DATE: 16-May-2024

TO: EMA

FROM: InDex Pharmaceuticals

SUBJECT: Early terminated study in EU CTR

To Whom It May Concern:

InDex Pharmaceuticals is committed to the disclosure of results for interventional clinical trials conducted in the EU/EEA per the requirements of Commission Guideline 2012/C 302/03.

The trial listed below was registered with the EudraCT database but **was early terminated** on November 21, 2023 based on the advice from an independent Data Monitoring Committee (DMC). The DMC had performed a pre-specified and independent analysis including 130 patients who had completed the 6-week Induction study. A futility assessment showed that cobitolimod was unlikely to meet the primary objective upon completion of Induction Study 1.

Therefore, results cannot/should not be posted using the EudraCT full results/data set module. Instead, an *abbreviated Clinical Study Report* containing partial study results (dated 15-May-2024) is posted as a summary attachment (enclosed).

EudraCT#:	Protocol No.:	Study Title:	Sponsor Name:
2021-002549-13	CSUC-01/21	A Randomised Double-Blind Placebo-Controlled Phase III Clinical Study to Evaluate the Efficacy and Safety of Cobitolimod as an Induction and Maintenance Therapy in Participants with Moderate to Severe Active Left-Sided Ulcerative Colitis	InDex Pharmaceuticals

Sincerely,

Jenny Sundqvist

Chief Executive Officer

InDex Pharmaceuticals AB
Berzelius väg 13, SE-171 65 Solna, Sweden
Tel +46 (0)8 122 038 50
Org nr 556704-5140
www.indexpharma.com

Title Page

Study Title:	A Randomised Double-Blind Placebo-Controlled Phase III Clinical Study to Evaluate the Efficacy and Safety of Cobitolimod as an Induction and Maintenance Therapy in Participants with Moderate to Severe Active Left-Sided Ulcerative Colitis
Short Title:	A Phase III Study to Evaluate the Efficacy and Safety of Cobitolimod as an Induction and Maintenance Therapy in Participants with Moderate to Severe Active Left-Sided Ulcerative Colitis
Study Intervention:	Cobitolimod
Indication:	Ulcerative colitis
Brief Study Description:	A randomised, double-blind, placebo-controlled study to assess the safety and efficacy of 250 mg and 500 mg doses of cobitolimod in inducing or maintaining clinical remission in participants with moderate to severe active left-sided ulcerative colitis
Study Sponsor:	InDex Pharmaceuticals AB Berzelius väg 13 171 65 Solna, Sweden
Study Number:	CSUC-01/21
Study Phase:	III
Date of First Enrollment:	24 Nov 2021
Date of Early Study Termination:	21 Nov 2023
Date of Last Participant Completed:	20 Dec 2023
Report Version:	Final; Date: 15 May 2024

The study was conducted according to the protocol and in compliance with Good Clinical Practice (GCP) and other applicable regulatory requirements.

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2 Clinical Study Synopsis

Name of Sponsor: InDex Pharmaceuticals AB	**Volume:**	(For national authority use only)
Intervention Name: Cobitolimod **Name of Active Ingredient(s):** Cobitolimod	**Page:**	
Title of Study: A Randomised Double-Blind Placebo-Controlled Phase III Clinical Study to Evaluate the Efficacy and Safety of Cobitolimod as an Induction and Maintenance Therapy in Participants with Moderate to Severe Active Left-Sided Ulcerative Colitis.		
Study/Protocol Number: CSUC-01/21	**Phase of Development:** III	
Number of Study Centre(s) and Countries: This study was conducted at 129 centres that screened participants in 30 countries.		
Publications (if applicable): None		
Study Period: **Date of First Enrollment**: 24 Nov 2021 **Date of Last Participant Completed:** 20 Dec 2023		
Ulcerative colitis (UC) is a disease characterised by chronic inflammation of the rectal and colonic mucosa. The disease is recurrent, with both active (flares) and inactive stages that differ in pathology, symptoms, and treatment. Current therapy for UC encompasses the treatment of active disease and the maintenance of remission. Treatment options for UC have rapidly expanded in recent years, and now include multiple biologic agents and the small molecule drug tofacitinib in addition to the non-biologic options. However, a significant proportion of participants do not respond to these treatments or lose response to biologics over time. TNFα inhibitors carry potential risks associated with their use, and the JAK-inhibitor tofacitinib has also been associated with serious side effects. There is an enduring unmet need for alternative safe and efficacious treatments with new mechanisms of action. Cobitolimod (rINN) is a fully synthetic DNA-based 19-mer ODN. The drug functions as an immunomodulatory agent by targeting the toll-like receptor 9 (TLR9) present inside immune cells or on the surface of epithelial cells.		

