

Effect of tight control management of Crohn's disease (CALM): a multicentre randomised controlled study

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Summary

Background: Biomarkers of intestinal inflammation, faecal calprotectin (FC) and C-reactive protein (CRP), have been recommended to monitor patients with Crohn's disease (CD), but whether their use in treatment decisions improves outcomes remains unknown. In CALM, we compared endoscopic and clinical outcomes at 48 weeks in moderate to severe CD managed with a tight control (TC) algorithm utilising clinical symptoms and biomarkers versus clinical management (CM) algorithm.

Methods: CALM (ClinicalTrial.gov number NCT01235689) was an open-label, multicentre, Phase 3 study in adult patients naïve to immunomodulator and biologics with active endoscopic CD (CD Endoscopic Index of Severity (CDEIS) >6 and sum of CDEIS subscores >6 in ≥ 1 segment with ulcers). Patients were randomised 1:1 to TC or CM groups after 8 weeks of prednisone induction therapy or earlier if they had active disease. In both groups, treatment was escalated in a step-wise manner from no treatment to adalimumab induction+every other week, every week (EW), and EW+azathioprine based on meeting failure criteria ($FC \geq 250 \mu\text{g/g}$, $CRP \geq 5\text{mg/L}$, Crohn's Disease Activity Index [CDAI] ≥ 150 , and/or prednisone for TC and CDAI and/or prednisone for CM). De-escalation was possible for adalimumab EW \pm azathioprine if failure criteria were not met. The primary endpoint of mucosal healing (CDEIS <4) with absence of deep ulcers was assessed 48 weeks post-randomisation.

Findings: A total of 244 patients (mean disease duration approximately 1 year) were randomised. Significantly higher proportion of patients in TC achieved the primary endpoint at week 48 (45.9%, $n=56$) than in CM (30.3%, $n=37$) with CMH adjusted risk difference of 16.1%

61 (95% CI 3·9–28·3), $p=0\cdot010$). The overall rate of adverse events was similar between TC and
62 CM.

63 **Interpretation:** Monitoring therapy using symptoms and biomarkers of inflammation led to
64 superior endoscopic and clinical outcomes in CD after 48 weeks post-randomisation compared
65 with symptom-driven decisions alone.

66 **Funding:** AbbVie.

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68

69 **Introduction**

70 Crohn's disease (CD) is a chronic, progressive, and disabling condition resulting in inflammation
71 of any segment in the gastrointestinal tract and, eventually, in development of strictures, fistulas,
72 or abscesses that require surgery in about half of patients within 10 years of diagnosis.¹⁻³

73 Conventional management of CD using corticosteroids, immunomodulators, and tumor necrosis
74 factor (TNF) inhibitors and other biologics in sequence may not adequately control the
75 underlying inflammation and may delay starting the most effective treatment.⁴ It may also put
76 patients at risk of infections, morbidity, and mortality due to the prolonged use of
77 corticosteroids.^{5,6} In addition, symptoms correlate poorly with endoscopic status in patients with
78 CD and might not be a reliable criterion for treatment adjustments to control persistent mucosal
79 inflammation.

80 Treatment goals have evolved to treat beyond symptoms.⁷ In 2015, the Selecting Therapeutic
81 Targets in Inflammatory Bowel Disease (STRIDE) program initiated by the International
82 Organisation for the Study of Inflammatory Bowel Diseases (IOBD) defined a treat-to-target
83 approach for CD with the aim of achieving both clinical and endoscopic remission.⁸ The IOBD
84 expert consensus also concluded that biomarkers of inflammation, faecal calprotectin (FC)
85 and/or C-reactive protein (CRP), may be useful to detect residual intestinal inflammation and
86 might facilitate patient monitoring. However, the panel noted that persistent elevations in these
87 biomarkers should not be used alone to adjust therapy based upon limited evidence available at
88 the time.

89 CALM was designed to evaluate the impact of two treatment algorithms to achieve mucosal
90 healing in patients with CD, escalating treatment based on pre-specified failure criteria: clinical

symptoms and biomarkers of inflammation in the tight control (TC) algorithm and clinical symptoms alone in the clinical management (CM) algorithm.

Methods

Study design

CALM was a multiCentre, randomised, open-label, active-controlled, two-group, Phase 3, efficacy and safety study to evaluate two treatment Algorithms, TC and CM, in patients with Moderate to severe CD that was conducted in 22 countries involving 74 sites. The study protocol was approved by the responsible ethics committees or internal review boards and was executed in compliance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines, and applicable local regulations.

Protocol deviations were monitored at study entry and throughout the study. A total of 8697 patients (35.29.8%) had reportable protocol deviations, including inclusion/exclusion criteria violations, received wrong treatment or incorrect dose, or received excluded concomitant treatment. No patients developed withdrawal criteria without being withdrawn. [Table S2 details types of deviations and number of affected patients per group. All protocol deviations were assessed in real time for impact on data integrity and patient safety to determine if the patient was to continue in the study. None of the deviations was considered to have affected the study outcome or interpretation of the study results.](#)

Study participants

Adult patients 18-75 years old with CD at baseline and diagnosis of ileal, colonic (including rectal) or ileocolonic CD confirmed by endoscopy not more than 6 years prior to baseline were enrolled in the study. Key inclusion criteria were (1) moderate to severe CD at baseline, defined

as Crohn's Disease Activity Index (CDAI) ≥ 220 to ≤ 450 for patients not receiving prednisone at baseline, ≥ 200 to ≤ 450 for patients receiving ≤ 20 mg prednisone for ≥ 7 days before baseline, and > 150 to ≤ 450 for patients receiving > 20 mg prednisone for ≥ 7 days before baseline, (2) active endoscopic disease, defined as total CD Endoscopic Index of Severity (CDEIS) > 6 and sum of CDEIS subscores > 6 in ≥ 1 segment with ulcers and (3) CRP ≥ 5 mg/L and/or FC ≥ 250 $\mu\text{g/g}$. Key exclusion criteria were previous or current biologic or immunomodulator use, > 2 previous courses of corticosteroids or current corticosteroids for > 3 months before screening. Patients with any fibrotic stricture (passable or non-passable and regardless of symptoms), draining perianal fistulas, or non-perianal fistulas were excluded (see appendix p.2 for complete list of inclusion and exclusion criteria).

