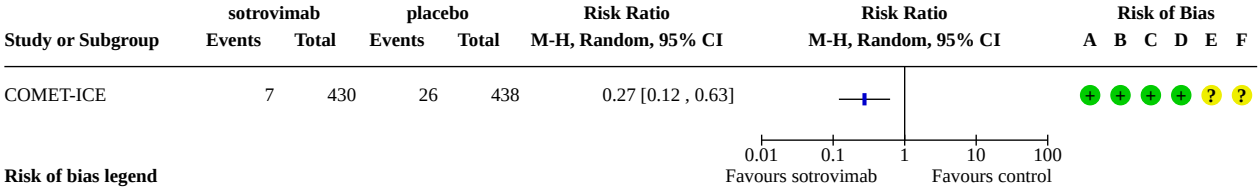
Analysis 4.7. Comparison 4: Sotrovimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 7: Adverse events: grade 3 and 4

Study or Subgroup	sotrovimab Events	sotrovimab Total	placebo Events	placebo Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
COMET-ICE	7	430	27	438	0.26 [0.12 , 0.60]		+	+	+	+	?	?



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.8. Comparison 4: Sotrovimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 8: Serious adverse events



Risk of bias legend

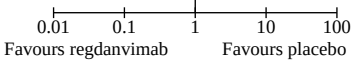
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 5. Regdanvimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Mortality by day 30	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.2 Development of severe symptoms according to WHO scale (≥ score 7, IMV, incl. death)	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.3 Admission to hospital or death by day 30	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.4 Admission to ICU by day 30	2	410	Risk Ratio (M-H, Random, 95% CI)	Not estimable
5.5 Viral clearance at day 15	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.6 Adverse events: all grades	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.7 Adverse events: grade 3 and 4	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.8 Serious adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5: Regdanvimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 1: Mortality by day 30

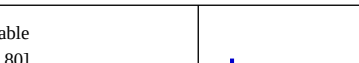
Study or Subgroup	regdanvimab Events	regdanvimab Total	placebo Events	placebo Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Eom 2021 (40 mg/kg)	0	101	0	103	Not estimable		+ + + + + +
Eom 2021 (80 mg/kg)	0	103	0	103	Not estimable		+ + + + + +



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 5.2. Comparison 5: Regdanvimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 2: Development of severe symptoms according to WHO scale (≥ score 7, IMV, incl. death)

Study or Subgroup	regdanvimab Events	regdanvimab Total	placebo Events	placebo Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Eom 2021 (40 mg/kg)	0	101	0	103	Not estimable		+ + + + + +
Eom 2021 (80 mg/kg)	1	103	0	103	3.00 [0.12 , 72.80]		+ + + + + +



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 5.3. Comparison 5: Regdanvimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 3: Admission to hospital or death by day 30

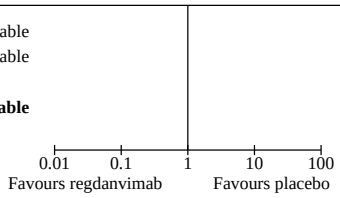
Study or Subgroup	regdanvimab Events	regdanvimab Total	placebo Events	placebo Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Eom 2021 (40 mg/kg)	4	101	9	103	0.45 [0.14 , 1.42]		+ + + + + +
Eom 2021 (80 mg/kg)	5	103	9	103	0.56 [0.19 , 1.60]		+ + + + + +

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 5.4. Comparison 5: Regdanvimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 4: Admission to ICU by day 30

Study or Subgroup	regdanvimab Events	regdanvimab Total	placebo Events	placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Eom 2021 (40 mg/kg)	0	101	0	103		Not estimable
Eom 2021 (80 mg/kg)	0	103	0	103		Not estimable
Total (95% CI)		**204**		**206**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

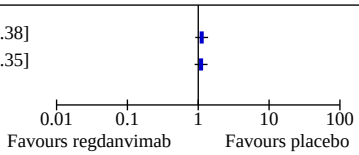


Risk of Bias: A B C D E F

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 5.5. Comparison 5: Regdanvimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 5: Viral clearance at day 15

Study or Subgroup	CT-P59 Events	CT-P59 Total	placebo Events	placebo Total	Risk Ratio M-H, Random, 95% CI
Eom 2021 (40 mg/kg)	68	101	62	103	1.12 [0.91 , 1.38]
Eom 2021 (80 mg/kg)	68	103	62	103	1.10 [0.89 , 1.35]

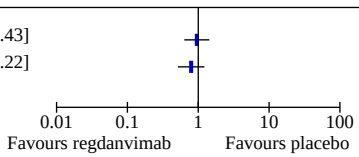


Risk of Bias: A B C D E F

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 5.6. Comparison 5: Regdanvimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 6: Adverse events: all grades

Study or Subgroup	CT-P59 Events	CT-P59 Total	placebo Events	placebo Total	Risk Ratio M-H, Random, 95% CI
Eom 2021 (40 mg/kg)	31	105	34	110	0.96 [0.64 , 1.43]
Eom 2021 (80 mg/kg)	27	110	34	110	0.79 [0.52 , 1.22]

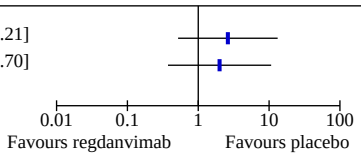


Risk of Bias: A B C D E F

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 5.7. Comparison 5: Regdanvimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 7: Adverse events: grade 3 and 4

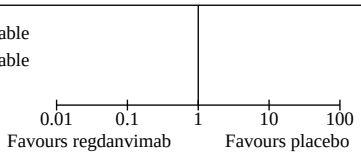
Study or Subgroup	CT-P59 Events	CT-P59 Total	placebo Events	placebo Total	Risk Ratio M-H, Random, 95% CI
Eom 2021 (40 mg/kg)	5	105	2	110	2.62 [0.52 , 13.21]
Eom 2021 (80 mg/kg)	4	110	2	110	2.00 [0.37 , 10.70]



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 5.8. Comparison 5: Regdanvimab in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease), Outcome 8: Serious adverse events

Study or Subgroup	CT-P59 Events	CT-P59 Total	placebo Events	placebo Total	Risk Ratio M-H, Random, 95% CI
Eom 2021 (40 mg/kg)	0	105	0	110	Not estimable
Eom 2021 (80 mg/kg)	0	110	0	110	Not estimable



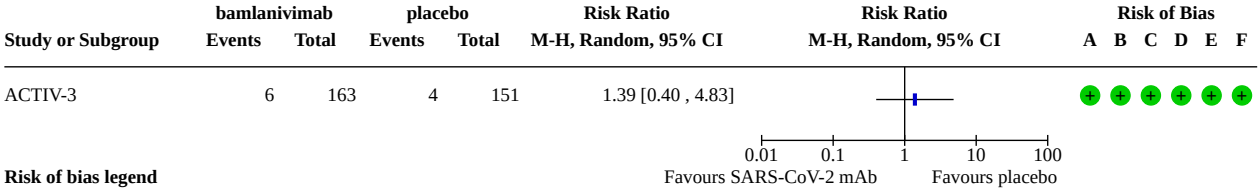
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 6. Bamlanivimab in hospitalised individuals with COVID-19 (moderate and severe disease)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Mortality by day 30	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.2 Mortality by day 90	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
6.3 Development of severe symptoms: need for NIV, IMV, ECMO, or renal replacement therapy at day 5 (group 5, 6 or 7)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.4 Development of severe symptoms: clinical status at day 5, intubation (group 6 at pulmonary scale)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.5 Hospital discharge up to 26 October 2020	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.6 Hospital discharge: at day 5	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.7 Adverse events: grade 3 and 4 by day 30	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.8 Serious adverse events by day 30	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.9 Serious adverse events (90 day follow-up)	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
6.10 Sustained recovery (90 day follow-up)	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
6.11 Neurological dysfunction by day 30: transient ischemic events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.12 Neurological dysfunction by day 30: acute delirium CVA	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.13 Neurological dysfunction by day 30: cerebrovascular event	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.14 Thromboembolic events by day 30	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.15 Renal dysfunction (or need for dialysis) by day 30	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

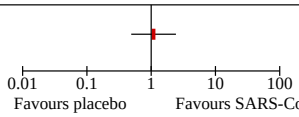
Analysis 6.1. Comparison 6: Bamlanivimab in hospitalised individuals with COVID-19 (moderate and severe disease), Outcome 1: Mortality by day 30



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.2. Comparison 6: Bamlanivimab in hospitalised individuals with COVID-19 (moderate and severe disease), Outcome 2: Mortality by day 90

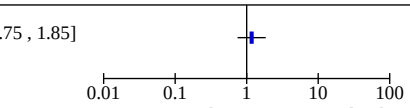
Study or Subgroup	log[Hazard Ratio]	SE	bamlanivimab Total	placebo Total	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI	Risk of Bias A B C D E F
ACTIV-3	0.086178	0.408487	163	151	1.09 [0.49 , 2.43]		+ + + + + +



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.3. Comparison 6: Bamlanivimab in hospitalised individuals with COVID-19 (moderate and severe disease), Outcome 3: Development of severe symptoms: need for NIV, IMV, ECMO, or renal replacement therapy at day 5 (group 5, 6 or 7)

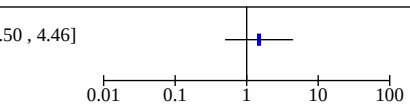
Study or Subgroup	bamlanivimab Events	bamlanivimab Total	placebo Events	placebo Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
ACTIV-3	34	161	27	150	1.17 [0.75 , 1.85]		+ + + + + +



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.4. Comparison 6: Bamlanivimab in hospitalised individuals with COVID-19 (moderate and severe disease), Outcome 4: Development of severe symptoms: clinical status at day 5, intubation (group 6 at pulmonary scale)

Study or Subgroup	bamlanivimab Events	bamlanivimab Total	placebo Events	placebo Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
ACTIV-3	8	161	5	150	1.49 [0.50 , 4.46]		+ + + + + +



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

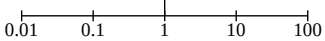
Analysis 6.5. Comparison 6: Bamlanivimab in hospitalised individuals with COVID-19 (moderate and severe disease), Outcome 5: Hospital discharge up to 26 October 2020

Study or Subgroup	log[Hazard Ratio]	SE	bamlanivimab Total	placebo Total	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI	Risk of Bias A B C D E F
ACTIV-3	-0.0305	0.1086	163	151	0.97 [0.78 , 1.20]		+ + + + + +

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.6. Comparison 6: Bamlanivimab in hospitalised individuals with COVID-19 (moderate and severe disease), Outcome 6: Hospital discharge: at day 5

Study or Subgroup	bamlanivimab Events	Total	placebo Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
ACTIV-3	90	163	85	151	0.98 [0.81 , 1.19]		+ + + + + +



