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Early, very high-titre convalescent plasma therapy in clinically vulnerable individuals with mild COVID-19 (COVIC-19): protocol for a randomised, open-label trial

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ABSTRACT

Introduction COVID-19 convalescent plasma (CCP) is a possible treatment option for COVID-19. A comprehensive number of clinical trials on CCP efficacy have already been conducted. However, many aspects of CCP treatment still require investigations: in particular (1) Optimisation of the CCP product, (2) Identification of the patient population in need and most likely to benefit from this treatment approach, (3) Timing of administration and (4) CCP efficacy across viral variants in vivo. We aimed to test whether high-titre CCP, administered early, is efficacious in preventing hospitalisation or death in high-risk patients.

Methods and analysis COVIC-19 is a multicentre, randomised, open-label, adaptive superiority phase III trial comparing CCP with very high neutralising antibody titre administered within 7 days of symptom onset plus standard of care versus standard of care alone. We will enrol patients in two cohorts of vulnerable patients [(1) elderly 70+ years, or younger with comorbidities; (2) immunocompromised patients]. Up to 1020 participants will be enrolled in each cohort (at least 340 with a sample size re-estimation after reaching 102 patients). The primary endpoint is the proportion of participants with (1) Hospitalisation due to progressive COVID-19, or (2) Who died by day 28 after randomisation. Principal analysis will follow the intention-to-treat principle.

Ethics and dissemination Ethical approval has been granted by the University of Ulm ethics committee (#41/22) (lead ethics committee for Germany), Comité de protection des personnes Sud-Est I (CPP Sud-Est I) (#2022-A01307-36) (ethics committee for France), and ErasmusMC ethics committee (#MEC-2022-0365) (ethics committee for the Netherlands). Signed informed consent will be obtained from all included patients. The findings will be published in peer-reviewed journals and presented at relevant stakeholder conferences and meetings.

Trial registration Clinical Trials.gov (NCT05271929), EudraCT (2021-006621-22)

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The trial evaluates the efficacy of plasma from convalescent, vaccinated donors with very high antibody titres against COVID-19 in outpatients with the omicron SARS-CoV-2 variant.
⇒ The design of the study is pragmatic, with broad inclusion criteria, and a comparison with the current standard of care.
⇒ The adaptive design accounts for uncertainty in the frequency of the primary outcome.
⇒ The trial addresses the needs of underserved vulnerable patients.
⇒ The open-label design is a limitation of the study.

INTRODUCTION

The SARS-CoV-2 pandemic has caused more than 6.5 million deaths worldwide. Mortality has been 40% or more for hospitalised patients from clinically vulnerable groups.[1–4] Clinically vulnerable patients, such as those with congenital immunodeficiency or patients who are immunocompromised due to underlying disease and/or immunosuppressive therapy, are at high risk of progression to severe COVID-19. These patients are also likely to develop persistent SARS-CoV-2 infection and may shed infectious SARS-CoV-2 particles for a prolonged time.[5 6] Furthermore, immunosuppressed or immunodeficient patients are less likely to mount an effective immune response to SARS-CoV-2 vaccination.[7] Consequently, treatment is urgently needed to prevent COVID-19 disease progression and hospitalisation in this population. To date, antiviral treatments are available, but their use is limited due to

adverse events (AE), drug interactions and availability. Besides, the emergence of virus variants means that the newly developed anti-SARS-CoV-2 monoclonal antibodies (MoAb) may not sufficiently neutralise SARS-CoV-2.[8]

The use of COVID-19 convalescent plasma (CCP) has been considered a possible treatment strategy: early CCP could reduce morbidity and mortality from COVID-19, avoiding complications such as secondary bacterial infections, and the need for hospitalisation.[9–13] In addition, CCP may benefit patients in whom SARS-CoV-2 vaccination may not elicit effective immune responses, such as the elderly, those with immunodeficiencies or those whose immune system is weakened due to an underlying disease or immunosuppressive therapy.[11]

Also, CCP administration in early COVID-19 may reduce long-term COVID-19 symptoms and improve quality of life. Other benefits could include a reduced strain on limited healthcare resources by reducing the number of COVID-19 hospitalisations and increasing resources for other urgent care in hospitals.

Many clinical trials on CCP have been conducted; however, data on efficacy has been heterogeneous. A recent systematic review and meta-analysis concluded that CCP was not significantly associated with a decrease in all-cause mortality or with any other benefit for other clinical outcomes compared with placebo or standard of care in unselected hospitalised patients with moderate to severe COVID-19. The overall certainty of evidence was high but the reported outcomes were variable in different groups of patients.[11]

These heterogeneous results could be explained by various aspects of the study design, methodology and patient characteristics. The volume of transfused CCP was low in some of the trials (≤400 mL), only a few studies defined a minimum anti-SARS-CoV-2 titre or the content of antibodies in CCP units was poorly characterised or only measured post hoc in some of the trials. The assays used for measuring anti-SARS-CoV-2 antibody concentrations and neutralisation titres varied substantially. Besides, most of these trials were initiated in spring 2020 when availability and information on comparability of antibody tests were limited.

In the planning period of the 'first generation' of clinical trials it was assumed that enrolled patients would be SARS-CoV-2 antibody-negative and that the passive transfer of CCP would convert patients from an antibody-negative to a positive status. It became apparent that a substantial proportion of patients in trials which enrolled hospitalised patients had already mounted a humoral immune response by the time of inclusion in the CCP trials.[9 14–18] Among hospitalised patients who lacked SARS-CoV-2 antibodies at baseline, CCP decreased the need for mechanical ventilation or mortality compared with standard of care or placebo.[9 11 14 19–21]

The majority of trials allowed the inclusion of patients in stages 4–7 of the WHO 8-point Ordinal Severity Scale and a common feature in most of the trials published so far is the inclusion of hospitalised patients only.[9 14–18 20–35] Only a few trials enrolled outpatients.[9 12 13 36 37] In the Fundación INFANT COVID-19 Randomised Clinical Trial from Argentina, the administration of CCP less than 3 days after the onset of symptoms of COVID-19 in vulnerable patients reduced the risk of disease worsening compared with a control group by about 50% (16% after CCP vs 31% in the control group).[38] A subgroup analysis by the concentration of SARS-CoV-2 Spike IgG titres in the transfused CCP units demonstrated that a significant reduction of progression to severe respiratory disease was observed in recipients of CCP with a titre at or above the median.[38] A dose effect was observed also in other trials.[16 38–41] Another large randomised study in the USA also demonstrated a reduced hospitalisation rate in patients with COVID-19 treated early with CCP.[14]

Based on the lessons learnt from past CCP trials, the COVIC-19 Clinical Trial combines several features, which distinguish it from previous CCP trials and constitute an innovative optimised treatment approach:

- Immunotherapy with plasma containing very high concentrations of neutralising SARS-CoV-2 antibodies elicited by a combination of SARS-CoV-2 infection and vaccination;
- Administration of CCP very early after onset of symptoms (within 7 days);
- Viral sequencing and cross-neutralisation analyses in the patient population to study potential implications of viral evolution and immune escape.