Randomisation and Blinding

Nine weeks after baseline, patients were randomised to TC or CM groups in a 1:1 ratio (figure 1), stratified by smoking status (yes or no), weight (< 70 kg or ≥ 70 kg), and disease duration (≤ 2 years or > 2 years). To facilitate recruitment, an amendment allowed patients with active disease (CDAI > 220) to be randomised early (between baseline and originally scheduled randomisation) if one of the following conditions were met: (1) receipt of corticosteroid therapy for four weeks duration, including two weeks of prednisone ≥ 40 mg or equivalent per day (or budesonide ≥ 9 mg per day), (2) intolerance or a medical contraindication to steroid therapy, or (3) the investigator assessed that it was in the best interest of the patient. The patient number and group of each stratum were assigned by a central randomisation schedule generated by AbbVie, utilising WebRando software for randomisation and IVRS/IWRS for patient allocation. The investigators and patients were blinded to post-screening FC/CRP results; treatments were open-label.

136 *Procedures*

137 Eligible patients received a prednisone burst of up to 40 mg/day at baseline. Prednisone was
138 tapered with a schedule per investigator discretion. One week prior to randomisation, patients'
139 lab samples, CDAI, and prednisone use were assessed during a site visit (figure 1). At
140 randomisation, open-label treatment options were determined based on meeting failure criteria
141 listed in figure 1. Patients who randomised early and who met any of the failure criteria 1 week
142 prior to randomisation received 160/80 mg adalimumab at weeks 0/2 followed by 40 mg every
143 other week (EOW, [adalimumab EOW]). Patients who did not meet the failure criteria at
144 randomisation did not receive adalimumab. All patients could continue prednisone treatment per
145 investigator discretion (based on the rapidity and tolerance of the taper).

146 During the post-randomisation treatment period, open-label treatment in both groups was
147 escalated in a step-wise manner at 12, 24, and 36 weeks based on results of lab assessments at
148 11, 23, and 35 weeks if patients met any of the post-randomisation failure criteria (figure 1). The
149 CDAI threshold for the CM group was different than the TC group because it was meant to
150 mirror treatment in clinical practice at the time the study was designed, whereas the more
151 stringent criteria in the TC group were meant to guide treatment escalation decisions using
152 clinical remission, normalized biomarkers, and discontinuation of corticosteroids. Patients who
153 did not meet the failure criteria stayed on their previously assigned treatment option. At 24 and
154 36 weeks post-randomisation, patients on adalimumab EW and adalimumab EW+azathioprine
155 de-escalated to adalimumab EOW and adalimumab EOW+azathioprine, respectively. Patients
156 who did not complete prednisone taper, could continue to receive prednisone throughout the
157 post-randomisation treatment period, but could not re-initiate once tapered-off. Only patients
158 with $CDAI \geq 300$ who were initiating treatment with adalimumab EW+azathioprine could restart

prednisone. Final assessment of patients occurred at 48 weeks post-randomisation. CDAI was collected at unscheduled visits.

Patients who needed treatment escalation before the next site visit and who had CDAI>300 for two consecutive visits seven days apart (the first CDAI>300 at/after 4 weeks from initiation of the current therapeutic option) or per investigator discretion moved to a rescue group and followed the TC management algorithm. Rescue therapy was not allowed if patients were within 6 weeks of the final study visit.

Ileocolonoscopies to assess CDEIS were performed at study sites during screening and at 48 weeks after randomisation or early termination. Endoscopists were trained to evaluate endoscopies in a standardized manner.

A central lab measured FC using the Genova method and CRP using Particle-enhanced Immunoturbidimetric Assay and Turbidimetric/Immunoturbidimetric Assay. FC has been shown to have a sensitivity of 87% and specificity of 67% for endoscopically active CD, whereas, CRP levels have demonstrated a sensitivity and specificity of 49% and 92%, respectively, for IBD.⁹

Outcomes

The primary endpoint of the study was the proportion of patients with mucosal healing, defined as CDEIS<4, and no deep ulcers 48 weeks after randomisation. Since there were numerous secondary endpoints (unranked) in the study, we report those most relevant to the primary endpoint. These included the following assessments 48 weeks after randomisation: (1) deep remission (CDAI<150, CDEIS<4 and no deep ulcers, absence of draining fistula, discontinuation of corticosteroids \geq 8 weeks), (2) biologic remission (FC<250 μ g/g, CRP<5mg/L, and CDEIS<4), (3) CDEIS<4, (4) overall CDEIS<4 plus CDEIS<4 in every segment, (5)

complete endoscopic remission (CDEIS=0), and (6) endoscopic response (CDEIS decrease >5 points). Steroid-free remission (CDAI<150 and discontinuation of steroid use \geq 8 weeks) and clinical remission (CDAI<150), mean change from baseline in CDAI, and mean change from baseline in CRP were assessed over time. Additional secondary endpoints will be reported in subsequent manuscripts.

Safety evaluation

Adverse events (AE) were monitored in all patients who were randomised from the time of administration up to 70 days of discontinuation of study drugs, except patients who continued on adalimumab after the end of the study. New AEs in these patients were reported through the post-marketing reporting mechanism. Serious AEs (SAE) were collected from the time patients signed the informed consent. Tuberculosis was tested using a Purified Protein Derivative skin test or Interferon-Gamma Release Assay and confirmed using chest X-ray during screening for all patients and then annually for patients who completed the study.

AEs were tabulated by system organ class and preferred term using MedDRA dictionary version 19.0.