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

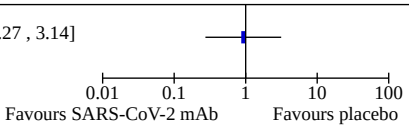
Analysis 6.7. Comparison 6: Bamlanivimab in hospitalised individuals with COVID-19 (moderate and severe disease), Outcome 7: Adverse events: grade 3 and 4 by day 30

Study or Subgroup	bamlanivimab Events	Total	placebo Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
ACTIV-3	37	163	27	151	1.27 [0.81 , 1.98]		+ + + + + +

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.8. Comparison 6: Bamlanivimab in hospitalised individuals with COVID-19 (moderate and severe disease), Outcome 8: Serious adverse events by day 30

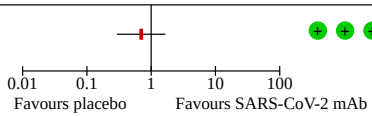
Study or Subgroup	bamlanivimab Events	bamlanivimab Total	placebo Events	placebo Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
ACTIV-3	5	163	5	151	0.93 [0.27 , 3.14]		+	+	+	+	+	+



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.9. Comparison 6: Bamlanivimab in hospitalised individuals with COVID-19 (moderate and severe disease), Outcome 9: Serious adverse events (90 day follow-up)

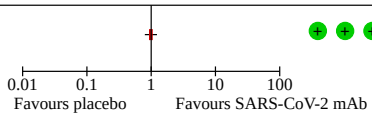
Study or Subgroup	log[Hazard Ratio]	SE	bamlanivimab Total	placebo Total	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI	Risk of Bias A	B	C	D	E	F
ACTIV-3	-0.356675	0.443541	163	151	0.70 [0.29 , 1.67]		+	+	+	+	+	+



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.10. Comparison 6: Bamlanivimab in hospitalised individuals with COVID-19 (moderate and severe disease), Outcome 10: Sustained recovery (90 day follow-up)

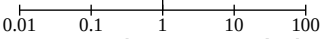
Study or Subgroup	log[Hazard Ratio]	SE	bamlanivimab Total	placebo Total	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI	Risk of Bias A	B	C	D	E	F
ACTIV-3	-0.01005	0.110863	163	151	0.99 [0.80 , 1.23]		+	+	+	+	+	+



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.11. Comparison 6: Bamlanivimab in hospitalised individuals with COVID-19 (moderate and severe disease), Outcome 11: Neurological dysfunction by day 30: transient ischemic events

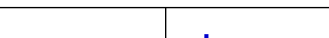
Study or Subgroup	bamlanivimab Events	bamlanivimab Total	placebo Events	placebo Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
ACTIV-3	0	152	0	141	Not estimable		+	+	+	+	+	+



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.12. Comparison 6: Bamlanivimab in hospitalised individuals with COVID-19 (moderate and severe disease), Outcome 12: Neurological dysfunction by day 30: acute delirium CVA

Study or Subgroup	bamlanivimab Events	bamlanivimab Total	placebo Events	placebo Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
ACTIV-3	4	152	1	141	3.71 [0.42 , 32.80]		+	+	+	+	+	+



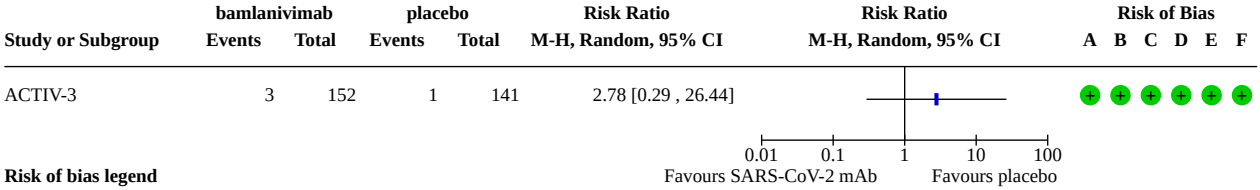
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.13. Comparison 6: Bamlanivimab in hospitalised individuals with COVID-19 (moderate and severe disease), Outcome 13: Neurological dysfunction by day 30: cerebrovascular event

Study or Subgroup	bamlanivimab Events	bamlanivimab Total	placebo Events	placebo Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A	B	C	D	E	F
ACTIV-3	0	152	1	141	0.31 [0.01 , 7.53]		+	+	+	+	+	+

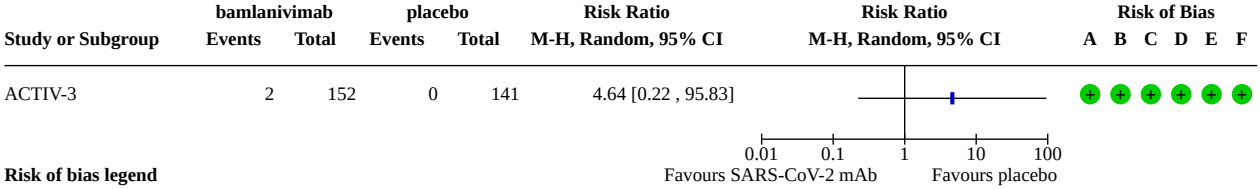
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.14. Comparison 6: Bamlanivimab in hospitalised individuals with COVID-19 (moderate and severe disease), Outcome 14: Thromboembolic events by day 30



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.15. Comparison 6: Bamlanivimab in hospitalised individuals with COVID-19 (moderate and severe disease), Outcome 15: Renal dysfunction (or need for dialysis) by day 30



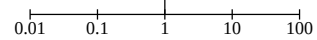
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 7. Casirivimab/imdevimab in hospitalised individuals with COVID-19 (moderate and severe disease)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Mortality by day 30	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.2 Development of severe symptoms: requirement for IMV or death by day 28 (WHO ≥ 7)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.3 Hospital discharge alive by day 30	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
7.4 Thromboembolic events by day 30	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.5 Renal dysfunction (or need for dialysis) by day 30	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 7.1. Comparison 7: Casirivimab/imdevimab in hospitalised individuals with COVID-19 (moderate and severe disease), Outcome 1: Mortality by day 30

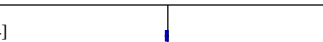
Study or Subgroup	casirivimab/imdevimab Events	Total	usual care alone Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
RECOVERY	944	4839	1026	4946	0.94 [0.87 , 1.02]		+ - + + + -



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 7.2. Comparison 7: Casirivimab/imdevimab in hospitalised individuals with COVID-19 (moderate and severe disease), Outcome 2: Development of severe symptoms: requirement for IMV or death by day 28 (WHO ≥ 7)

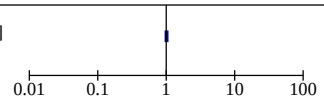
Study or Subgroup	casirivimab/imdevimab Events	Total	usual care alone Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
RECOVERY	1089	4556	1151	4642	0.96 [0.90 , 1.04]		+ - + + + -



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 7.3. Comparison 7: Casirivimab/imdevimab in hospitalised individuals with COVID-19 (moderate and severe disease), Outcome 3: Hospital discharge alive by day 30

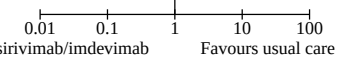
Study or Subgroup	casirivimab/imdevimab Events	Total	usual care alone Events	Total	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI	Risk of Bias A B C D E F
RECOVERY	3375	4839	3413	4946	1.01 [0.98 , 1.04]		+ - + + + -



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 7.4. Comparison 7: Casirivimab/imdevimab in hospitalised individuals with COVID-19 (moderate and severe disease), Outcome 4: Thromboembolic events by day 30

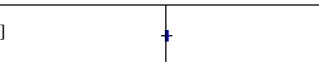
Study or Subgroup	casirivimab/imdevimab Events	Total	usual care alone Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
RECOVERY	249	4839	248	4946	1.03 [0.86 , 1.22]		+ - + + + -



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 7.5. Comparison 7: Casirivimab/imdevimab in hospitalised individuals with COVID-19 (moderate and severe disease), Outcome 5: Renal dysfunction (or need for dialysis) by day 30

Study or Subgroup	casirivimab/imdevimab Events	Total	usual care alone Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
RECOVERY	203	4783	201	4887	1.03 [0.85 , 1.25]		+ - + + + -



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

ADDITIONAL TABLES

Table 1. Main study characteristics of included RCTs

Study	Intervention	Population	Country	N randomised up to data cut-off	Status
ACTIV-3	Bamlanivimab (7.0 g)	Inpatients, moderate disease	USA, Denmark, Singapore, Spain, India, Poland, Switzerland, UK	314	Interim analysis, bamlanivimab arm stopped for futility, recruitment ongoing for other arms
BLAZE-1 (phase 2)	Bamlanivimab (0.7 g, 2.8 g, 7.0 g) bamlanivimab/etesevimab (2.8 g + 2.8 g)	Outpatients, mild disease	USA, Puerto Rico (added after publication of interim results)	592	Recruiting, estimated enrolment 4000 participants Estimated study completion: May 2021
Weinreich (phase 1/2)	Casirivimab/imdevimab (REGN10933/	Outpatients, mild disease	USA, Chile, Mexico, Romania	275	Interim analysis, recruiting, estimated enrolment 6420 participants

Table 1. Main study characteristics of included RCTs *(Continued)*

	REGN10987; 2.4 g, 8 g)				Estimated study completion: August 2021
Weinreich (phase 3)	Casirivimab/imdevimab (REGN10933/ REGN10987; 1200 mg, 2400 mg,)	Outpatients, mild disease	USA, Mexico, Chile, Romania	592	Interim analysis, recruiting, estimated enrolment 6420 participants Estimated study completion: August 2021
RECOVERY	Casivirimab/imdevimab (4g, 4g)	Hospitalised patients, moderate or severe disease	UK	9185	Preprint publication, recruiting, estimated enrolment 40000 participants, estimated study completion: December 2031
COMET-ICE	Sotrovimab (VIR-7831; GSK4182136; 500 mg)	Outpatients, mild disease	USA, Brazil, Canada, Spain	583	Preprint publication, interim analysis, data collection ongoing; Estimated completion date: July 2021
Eom 2021	Regdanvimab (CT-P59; 40 mg/kg, 80 mg/kg)	Outpatients, mild disease	South Korea, Romania, Spain and USA	327	recruiting, estimated enrolment: 1020 participants Estimated completion date: September 2021

APPENDICES

Appendix 1. Search strategy: MEDLINE via Ovid

Searches

1 "spike protein, SARS-CoV-2".mp.

2 Coronavirus Infections/ or Coronavirus/

3 SARS-CoV-2/ or COVID-19/

4 ("2019 nCoV" or 2019nCoV or coronavir* or coronovir* or COVID or COVID19 or HCoV* or "nCov 2019" or "SARS CoV2" or "SARS CoV 2" or SARSCoV2 or "SARSCoV 2").tw,kf.

5 "severe acute respiratory syndrome coronavirus 2".tw,kf,nm.

6 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).tw,kf.