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This was a randomised double-blind placebo-controlled phase III clinical study to evaluate the efficacy and safety of cobitolimod as an Induction and maintenance therapy in participants with moderate to severe active left-sided UC.

The independent Data Monitoring Committee (DMC) completed the planned dose selection interim analysis including a safety review and futility assessment in induction study of the phase III programme CONCLUDE on 21 Nov 2023, and their recommendation was to terminate the study as cobitolimod was unlikely to meet the primary objective. The Sponsor decided to terminate the CONCLUDE CSUC-01/21 study based on the independent DMC advice and recruitment of participants was stopped, and no more participants were dosed. Therefore, an abbreviated clinical study report (CSR) is written.

Methodology: The full phase III programme for cobitolimod in the treatment of moderate to severe UC was intended to include two induction studies (induction study 1 and induction study 2) and one maintenance study. This CSR (CSUC-01/21 CONCLUDE) covers stage 1 of induction study and the resulting maintenance study. The maintenance study was supposed to include participants from both induction study 1 and induction study 2. Approximately, 800 participants in the induction studies (440 in induction study 1 and 300 to 400 in induction study 2) and at least 250 participants in the maintenance study were planned to be enrolled.

Induction Study

Induction study was a randomised, double-blind, placebo-controlled, parallel-group, multicentre study, with an adaptive design in two stages that enrolled participants with moderate to severe active left-sided UC who demonstrated an inadequate response to or intolerance of conventional, biologics (infliximab, adalimumab, golimumab, vedolizumab, ustekinumab) or JAK-inhibitors (tofacitinib), or other approved advanced therapy for UC.

Stage 1 explored the efficacy of two different doses of cobitolimod (250 mg and 500 mg, administered twice 3 Weeks apart) with placebo as a control, to select the most effective and safe dose. In stage 2, the study was supposed to continue with the winning dose of cobitolimod. The primary objective of the induction study was to confirm superior efficacy in the selected (winning) dose arm compared with placebo at induction (I)-Week 6.

In stage 1, participants were randomly assigned in a 1:1:1 allocation to receive rectal doses of cobitolimod 250 mg, cobitolimod 500 mg, or placebo. After approximately 44 participants were randomised into each arm and had eligible efficacy data for the primary endpoint, an interim analysis was performed. A total of 133 participants (i.e., approximately 30% of the total 440 participants enrollment target in induction study) completed the 6-Week induction

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study and were included in the induction study interim analysis. The independent DMC completed the planned dose selection interim analysis including a safety review and futility assessment and advised to terminate the study because cobitolimod was unlikely to meet the primary objective upon completion of induction study. The Sponsor decided to terminate the study on 21 Nov 2023 based on the advice from the independent DMC.

Randomisation in the induction study was stratified for concomitant use of GCS treatment at I-Week 0 and previous treatment with biologics, JAK inhibitors, or other approved advanced therapy.

Visits during the induction study were performed during the screening period, with approximately 10 days from endoscopy until randomisation, and at I-Week 0 (day 1), I-Week 3, and I-Week 6.

Participants self-administered the study intervention rectally using an enema at the clinic under the supervision of the study staff, to ensure they managed to administer the study intervention appropriately.

Maintenance Study

Participants who achieved clinical response at I-Week 6 after starting induction treatment were eligible for participation in the maintenance study. Eligible participants (I-Week 6 responders) were re-randomised in a 1:1 allocation to cobitolimod (250 mg or 500 mg) or placebo, administered once every 3 Weeks for up to 46 Weeks. Participants in the placebo group during the induction study continued with placebo in the maintenance study. Randomisation should have been stratified for clinical remission at I-Week 6 and concomitant use of GCS at I-Week 6. However, as the electronic data capture (EDC) system was non-functioning for clinical remission parameter, no participants were stratified for clinical remission status. The study was terminated before the EDC system could be updated to rectify the issue.