Statistical Analysis

Sample size was calculated using nQuery Advisor 6.0. To achieve 90% power, assuming 44.0%¹⁰ and 23.5%¹¹ mucosal healing and no deep ulceration rates in the TC and CM groups through the end of the 48 week post-randomisation treatment period, respectively, 120 subjects per group were needed using the Fisher's exact test (2-sided) at 0.05 alpha level. Patients who were in screening or who had been enrolled into the prednisone burst/taper portion of the study

when the minimum sample size was met were able to enrol in the study, resulting in 122 patients per group.

Efficacy endpoints and safety were analysed in the modified intent-to-treat population, defined as all randomised patients. Missing values after randomisation for primary and secondary endpoints and for remission over time were imputed using non-responder imputation (NRI); data for patients who discontinued the study or who moved to the rescue group were also subject to NRI. Change from baseline in CDAI and CRP were imputed using last observation carried forward method (LOCF).

Primary endpoint and categorical secondary endpoints were compared in the TC and CM groups using Cochran-Mantel-Haenszel (CMH) test stratified by smoking status (yes or no) and weight (<70 kg or \geq 70 kg) at screening. The CMH-based two-sided 95% confidence intervals (CI) for the difference in proportions between groups were calculated. The secondary endpoints for the difference in change from baseline between groups were analysed using an ANCOVA model including factors of treatment, screening smoking status (yes or no), weight (<70 kg or \geq 70 kg), and baseline scores as covariate. While disease duration (\leq 2 years or > 2 years) was a randomization stratum, it was not used in CMH or ANCOVA analyses to avoid zero cell issue because the majority of patients had disease duration of \leq 2 years. The secondary endpoints were tested at nominal significance level of 0.05 with no adjustment of multiplicity. Safety analyses were summarized by study group and presented as incidences (%) and rates (events [E]/100 patient-years [PY]).

Role of Funding Source

AbbVie funded the study, contributed to design, participated in the collection, analysis, and interpretation of the data, and in preparation and approval of this report. All authors had access to study data, reviewed and approved the final report, and take full responsibility for the accuracy of the data and statistical analysis. The corresponding author had full access to study data and had final responsibility for the decision to submit for publication.

Findings

Between March 2011 and November 2016, 460 patients were screened, 205 were excluded, 11 were enrolled, but not randomised, and 244 were randomised to TC (n=122) and CM (n=122) (figure 2). The most common reason for screen failure was not meeting inclusion or meeting exclusion criteria. Among patients who screen-failed, 65 (32%) did not meet elevated FC or CRP criteria. 3/122 (2%) patients in TC and 24/122 (20%) patients in CM moved to rescue therapy. 93/122 (76%) patients in TC and 90/122 (74%) patients in CM completed the study. Primary reasons for discontinuation in both groups were similar.

Patient characteristics in both groups were similar at baseline (table 1). Mean (SD) disease duration was comparable in both groups: 1.04 (2.25) years in TC and 0.86 (1.68) years in CM. 98 (80.3%) patients in TC and 97 (79.5%) in CM were exposed to prednisone at/after screening. Mean (SD) exposure of prednisone during the entire study excluding the use prior to randomisation was 1369.9 (1137.7) mg/patient in TC and 1505.7 (1029.8) mg/patient in CM. 69 (57%) patients in TC and 63 (52%) patients in CM were randomised early. Table S23 shows the timing of randomisation.

The study's primary endpoint of mucosal healing (CDEIS<4) and no deep ulcers at 48 weeks post-randomisation was met in 56 (46%) patients in TC compared with 37 (30%) patients in CM;

CMH adjusted risk difference of 16.1% (95% CI 3.9–28.3), $p=0.010$ (figure 3A). A higher proportion of patients in the TC group achieved deep remission (CMH adjusted risk difference of 14.5% [95% CI 2.9–26.0], $p=0.014$), biologic remission (CMH adjusted risk difference of 14.5% [95% CI 4.1–25.0], $p=0.006$), and CDEIS<4 at 48 weeks after randomisation (CMH adjusted risk difference of 16.1% [95% CI 3.9–28.3], $p=0.010$) compared with the CM group (figure 3B). No statistically significant differences were observed for overall CDEIS<4 plus CDEIS<4 in every segment (CMH adjusted risk difference of 5.9% [95% CI -5.2–17.0], $p=0.299$), complete endoscopic remission (CMH adjusted risk difference of 1.7% [95% CI -7.9–11.3], $p=0.728$), and endoscopic response (CMH adjusted risk difference of 11.5% [95% CI -0.8–23.9], $p=0.067$) (figure 3B). A significantly higher proportion of patients in TC than CM achieved steroid-free remission (figure 3C) and clinical remission (CDAI<150) (figure S1) at 11, 23, 35, and 48 weeks after randomisation. A significantly greater mean change from baseline in CDAI was observed in TC compared with CM at 11, 35, and 48 weeks (figure S2). Mean change from baseline in CRP was not statistically different between TC and CM (figure S3).

The number of patients receiving each treatment option at randomization and 12, 24, and 36 weeks after randomisation are shown in figure 4 for patients who completed the study and did not move to the rescue group ($n=88$ in TC and $n=78$ in CM). At randomisation, numerically more patients in the TC group than in the CM group received adalimumab EOW. Over time, more patients in TC advanced in the treatment algorithm earlier than in CM. For example, more patients in TC escalated to adalimumab EW at 12 weeks and to adalimumab EW+azathioprine at 24 weeks than in CM. In addition, more patients de-escalated from the EW dosing to EOW at 24 weeks and from adalimumab EW+azathioprine to adalimumab EOW+azathioprine at 36 weeks in TC than in CM (figure 4). Overall, more treatment adjustments occurred in TC than in CM.