7 or/2-6

8 *Antibodies, Monoclonal/

9 Antibodies, Neutralizing/

10 Antibodies, Viral/

11 ((antibod* or mAb* or nAb*) adj2 (therap* or treatment* or neutrali?ing or prevent* or protect* or prophylax*)).tw,kf.

12 Spike Glycoprotein, Coronavirus/

13 Binding, Competitive/

14 (compet* adj1 bind*).tw,kf.

15 ("spike protein*" or "s protein*" or "Spike (S) protein").mp.

16 ((cocktail* or mixture* or combination*) adj3 (mAb* or antibod* or nAb*)).tw,kf.

17 (LY3832479* or LY-CoV016* or LY-3832479* or LYCoV016* or JS016* or JS-016* or etesevimab*).mp.

18 (REGN-COV2* or REGN-COV-2* or REGN10933* or REGN10987* or REGN-10933* or REGN-10987* or REGEN-COV2* or REGEN-COV-2* or REGEN10933* or REGEN10987* or REGEN-10933* or REGEN-10987* or casirivimab* or imdevimab*).mp.

19 (LY3819253* or LY-3819253* or LY-CoV555* or LYCoV555* or bamlanivimab* or banlanivimab*).mp.

20 (VIR7831* or VIR-7831* or GSK4182136* or GSK-4182136* or sotrovimab*).mp.

21 (AZD7442* or AZD-7442* or AZD8895* or AZD-8895* or tixagevimab* or COV2-2196 or COV22196* or AZD1061* or AZD-1061* or cilgavimab* or COV2-2130* or COV22130*).mp.

22 (DXP-593* or DXP593* or BGB-DXP593* or BGBDXP593* or BGB-DXP-593*).mp.

23 (TY027* or TY-027*).mp.

24 (CTP59* or CTP-59* or regdanvimab*).mp.

25 (STI1499* or STI-1499* or covi-shield* or covishield* or COVI-GUARD* or COVIguard*).mp.

26 (BRII196* or BRII-196*).mp.

27 (SCTA01* or SCTA-01*).mp.

28 (MW33* or MW-33*).mp.

29 (BRII198* or BRII-198*).mp.

30 (HFB30132A* or HFB-30132A*).mp.

31 (ADM03820* or ADM-03820*).mp.

32 (HLX70* or HLX-70*).mp.

33 (STI2020* or STI-2020* or COVIAMG* or COVI-AMG*).mp.

34 (DZIF10c* or DZIF-10c* or BI767551* or BI-767551*).mp.

35 (COV2-2381* or COV22381*).mp.

36 (ABBV-47D11* or 47D11* or ABBV47D11*).mp.

37 (COR-101* or COR101* or STE90-C11*).mp.

38 (DXP-604* or DXP604* or BGB-DXP604* or BGBDXP604* or BGB-DXP-604*).mp.

39 (Chicken egg antibod* or egg yolk antibod* or IgY*).mp.

40 (VIR-7832 or VIR7832 or GSK4182137* or GSK-4182137*).mp.

41 (IDB003 or MD65 or MTX-COVAB).mp.

42 (C144-LS or C144LS or C-135-LS or C135-LS or C135LS or SAB-185 or SAB185 or JMB2002 or JMB-2002 or TATX-03 or TATX03 or NOVOAB-20 or NOVOAB20 or NOVO-AB-20 or ABP-300 or ABP300 or MW05 or MW-05 or MW07 or MW-07 or ACmab1 or covimax or adimab or CPI-006 or CPI006).tw,kf,nm.

43 Single-Chain Antibodies/

44 (nmabs or diabod* or dia-bod* or nanobod* or nano-bod* or microbod* or micro-bod* or monobod* or mono-bod*).tw,kf,nm.

45 (scFv* or "single-chain*" or "heavy chain*" or HCAbs or SCAbs or FAB).tw,kf,nm.

46 or/8-45

47 7 and (1 or 46)

48 (exp Animals/ or exp Animal Experimentation/ or exp Models, Animal/) not Humans/

49 47 not 48

50 limit 49 to yr="2020-Current"

Appendix 2. Search strategy: Embase via Ovid

Searches

1 coronavirinae/ or coronaviridae/ or coronaviridae infection/

2 coronavirus disease 2019/

3 Coronavirus infection/

4 sars-related coronavirus/

5 "Severe acute respiratory syndrome coronavirus 2"/

6 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).tw,kw.

7 ("2019 nCoV" or 2019nCoV or coronavir* or coronovir* or COVID or COVID19 or HCoV* or "nCov 2019" or "SARS CoV2" or "SARS CoV 2" or SARSCoV2 or "SARSCoV 2").tw,kw.

8 "Severe acute respiratory syndrome coronavirus 2".mp.

9 or/1-8

10 Antibodies, Monoclonal/

11 Antibodies, Neutralizing/

12 Antibodies, Viral/

13 ((antibod* or mAb* or nAb*) adj2 (therap* or treatment* or neutrali?ing or prevent* or protect* or prophylax*)).tw,kw.

14 Spike Glycoprotein, Coronavirus/

15 Binding, Competitive/

16 (compet* adj1 bind*).tw,kw.

17 ("spike protein*" or "s protein*" or "Spike (S) protein").mp.

18 ((cocktail* or mixture* or combination*) adj3 (mAb* or antibod* or nAb*)).tw,kw.

19 (LY3832479* or LY-CoV016* or LY-3832479* or LYCoV016* or JS016* or JS-016* or etesevimab*).mp.

20 (REGN-COV2* or REGN-COV-2* or REGN10933* or REGN10987* or REGN-10933* or REGN-10987* or REGEN-COV2* or REGEN-COV-2* or REGEN10933* or REGEN10987* or REGEN-10933* or REGEN-10987* or casirivimab* or imdevimab*).mp.

21 (LY3819253* or LY-3819253* or LY-CoV555* or LYCoV555* or bamlanivimab* or banlanivimab*).mp.

22 (VIR7831* or VIR-7831* or GSK4182136* or GSK-4182136* or sotrovimab*).mp.

23 (AZD7442* or AZD-7442* or AZD8895* or AZD-8895* or tixagevimab* or COV2-2196 or COV22196* or AZD1061* or AZD-1061* or cilgavimab* or COV2-2130* or COV22130*).mp.

24 (DXP-593* or DXP593* or BGB-DXP593* or BGBDXP593* or BGB-DXP-593*).mp.

25 (TY027* or TY-027*).mp.

26 (CTP59* or CTP-59* or regdanvimab*).mp.

27 (STI1499* or STI-1499* or COVI-shield* or COVIshield* or COVI-GUARD* or COVIguard*).mp.

28 (BRII196* or BRII-196*).mp.

29 (SCTA01* or SCTA-01*).mp.

30 (MW33* or MW-33*).mp.

31 (BRII198* or BRII-198*).mp.

32 (HFB30132A* or HFB-30132A*).mp.

33 (ADM03820* or ADM-03820*).mp.

34 (HLX70* or HLX-70*).mp.

35 (STI2020* or STI-2020* or COVIAMG* or COVI-AMG*).mp.

36 (DZIF10c* or DZIF-10c* or BI767551* or BI-767551*).mp.

37 (COV2-2381* or COV22381*).mp.

38 (ABBV-47D11* or 47D11* or ABBV47D11*).mp.

39 (COR-101* or COR101* or STE90-C11*).mp.

40 (DXP-604* or DXP604* or BGB-DXP604* or BGBDXP604* or BGB-DXP-604*).mp.

41 (Chicken egg antibod* or egg yolk antibod* or IgY*).mp.

42 (VIR-7832* or VIR7832* or GSK4182137* or GSK-4182137*).mp.

43 (IDB003 or MD65 or MTX-COVAB).mp.

44 (C144-LS or C144LS or C-135-LS or C135-LS or C135LS or SAB-185 or SAB185 or JMB2002 or JMB-2002 or TATX-03 or TATX03 or NOVOAB-20 or NOVOAB20 or NOVO-AB-20 or ABP-300 or ABP300 or MW05 or MW-05 or MW07 or MW-07 or ACmab1 or covimax or adimab or CPI-006 or CPI006).tw,kw.

45 single chain fragment variable antibody/

46 (nmabs or diabod* or dia-bod* or nanobod* or nano-bod* or microbod* or micro-bod* or monobod* or mono-bod*).mp.

47 (scFv* or "single-chain*" or "heavy chain*" or HCAbs or SCAbs or FAB).tw,kw.

48 or/10-47

49 9 and 48

50 (exp animal/ or nonhuman/) not exp human/

51 Animal experiment/ not (human experiment/ or human/)

52 or/50-51

53 49 not 52

54 limit 53 to yr="2020 -Current"

55 limit 54 to medline

56 54 not 55

Appendix 3. Search strategy: Cochrane Covid-19 Study Register

"Ly-3832479" OR Ly3832479 OR "LY-3832479" OR LY3832479 OR "LY-CoV016" OR "REGN-COV2" OR "REGEN-COV2" OR REGN10933 OR REGN10987 OR REGEN10933 OR REGEN10987 OR casirivimab OR imdevimab OR "LY-3819253" OR LY3819253 OR "LY-CoV555" OR Bamlanivimab OR Banlanivimab OR "VIR-7831" OR VIR7831 OR GSK4182136 OR "GSK-4182136" OR sotrovimab OR AZD7442 OR "AZD-7442" OR AZD8895 OR "AZD-8895" OR tixagevimab OR "COV2-2196" OR COV22196 OR AZD1061 OR "AZD-1061" OR cilgavimab OR "COV2-2130" OR COV22130 OR DXP593 OR "DXP-593" OR "BGB-DXP-593" OR BGBDXP593 OR JS016 OR "JS-016" OR etesevimab OR TY027 OR "TY-027" OR CTP59 OR "CTP-59" OR "CT-P59" OR regdanvimab OR STI1499 OR "STI-1499" OR "COVI-guard" OR COVIguard OR BRII196 OR "BRII-196" OR SCTA01 OR "SCTA-01" OR MW33 OR "MW-33" OR BRII198 OR "BRII-198" OR HFB30132A OR "HFB-30132A" OR ADM03820 OR "ADM-03820" OR HLX70 OR "HLX-70" OR STI2020 OR "STI-2020" OR COVIAMG OR "COVI-AMG" OR DZIF10c OR "DZIF-10c" OR BI767551 OR "BI-767551"