Objectives

The COVIC-19 Trial is assessing whether administration of high-titre CCP in people with mild COVID-19 aged 70+ years, or under 70 years with comorbidities or immunosuppression, reduces the risk of hospitalisation or death within 28 days. Additional objectives are to demonstrate whether CCP benefits clinically vulnerable patients (including long-term complications) and to provide a framework for the administration of CCP for outpatient care. Moreover, COVIC-19 will monitor the virological response to CCP by measuring SARS-CoV-2 RNA levels, anti-SARS-CoV-2 antibody titres, and the emergence of virus variants by whole-genome sequencing and virus isolation.

Demonstrating the effectiveness of CCP in the outpatient settings may inform future lockdown policy and influence healthcare resource planning. Importantly, at the onset of a pandemic, or in case of the emergence of a variant resistant to all available MoAB, CCP may be the only passive immunotherapy approach widely available.

METHODS AND ANALYSIS

Design

COVIC-19 is a multicentre international, randomised, open-label adaptive superiority phase III trial to evaluate the efficacy and safety of high-titre CCP in the early treatment of SARS-CoV-2 infected patients who are at risk of progression to severe COVID-19. It is conducted

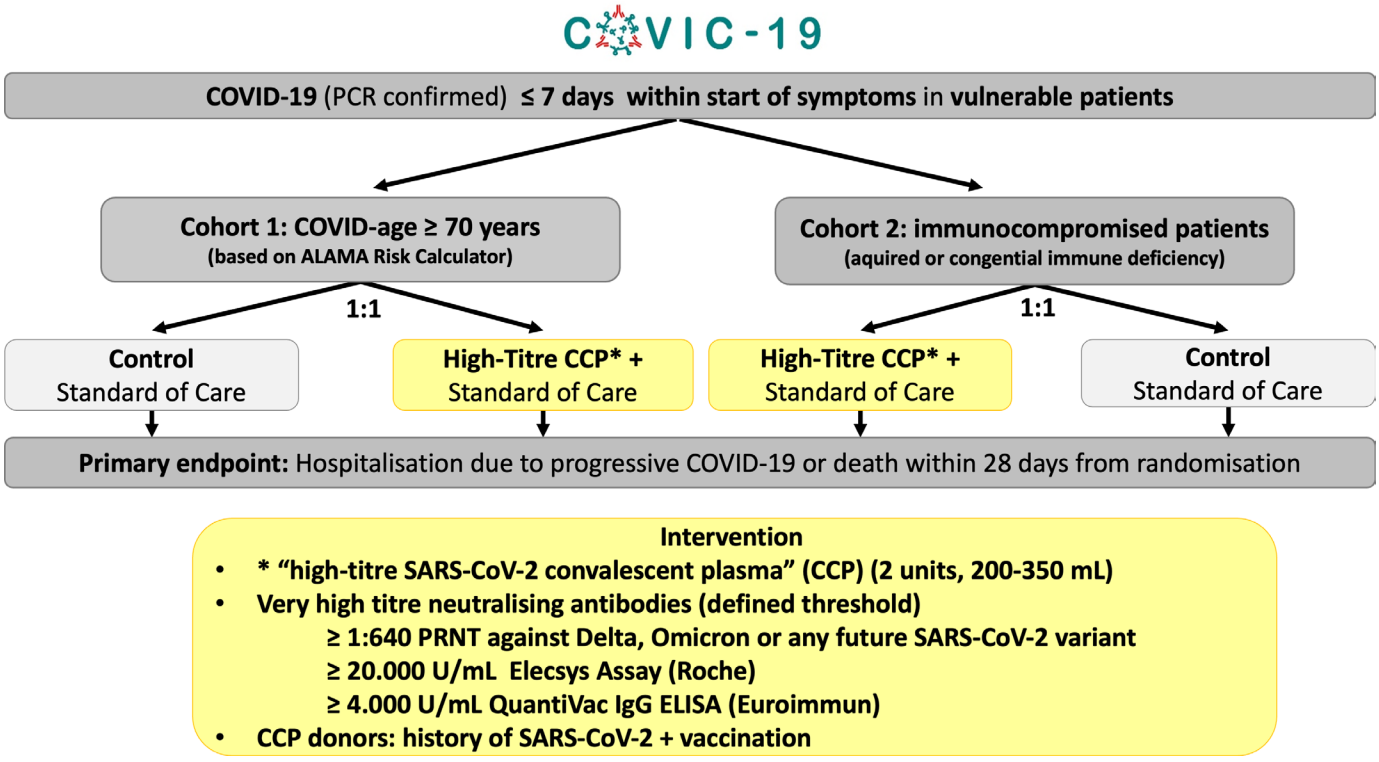

Figure 1 Trial design schematic. PRNT, Plaque reduction neutralisation test.

in a harmonised approach in Germany, the Netherlands, France and the UK. COVIC-19 will evaluate the efficacy of CCP collected from donors with high-titre neutralising SARS-CoV-2 antibodies plus standard care in reducing the risk of hospitalisation in people with early COVID-19 compared with standard care alone.

The study will randomise adult patients with COVID-19 into one of two arms (1:1): standard of care or CCP with very high neutralising antibody titre in addition to standard of care. Randomisation will be stratified by centre and by cohort. Patients will be included in two cohorts of vulnerable patients. Cohort 1 consists of unvaccinated elderly patients ≥70 years and cohort 2 comprises immunosuppressed patients (figure 1). All subjects will undergo a series of efficacy and safety assessments, including laboratory assays (at baseline, days 3, 14, 28, 90 and 180).

Nasopharyngeal swabs or oral samples will be obtained at day 1 (baseline/pretreatment), and at days 3, 14, 28 and 180 (and monthly in case of positivity till clearance) for cohort 2 and on the day of hospitalisation (if applicable).