In the TC group, 50, 39, and 20 patients met failure criteria at 11, 23, and 35 weeks after randomisation, respectively (table S43). Post-hoc exploratory analyses demonstrated that at 11 and 23 weeks, the decision to escalate included elevated FC for 31/50 (62%) and 22/39 (56%) patients and elevated CRP for 23/50 and 18/39 (both 46%) patients. At week 35, both FC and CRP equally contributed to the decision to escalate in 45% of patients. Lesser proportions of patients escalated based on the decision that included CDAI and use of prednisone. In the CM group, 24, 9, and 7 patients met failure criteria at 11, 23, and 35 weeks, respectively (table S54). Prednisone use was the main driver of the decision to escalate at 11 and 23 weeks. At 35 weeks, all patients were escalated based on elevated CDAI.

Overall, 105 patients (86·1%) in the TC group and 100 patients (82·0%) in the CM group reported treatment-emergent AEs (table 4). AE rates in the both groups were similar: 643·1 E/100 PY in TC and 694·4 E/100 PY in CM. A similar proportion of patients reported SAEs: 22 patients (18·0%) and 25 patients (20·5%) in TC and CM, respectively. SAE rates in TC were numerically lower (32·4 E/100 PYs) than in CM (49·3 E/100 PY). The proportion of patients reporting serious infections in TC (4·9%, n=6) and in CM (9·8%, n=12) were not significantly different. Among patients with serious infection, 2 in TC and 7 in CM reported abdominal/anal abscesses. The serious infection rate was 7·1 E/100 PY (7 events) in TC and 16·4 E/100 PY (15 events) in CM. Incidences and rates of other AEs from patients in the TC and CM groups were similar. No new safety signals were found in either group.

Discussion

The CALM study demonstrates that a treatment algorithm based on FC and CRP (tight control) to monitor inflammatory activity in addition to clinical symptoms led to superior outcomes

290 compared to the algorithm based on clinical management alone in a patient population with early
291 CD. The TC algorithm led to rapid optimisation of therapy and therefore to a higher rate of
292 mucosal healing (CDEIS<4) with a lack of deep ulcers on endoscopy, deep remission
293 (CDAI<150 and CDEIS<4 and no deep ulcers, no draining fistula, and no prednisone use for 8
294 weeks), biological remission (FC<250 µg/g, CRP<5 mg/L, and CDEIS<4), and steroid-free
295 remission (CDAI<150 with no prednisone for 8 weeks).

296 Early use of anti-TNF therapy has been advocated based on a greater chance of achieving
297 clinical remission, mucosal healing, and preserving bowel integrity.¹² In a subgroup analysis of
298 patients with moderately to severely active CD treated with adalimumab, patients with disease
299 duration of <2 years maintained higher remission rates than patients with longer disease duration
300 during 3 years of continued treatment.¹³ Higher rates of combined clinical and endoscopic
301 remission (“deep remission”) were observed among patients with <2 years of CD in another
302 study.¹⁴ Our study results reinforce previous findings that patients with recent onset of disease
303 (mean disease duration of 0·84–1·04 years) benefited from early biologic treatment as noted by
304 higher overall rates of mucosal healing and steroid-free remission in the clinically managed
305 group compared with historical rates observed with adalimumab used in a traditional step-up
306 manner in patients with a longer average disease duration.^{11,15} Even in these early patients, in
307 whom the high rates of endoscopic and clinical outcomes are anticipated, the tight control
308 approach led to even greater clinical benefits without an increased risk.

309 Delaying administration of effective therapy for CD can put patients at a greater risk of
310 developing complications. A concept of early immunosuppression addressing this concern by
311 administering biologics combined with immunomodulators after corticosteroid induction has
312 shown superior outcomes than a conventional step-up therapy in both referral centres and

community-based practices.^{4,10,16} In our study, we used a novel approach to optimize adalimumab dosing before adding azathioprine based upon individual response in order to minimize exposure to azathioprine and improve outcomes.

The REACT study showed a decrease in the risk of major adverse outcomes, including surgeries and hospitalisations, with early combined immunosuppression based upon a rapid step-up algorithm using adalimumab combined with an antimetabolite as first-line in patients with established CD after failure of corticosteroids versus conventional management.⁴ It needs to determine if early individualised optimisation of therapy based upon biomarkers and symptoms like in CALM will also lead to fewer irreversible disease-related structural complications compared to therapy individualisation based upon symptoms alone.

The STRIDE consensus recommended a treat-to-target goal in CD to be an endoscopic remission (resolution of ulceration as observed by ileocolonoscopy) in addition to clinical remission (resolution of abdominal pain and diarrhoea/altered bowel habit).⁸ Endoscopic remission and deep remission defined as the absence of mucosal ulceration and CDAI<150 have shown to be consistently associated with better long-term outcomes.¹⁴ However, the ability to perform repeated endoscopic evaluations and the patient acceptance of this are probably prohibitive. Studies have demonstrated that inflammatory biomarkers, such as CRP and FC, may be useful adjuncts to identify patients at risk for negative outcomes. In a study of 43 patients with CD, elevated levels of FC predicted relapse of disease activity.¹⁷ A recent systematic analysis of six studies in inflammatory bowel disease (IBD), including CD, has showed that elevated levels of FC on at least two consecutive measurements were associated with a higher risk of relapse within 2–3 months in asymptomatic patients and normal FC values were associated with a lower risk of relapse.¹⁸ In another study of 87 patients with CD, the FC levels of >250 µg/g were

336 associated with the presence of large ulcers and levels of ≤ 250 $\mu\text{g/g}$ predicted endoscopic
337 remission.¹⁹ Elevation of CRP levels has been shown to be associated with clinical disease
338 activity, endoscopic inflammation, and severely active histologic inflammation in CD patients.²⁰
339 However, the utility of CRP, a nonspecific marker of intestinal inflammation, in monitoring
340 patients with CD remains unclear. While CRP has been shown to be a predictive factor of CD
341 relapse in patients with elevated CRP levels at diagnosis,²¹ some patients with low CRP levels
342 still have active disease²² and an elevated CRP is not always due to active disease.²³ Our study
343 showed better outcomes due to a quicker treatment escalation guided by elevated FC and/or CRP
344 levels and clinical symptoms in the TC group compared with decisions based on clinical
345 symptoms alone. These findings emphasize the role biomarkers can play in identifying
346 underlying inflammation in CD and the need for monitoring patients using objective criteria.