OR "COV2-2381" OR COV22381 OR "ABBV-47D11" OR 47D11 OR ABBV47D11 OR "COR-101" OR COR101 OR "STE90-C11" OR "DXP-604" OR DXP604 OR "BGB-DXP604" OR BGBDXP604 OR "BGB-DXP-604" OR "chicken egg antibody" OR "egg yolk antibody" OR IgY* OR "VIR-7832" OR VIR7832 OR GSK4182137 OR "GSK-4182137" OR IDB003 OR MD65 OR "MTX-COVAB" OR "C144-LS" OR C144LS OR "C-135-LS" OR "C135-LS" OR C135LS OR "SAB-185" OR SAB185 OR JMB2002 OR "JMB-2002" OR "TATX-03" OR TATX03 OR "NOVOAB-20" OR NOVOAB20 OR "NOVO-AB-20" OR "ABP-300" OR ABP300 OR MW05 OR "MW-05" OR MW07 OR "MW-07" OR ACmab1 OR covimax OR adimab OR "CPI-006" OR CPI006 OR ADG20 OR "ADG 20" OR diabod* OR nanobod* OR microbod* OR monobod* OR scFv* OR "single-chain" OR "heavy chain" OR HCAbs OR SCAbs OR nmAb* OR "f(ab)"

Appendix 4. Search strategy: PubMed (ahead of print only)

#1 2019 nCoV[tiab] OR 2019nCoV[tiab] OR corona virus[tiab] OR corona viruses[tiab] OR coronavirus[tiab] OR coronaviruses[tiab] OR COVID[tiab] OR COVID19[tiab] OR nCov 2019[tiab] OR SARS-CoV2[tiab] OR SARS CoV-2[tiab] OR SARSCoV2[tiab] OR SARSCoV-2[tiab] OR "COVID-19"[Mesh] OR "Coronavirus"[Mesh:NoExp] OR "SARS-CoV-2"[Mesh] OR "COVID-19"[nm] OR "severe acute respiratory syndrome coronavirus 2"[nm]

#2 (antibod*[Title/Abstract] OR mAb[Title/Abstract] OR mAbs[Title/Abstract] OR nAb[Title/Abstract] OR nAbs[Title/Abstract]) AND (therap*[Title/Abstract] OR treat*[Title/Abstract] OR neutrali*[Title/Abstract] OR prevent*[Title/Abstract] OR protect*[Title/Abstract] OR prophylax*[Title/Abstract]) OR (compet*[Title/Abstract] AND bind*[Title/Abstract]) OR (cocktail*[Title/Abstract] OR mixture*[Title/Abstract] OR combination*[Title/Abstract]) AND (mAb[Title/Abstract] OR mAbs[Title/Abstract] OR antibod*[Title/Abstract] OR nAb[Title/Abstract] OR nAbs[Title/Abstract]) OR "spike protein*"[Title/Abstract] OR "s protein*"[Title/Abstract] OR "Spike (S) protein"[Title/Abstract]

#3 (LY-3832479 OR LY3832479 OR LY-CoV016 OR REGN-COV2 OR REGN10933 OR REGN10987 OR REGN-10933 OR REGN-10987 OR REGEN10933 OR REGEN10987 OR REGEN-10933 OR REGEN-10987 OR REGN-CoV2* OR REGN-CoV-2* OR REGEN-CoV2* OR REGEN-CoV-2* OR casirivimab OR imdevimab OR LY-3819253 OR LY3819253 OR LY-CoV555 OR Bamlanivimab OR Banlanivimab OR VIR-7831 OR VIR7831 OR GSK4182136 OR GSK-4182136 OR sotrovimab OR AZD7442 OR AZD-7442 OR AZD1061 OR AZD-1061 OR AZD8895 OR AZD-8895 OR tixagevimab OR cilgavimab OR DXP593 OR DXP-593 OR BGB-DXP-593 OR BGBDXP593 OR JS016 OR JS-016 OR LY-CoV016 OR etesevimab OR TY027 OR TY-027 OR CTP59 OR regdanvimab OR STI1499 OR STI-1499 OR COVI-guard OR COVIguard OR BRII196 OR BRII-196 OR SCTA01 OR SCTA-01 OR MW33 OR MW-33 OR BRII198 OR BRII-198 OR HFB30132A OR HFB-30132A OR ADM03820 OR ADM-03820 OR HLX70 OR HLX-70 OR STI2020 OR STI-2020 OR COVIAMG OR COVI-AMG OR DZIF10c OR DZIF-10c OR BI767551 OR BI-767551 COV2-2381 OR COV22381 OR ABBV-47D11 OR 47D11 OR ABBV47D11 OR COR-101 OR COR101 OR STE90-C11 OR DXP-604 OR DXP604 OR BGB-DXP604 OR BGBDXP604 OR BGB-DXP-604 OR „chicken egg antibod*" OR "egg yolk antibod*" OR IgY OR IgYs OR VIR-7832 OR VIR7832 OR GSK4182137 OR GSK-4182137 OR IDB003 OR MTX-COVAB OR MD65 OR TATX-03 OR NOVOAB-20 OR "C144-LS" OR C144LS OR "C-135-LS" OR "C135-LS" OR C135LS OR "SAB-185" OR SAB185 OR JMB2002 OR "JMB-2002" OR "TATX-03" OR TATX03 OR "NOVOAB-20" OR NOVOAB20 OR "NOVO-AB-20" OR "ABP-300" OR ABP300 OR MW05 OR "MW-05" OR MW07 OR "MW-07" OR ACmab1 OR covimax OR adimab OR "CPI-006" OR CPI006 OR diabod* OR nanobod* OR microbod* OR monobod* OR scFv* OR "single-chain" OR "heavy chain" OR HCAbs OR SCAbs OR nmAbs OR FAB)

#4 "spike protein*"[Title/Abstract] OR "s protein*"[Title/Abstract] OR "Spike (S) protein"[Title/Abstract]

#5 #1 AND (#2 OR #3)

#6 #4 OR #5

#7 (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])

#8 *("animals"[mh] NOT "humans"[mh])*

#9 #6 NOT (#7 OR #8) Filters: from 2020/1/1 - 3000/12/12

Appendix 5. Search strategy: Epistemonikos COVID-19 L*VE Platform

https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d?utm=epdb_en

the Coronavirus disease (COVID-19) L*OVE by PICO: Prevention or treatment > Pharmacological interventions > Targeted therapies > Anti-SARS-CoV-2 Mab > primary studies.

Appendix 6. Search strategy: World Health Organization COVID-19 global literature on coronavirus disease

Advanced search and in the search field: title, abstract, subject

("Ly-3832479" OR ly3832479 OR "LY-3832479" OR ly3832479 OR "LY-CoV016" OR "REGN-COV2" OR "REGEN-COV2" OR regn10933 OR regn10987 OR regen10933 OR regen10987 OR casirivimab OR imdevimab OR "LY-3819253" OR ly3819253 OR "LY-CoV555" OR bamlanivimab OR banlanivimab OR "VIR-7831" OR vir7831 OR gsk4182136 OR "GSK-4182136" OR sotrovimab OR azd7442 OR "AZD-7442" OR azd8895 OR "AZD-8895" OR tixagevimab OR "COV2-2196" OR cov22196 OR azd1061 OR "AZD-1061" OR cilgavimab OR "COV2-2130" OR cov22130 OR dxp593 OR "DXP-593" OR "BGB-DXP-593" OR bgbdxp593 OR js016 OR "JS-016" OR etesevimab OR ty027 OR "TY-027" OR ctp59 OR "CTP-59" OR "CT-P59" OR regdanvimab OR sti1499 OR "STI-1499" OR "COVI-guard" OR coviguard OR brii196 OR "BRII-196" OR scta01 OR "SCTA-01" OR mw33 OR "MW-33" OR brii198 OR "BRII-198" OR hfb30132a OR "HFB-30132A" OR adm03820 OR "ADM-03820" OR hlx70 OR "HLX-70" OR

sti2020 OR "STI-2020" OR coviamg OR "COVI-AMG" OR dzif10c OR "DZIF-10c" OR bi767551 OR "BI-767551" OR "COV2-2381" OR cov22381 OR "ABBV-47D11" OR 47d11 OR abbv47d11 OR "COR-101" OR cor101 OR "STE90-C11" OR "DXP-604" OR dxp604 OR "BGB-DXP604" OR bgbdxp604 OR "BGB-DXP-604" OR "chicken egg antibody" OR "egg yolk antibody" OR igy* OR "VIR-7832" OR vir7832 OR gsk4182137 OR "GSK-4182137" OR idb003 OR md65 OR "MTX-COVAB" OR "C144-LS" OR c144ls OR "C-135-LS" OR "C135-LS" OR c135ls OR "SAB-185" OR sab185 OR jmb2002 OR "JMB-2002" OR "TATX-03" OR tatx03 OR "NOVOAB-20" OR novoab20 OR "NOVO-AB-20" OR "ABP-300" OR abp300 OR mw05 OR "MW-05" OR mw07 OR "MW-07" OR acmab1 OR covimax OR adimab OR "CPI-006" OR cpi006 OR ADG20 OR "ADG20" OR diabod* OR nanobod* OR microbod* OR monobod* OR scfv* OR "single-chain" OR "heavy chain" OR hcabs OR scabs OR "F(ab)2" OR nmAb*)

Appendix 7. Search strategy: Cochrane Covid-19 Study Register, search strategy for platform trials

Cochrane COVID-19 Study Register via the Cochrane Register of Studies http://crsweb.cochrane.org/

1 (adaptive clinical trial):PT AND INREGISTER

2 (adaptive NEAR7 (trial OR stud*)) AND INREGISTER

3 (adaptive NEAR5 (design)) AND INREGISTER

4 master protocol OR master study AND INREGISTER

5 "cohort multiple randomized controlled trial*" AND INREGISTER

6 "cohort multiple randomised controlled trial*" AND INREGISTER

7 "cmRCT" AND INREGISTER

8 (("multi-factorial" OR multifactorial) NEAR7 (trial OR stud*)) AND INREGISTER

9 (network NEAR2 trial) AND INREGISTER

10 (network NEAR2 stud*):ti AND INREGISTER

11 (additional NEAR2 (arm* OR drug* OR agent* OR treatment* OR intervention*)): TI,AB AND INREGISTER

12 "candidate agents": TI,AB AND INREGISTER

13 (new NEAR2 (arm* OR drug*)): TI,AB AND INREGISTER

14 (different NEXT (agent* OR drug* OR treatment*)): TI,AB AND INREGISTER

15 (multiple NEXT (agent* OR treatment* OR intervention*)): TI,AB AND INREGISTER

16 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15

Appendix 8. Search strategy: RCT search between 18 June and 30 July 2021

MEDLINE (via Ovid)

1. "spike protein, SARS-CoV-2".af.

2. Coronavirus Infections/ or Coronavirus/

3. SARS-CoV-2/ or COVID-19/

4. ("2019 nCoV" or 2019nCoV or coronavir* or coronovir* or COVID or COVID19 or HCoV* or "nCov 2019" or "SARS CoV2" or "SARS CoV 2" or SARSCoV2 or "SARSCoV 2").tw,kf.

5. "severe acute respiratory syndrome coronavirus 2".tw,kf,nm.

6. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).tw,kf.

7. or/2-6

8. *Antibodies, Monoclonal/

9. Antibodies, Neutralizing/

10. Antibodies, Viral/

11. ((antibod* or mAb* or nAb*) adj2 (therap* or treatment* or neutrali?ing or prevent* or protect* or prophylax*)).tw,kf.