Blood samples will be obtained at day 1 (baseline), 14 and 28 and on the day of hospitalisation (if applicable).

Trial participants

The main eligibility criteria for the two patient cohorts are: men or women currently displaying symptoms of COVID-19 but not requiring admission to hospital for COVID-19 disease or oxygen support; SARS-CoV-2 RNA detected in a specimen within 7 days of onset of symptoms. Specific criteria for each cohort are: (1) Elderly and high COVID-age population: patients, aged 70 years or older, or under 70 years with significant comorbidities resulting in a COVID-age of 70 years or more according to the Association of Local Authority Medical Advisors (ALAMA) risk calculator, and (2) High-risk immunocompromised population: patients with primary (B, T, combined) or acquired (lymphoid or myeloid malignancies, solid tumour with ongoing chemotherapy, allogenic haematopoietic stem cell transplantation, organ transplantation, immunosuppressive treatments, AIDS, etc), immunodeficiencies or patients without detectable seroconversion ≥3 weeks after complete vaccination schedule with an approved vaccine. Patients eligible for either cohort will be included in the immunocompromised cohort.

The main exclusion criteria are: age <18 years (except in the UK); history of documented SARS-CoV-2 infection in the last 90 days prior to enrolment; unauthorised prior or concurrent treatment for COVID-19 (currently MoAb and nirmatrelvir-ritonavir/Paxlovid are authorised in the trial); patients for whom transfusion will not be completed within 7 days of symptom onset; and prior SARS-CoV-2 vaccination (only for cohort 1).

Interventions

Convalescent plasma

The intervention consists of two plasma units provided by COVID-19 convalescent donors, fully compliant with national regulations. The intervention will be administered in addition to the standard of care at the time of randomisation. The first unit of ABO compatible convalescent plasma (200–350 mL per unit) will be infused intravenously as soon as possible after randomisation and the second on the same day or the next day according to anticipated patient tolerance. Plasma has been obtained

by apheresis from donors who have recovered from COVID-19 infection (at least 14 days after recovery) and have been vaccinated (at least 3 weeks after first dose of vaccine). As far as availability allows, the plasma units should have been donated by two different convalescent donors. Plasma should contain a minimum neutralising antibody titre of 1:640 against delta (B1.617.2), omicron or any future SARS-CoV-2 variant, or an anti-SARS-CoV-2 antibody concentration ≥4.000 binding antibody units/mL (BAU/mL) measured by the QuantiVac anti-SARS-CoV-2 IgG ELISA (Euroimmun) or ≥20.000U/mL measured by the anti-SARS-CoV-2 Elecsys test (Roche).

Standard of care

The standard of care for COVID-19 is evolving rapidly. We will take specific measures to ensure that the standard of care used in participating patients remains comparable in both arms over the inclusion period. Whenever necessary, the trial steering committee will provide updated guidelines regarding the standard of care and will strongly recommend that participating centres observe them. These recommendations may consider the local availability of COVID-19-specific medications such as MoAb.

Currently, the following COVID-19 medications are authorised for use as standard of care in patients enrolled in the study as pre-exposure prophylaxis, post-exposure prophylaxis, as well as early treatment: MoAb (including casirivimab/imdevimab, regdanvimab, sotrovimab and tixagevimab/cilgavimab) and antiviral drugs (molnupiravir, nirmatrelvir/ritonavir and remdesivir).

Randomisation

Patients will be enrolled by their treating physician in the participating centres. Eligible patients will be allocated using a central web-based randomisation service (CleanWeb, Telemedicine Technologies, Boulogne Billancourt, France). The randomisation service will allocate the treatment based on a prespecified randomisation list generated by the data manager. Separate randomisation lists will be used for each patient population. Randomisation will be performed at a 1:1 ratio, blocked (with randomly varying block sizes of two and four) and stratified by centre.

Outcomes

The primary endpoint is the proportion of participants with (1) At least one overnight stay in hospital for progressive COVID-19 symptoms, or (2) Who died, by day 28 after randomisation. COVID-19 related hospitalisations will be adjudicated using a three-member panel. Each member will independently come to a decision on whether the hospitalisation or decision to extend a hospitalisation was or was not related to COVID-19 using as much information that could be provided such as hospital discharge forms but remain blinded to the randomisation group. Classification of whether the hospitalisation was due to COVID-19 will be by majority decision of the panel.

Secondary outcome measures include core outcomes from the meta-core outcome set (COS) for hospitalised patients (http://www.comet-initiative.org/Studies/Details/1538), and the WHO progression scale.[42] There is no COS for patients with COVID-19 managed in the community. Viral outcome measures will enable assessment of mechanism.

Efficacy secondary endpoints are: proportion of participants with hospitalisation for progressive COVID-19 symptoms, or death by day 14 after randomisation; proportion of participants with hospitalisation for progressive COVID-19 symptoms requiring O_2 support (requirement based on O_2 saturation level on room air ≤93% and/or respiratory rate >30), or death by days 14 and 28 after randomisation; all-cause mortality by days 28, 90 and 180 after randomisation; proportion of patients with supplemental oxygen by days 14 and 28 after randomisation; proportion of patients with non-invasive ventilation by days 14 and 28 after randomisation; proportion of patients with intubation and mechanical ventilation by days 14 and 28 after randomisation; change in 10-point WHO Clinical Progression Scale Score by days 14 and 28 after randomisation; duration of hospital admission censored at 28 days after randomisation (for participants reaching primary endpoint); proportion of patients with admission to Intensive Therapy Unit (ITU)by days 14 and 28 after randomisation; duration of ITU admission censored at 28 days after randomisation; proportion of patients with long COVID-19 symptoms and time to recovery assessed by questionnaire at days 28 and 180 postrandomisation; health-related quality of life assessed using the EQ-5D-5L at days 28 and 180 after randomisation

Safety outcomes are: number of serious AE at 72 hours after randomisation (Grade 3/4 AE and AE unexpected for their nature, onset, evolution, severity or frequency); number of participants with arterial and venous thromboembolic events at days 28, 90 and 180 after randomisation.

Exploratory endpoints are: change in SARS-CoV-2 RNA level (PCR, cycle threshold value) in oral or nose/throat swab samples at days 3, 14, 28 and 180 after randomisation (cohort 2 only); change in anti-SARS-CoV-2 spike antibody levels in blood at days 14 and 28 after randomisation; SARS-CoV-2 whole-genome sequence analysis in oral or nose/throat swab samples at days 1 and 28 after randomisation; proportion and clinical characteristics of patients with cultivable virus at day 28, hospitalisation and day 180; virus sequence variation and cultivability over time, overall and in individuals receiving versus not receiving CCP.