347 In spite of more intensive immunosuppression based upon faster treatment escalation to
348 adalimumab EW \pm azathioprine in TC than in CM, the frequency and rates of AEs at 48 weeks of
349 treatment in the both groups were similar, and the rates of SAEs and serious infections were
350 numerically lower in TC than in CM. Adalimumab EW has previously been shown to be well-
351 tolerated and have a safety profile similar to the EOW dosing at 56 weeks.¹⁵ Similar adverse
352 event rates have been observed in patients treated with adalimumab monotherapy or combination
353 therapy in short-term studies,²⁴ but combined use was associated with a greater risk of
354 malignancy in an analysis that included longer follow up.²⁵ The lower exposure-adjusted rates of
355 SAEs in the TC group may be related to superior control of CD activity. This is noted by a
356 lower number of subjects who experienced serious infections due to abscess in TC than CM. A
357 recent analysis of patients with CD treated with adalimumab found that higher disease activity
358 was associated with significantly increased risks of both serious and opportunistic infections.⁶

The frequency and rates of AEs and SAEs in CALM were consistent with the adalimumab safety profile from global clinical trials in patients with CD and across approved indications;^{26,27} no new safety signals were identified.

Our study has several limitations. First, endoscopies were evaluated by site readers that could have created an inclusion bias and scoring heterogeneity. On the other hand, inter-observer agreement in measuring CDEIS has been shown to be good.^{28,29} In addition, agreement between CDEIS determined by trained site and central readers has been shown to be excellent, suggesting that site readings by trained endoscopists could be used in clinical trials.³⁰ In CALM, investigators were trained to evaluate endoscopies in a standardized manner and the same endoscopist was to perform evaluation of endoscopies from an individual patient. Another limitation of CALM was its open-label design (which could have biased clinical and endoscopic assessments) and limited duration of follow up (48 weeks), which did not allow assessment of whether the superior efficacy findings with TC would lead to better long-term outcomes or if the safety profile would change with longer use. The CALM entry criteria specified a maximum disease duration of 6 years as well as no exposure to anti-TNF agents and immunomodulators in order to identify patients with a lower likelihood of accumulated bowel damage who would be more responsive to the study treatments. Whether the findings of CALM could be expected in a population of patients with longer disease duration or more treatment experience is unknown. Lastly, the prednisone taper schedule and continuation of prednisone treatment was at the investigator's discretion. Because the duration of taper could influence the treatment option at randomisation differentially between treatment groups (due to the use of prednisone defining failure at randomization only in the TC group), it is possible that earlier introduction of adalimumab could have affected the outcomes observed 48 weeks post randomisation.

The CALM study has shown for the first time that tight control of inflammation in patients with CD, using objective markers of disease activity in addition to clinical symptoms to drive treatment decisions, achieved better endoscopic and clinical outcomes than conventional care based on symptoms alone. Early treatment escalation to adalimumab was well tolerated and proactive biomarker monitoring reduced the use of corticosteroids.

PANEL: RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed for articles published up to August 2017 in any language using search terms of “Crohn’s disease”, “early combined immunosuppression”, “azathioprine combination”, “therapeutic goals”. We identified three publications of randomised controlled trials using biologics in combination with azathioprine in treatment of CD (Top-Down, SONIC, and REACT) and one publication of recommendations from expert panel determining treat-to-target goals in CD (STRIDE). The Top-Down and REACT trials have showed that combined immunosuppression was effective in inducing clinical remission, decreasing corticosteroid use, and decreasing the risk of major adverse outcomes defined as occurrence of surgery, hospital admission or serious disease-related complication in patients with CD. Recent recommendations by an expert panel (STRIDE) have defined the therapeutic goal in CD as clinical and endoscopic remission but lacked a practical algorithm of achieving this goal. The panel recommended using biomarkers of inflammation, FC and CRP, to assist in monitoring patients to achieve the goal; however, there is insufficient evidence to recommend treatment optimisation based on

403 *biomarkers alone. Indeed, few studies have shown the utility of FC and CRP in monitoring*
404 *patients with CD.*

405 *Added value of this study*

406 *CALM was a Phase 3, multicentre, randomised, open-label, active-controlled efficacy and safety*
407 *study in patients with moderate to severe CD naïve to immunomodulators and biologics. This is*
408 *the first study that demonstrated that a tight control algorithm of disease activity using stringent*
409 *criteria including CRP, FC, CDAI, and prednisone use improves the rate of mucosal healing*
410 *(CDEIS < 4) and no deep ulcers at 48 weeks post-randomisation in patients with CD compared*
411 *with clinical management using CDAI and prednisone use. Tight control of disease activity*
412 *based on biomarkers also improved other endoscopic and clinical outcomes, including steroid-*
413 *free remission. The safety profile was similar between treatment groups and consistent with the*
414 *known safety profile of adalimumab in CD.*

415 *Interpretation: Implications of all the available evidence*

416 *Results from this study indicate that treatment escalation based on tight monitoring of patients*
417 *with CD using biomarkers of inflammation and clinical management improves endoscopic and*
418 *clinical outcomes. No new safety signals were identified with treatment escalation; the safety*
419 *profile of study treatments was comparable with the known safety of adalimumab mono- and*
420 *combination therapy as well as adalimumab dosing schedules in CD.*

421 **CONTRIBUTORS**

422 *JFC, RP, PB, ML, FB, TV, AD, GN, AA, XH, ST, SD, WR, WJS, PR, DH, SS, GD participated*
423 *in the conception and study design, conduct of the study, including selection, treatment, and*