It was planned that after the winning dose was selected, the participants that had been enrolled into the maintenance study based on clinical response in the losing dose arm, should be switched to the winning dose in the maintenance study at the next visit to the clinic, with the justification to collect further safety data for the winning dose. These participants would not have been part of the efficacy evaluation in the maintenance study.

Participants were scheduled for clinic or virtual visits at M-Weeks 0, 7, 15, 23, 31, 39 and 45.

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At the first administration in the maintenance study (following re-randomisation), the study intervention was self-administered at the clinic by the participant under supervision of study staff. During all subsequent administration occasions, the study intervention was self-administered by the participant at home every third Week.

The study was terminated based on the advice from independent DMC and recruitment of participants was stopped. The participants that were ongoing in the study (induction and maintenance) did not receive any new dose of study intervention but were followed up and all study assessments were to be performed as planned for a termination visit, as per the Study Protocol.

Number of Participants (planned and analysed):

It was planned to include approximately 440 participants in induction study and at least 250 participants in the maintenance study.

Of the 466 participants screened, 171 participants were randomised into the induction study, of whom 168 (98.2%) participants were treated with at least one dose and 142 (83%) completed the induction study.

There were 149 participants included in the Full Analysis Set (FAS), defined as all participants randomised who received at least one dose of study intervention, did not violate important inclusion/exclusion criteria, and did not terminate the study based on the interim analysis-decision.

There were 168 participants included in the Safety Analysis Set, defined as all participants who received at least one dose of study intervention.

In the maintenance study, 59 participants were randomised. Among the randomised participants, 58 (98.3%) participants received the study intervention, and 8 (13.6%) participants completed the maintenance study.

Objectives and Endpoints:

This section is not applicable as this is an abbreviated CSR. For details, please refer to the Study Protocol.

Statistical Analyses:

Planned analyses were reduced due to early termination of the study. All changes in the planned analyses for the study were implemented by SAP addendum.
In the induction study, the primary analysis of the primary endpoint was based on the FAS population and was performed using logistic regression adjusting for randomisation strata GCS use at I-Week 0 and prior use of biologics or JAK-inhibitors.

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Key secondary endpoints were analysed using the same principles. The testing procedure was controlled using the overall type I error rate of 0.05 with a two-sided test. Adjustment for multiplicity was done for the key secondary endpoints. No imputation was done except for the principle of non-responder imputation that was used in the analysis of the DMC data set i.e., for the endpoints, clinical remission, endoscopic improvement, and symptomatic remission. Data from participants that exited the study due to the study termination were not imputed as non-responder but excluded from the final efficacy analysis.

Full details of the original planned analyses are given in the Study Protocol.

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Summary of Results and Conclusions:

- Among the randomised participants, for the induction study, 142 (83%) participants completed the induction study, and among the randomised participants for the maintenance study, 8 (13.6%) participants completed the maintenance study; the most common reason for discontinuation from the study was study termination by the Sponsor (10.5% in the induction study and 67.8% in the maintenance study).
- Induction study did not meet the primary objective of demonstrating clinically relevant and statistically significant efficacy in inducing clinical remission in participants who received cobitolimod compared to placebo.
- Induction study did not meet the key secondary objectives of demonstrating statistically significant efficacy in inducing endoscopic improvement and symptomatic remission in participants who received cobitolimod compared to placebo.
- In the induction study, overall, 52 (31.0%) participants experienced at least one AE with similar distribution among the treatment groups. Overall, 42 (25.0%) participants were noted with treatment-emergent adverse events (TEAEs), and 4 (2.4%) participants had TEAEs which were likely related to the study intervention. Four (2.4%) participants reported serious TEAEs, all of which were unlikely related to the study intervention. A total of 4 (2.4%) participants discontinued the study intervention due to TEAEs and 2 (1.2%) participants discontinued the induction study due to TEAEs.
- In the maintenance study, overall, 18 (31.0%) participants experienced at least one TEAE. The highest incidence of TEAEs reported during the maintenance study was in the placebo group. One (1.7%) participant had a TEAE which was likely related to the study intervention. Three (5.2%) participants reported serious TEAEs, all of which were unlikely related to the study intervention. A total of 3 (5.2%) participants discontinued the study intervention followed by discontinuation of the maintenance study.
- Cobitolimod at doses of 250 mg and 500 mg was well tolerated in the treatment of moderate to severe active UC and no safety concerns were observed during the study.