Data collection

For all participating centres, patient characteristics and outcome data will be obtained from the patient records and collected via CleanWeb e-Case Report Form (e-CRF). CleanWeb is Good Clinical Practice (GDP), International Council for Harmonisation (ICH), General Data Protection Regulation (GDPR) and 21 CFR part 11 (Food and Drug Administration) compliant. All data collection and

management will be performed in accordance with the European Union's GDPR. A unique de-identified number will identify all patients, and no patient identifiers will be kept with clinical data. Data can only be accessed by the site investigator and supporting staff. In each country, the country's final data set will be available to the principal investigator. The research data will be stored at the coordinating centre for 2 years after the last publication of the research results or, without publication, after the final research report is signed.

Sample size

Libster *et al* observed a 31% risk of severe COVID-19 disease in the control group of their study in an elderly high-risk population with a similar intervention of convalescent plasma.[12] The relative risk of severe COVID-19 in treated patients was 0.52 (95% CI 0.29 to 0.94). We estimate that the risk of severe COVID-19 in the elderly population will be 30% and that our intervention will reduce the risk of hospitalisation by 50%. Sample size calculations based on a Z-test, a two-tailed α of 0.05, a 1-β of 0.90, and a relative risk of 0.5 require 316 patients per cohort (632 in the trial). The sample size is increased to 340 (680 total) to account for missing data/loss to follow-up.

The SARS-CoV-2 pandemic is a constantly evolving situation and with the appearance of new variants, there is considerable uncertainty as to the real risk of severe COVID-19 in the population. There is little data regarding the risk of severe COVID-19 in the immunocompromised population. Moreover, the effect observed by Libster *et al* may be overly optimistic by chance and may be different in our trial. If the effect is overestimated, the trial may not achieve the desired power. Thus, we will include a sample size re-estimation during the course of the trial as a form of adaptive design. For each cohort, sample size re-estimation will be planned using the method proposed by Mehta and Pocock.[43] Specifically, an interim analysis will be conducted when 30% of the patients have reached the primary endpoint. The conditional power for detecting the difference in primary outcome between the two arms in the final analysis will then be estimated. If the conditional power is between 50% and 90%, the sample size will be increased in order to achieve 90% power to detect the effect observed at the interim analysis with a maximum sample size of 1020 per cohort. Otherwise, the trial will continue using the planned sample size.

Recruitment schedule

Enrolment in the study is ongoing in Germany, the Netherlands and France. The first participant was enrolled in Germany on 11 April 2022, at Charité Hospital in Berlin. We anticipate the recruitment period will last 2 years for an estimated study completion date of 30 June 2024.

Statistical methods

The analyses will be performed according to the intention-to-treat (ITT) principle. The ITT population (by patient cohort) will be used for all efficacy analyses. A modified ITT population excluding patients who were randomised in error will be considered.

A detailed statistical analysis plan will be developed by the investigators while still blind to any analyses of aggregated data on study outcomes by treatment allocation.

Although conducted as a single trial separate randomisation lists for each cohort, the findings in each cohort are considered as separate trials and will be analysed separately.

All outcomes will be analysed in superiority (two-sided) analyses using simple hypothesis tests. As sensitivity analyses, generalised linear models will be used to account for stratification on the centre. No correction for multiplicity and no hierarchical testing procedures are planned in analysing secondary outcomes. These analyses will therefore be considered as exploratory in nature.

Primary endpoint analysis

The primary outcome will be analysed using a two-sided Z-test to compare proportions of events in the randomisation groups. The risk difference will be provided with its 95% CI. As a sensitivity analysis accounting for stratification on the centre, the endpoint will be analysed using a generalised linear mixed model (with logit link) with a random centre effect. Adjustment for major prognostic factors will be considered depending on the evolution of medical knowledge on the prognosis of patients infected by SARS-CoV-2.

Chen *et al* have shown that if one increases the sample size only when the interim result is promising, the type 1 error is not inflated by use of the conventional Wald statistic.[44] The significance level of the primary analysis will therefore remain at 0.05.

Secondary endpoints analysis

Binary outcomes will be analysed using Z-tests or Fisher's exact tests. When appropriate, risk differences will also be provided with their 95% CIs. As a sensitivity analysis, generalised linear mixed models (with logit link) with a random centre effect will be performed. Time-to-event outcomes will be analysed using log-rank tests with sensitivity analyses based on Cox regression models with a random centre effect (results will be expressed as HRs with 95% CIs). Finally, quantitative outcomes will be analysed using Student's t-tests or Mann-Whitney tests, as appropriate. Sensitivity analyses will consist of mixed linear regression with a random centre effect (results will be expressed as mean differences with 95% CIs).

Subgroup analyses

Exploratory analyses of the primary endpoint and other safety and efficacy endpoints will be conducted in subgroups of subjects including but not limited to SARS-CoV-2 variant identified at inclusion, SARS-CoV-2 vaccinal status at inclusion, anti-SARS-CoV-2 MoAb received, and the cumulative dose of antibody received. The interactions between experimental treatment and vaccinal status

as well as the dose of antibody received will be explored and tested.

Data safety and monitoring

An independent data safety and monitoring board will review annual safety reports of patient baseline characteristics, serious AE and safety outcomes including all-cause mortality. No formal stopping rules were implemented.

Study management

A steering committee has been established with the overall responsibility for the design, execution and analysis of the trial. The coordinating centre is located at the clinical investigation centre, *Centre Hospitalier Universitaire* (CHU) de Besançon, Besançon, France. Personnel at the coordinating centre include the study principal investigator for France, study coordinators, biostatisticians and data managers. The coordinating centre is responsible for international coordination of the trial, centralised data collection and analysis. In each participating country a coordinating centre is responsible for day-to-day management of the trial. The study coordinator is responsible for checking protocol adherence weekly and address trial-related issues that may arise during the study.

Patient and public involvement

Representatives of a patients and public involvement group of immunosuppressed patients were involved in the early stages of study design in the UK. The study protocol was also presented to patient representatives involved in the Support-e project.