12. Spike Glycoprotein, Coronavirus/

13. Binding, Competitive/

14. (compet* adj1 bind*).tw,kf.

15. ("spike protein*" or "s protein*" or "Spike (S) protein").mp.

16. ((cocktail* or mixture* or combination*) adj3 (mAb* or antibod* or nAb*)).tw,kf.

17. ("two mab" or "mabs" or "two nab" or "two nabs").tw,kw.

18. (LY3832479* or LY-CoV016* or LY-3832479* or LYCoV016* or JS016* or JS-016* or etesevimab*).mp.

19. (REGN-COV2* or REGN-COV-2* or REGN10933* or REGN10987* or REGN-10933* or REGN-10987* or REGEN-COV2* or REGEN-COV-2* or REGEN10933* or REGEN10987* or REGEN-10933* or REGEN-10987* or casirivimab* or imdevimab*).mp.

20. (LY3819253* or LY-3819253* or LY-CoV555* or LYCoV555* or bamlanivimab* or banlanivimab*).mp.

21. (VIR7831* or VIR-7831* or GSK4182136* or GSK-4182136* or sotrovimab*).mp.

22. (AZD7442* or AZD-7442* or AZD8895* or AZD-8895* or tixagevimab* or COV2-2196 or COV22196* or AZD1061* or AZD-1061* or cilgavimab* or COV2-2130* or COV22130*).mp.

23. (DXP-593* or DXP593* or BGB-DXP593* or BGBDXP593* or BGB-DXP-593*).mp.

24. (TY027* or TY-027*).mp.

25. (CTP59* or CTP-59* or CT-P59* or regdanvimab*).mp.

26. (STI1499* or STI-1499* or COVI-GUARD* or COVIguard*).mp.

27. (BRII196* or BRII-196*).mp.

28. (SCTA01* or SCTA-01*).mp.

29. (MW33* or MW-33*).mp.

30. (BRII198* or BRII-198*).mp.

31. (HFB30132A* or HFB-30132A*).mp.

32. (ADM03820* or ADM-03820*).mp.

33. (HLX70* or HLX-70*).mp.

34. (STI2020* or STI-2020* or COVIAMG* or COVI-AMG*).mp.

35. (DZIF10c* or DZIF-10c* or BI767551* or BI-767551*).mp.

36. (COV2-2381* or COV22381*).mp.

37. (ABBV-47D11* or 47D11* or ABBV47D11*).mp.

38. (COR-101* or COR101* or STE90-C11*).mp.

39. (DXP-604* or DXP604* or BGB-DXP604* or BGBDXP604* or BGB-DXP-604*).mp.

40. (Chicken egg antibod* or egg yolk antibod* or IgY*).mp.

41. (VIR-7832 or VIR7832 or GSK4182137* or GSK-4182137*).mp.

42. (IDB003 or MD65 or MTX-COVAB).mp.

43. (C144-LS or C144LS or C-135-LS or C135-LS or C135LS or SAB-185 or SAB185 or JMB2002 or JMB-2002 or TATX-03 or TATX03 or NOVOAB-20 or NOVOAB20 or NOVO-AB-20 or ABP-300 or ABP300 or MW05 or MW-05 or MW07 or MW-07 or ACmab1 or covimax or adimab or CPI-006 or CPI006 or ADG20 or "ADG20").mp.

44. Single-Chain Antibodies/

45. (nmabs or diabod* or dia-bod* or nanobod* or nano-bod* or microbod* or micro-bod* or monobod* or mono-bod*).tw,kf,nm.

46. (scFv* or "single-chain*" or "heavy chain*" or HCAbs or SCAbs or FAB).tw,kf,nm.

47. or/8-46

48. 7 and (1 or 47)

49. randomized controlled trial.pt.

50. controlled clinical trial.pt.

51. randomi?ed.ab.

52. placebo.ab.

53. drug therapy.fs.

54. randomly.ab.

55. trial.ab.

56. groups.ab.

57. or/49-56

58. exp animals/ not humans/

59. 57 not 58

60. clinical trial, phase iii/

61. ("Phase 3" or "phase3" or "phase III" or P3 or "PIII").ti,ab,kw.

62. (60 or 61) not 58

63. 59 or 62

64. 7 and (1 or 47) and 63

65. limit 64 to yr="2020-Current"

PubMed

#1 2019 nCoV[tiab] OR 2019nCoV[tiab] OR corona virus[tiab] OR corona viruses[tiab] OR coronavirus[tiab] OR coronaviruses[tiab] OR COVID[tiab] OR COVID19[tiab] OR nCov 2019[tiab] OR SARS-CoV2[tiab] OR SARS CoV-2[tiab] OR SARSCoV2[tiab] OR SARSCoV-2[tiab] OR "COVID-19"[Mesh] OR "Coronavirus"[Mesh:NoExp] OR "SARS-CoV-2"[Mesh] OR "COVID-19"[nm] OR "severe acute respiratory syndrome coronavirus 2"[nm]

#2 (antibod*[Title/Abstract] OR mAb[Title/Abstract] OR mAbs[Title/Abstract] OR nAb[Title/Abstract] OR nAbs[Title/Abstract]) AND (therap*[Title/Abstract] OR treat*[Title/Abstract] OR neutrali*[Title/Abstract] OR prevent*[Title/Abstract] OR protect*[Title/Abstract] OR prophylax*[Title/Abstract]) OR (compet*[Title/Abstract] AND bind*[Title/Abstract]) OR (cocktail*[Title/Abstract] OR mixture*[Title/Abstract] OR combination*[Title/Abstract]) AND (mAb[Title/Abstract] OR mAbs[Title/Abstract] OR antibod*[Title/Abstract] OR nAb[Title/Abstract] OR nAbs[Title/Abstract]) OR "spike protein*"[Title/Abstract] OR "s protein*"[Title/Abstract] OR "Spike (S) protein"[Title/Abstract]

#3 (LY-3832479 OR LY3832479 OR LY-CoV016 OR REGN-COV2 OR REGN10933 OR REGN10987 OR REGN-10933 OR REGN-10987 OR REGEN10933 OR REGEN10987 OR REGEN-10933 OR REGEN-10987 OR REGN-CoV2* OR REGN-CoV-2* OR REGEN-CoV2* OR REGEN-CoV-2* OR casirivimab OR imdevimab OR LY-3819253 OR LY3819253 OR LY-CoV555 OR Bamlanivimab OR Banlanivimab OR VIR-7831 OR VIR7831 OR GSK4182136 OR GSK-4182136 OR sotrovimab OR AZD7442 OR AZD-7442 OR AZD1061 OR AZD-1061 OR AZD8895 OR AZD-8895 OR tixagevimab OR cilgavimab OR DXP593 OR DXP-593 OR BGB-DXP-593 OR BGBDXP593 OR JS016 OR JS-016 OR LY-CoV016 OR etesevimab OR TY027 OR TY-027 OR CTP59 OR CT-P59 OR regdanvimab OR STI1499 OR STI-1499 OR COVI-guard OR COVIguard OR BRII196 OR BRII-196 OR SCTA01 OR SCTA-01 OR MW33 OR MW-33 OR BRII198 OR BRII-198 OR HFB30132A OR HFB-30132A OR ADM03820 OR ADM-03820 OR HLX70 OR HLX-70 OR STI2020 OR STI-2020 OR COVIAMG OR COVI-AMG OR DZIF10c OR DZIF-10c OR BI767551 OR BI-767551 COV2-2381 OR

COV22381 OR ABBV-47D11 OR 47D11 OR ABBV47D11 OR COR-101 OR COR101 OR STE90-C11 OR DXP-604 OR DXP604 OR BGB-DXP604 OR BGBDXP604 OR BGB-DXP-604 OR „chicken egg antibod*" OR "egg yolk antibod*" OR IgY OR IgYs OR VIR-7832 OR VIR7832 OR GSK4182137 OR GSK-4182137 OR IDB003 OR MTX-COVAB OR MD65 OR TATX-03 OR NOVOAB-20 OR "C144-LS" OR C144LS OR "C-135-LS" OR "C135-LS" OR C135LS OR "SAB-185" OR SAB185 OR JMB2002 OR "JMB-2002" OR "TATX-03" OR TATX03 OR "NOVOAB-20" OR NOVOAB20 OR "NOVO-AB-20" OR "ABP-300" OR ABP300 OR MW05 OR "MW-05" OR MW07 OR "MW-07" OR ACmab1 OR covimax OR adimab OR "CPI-006" OR CPI006 OR diabod* OR nanobod* OR microbod* OR monobod* OR scFv* OR "single-chain" OR "heavy chain" OR HCAbs OR SCAbs OR nmAbs OR ADG20 OR ADG 20 OR MAD0004J08)

#4 "spike protein*"[Title/Abstract] OR "s protein*"[Title/Abstract] OR "Spike (S) protein"[Title/Abstract]

#5 #1 AND (#2 OR #3)

#6 #4 OR #5

#7 (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])

#8 randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab] OR randomized controlled trial [pt] OR controlled clinical trial [pt]

#9 #6 AND #7 AND #8

#10 *("animals"[mh] NOT "humans"[mh])*

#11 #9 NOT #10 Filters: from 2020/1/1 - 3000/12/12

Embase (via Ovid)

#	Searches
1	coronavirinae/ or coronaviridae/ or coronaviridae infection/
2	coronavirus disease 2019/
3	Coronavirus infection/
4	sars-related coronavirus/
5	"Severe acute respiratory syndrome coronavirus 2"/
6	((corona* or corono*) adj1 (virus* or viral* or virinae*)).tw,kw.
7	("2019 nCoV" or 2019nCoV or coronavir* or coronovir* or COVID or COVID19 or HCoV* or "nCov 2019" or "SARS CoV2" or "SARS CoV 2" or SARSCoV2 or "SARSCoV 2").tw,kw.
8	"Severe acute respiratory syndrome coronavirus 2".mp.
9	or/1-8
10	Antibodies, Monoclonal/
11	Antibodies, Neutralizing/
12	Antibodies, Viral/
13	((antibod* or mAb* or nAb*) adj2 (therap* or treatment* or neutrali?ing or prevent* or protect* or prophylax*)).tw,kw.
14	Spike Glycoprotein, Coronavirus/
15	Binding, Competitive/
16	(compet* adj1 bind*).tw,kw.
17	("spike protein*" or "s protein*" or "Spike (S) protein").mp.
18	((cocktail* or mixture* or combination*) adj3 (mAb* or antibod* or nAb*)).tw,kw.

19 ("two mab" or "mabs" or "two nab" or "two nabs").tw,kw.

20 (LY3832479* or LY-CoV016* or LY-3832479* or LYCoV016* or JS016* or JS-016* or etesevimab*).mp.