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558 issued, a patent Colonic delivery of nicotine to treat inflammatory bowel disease (South African
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560 0954337 and 893998; Hong Kong patent HK1019043; China patent ZL97192177; Czech patent
561 293616; Canada patent 2,246,235) issued, a patent The use of azathioprine to treat Crohn's
562 disease (US 5,733,915) issued, a patent Azathioprine compositions for colonic administration
563 (New Zealand patent 306062; Singapore patent 45647; Australia patent 707168; Czech patent
564 290428) issued, a patent Intestinal absorption of nicotine to treat nicotine responsive conditions
565 (Australia patent 718052; US 6,238,689) issued, a patent The use of topical azathioprine and
566 thioguanine to treat colorectal adenomas (US 6,166,024) issued, a patent Enema and enterically
567 coated oral dosage forms of azathioprine (US 6,432,967) issued, a patent A pharmaceutical
568 composition for the treatment of inflammatory bowel disease (US 7,341,741) issued, a patent
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Figure legends

Figure 1. CALM study design

CM=clinical management. CDAI= Crohn's Disease Activity Index. ADA=adalimumab. EOW=every other week. EW=every week. AZA=azathioprine. TC=Tight Control. FC=faecal calprotectin. CRP=C-reactive protein.

Figure 2. Patient flow diagram of CALM study

Figure 3. Study endpoints at 48 weeks after randomisation

Proportion of patients with mucosal healing (CDEIS<4) and no deep ulcers at 48 weeks after randomisation (A); number of patients analyzed over total number in each group is shown in bars. Secondary endoscopic endpoints at 48 weeks after randomisation (B); number of patients analyzed is shown in bars. Steroid-free remission (CDAI<150 and no corticosteroids for >8 weeks) during the post-randomisation period (C); number of patients analyzed is shown in bars.

CDEIS=Crohn's Disease Endoscopic Index of Severity.

Figure 4: Treatment options during the post-randomisation period in patients who completed the study and did not move to the rescue group

Total number of patients in each group is shown under bars; proportion of patients and number of patients with a specific treatment is shown in each bar as % (n).

ADA=adalimumab. EW=every week. AZA=azathioprine. EOW=every other week. CM=Clinical Management. TC=Tight Control.

	Clinical Management n=122	Tight Control n=122
Sex		
Female (n, %)	69 (56·6)	72 (59·0)
Race		
White, n (%)	113 (92·6)	113 (92·6)
Age, year; mean (SD)	31·1 (11·4)	32·1 (12·0)
Weight, kg; mean (SD)	66·3 (12·3)	66·3 (13·7)
Disease duration, year		
mean, (SD)	0·86 (1·68)	1·04 (2·25)
median (range)	0·22 (0·0—12·7)	0·20 (0·0—13·2)
CDAI, mean (SD)	267·7 (58·4)	273·3 (59·5)
CDEIS, mean (SD)	14·3 (6·9)	13·4 (6·0)
Disease Location n (%)		
Ileal	14 (11·5)	21 (17·2)
Colonic	37 (30·3)	34 (27·9)
Ileal-colonic	65 (53·3)	64 (52·5)
Surgeries, n (%)	8 (6·6)	12 (9·8)
FC, n (%)		
< 250 µg/g	17 (13·9)	24 (20·0)
≥ 250 µg/g	105 (86·1)	96 (80·0)

CRP		
mean (SD)	27·0 (30·6)	26·4 (32·3)
median (range)	16·1 (0·4—172·6)	13·6 (0·2—157·1)
n (%)		
< 5 mg/L	19 (15·6)	27(22·1)
≥ 5 mg/L	103 (84·4)	95 (77·9)
Smoker, n (%)	33 (27·0)	31 (25·4)

711 SD=Standard deviation. CDAI=Crohn's Disease Activity Index. CDEIS=Crohn's Disease

712 Endoscopic Index of Severity. FC=faecal calprotectin.CRP=C-reactive protein.

713

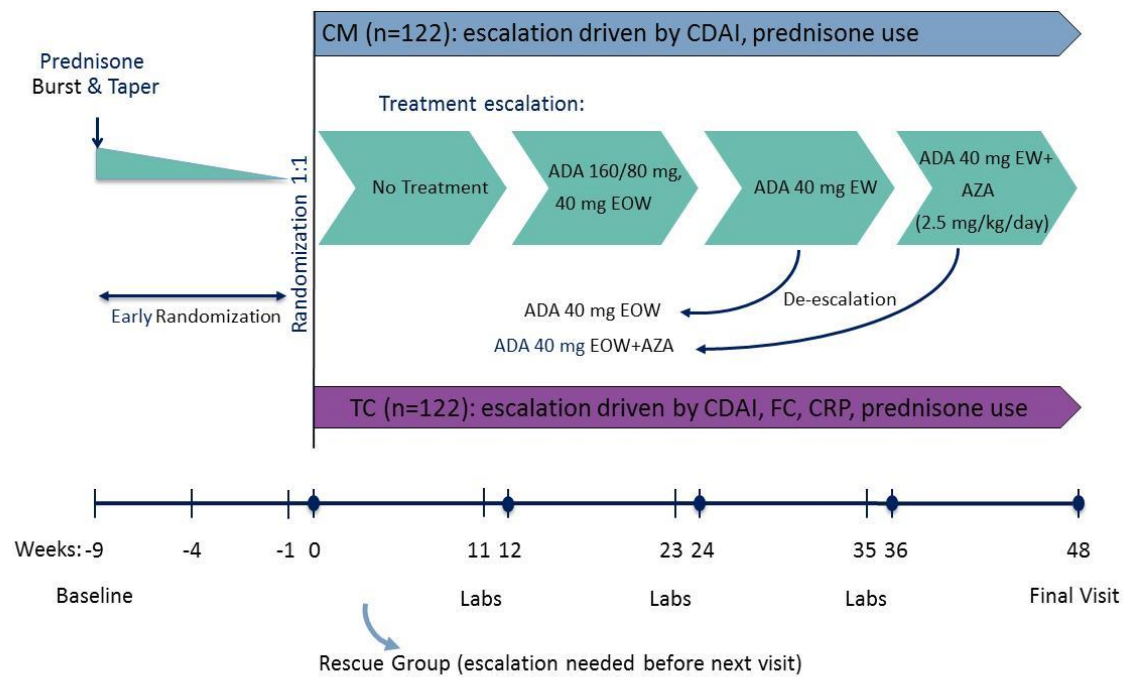
714 **Table 2.** Adverse events.