ETHICS AND DISSEMINATION

Approval has been obtained from research ethics board of all involved institutions (University of Ulm ethics committee decision #41/22 on 12 April 2022; *Comité de protection des personnes Sud-Est I* #2022-A01307-36 on 11 July 2022; ErasmusMC ethics committee decision #MEC-2022–0365 on 2 August 2022). The amendments to the protocol are described in table 1. Protocol V.2.2 is the one described here. No patient will be recruited before institutional approval is obtained. Signed informed consent will be obtained from all included patients (see online supplemental material).

From the early development of the trial, we have involved experts in the care of patients with COVID-19 as well as blood establishment stakeholders, specialists in the organisation and research of transfusion (haematologists, transfusion specialists, healthcare researchers, epidemiologists, blood organisation decision makers and senior scientists). This diversity of expertise will ensure that the objectives, methods, and results analysis and interpretation answer pertinent questions for clinicians and patients.

For clinicians and researchers, traditional dissemination will be used, including publication in relevant peer-reviewed medical journals and presentations at local, national and international conferences and meetings. We will work closely with the stakeholders of the blood establishments involved and the different clinical specialties to provide reports for the specific needs of their organisations/disciplines. We plan to reach out to these organisations to present our results, and the team members will be readily available for further discussions, meetings or presentations to answer their specific needs and questions.

Table 1 Protocol amendments

Version no.	Date	Main changes
V1.0	16 February 2022	First version
V1.1	18 March 2022	Added annex describing current standard of care
V2.0	12 May 2022	Removed O_2 requirement from primary endpoint and added adjudication of primary endpoint. Added neutralisation assay against current and future variants for donor selection. Added viral cultivability objectives
V2.1	19 May 2022	Update Trial Steering Committee
V2.2	20 July 2022	Clarification of the statistical methods and sample size calculation

DISCUSSION

The ongoing trial is the first to include convalescent plasma with very high antibody titres from convalescent and vaccinated donors. Antibody titres in CCP may vary significantly and higher titres may address previous inconsistencies in CCP efficacy observed in prior studies. We also took specific steps to standardise the CCP titres across antibody assays to improve antibody dose standardisation.

High-titre CCP may represent a therapeutic modality superior to MoAb, in that it stems from a polyclonal immune response which covers a broader range of viral epitopes and may prevent the selection of immune resistance. CCP can also readily be adapted to emerging viral variants since collection can occur as early as 4 weeks after symptom resolution in a donor.

Promising results from non-randomised studies[45–47] or subgroup analyses of randomised trials[11 19 48 49] and recent meta-analyses[11 50] show that immunocompromised patients may benefit from the use of CCP in COVID-19. COVIC-19 is the first randomised study to specifically address this population. Long-term viral persistence has been observed in immunocompromised patients and is associated with SARS-CoV-2 immune evasion. COVIC-19 will also provide data regarding the emergence of resistant variants in immunocompromised patients treated with CCP and other treatments.

We acknowledge that patients in the unvaccinated, elderly or high COVID-age cohort are currently unlikely to participate in COVIC-19. The trial was conceived at a time where the likelihood of variants resistant to treatment was of concern (and may still be). However, the risk of resistant variants is still very much present. The open-label design is also a limitation of the study.

Overall, COVIC-19 will provide needed robust evidence regarding the use of CCP in COVID-19 in currently underserved segments of the population.

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Contributors LE, DJR, DB, HS, PT, conceived the study. LE, DJR, DB, HS, PT, ET, MD initiated the study design and CV, GB, CEV, HH, AD, SK, ESc, BJAR, TA, ESe helped with implementation. HS and BJAR are grant holders. MD provided expertise in clinical trial design and will conduct the primary statistical analysis. MD, SH and HS wrote the initial manuscript. All authors contributed to refinement of the study protocol and approved the final manuscript

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Competing interests PT is an employee of Établissement Français du Sang, the blood establishment responsible for blood collection, qualification and supply in France. HS, SH, SK, TA and ES are employees of the German Red Cross Blood Transfusion Service Baden-Württemberg-Hessen (or its affiliates), the establishment responsible for blood collection, qualification and supply in Baden-Württemberg and Hesse, Germany. CEV, is an employee of Sanquin, the establishment responsible for blood collection, qualification and supply in the Netherlands. The authors declare no other competing interests.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

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CHU BESANÇON DRCI	**Information notice and informed consent CAT 1 - PATIENT**		098 DRC 210 ER03 018 Version 2.0 Page 1 / 14
	REGISTRATION	COVIC-19	

Patient ID:

COVIC-19

INFORMATION NOTICE

« A Randomised Open-Label Trial of Early, Very High-Titre Convalescent Plasma Therapy in Clinically Vulnerable Individuals with Mild COVID-19 »

REF.: 2022/703 No. IDRCB: 2022-A01307-36 / NCT 05271929

Sponsor and responsible for the processing of personal data	**University Hospital of Besançon** 3 A. Fleming Blvd. 25030 Besançon cedex DRCI recherche & innovation
Principal Investigator	**Prof. Eric Toussirot** INSERM Clinical Investigation Centre CIC 1431, CHU Besançon
Proposed study	**COVIC-19** ***Research of public interest involving the human person of category 1*** ***Version 2 of 15/07/2022***

Dear Madam, Sir,
You are invited to participate in the COVIC-19 study.

Herein, you will find all the information necessary to understand the objectives of the study, what your participation entails, including the expected benefits, drawbacks, and the foreseeable risks.

Read this notice carefully.
Ask all the questions you may have.
After having obtained satisfactory answers to your questions and having had sufficient time for reflection, you can then decide whether you want to participate in this study or not.

What is the purpose of this study?

There is an ongoing international pandemic due to a novel coronavirus (SARS-CoV-2). The disease associated with SARS-CoV-2 infection is called COVID-19. While the care of patients with COVID-19 has improved considerably since the beginning of 2020 and vaccination has limited the occurrence of severe forms, it is still necessary to prevent them in at risk populations.
The purpose of COVIC-19 is to determine if a transfusion of plasma collected from convalescent donors for COVID-19 (i.e. people who have had COVID-19 disease and are now cured) and vaccinated can prevent the occurrence of a severe form in the elderly, or people with risk factors for a severe form of the disease, who have shown symptoms of COVID-19 in the last few days. Convalescent plasma contains antibodies capable of neutralizing the SARS-CoV-2 virus which causes COVID-19.
For this, the patients participating in the project will be divided into 2 groups, the first receiving standard care for COVID-19, according to current recommendations, and the second receiving this standard care and also a transfusion with convalescent plasma.