21 (REGN-COV2* or REGN-COV-2* or REGN10933* or REGN10987* or REGN-10933* or REGN-10987* or REGEN-COV2* or REGEN-COV-2* or REGEN10933* or REGEN10987* or REGEN-10933* or REGEN-10987* or casirivimab* or imdevimab*).mp.

22 (LY3819253* or LY-3819253* or LY-CoV555* or LYCoV555* or bamlanivimab* or banlanivimab*).mp.

23 (VIR7831* or VIR-7831* or GSK4182136* or GSK-4182136* or sotrovimab*).mp.

24 (AZD7442* or AZD-7442* or AZD8895* or AZD-8895* or tixagevimab* or COV2-2196 or COV22196* or AZD1061* or AZD-1061* or cilgavimab* or COV2-2130* or COV22130*).mp.

25 (DXP-593* or DXP593* or BGB-DXP593* or BGBDXP593* or BGB-DXP-593*).mp.

26 (TY027* or TY-027*).mp.

27 (CTP59* or CTP-59* or CT-P59* or regdanvimab*).mp.

28 (STI1499* or STI-1499* or COVI-GUARD* or COVIguard*).mp.

29 (BRII196* or BRII-196*).mp.

30 (SCTA01* or SCTA-01*).mp.

31 (MW33* or MW-33*).mp.

32 (BRII198* or BRII-198*).mp.

33 (HFB30132A* or HFB-30132A*).mp.

34 (ADM03820* or ADM-03820*).mp.

35 (HLX70* or HLX-70*).mp.

36 (STI2020* or STI-2020* or COVIAMG* or COVI-AMG*).mp.

37 (DZIF10c* or DZIF-10c* or BI767551* or BI-767551*).mp.

38 (COV2-2381* or COV22381*).mp.

39 (ABBV-47D11* or 47D11* or ABBV47D11*).mp.

40 (COR-101* or COR101* or STE90-C11*).mp.

41 (DXP-604* or DXP604* or BGB-DXP604* or BGBDXP604* or BGB-DXP-604*).mp.

42 (Chicken egg antibod* or egg yolk antibod* or IgY*).mp.

43 (VIR-7832* or VIR7832* or GSK4182137* or GSK-4182137*).mp.

44 (IDB003 or MD65 or MTX-COVAB).mp.

45 (C144-LS or C144LS or C-135-LS or C135-LS or C135LS or SAB-185 or SAB185 or JMB2002 or JMB-2002 or TATX-03 or TATX03 or NOVOAB-20 or NOVOAB20 or NOVO-AB-20 or ABP-300 or ABP300 or MW05 or MW-05 or MW07 or MW-07 or ACmab1 or covimax or adimab or CPI-006 or CPI006 or ADG20 or ADG 20 or MAD0004J08).mp.

46 single chain fragment variable antibody/

47 (nmabs or diabod* or dia-bod* or nanobod* or nano-bod* or microbod* or micro-bod* or monobod* or mono-bod*).mp.

48 (scFv* or "single-chain*" or "heavy chain*" or HCAbs or SCAbs).mp.

49 or/10-48

50 Randomized controlled trial/

51 Controlled clinical study/

52 random*.ti,ab.

53 randomization/

54 intermethod comparison/

55 placebo.ti,ab.

56 (compare or compared or comparison).ti.

57 (open adj label).ti,ab.

58 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.

59 double blind procedure/

60 parallel group$1.ti,ab.

61 (crossover or cross over).ti,ab.

62 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant $1)).ti,ab.

63 (controlled adj7 (study or design or trial)).ti,ab.

64 (volunteer or volunteers).ti,ab.

65 trial.ti.

66 or/50-65

67 phase 3 clinical trial/

68 ("Phase 3" or "phase3" or "phase III" or P3 or "PIII").tw,kw.

69 or/67-68

70 (animal experiment/ or Animal experiment/) not (human experiment/ or human/)

71 (66 or 69) not 70

72 9 and 49 and 71

73 limit 72 to yr="2020 -Current"

74 limit 73 to medline

75 73 not 74

Cochrane Covid-19 study register (https://covid-19.cochrane.org/)

"Ly-3832479" OR Ly3832479 OR "LY-3832479" OR LY3832479 OR "LY-CoV016" OR "REGN-COV2" OR "REGEN-COV2" OR REGN10933 OR REGN10987 OR REGEN10933 OR REGEN10987 OR casirivimab OR imdevimab OR "LY-3819253" OR LY3819253 OR "LY-CoV555" OR Bamlanivimab OR Banlanivimab OR "VIR-7831" OR VIR7831 OR GSK4182136 OR "GSK-4182136" OR sotrovimab OR AZD7442 OR "AZD-7442" OR AZD8895 OR "AZD-8895" OR tixagevimab OR "COV2-2196" OR COV22196 OR AZD1061 OR "AZD-1061" OR cilgavimab OR "COV2-2130" OR COV22130 OR DXP593 OR "DXP-593" OR "BGB-DXP-593" OR BGBDXP593 OR JS016 OR "JS-016" OR etesevimab OR TY027 OR "TY-027" OR CTP59 OR "CTP-59" OR "CT-P59" OR regdanvimab OR STI1499 OR "STI-1499" OR "COVI-guard" OR COVIguard OR BRII196 OR "BRII-196" OR SCTA01 OR "SCTA-01" OR MW33 OR "MW-33" OR BRII198 OR "BRII-198" OR HFB30132A OR "HFB-30132A" OR ADM03820 OR "ADM-03820" OR HLX70 OR "HLX-70" OR STI2020 OR "STI-2020" OR COVIAMG OR "COVI-AMG" OR DZIF10c OR "DZIF-10c" OR BI767551 OR "BI-767551" OR "COV2-2381" OR COV22381 OR "ABBV-47D11" OR 47D11 OR ABBV47D11 OR "COR-101" OR COR101 OR "STE90-C11" OR "DXP-604" OR DXP604 OR "BGB-DXP604" OR BGBDXP604 OR "BGB-DXP-604" OR "chicken egg antibody" OR "egg yolk antibody" OR IgY* OR "VIR-7832" OR VIR7832 OR GSK4182137 OR "GSK-4182137" OR IDB003 OR MD65 OR "MTX-COVAB" OR "C144-LS" OR C144LS OR "C-135-LS" OR "C135-LS" OR C135LS OR "SAB-185" OR SAB185 OR JMB2002 OR "JMB-2002" OR "TATX-03" OR TATX03 OR "NOVOAB-20" OR NOVOAB20 OR "NOVO-AB-20" OR "ABP-300" OR ABP300 OR MW05 OR "MW-05" OR MW07 OR "MW-07" OR ACmab1 OR covimax OR adimab OR "CPI-006" OR CPI006

OR ADG20 OR "ADG 20" OR diabod* OR nanobod* OR microbod* OR monobod* OR scFv* OR "single-chain" OR "heavy chain" OR HCAbs OR SCAbs OR nmAb* OR "two mab" OR "mabs" OR "two nab" OR "two nabs" OR "ADG20" OR "ADG 20" OR "MAD0004J08"

Study characteristics: "Intervention assignment": Randomised/quasi-randomised/unclear

1) "Intervention assignment": “Randomised” OR „unclear“

2) "Study design": "Parallel/Crossover" AND "Unclear"

WHO database (without Embase, ICTRP, Medline and PubMed)

Advanced search and in the search field: title, abstract, subject

("Ly-3832479" OR Ly3832479 OR "LY-3832479" OR LY3832479 OR "LY-CoV016" OR "REGN-COV2" OR "REGEN-COV2" OR REGN10933 OR REGN10987 OR REGEN10933 OR REGEN10987 OR casirivimab OR imdevimab OR "LY-3819253" OR LY3819253 OR "LY-CoV555" OR Bamlanivimab OR Banlanivimab OR "VIR-7831" OR VIR7831 OR GSK4182136 OR "GSK-4182136" OR sotrovimab OR AZD7442 OR "AZD-7442" OR AZD8895 OR "AZD-8895" OR tixagevimab OR "COV2-2196" OR COV22196 OR AZD1061 OR "AZD-1061" OR cilgavimab OR "COV2-2130" OR COV22130 OR DXP593 OR "DXP-593" OR "BGB-DXP-593" OR BGBDXP593 OR JS016 OR "JS-016" OR etesevimab OR TY027 OR "TY-027" OR CTP59 OR "CTP-59" OR "CT-P59" OR regdanvimab OR STI1499 OR "STI-1499" OR "COVI-guard" OR COVIguard OR BRII196 OR "BRII-196" OR SCTA01 OR "SCTA-01" OR MW33 OR "MW-33" OR BRII198 OR "BRII-198" OR HFB30132A OR "HFB-30132A" OR ADM03820 OR "ADM-03820" OR HLX70 OR "HLX-70" OR STI2020 OR "STI-2020" OR COVIAMG OR "COVI-AMG" OR DZIF10c OR "DZIF-10c" OR BI767551 OR "BI-767551" OR "COV2-2381" OR COV22381 OR "ABBV-47D11" OR 47D11 OR ABBV47D11 OR "COR-101" OR COR101 OR "STE90-C11" OR "DXP-604" OR DXP604 OR "BGB-DXP604" OR BGBDXP604 OR "BGB-DXP-604" OR "chicken egg antibody" OR "egg yolk antibody" OR IgY* OR "VIR-7832" OR VIR7832 OR GSK4182137 OR "GSK-4182137" OR IDB003 OR MD65 OR "MTX-COVAB" OR "C144-LS" OR C144LS OR "C-135-LS" OR "C135-LS" OR C135LS OR "SAB-185" OR SAB185 OR JMB2002 OR "JMB-2002" OR "TATX-03" OR TATX03 OR "NOVOAB-20" OR NOVOAB20 OR "NOVO-AB-20" OR "ABP-300" OR ABP300 OR MW05 OR "MW-05" OR MW07 OR "MW-07" OR ACmab1 OR covimax OR adimab OR "CPI-006" OR CPI006 OR ADG20 OR "ADG 20" OR diabod* OR nanobod* OR microbod* OR monobod* OR scFv* OR "single-chain" OR "heavy chain" OR HCAbs OR SCAbs OR nmAb* OR "two mab" OR "mabs" OR "two nab" OR "two nabs" OR "ADG20" OR "ADG 20" OR "MAD0004J08")

AND

(random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII")

Epistemonikos

Covid-19 àprevention or treatment à procedures à passive immunization à Anti-SARS-CoV-2 MaB à primary studies

results filtered by RCT

Appendix 9. Characteristics of studies for tracking (listed in excluded studies)