	Clinical Management		Tight Control	
	n=122 n (%)	PY=91·3 Events (E/100 PY)	n=122 n (%)	PY=98·9 Events (E/100 PY)
AE	100 (82·0)	634 (694·4)	105 (86·1)	636 (643·1)
Serious AE	25 (20·5)	45 (49·3)	22 (18·0)	32 (32·4)
AE leading to adalimumab discontinuation	16 (13·1)	25 (27·4)	17 (13·9)	18 (18·2)
Infection	57 (46·7)	110 (120·5)	61 (50·0)	116 (117·3)
Serious infection	12 (9·8)	15 (16·4)	6 (4·9)	7 (7·1)
Opportunistic infection excluding oral candidiasis and TB	0	0	0	0
Active TB	0	0	1* (0·8)	1(1·0)
Latent TB	2 (1·6)	2 (2·2)	1 (0·8)	1(1·0)
Malignancy	0	0	1 (0·8)	1 (1·0)
Deaths	0	0	0	0

715 *Pulmonary TB.

716 PY=Patient-years. E=events. AE=adverse events. TB=tuberculosis

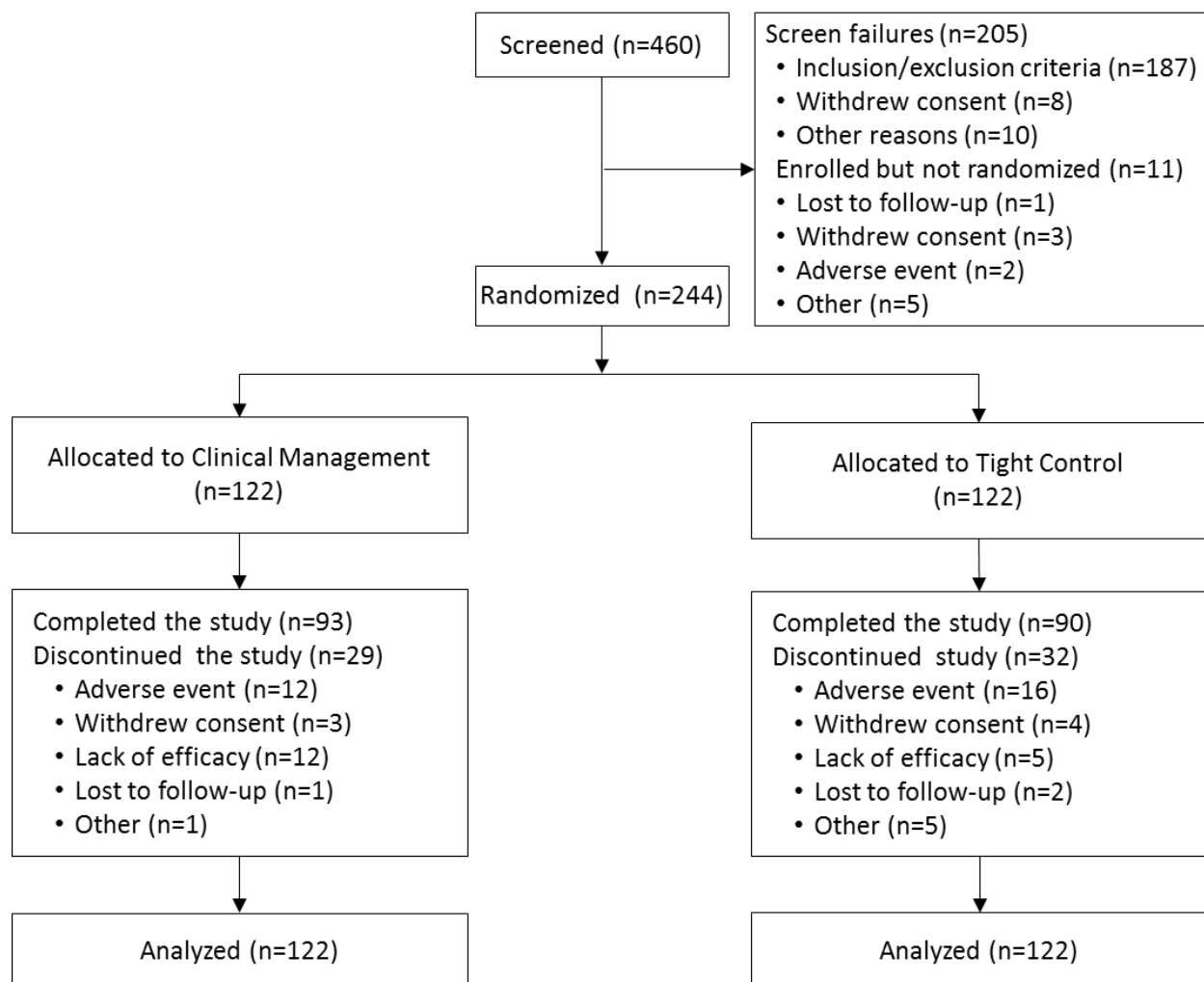
717 **Figure 1.**



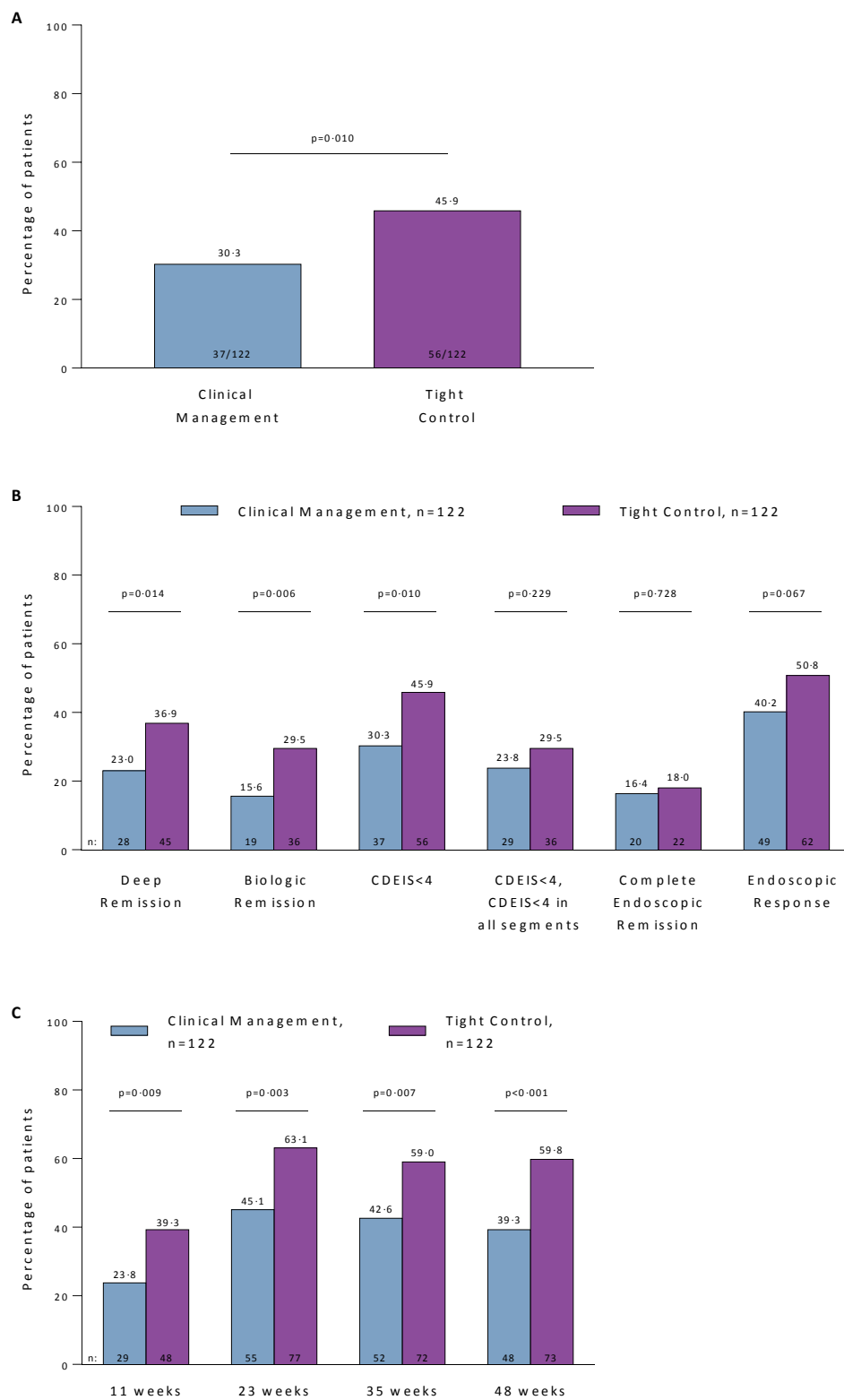
Failure criteria:

Lab visits	Clinical Management	Tight Control
Week -1 (prior to randomization)	CDAI decrease < 70 points compared to BL or CDAI > 200	1. CDAI ≥ 150 2. CRP ≥ 5mg/L 3. FC ≥ 250 µg/g 4. Prednisone use at week 0
Weeks 11, 23, and 35	CDAI decrease < 100 points compared to BL or CDAI ≥ 200 Prednisone use a week prior to visit	1. CDAI ≥ 150 2. CRP ≥ 5mg/L 3. FC ≥ 250 µg/g 4. Prednisone use a week prior to visit

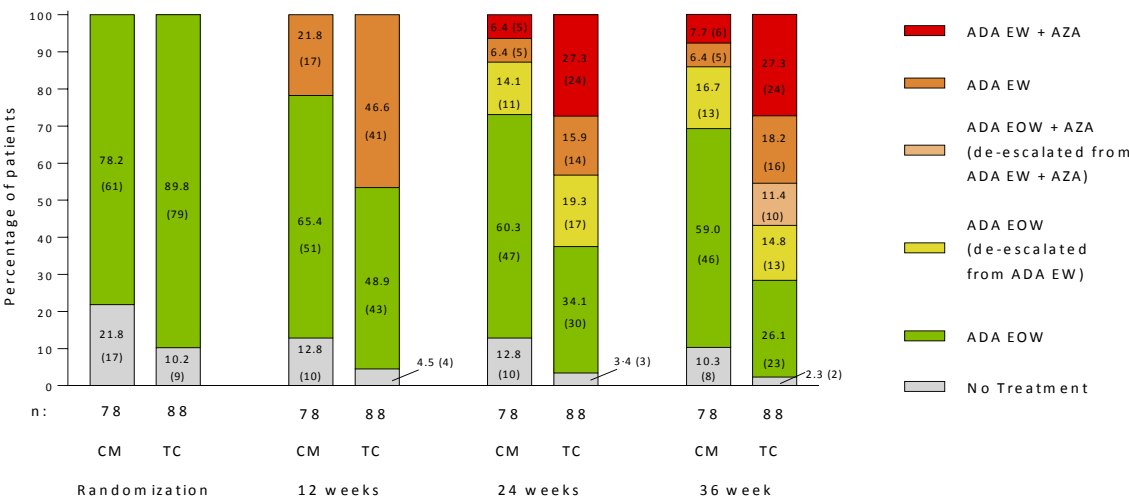
719 **Figure 2.**



720



723 **Figure 4.**



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725