How will the study unfold?

COVIC-19 is an international multicentre interventional study. Multicentre because it involves multiple healthcare centres). It is interventional because it involves interventions in addition to those of standard care.

These additional interventions consist, firstly, in your allocation to one of the 2 groups of the study (standard treatment of your COVID-19 infection or standard treatment with transfusion with plasma from convalescent and vaccinated donors) by random drawing. This random drawing (or randomisation) allows the treatment to be allocated randomly, in order to obtain homogeneous groups and so the final result can only be the result of the studied intervention. You as well as your doctor will know the group to which you will be allocated.
The main specific intervention in the study is the transfusion of **two units of plasma** convalescent, only if you are included in that group. This is the treatment the study aims to show the effectiveness of compared to the usual treatment.

These plasma transfusions will most often take place on an outpatient basis, that is to say without spending one night or more in the hospital. The transfusion may take place in the clinical ward of a hospital involved in the study, a primary healthcare centre, or at your home under the home hospitalization scheme (HAD). The two transfusions may take place on the same day or over two consecutive days. More exceptionally, these transfusions may take place during a hospital stay motivated by a condition other than COVID-19.
After randomisation, regardless of your treatment group, you will be cared for and observed according to the same procedures. The only difference between the two groups is the treatment strategy you will receive. Blood samples (3 to 6, depending on your course in the study) and nasopharyngeal or salivary

samples will also be taken over the 6 months of study follow-up. You will also be asked three times to complete questionnaires to assess your health-related quality of life and the potential signs of a long COVID.

The number of patients participating in this study will be at least 226 and up to 680 in France. It is indeed an adaptive study (in two phases) which makes it possible to stop or continue the inclusions depending on the results obtained during an interim analysis of the trial.

What will happen during the study step by step?

Enrolment in the study

You are invited to participate in the study because you have symptoms of COVID-19 and a positive PCR test. After presentation of the study, you will be able to ask all the questions you deem necessary, and you will have a minimum reflection period of 2 hours to choose whether to participate (in the event that you are approaching 7 days from symptom onset). This time may be longer if time allows. If you agree to participate and after obtaining your written consent, you will receive a medical examination suitable for the study in accordance with article L1121-11 of the Public Health Code. The results of this examination will be communicated to you directly or through a doctor of your choice. Your doctor will also ask you about your health (medical history, treatments, etc.). If necessary, a pregnancy test will be performed (β-HCG assay, a 6 mL tube of blood will be drawn).

During this first visit, you will be allocated to the control group or to the group receiving plasma. The presence of a control group makes it possible to make an objective evaluation of the study results. Indeed, the research aims to determine whether one treatment is superior to the other. To find out, the improvement in the symptoms of the disease as well as the presence of the virus in the nasopharyngeal secretions or in the blood will be compared in the participants of the 2 groups.

If you are allocated to the plasma group, the infusion of two units of 200 to 240 mL will be carried out soon as possible after your enrolment, at the hospital, the primary healthcare centre, or at your home.

All the other procedures performed during the study will be the same for both groups. For the enrolment visit, these procedures will be:

- A blood draw with:
  - 3 tubes (13 mL) to carry out a laboratory assessment (complete blood count, liver function, renal function, calcium, glucose, etc.),
  - 1 tube of 10 mL to constitute a biobank of serum (optional),
  - 1 tube of 10 mL to constitute a plasma biobank (optional),
  - 1 tube of 10 mL to constitute a biobank of cells (optional),
  - 1 tube of 5 mL to test for the presence of specific SARS-CoV-2 antibodies in your blood.
- A nasopharyngeal swab using a cotton swab to test for the presence of SARS-CoV-2, using a PCR technique, and a second to isolate the virus (optional)
- The completion of two questionnaires to assess your health-related quality of life and determine the existence and, during follow-up, the persistence of certain symptoms related to COVID19.

Follow-up

Your participation in the study will last 180 days (6 months) ± 14 days or 194 days maximum after signing the consent, with 5 follow-up visits at days 3, 14, 28, 90, and 180 after your enrolment in the study. An additional visit will take place if you were to be hospitalized during the study follow-up.

During these visits, which may be done by telephone, medical data (need for hospitalisation or oxygen supplementation, treatments, etc.) will be recorded. The persistence of COVID symptoms will also be recorded.

You will be invited to complete a questionnaire to assess your health-related quality of life and determine the persistence of certain symptoms related to COVID-19 at 28 days and 180 days after enrolment in the study.
The blood draw for biological assessment may be repeated 14 days after inclusion and in the event of hospitalisation. Blood samples for biobanks may be repeated at days 14 and 28 of follow-up, and during hospitalisation, if applicable. The search for specific SARS-CoV-2 antibodies in your blood will also be repeated in the event of hospitalisation (for all), and at days 14 and 28 after enrolment (immunocompromised patients only). For immunocompromised patients or in whom the SARS-CoV-2 virus may persist, nasopharyngeal samples will be taken at days 3, 14, 28 and 180 days after enrolment.

Summary of the samples taken for the study:

		Day 1	Day 3	Day 14	Day 28	Hospitalisation	Day 180
Blood draw	Lab tests	X (13 mL)		X[1] (13 mL)		X (13 mL)	
	Anti-SARS CoV 2 antibodies	X (5 mL)	X (5 mL)[1]	X[2] (5 mL)	X[2] (5 mL)	X (5 mL)	
	Biobanks	X (30mL)		X (30mL)	X (30mL)	X (30mL)	
Nasopharyngeal swab	Detection and sequencing of SARS-CoV-2	X	X[2]	X[2]	X[2]	X	X[2]
	Culture of SARS-CoV-2	X[1]			X[1]	X1	X[1]

[1] optional
[2] immunocompromised patients or elderly patients who are still positive for SARS-CoV-2 by PCR

Information on possible treatment alternatives

At the time of preparation of this proposal, individuals at high risk of developing a severe form of COVID-19 are also eligible for administration of monoclonal antibodies under temporary cohort use authorisations, early access clearance or marketing authorisation.
High-risk patients are also eligible for administration of antiviral therapies, such as Paxlovid.
These monoclonal antibodies, combination of monoclonal antibodies, and antiviral therapies are authorised in the standard treatment, for all the patients enrolled in the study.