Study, drug name	Sponsor/developer	Target	Phase	Design	Population/disease severity	Patient status	Time of administration	Route of administration	Number of participants	Status, planned completion date, or DOI if published
Prospectively registered, non-randomised studies examining SARS-CoV-2-neutralising mAbs										
Track: NCT04603651, Bamlanivimab	Eli Lilly and Company	SARS-CoV-2 S protein	Expanded access	Non-randomised, expanded access	Mild	Outpatients	Within 3 days of confirmation of disease	Infusion (IV)	Not reported	Cinicaltrials.gov: no longer available (was available previously)
Track: NCT04701658 Bamlanivimab	Eli Lilly and Company	SARS-CoV-2 S protein	Phase 2	Non-randomised prospective cohort Study	Mild	Outpatients	Not reported	Infusion (IV)	Estimated enrollment: 3000 participants	Recruiting Estimated completion date: June 2021
Track: NCT04617535, Casirivimab plus imdevimab	Regeneron Pharmaceuticals	SARS-CoV-2 S protein	Expanded access	Non-randomised, compassionate use	Mild	Outpatients	Not reported	Infusion (IV), single-dose	Not reported	Available
Track: NCT04656691 Bamlanivimab	Daniel Griffin, United Health Group; Eli Lilly and Company; Optum, Inc.	SARS-CoV-2 S protein	Phase 4	Single-dose study using matched controls	Mild to moderate	Outpatients	Not reported	Infusion (IV), single dose	Actual enrolment: 4000 participants	Completed in April 2021

(Continued)

RCTs in healthy participants

Track: NCT04592549, ADM03820	Ology Bioservices	A mixture of 2 human IgG1 non-competitive binding anti-SARS-CoV-2 antibodies	Phase 1	Randomised, sequential assignment, quadruple-blind (participant, care provider, investigator, outcome assessor), placebo-controlled, dose-escalation trial	Healthy	Not applicable	Not applicable	Infusion (IV), infusion (IM) (4 subcohorts with different injection/dose)	Estimated enrolment: 40 participants	Recruiting Estimated completion date 30 September 2021
Track: NCT04567810, Anti-SARS-CoV-2 chicken egg IgY	Stanford University	Not specified	Phase 1	Randomised, double-blind, sequential-assignment	Healthy	Not applicable	Not applicable	Intranasally, multiple doses	Actual enrolment: 48 participants	Completed in December 2020, no results posted yet
Track: NCT04507256, AZD7442 (AZD8895 + AZD1061)	AstraZeneca, Parexel	SARS-CoV-2 S protein	Phase 1	Randomised, double-blind, placebo-controlled and dose-escalation study	Healthy	Not applicable	Not applicable	Infusion (IV and IM), 3 cohorts sequentially, 1 cohort co-administration of AZD8895 + AZD1061	Actual enrolment: 60 participants	Active, not recruiting Estimated completion date 25 October 2021 Press release: https://doi.org/10.1021/cen-09843-buscon13
Track: NCT04896541 AZD7442 (AZD8895 + AZD1061)	AstraZeneca	SARS-CoV-2 S protein	Phase 1	Randomised, double-blinded, placebo controlled, single dose	Healthy	Not applicable	On day 1	IM injections or IV administration	Estimated enrolment: 40 participants	Active, not recruiting, Estimated completion date July 4, 2022
Track: NCT04537910, Bamlanivimab	Eli Lilly and Company	SARS-CoV-2 S protein	Phase 1	Randomised, placebo-controlled, participant- and investigator-blind	Healthy	Not applicable	Not applicable	Subcutaneously	Actual enrolment: 25 participants	Completed, December 28, 2020

(Continued)

Track: NCT04532294, BGB-DXP593	BeiGene	SARS-CoV-2 S protein	Phase 1	Randomised, double-blind, placebo-controlled, single-dose escalation study	Healthy	Not applicable	Not applicable	Infusion (IV)	Estimated enrolment: 30 participants	Completed, estimated completion date February 13, 2021
Track: NCT04479631, BRII-196	Brii Biosciences Limited, TSB Therapeutics (Beijing) CO.LTD	SARS-CoV-2 S protein	Phase 1	Randomised, single-blind, placebo-controlled, single ascending dose-escalation study	Healthy	Not applicable	Not applicable	Infusion (IV), single dose	Estimated enrolment: 16 participants	Completed Completion dateJanuary 29, 2021
Track: NCT04691180 BRII-196 and BRII-198 (2 arms with different dose)	Brii Biosciences Limited, TSB Therapeutics (Beijing) CO.LTD	SARS-CoV-2 S protein	Phase 1	Randomised, single-blind, placebo-controlled, single ascending dose-escalation study	Healthy	Not applicable	Not applicable	Infusion (IV), single dose	Estimated enrolment: 24 participants	Recruiting Estimated completion date: August 2021
Track: NCT04479644, BRII-198	Brii Biosciences Limited, TSB Therapeutics (Beijing) CO.LTD	SARS-CoV-2 S protein	Phase 1	Randomised, single-blind, placebo-controlled, single ascending dose-escalation study	Healthy	Not applicable	Not applicable	Infusion (IV), single dose	Estimated enrolment: 17 participants	Completed Completion date February 3, 2021
Track: jRCT2071200117 Casarivimab/ imdevimab	Chugai Pharmaceutical Co., Ltd.	SARS-CoV-2 S protein	Phase 1	Randomised, double-blind, placebo-controlled study	Not applicable	Healthy	Not applicable	Infusion (IV), single dose	Planned enrolment: 22 participants	Active, not recruiting
Track: NCT04519437, Casirivimab/ imdevimab	Regeneron Pharmaceuticals	SARS-CoV-2 S protein	Phase 1	Randomised, double-blind, placebo-controlled	Healthy	Not applicable	Not applicable	Subcutaneously, repeated dose	Actual enrolment: 974 participants	Active, not recruiting

(Continued)

										Estimated completion date October 2021 Press release: https://www.aljazeera-a.com/economy/2020/11/17/regeneron-roche-tested-manufacture-of-covid-drug-trump-used
Track: NCT04852978 Casirivimab/ imdevimab + vaccine	Regeneron Pharmaceuticals	SARS-CoV-2 S protein	Phase 2	Randomised, open-label, parallel group study	Healthy	Not applicable	Not applicable	Infusion (IV) or subcutaneous administration	Estimated enrolment: 180 participants	Recruiting Estimated completion date August 30, 2022
Track: NCT04525079, Regdanvimab	Celltrion	SARS-CoV-2 spike RBD	Phase 1	Randomised, double-blind, placebo-controlled, parallel-group, single ascending dose	Healthy	Not applicable	Not applicable	Not reported	Estimated enrolment: 32 participants	Recruiting Estimated completion date 30 November 2020
Track: NCT04441931, Etesevimab	Eli Lilly and Company	SARS-CoV-2 S protein	Phase 1	Randomised, placebo-controlled, double-blinded	Healthy	Not applicable	Not applicable	Infusion (IV)	Actual enrolment: 26 participants	Completed on October 2, 2020
Track: NCT04441918, Etesevimab	Shanghai Junshi Bioscience Co., Ltd.	SARS-CoV-2 S protein	Phase 1	Randomised, double-blind, placebo-controlled	Healthy	Not applicable	Not applicable	Infusion (IV), single dose	Estimated enrolment: 40 participants	Recruiting Estimated completion date December 2020
Track: ChiCTR2100042150 JMB-2002	Shu Lan (Hang Zhou) Hospital	SARS-CoV-2 S protein	Phase 1	Randomised, double-blind, placebo-controlled study	Not applicable	Healthy	Not applicable	Infusion (IV), single dose	Planned enrolment: 40 participants	Active, not yet recruiting

(Continued)

Track: NCT04590430, HFB30132A	HiFiBiO Therapeutics	SARS-CoV-2 S protein	Phase 1	Randomised, double-blind, placebo-controlled, single ascending dose	Healthy	Not applicable	Not applicable	Infusion (IV), single dose	Estimated enrolment: 24 participants	Active, not recruiting Estimated completion date July 2021
Track: NCT04561076 HLX70	Hengenix Biotech Inc., Sanyou Biopharmaceuticals (Shanghai) Co., Ltd Shanghai ZJ Bio-Tech Co., Ltd	SARS-CoV-2 S protein	Phase 1	Randomised, double-blind, placebo-controlled, dose-escalation study	Healthy	Not applicable	Not applicable	Infusion (IV), single dose	Estimated enrolment: 24 participants	Not yet recruiting Estimated completion date: September 2021
Track: NCT04533048, MW33	Mabwell (Shanghai) Bioscience Co., Ltd.	SARS-CoV-2 S protein	Phase 1	Randomised, double-blind, placebo-controlled	Healthy	Not applicable	Not applicable	Injection	Actual enrolment: 42 participants	Completed, on December 2, 2020 no results posted yet
Track: NCT04483375, SCTA01	Sinocelltech Ltd.	SARS-CoV-2 S protein	Phase1	Randomised, double-blinded, placebo-controlled, single ascending dose	Healthy	Not applicable	Not applicable	Not reported, single dose	Actual enrolment: 33 participants	Completed, on November 17, 2020 no results posted yet
Track: NCT04429529, TY027	Tychan Pte Ltd.	SARS-CoV-2 S protein	Phase 1	Randomised, placebo- controlled, double-blind, single ascending dose, time-lagged	Healthy	Not applicable	Not applicable	Infusion (IV), single dose	Estimated enrolment: 32 participants	Completed On NCT04429529

(Continued)

Track: NCT04700163, C144-LS and C-135-LS	Rockefeller University	SARS-CoV-2 S protein	Phase 1	Non-randomised, open -abel, single-dose, dose-escalation study	Healthy	Not applicable	Not reported	Infusion (IV) or SC; 5 arms with different injection/dose	Actual enrolment: 23 participants	Active, not recruiting Estimated completion date: June 2022
Track: NCT04932850, MAD0004J08	Toscana Life Sciences Sviluppo s.r.l.	SARS-CoV-2 S protein	Phase 1	Randomised, placebo-controlled, quadruple- blind, dose-escalation study	Healthy	Not applicable	Not reported	Injection (Cohort 1 (48 mg), Cohort 2 (100 mg) and Cohort 3 (400 mg))	Actual enrolment: 30 participants	Active, not recruiting Estimated completion date: October 2021