Expected benefits

A direct benefit is expected for patients treated with convalescent plasma. Indeed, it is a passive immunotherapy whose early administration may prevent the aggravation of COVID-19, and the risk of hospitalisation. No direct benefit is expected for patients in the control arm.
In terms of public health, if the effectiveness of convalescent plasma administered early is demonstrated, this therapeutic strategy could be used to prevent the worsening of COVID-19 in patients who cannot benefit from effective vaccination and with few therapeutic alternatives. This would also help reduce pressure on the hospital system.

Foreseeable risks

The foreseeable risks associated with any plasma transfusion are, from most to least common:

- Allergic reactions (114 events per 100,000 plasmas transfused, for reference)
- Febrile reactions
- Transfusion-related circulatory overload
- Acute respiratory syndrome post-transfusion

Clinical studies on plasma from donors who recovered from COVID-19 carried out during the emergency use authorisation period show that the product is well tolerated. Serious adverse events have been observed, according to published data, in 0 to 6.4% of people transfused, mainly allergic, respiratory, thrombotic or cardiac events. Among the 20,000 people who received convalescent plasma, 12 deaths were possibly and 1 probably related to the transfusion. The only study of early administration of convalescent plasma in 80 vulnerable patients mildly ill with COVID-19 (like patients to be included in COVIC-19) reported no adverse events. Three other studies recently published (also involving patients similar to those to be included in COVIC-19) reported no increase in frequency of adverse events in patients treated with convalescent plasma. . A transient increase in oxygen requirements soon after plasma transfusion and without evidence of circulatory overload has been observed in several immunocompromised patients hospitalised with severe COVID-19 in France. It is important to note that such occurrences, always transient, did not prevent a subsequent favorable effect of plasma on the course of COVID-19.

The drawing of blood samples can cause a minor hematoma at the puncture site, which will resolve spontaneously within a few days.

Placing the catheter required for plasma delivery can cause pain during insertion and might cause an infection.

Inserting the cotton swab (q-tip) into the nostril for taking nasopharyngeal swabs may be slightly painful and cause discomfort. This discomfort is temporary and without consequences.

Your participation is voluntary

Your participation in this study is entirely free and voluntary.

Refusing to participate will have no consequences on the type and quality of your treatment, or on your relationship with the investigating physician.

If you agree to participate, you can leave this study at any time without justification and with no consequence on the quality of your future care.

In addition, the investigating physician may also end your participation in the study in the following cases:

- ✓ if he considers that remaining in the study could be harmful to you,
- ✓ you if you need a treatment not authorised by the protocol,
- ✓ if you do not follow the instructions of your doctor or the study team.

Your participation may end if the study is terminated early.

Should you decide to withdraw your consent, the data obtained for the research based on the consent expressed before it was withdrawn may be used, unless you express your opposition to the investigating physician who takes care of you. You can make this objection at any time.

Throughout your participation, you will be informed of any new data about the study or its implementation that may change your decision regarding your participation in the study.

You have the option at any time of the study to contact the investigating physician (whose details are on the 1st page of this notice) to request additional information about the study, your participation or your personal healthcare data.

What are your rights?

Study results

You have the right to be informed, if you so wish, of the overall results of the research at the end of the study (Art L.1122-1 Public Health Code). To exercise this right, you may contact Pr Eric Toussirot, Clinical Investigation Centre, CHU, 2 place St Jacques 25000 Besançon; Phone: 03 81 21 89 97.

Doctor/patient confidentiality

Your health data will be collected in a computer file allowing their automated processing. Doctor/patient confidentiality will be respected (article L. 1110-4 of the Public Health Code) and the data analysis will respect your privacy in accordance with the rules of the national data protection agency (CNIL). The data analysis results may be written up in a report and / or presented in a scientific publication which will not reveal your identity.

Access to your medical records

In application of the law *2002-303 of March 4, 2002 relating to the rights of patients and the quality of the health system*, you have the right to access your medical records during and after the end of the study. The research data constitutes a communicable element of the patient's medical records, according to the terms of article L.1111-7 of the Public Health Code.

Your rights over your personal data

Regarding your health data used for this research, you have the right to:

- access your data;
- request the correction of your data if they are inaccurate or incomplete;
- to limit the processing of your data;
- object to the processing of your personal data, at any time, without having to justify your decision. In this case, the data that will have been processed prior to your opposition will be kept. No other data will be collected after your opposition.

  You can request that the data already collected be deleted. However, certain data previously collected may not be erased if their deletion is likely to make it impossible or seriously compromise the achievement of the study objective.

All rights concerning your personal data are exercised either through the investigating physician or directly to the data protection officer (DPO) of the study sponsor (CHU de Besançon): crdpd@chu-besancon.fr.
At any time, you can request additional information on the possible use of your data. Your requests will be answered as soon as possible. You also have the right to lodge a complaint with CNIL by following the link below: www.cnil.fr/fr/plaintes

Origin, nature, and recipients of your collected data

This study requires the processing of some of your personal data.
These data come exclusively from:
- your medical records
- yourself or your legal representative
- the professionals involved in the study;

It can be directly or indirectly identifying data.
Only data that is strictly relevant, adequate and limited to what is necessary with regard to the objectives of the study will be used. These data will be pseudonymised and you will be identified using a code (ID). Only the principal investigator of the study will be able to maintain the link between the pseudonymisation code and your identity.
For the purpose of the study, your personal data may be accessed by the personnel involved in the study and those acting under their responsibility. All are subject to professional secrecy. They may be employees

of the hospital sponsoring the study, other care centres participating in the study, or other organisations acting on behalf of the sponsor.
Unless you object, these data may be used for medical or scientific research, with due regard for confidentiality. You can express your opposition at any time without having to justify your decision and without consequences on your medical care.