Appendix 10. Ongoing RCTs investigating SARS-CoV-2 neutralising mAbs

Ongoing studies for SARS-CoV-2 neutralising mAbs

mAb or mAb combination	Number	RCTs	Phase	Status, planned completion
bamlanivimab	6 RCTs	NCT04411628	Phase 1	Completed
		NCT04840459	Phase 2	Recruiting, Jan 2022
		ACTIV-2	Phase 2/3 (platform)	Recruiting, May 2023
		OPTIMISE-C19	Phase 3 (platform)	Recruiting, Dec 2022
		NCT04748588	Phase 4	Recruiting, Mar 2023
		NCT04796402	Phase 4	Recruiting, Dec 2021
sotrovimab (VIR-7831)	4 RCTs	AGILE	Phase 1/2 (platform)	Recruiting, April 2023
		NCT04779879	Phase 2	Recruiting, April 2023
		ACTIV-3	Phase 3 (platform)	Arm stopped for futility, study continues, July 2022
		NCT04913675	Phase 3	Not yet recruiting, Nov 2022
AZD7442	4 RCTs	ACTIV-2	Phase 2/3 (platform)	Recruiting, May 2023
		NCT04723394	Phase 3	Recruiting, Sep 2022
		ACTIV-3	Phase 3 (platform)	Recruiting, July 2022
		DISCOVERY	Phase 3 (platform)	Active, not recruiting March 2023
BRII-196/ BRII-198	4 RCTs	NCT04770467	Phase 2	Withdrawn, Oct 2022
		NCT04787211	Phase 2	Recruiting, Dec 2021
		ACTIV-2	Phase 2/3 (platform)	Recruiting, May 2023
		ACTIV-3	Phase 3 (platform)	Arm stopped for futility, study continues, July 2022
casiriv-imab/imdevimab	4 RCTs	NCT04426695	Phase 1/2	Active not recruiting, June 2021
		NCT04666441	Phase 2	Active not recruiting, Aug 2021
		NCT04840459	Phase 2	Recruiting, Jan 2022
		OPTIMISE-C19	Phase 3	Recruiting, Dec 2022
DZIF-10c	3 RCTs	NCT04631666	Phase 1/2	Active not recruiting, Aug 2021
		NCT04631705	Phase 1/2	Recruiting, Sep 2021

(Continued)

		NCT04822701	Phase 2/3	Terminated, June 2021
SCTA01	3 RCTs	NCT04644185	Phase 2/3	Recruiting, Dec 2021
		NCT04683328	Phase 2/3	Not yet recruiting, Nov 2021
		NCT04709328	Phase 2/3	Not yet recruiting, March 2022
STI-2020 (COVI-AMG)	3 RCTs	NCT04584697	Phase 1/2	Withdrawn, April 2021
		NCT04734860	Phase 2	Recruiting, Nov 2021
		NCT04771351	Phase 2	Recruiting, Oct 2021
regdanvimab (CT-P59)	2 RCTs	NCT04593641	Phase 1	Active not recruiting, Dec 2021
		EU-DRACT2020-003401-60	Phase 2/3	Not updated
bam-lanivimab/etese-vimab	2 RCTs	NCT04634409	Phase 2	Recruiting, Nov 2021
		OPTIMISE-C19	Phase 3 (platform)	Recruiting, Dec 2022
ABBV-47D11	1 RCT	NCT04644120	Phase 1	Active not recruiting, Aug 2021
ADG20	1 RCT	NCT04840459	Phase 2/3	Recruiting, Jan 2022
bam-lanivimab/ete-sevimab/LY-CoV1404	1 RCT	NCT04634409	Phase 2	Recruiting, Nov 2021
bam-lanivimab/sotro-vimab	1 RCT	NCT04634409	Phase 2	Recruiting, Nov 2021
BGB-DXP593	1 RCT	NCT04551898	Phase 2	Completed
COR-101	1 RCT	NCT04674566	Phase 1b/2	Recruiting, June 2021
C135-LS/C144-LS	1 RCT	ACTIV-2	Phase 2/3 (platform)	Recruiting, May 2023
etesevimab alone	1 RCT	NCT04780321	Phase 1/2	Recruiting, Oct 2021
LY-CoV1404	1 RCT	NCT04634409	Phase 2	Recruiting, Nov 2021
MW33	1 RCT	NCT04627584	Phase 2	Recruiting, Sep 2021
STI-2099	1 RCT	NCT04900428	Phase 2	Not yet recruiting, March 2022
VIR-7832	1 RCT	AGILE	Phase 1/2 (platform)	Recruiting, April 2022
MAD0004J08	1 RCT	NCT04952805	Phase 2/3	Recruiting, August 2022

(Continued)

Abbreviations: **mAb:** monoclonal antibody; **RCT:** randomised controlled trial

HISTORY

Protocol first published: Issue 1, 2021

CONTRIBUTIONS OF AUTHORS

NK: screening, data extraction, risk of bias assessment, meta-analysis, writing the manuscript

CH: screening, data extraction, risk of bias assessment, meta-analysis, writing the manuscript

KLC: screening, risk of bias assessment, clinical expertise

ET: screening, risk of bias assessment

ZK: screening, risk of bias assessment, characteristics of studies

MP: screening, data extraction, risk of bias assessment, clinical expertise and advice

MN: risk of bias assessment, characteristics of studies

VP: risk of bias assessment, methodological expertise

SS: conception of the protocol and review

SJV: clinical expertise

IM: development of the search strategy

CS: clinical expertise and advice

EMW: clinical expertise and advice

CS-O: clinical expertise and advice

DJR: clinical expertise and advice

ZM: clinical expertise and advice

LJE: clinical and methodological expertise

NS: methodological expertise and advice, and conception and writing of the protocol and review

DECLARATIONS OF INTEREST

NK: is funded by the Federal Ministry of Education and Research, Germany (NaFoUniMedCovid19, funding number: 01KX2021; part of the project 'COVIM', which was paid to the institution).

CH: none known

KLC: none known

ET: none known

ZK: none known

MP: none known

MN: is funded by the Federal Ministry of Education and Research, Germany (NaFoUniMedCovid19, funding number: 01KX2021; part of the project 'COVIM', which was paid to the institution).

VP: none known

SS: is funded by the Federal Ministry of Education and Research, Germany (NaFoUniMedCovid19, funding number: 01KX2021; part of the project 'COVIM' which was paid to the institution).

SJV: receives a PhD scholarship from the not-for-profit Sanquin blood bank.

IM: none known

CS: none known

EMW: none known

CS-O: has declared to be employed by the not-for-profit Sanquin blood bank.

DJR: is a consultant haematologist for NHS Blood and Transplant.

ZM: is a haematologist at Monash University.

LJE: is a consultant haematologist for NHS Blood and Transplant.

NS: none known

SOURCES OF SUPPORT

Internal sources

- University Hospital of Cologne, Germany

  Cochrane Cancer, Department I of Internal Medicine
- NHS Blood and Transplant, UK

  NHS Blood and Transplant
- Monash University Australia, Australia

  Transfusion Research Unit, Department of Epidemiology and Preventive Medicine
- Haematology Society of Australia and New Zealand, Australia

  Leukaemia Foundation and HSANZ Australia

External sources

- Federal Ministry of Education and Research, Germany

  NaFoUniMedCovid19 (funding number: 01KX2021); part of the project "COVIM"
- Federal Ministry of Education and Research, Germany

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Assessment of reporting bias

As we did not pool the data in meta-analysis and included fewer than 10 trials, we did not generate a funnel plot to assess reporting bias.

Electronic searches

We stopped using the ‘Similar articles’ feature on PubMed, because we did not find new relevant references with this feature.

Data synthesis

We had planned to pool the data in meta-analysis if clinical and methodological characteristics of individual studies were sufficiently homogeneous. The included studies were too heterogeneous regarding different monoclonal antibody types, doses, populations, or settings. We decided not to perform meta-analyses and commented on the results instead.

We had planned at protocol stage to calculate Peto odds ratios for outcomes with few events (less than 5%). However, for interpretability and consistency throughout the review, we report risk ratios, and plan to do so for future updates of this review as well.

Assessment of risk of bias

We planned to use the Risk-of-bias VISualization tool (robvis) to generate risk of bias summary figures (McGuinness 2020), but instead we used Review Manager Web (RevMan Web 2020) to present risk of bias summary figures in the analysis and to produce interactive risk of bias tables for each outcome.

Types of participants

After discussion with clinical experts, we decided to perform separate analyses for populations with hospitalised individuals with COVID-19 and moderate to severe disease, and for populations with non-hospitalised individuals with COVID-19 with asymptomatic and mild disease.

Types of outcome measures

In a group discussion with clinical experts, we revised our outcomes. We decided to add the outcomes thromboembolic events and renal failure for both populations. For adverse events, we have added all grade adverse events and grades 1 to 2.

For hospitalised individuals with moderate to severe COVID-19, we changed the outcome hospital admission to hospital discharge. We added the outcomes time to sustained recovery and neurological dysfunction, as they were rated as important as part of a guideline consortium (CEOSys).

To account for possible bias due to competing events, we changed the outcome admission to hospital for non-hospitalised individuals to admission to hospital or death; and hospital discharge for hospitalised participants to hospital discharge and alive.

Assessment of heterogeneity

We have changed the description of how we quantify heterogeneity. We now base it on the I^2 statistic to better reflect the *Cochrane Handbook for Systematic Reviews of Interventions*. In the light of future updates of this review, and based on peer review advice, we changed our criterion on when to perform subgroup analysis from $I^2 > 80\%$ to $I^2 > 50\%$, reflecting substantial heterogeneity according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2021).

Measures of treatment effect

We had planned to use Peto odds ratio if the number of observed events was small (less than 5% of sample per group). However, for consistency throughout the review, better interpretability, and lacking impact on the findings, we have decided to report risk ratios instead.

Subgroup analysis and investigation of heterogeneity

The subgroup analyses planned to explore:

- age of participants (divided into applicable age groups, e.g. children; 18 to 65 years, 65 years and older)
- pre-existing conditions (diabetes, respiratory disease, hypertension, immunosuppression)
- timing of first dose administration with illness onset
- duration since symptom onset
- antibodies detected at baseline

Due to the limited number of RCTs providing relevant data and the variation of SARS-CoV-2-neutralising monoclonal antibodies used across the trials, we did not perform meta-analyses and thus no subgroup analyses.

For future updates of the review, we will combine the subgroups 'timing of first dose administration with illness onset' and 'duration since symptom onset' and specify the splits of interest to be 'timing of first dose administration since symptom onset (up to 3 days, 4 to 7 days and more than 7 days)'.

Summary of findings tables

During the protocol stage, we had listed the following outcomes eligible for display in the summary of findings tables:

- all-cause mortality, up to 30 days
- all-cause mortality, until longest follow-up (time-to-event)
- clinical COVID-19 symptoms, assessed with the WHO Clinical Progression Scale (Marshall 2020), within 30 days
- quality of life, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 30 days, and longest follow-up available
- adverse events (grade 3 to 4), including if possible, imputability of events
- serious adverse events, including if possible, imputability of events
- admission to hospital (for outpatients only)

Based on changes in the list of outcomes during protocol stage, we changed this to:

- all-cause mortality, up to 30 days
- all-cause mortality, up to 60 days
- clinical COVID-19 symptoms, assessed with the WHO Clinical Progression Scale (Marshall 2020), within 30 days, or development of severe symptoms if clinical progression scale not available; if available, we extracted IMV requirement or death
- quality of life, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 30 days, and longest follow-up available)
- admission to hospital (for outpatients only), hospital discharge (for inpatients only)
- adverse events (all grades, grade 1-2, grade 3-4)
- serious adverse events

NOTES

Parts of the review's methods section is adopted from templates of Cochrane Haematology and a similar protocol published by Piechotta 2020, and the corresponding reviews (Piechotta 2021).