The data collection will concern:

Indirectly identifying data	Recipients of the data
Indirectly identifying data *Excluding surname(s), first name(s) and registration number in the National Directory for the Identification of Individuals*	▸ the data controller and the natural or legal persons acting on his behalf ▸ scientific research manager ▸ professionals involved in research and personnel acting under their responsibility or authority, ▸ those responsible for data collection, quality control, processing, and analysis ▸ persons in charge of regulatory affairs and registration of the research with the competent authorities ▸ the personnel of health authorities and public control authorities legally authorized, within the framework of a particular mission or the exercise of a right of communication ▸ the authorised personnel acting under the responsibility of the insurance organization guaranteeing the promoter's civil liability, ▸ the independent experts in charge of re-analysing the data to verify the results of the research (scientific editor)
Health data	
Dates relating to the conduct of the research Date of inclusion, dates of visits	
Social Security Excluding the registration number in the National Directory for the Identification of Individuals	
Participation in other research or studies	
Lifestyle habits and behaviours	
Vital status Only if this information appears in the medical file or is known to the professional involved in the research	
Quality of life scale	

Directly identifying data	Recipients of the data
- name - first name - postal address - electronic contact details - telephone number	▸ professionals involved in the study ▸ the personnel responsible for quality control and assurance (clinical research associates), duly mandated by the sponsor. ▸ the members of the data monitoring committee (DMC) ▸ the data protection officer (DPO) only in the event that you voluntarily enter into contact with them ▸legally authorized personnel of health authorities and public control authorities, ▸ authorized personnel acting under the responsibility of the insurance organisation guaranteeing the promoter's civil liability

Retention and archival of your data

Your personal data may be kept until 2 years after the last publication of the results of the research or, without publication, until the signature of the final research report. Your data will then be archived on paper or electronically for a period in accordance with the current regulations.

Transfer of your data outside the European Union

Only pseudonymised data may be transferred outside the European Union to a country or organisation recognised by the European Commission as providing an adequate level of protection or presenting the appropriate guarantees. This transfer can only occur if strictly necessary for the implementation of the research or the exploitation of its results.

Compensation - coverage of study costs

All examinations and treatments associated with the study are covered.
You will not receive any financial compensation for your participation in the study.

Your duties

You must be affiliated to a social security scheme or equivalent. You cannot be under the protection of justice, nor under tutorship or curatorship, nor under any protection regime.

Exclusion period

It is forbidden to participate in another interventional trial within 28 (± 2 days) after your enrolment. You can then participate in any other clinical study.

The regulatory framework

This study is carried out according to:

- the public health code and the code of medical ethics,
- European regulation 2014-536 relating to clinical trials of medicinal products for human use of April 16, 2014;
- law n°2012-300 of March 5, 2012 relating to research involving the human person (known as the Jardé law) modified by ordinance n°2016-800 of June 16, 2016,
- the general European regulation 2016-679 on the protection of personal data (GD¨R) of April 27, 2016, in particular article 6.1.e on the basis of public interest for the processing of your personal data,
- Law No. 78-17 of January 6, 1978 relating to data processing, files and freedoms as amended, known as the Data Protection Act (LIL),
- the MR-001 Reference Methodology of the National Commission for Computing and Liberties (CNIL).

This study received for its implementation:

- a favorable opinion from the Committee for the Protection of Persons (CPP) Sud-Est I dated 20/07/2022
- an authorisation from ANSM (National Agency for the Safety of Medicines and Health Products) dated 10/18/2022.

The sponsor has taken out insurance guaranteeing its civil liability to cover the possible harmful consequences of this study (*Société Hospitalière d'Assurances Mutuelles*, SHAM, contract number 158326, 18 rue Edouard Rochet, 69372 Lyon Cedex 08).

What will happen to your biological samples?

The samples taken for the diagnosis, during follow-up of your illness, or as part of the COVIC-19 research program may be kept and / or used for research related to COVID-19, as part of this research program, or for future studies.

Purpose of the collection of biological samples

The biological samples will be used for research programs or projects about the treatment of COVID-19. If your samples are used later for a study unrelated to COVID-19, you will be informed, and your consent will be requested again. No examination of your identifying genetic characteristics will be carried out without first obtaining your written and signed consent.

Nature of the samples and quantity taken

Blood and nasopharyngeal samples which will be carried out will be used in priority for disease diagnostic purposes. If all the samples are not used, we would like to keep the remainders, instead of destroying them, for future use in this research program or other research about COVID-19.

Location, storage period and name of the person in charge of the conservation of the collection of biological samples

The samples will be kept at the CIC-1431 Biomonitoring Platform (8 rue du Dr Giroud 25000 Besançon) for 3 years. Professor Philippe Saas is responsible for the conservation of this collection. The analyses will be carried out in the hospital centre where you were included or at the CIC-1431 Biomonitoring Platform (Besançon). You may request the destruction of the stored samples at any time by sending a handwritten letter to the physician responsible for the study or to the person in charge of conservation mentioned above, without any prejudice to you. You will continue to benefit from the care you need.

Future research

Future research on the same topic may require the use of your data and / or your biological samples. This research will always be carried out with due regard for doctor/patient confidentiality. This research may be carried out in part now or later depending on the progress of scientific knowledge.
You can nevertheless withdraw your consent or oppose future use of your pseudonymised data with the investigating doctor who follows you within the framework of this study. You can withdraw your consent or assert this opposition at any time.

This information notice belongs to you, and you may share it and talk about it with your primary care physician and / or to your relatives for advice.

If you agree to participate in this study, we kindly ask you to sign the consent form below.

DRCI	**Information notice and informed consent CAT 1 - PATIENT**		098 DRC 210 ER03 018 Version 2.0 Page 10/10
	REGISTRATION	COVIC-19	

Patient ID:

INFORMED CONSENT FORM

"A RANDOMISED OPEN-LABEL TRIAL OF EARLY, VERY HIGH-TITRE, CONVALESCENT PLASMA THERAPY IN CLINICALLY VULNERABLE INDIVIDUALS WITH MILD COVID-19"

SPONSOR: CHU BESANÇON

REF: 2022/703 No. IDRCB: 2022-A01307-36. / NCT 05271929

I freely and voluntarily agree to participate in this study.

I have carefully read this information notice, the aims of the study, how it will unfold.

I understand that my personal data and my biological samples may be collected by the sponsor and used in the context of present and future research.

STUDY PARTICIPANT		
Date: …… / ….. / …….	First name LAST NAME: …… Date of birth: ……. /……./ ……	Signature:
If applicable: Attestation of consent by a trusted person, a family member or other relative in the event the study participant cannot provide written consent.		
Date: …… / ….. / …… ..	First name LAST NAME: …… Relationship with the participant (Spouse, Guardian, Curator, Parent, etc.): ……	Signature:
INVESTIGATOR *I certify that I have fully explained to the participant the aims, the methods, and the potential risks of the study*		
Date: …… / ….. / …….	First name LAST NAME: ……	Signature:

Made in triplicate: the information notice and a copy of the consent form is to be kept by you, the participant, a copy of the consent form is kept by the investigator (page 13), and one is filed by the organisation responsible for the collection of biological samples (page 14).