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Efficacy Results:

The primary endpoint of clinical remission at I-Week 6 was observed in 4 (8.0%) of participants in the cobitolimod 250 mg group, 3 (6.0%) of participants in the cobitolimod 500 mg group, and 3 (6.1%) of participants in the placebo group.

There was no statistically significant difference in the proportion of participants achieving clinical remission between the cobitolimod 250 mg and placebo treatment groups. Also, there was no statistically significant difference in the proportion of participants achieving clinical remission between the cobitolimod 500 mg and placebo treatment groups. The risk difference (standard error) for cobitolimod vs placebo (adjusted for stratification factors) was 2.0% (5.10%) in the cobitolimod 250 mg treatment group and -0.2% (4.76%) in the cobitolimod 500 mg treatment group. Thus, the primary endpoint for this study was not met.

There were no statistically significant differences between the cobitolimod 250 mg or 500 mg groups and the placebo treatment group for either of the key secondary efficacy endpoints, endoscopic improvement at I-Week 6 and symptomatic remission at I-Week 6.

No formal statistical analysis was done for the maintenance study.

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Safety Results:

Cobitolimod was well tolerated in the treatment of moderate to severe active UC participants at both 250 mg and 500 mg doses.

In the induction study, 42 (25.0%) participants experienced at least one TEAE.

The most commonly reported TEAEs (>5% overall) were in the system organ class (SOC) of infections and infestations (15 participants; 8.9%) and gastrointestinal disorders (12 participants; 7.1%), and the most commonly (> 1% overall or >1 participant) experienced TEAEs by preferred term (PT) were headache, colitis ulcerative, COVID-19, nasopharyngitis, pharyngitis, alanine aminotransferase increased, blood creatine phosphokinase increased, pyrexia, and cough.

In the maintenance study, 18 (31.0%) participants experienced at least one TEAE. The most commonly reported TEAEs (>5% overall) were in the SOCs of gastrointestinal disorders, infections and infestations (6 participants each; 10.3% each), and musculoskeletal and connective tissue disorders (5 participants; 8.6%), and the most commonly (>2% overall or >1 participant) experienced TEAEs by PT were colitis ulcerative, arthralgia, back pain, and seasonal allergy.

The severity of TEAEs was comparable across the treatment groups in the induction study and maintenance study.

No clinically meaningful trends were observed in changes from Baseline in the laboratory parameters and vital signs for both the induction and maintenance studies.

No safety concerns were observed during the study.

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Conclusions:

- The independent DMC completed the planned dose selection interim analysis including a safety review and futility assessment in induction study of the phase III programme CONCLUDE, and recommended to terminate the study as cobitolimod was unlikely to meet the primary objective of demonstrating clinically relevant and statistically significant efficacy in inducing clinical remission. The Sponsor decided to terminate CONCLUDE CSUC-01/21 study on 21 Nov 2023 based on the advice from the independent DMC.
- In the induction study, overall, 52 (31.0%) participants experienced at least one AE with similar distribution among the treatment groups. Overall, 42 (25.0%) participants were noted with TEAEs, and 4 (2.4%) participants had TEAEs which were likely related to the study intervention. Only 4 (2.4%) participants reported serious TEAEs, all of which were unlikely related to the study intervention. A total of 4 (2.4%) participants discontinued the study intervention due to TEAEs and 2 (1.2%) participants discontinued the induction study due to TEAEs.
- In the maintenance study, overall, 18 (31.0%) participants experienced at least one TEAE. The highest incidence of TEAEs reported during the maintenance study was in the placebo group. One (1.7%) participant had a TEAE which was likely related to the study intervention. Three (5.2%) participants reported serious TEAEs, all of which were unlikely related to the study intervention. A total of 3 (5.2%) participants discontinued the study intervention followed by discontinuation of the maintenance study.
- Cobitolimod at doses of 250 mg and 500 mg was well tolerated in the treatment of moderate to severe active UC and no safety concerns were observed during the study.

Date and Version of This Report:

Document Version	Date
Final	15 May 2024

3 Table of Contents

Tables in Text

Figures in Text

4 List of Abbreviations and Definitions of Terms

Abbreviation/Acronym	Definition/Expansion
5-ASA	5-Aminosalicylic Acid
6-MP	6-Mercaptopurine
AE	Adverse Event
AEDC	Adverse event leading to discontinuation
AZA	Azathioprine
CAI	Clinical Activity Index
CD	Crohn's disease
CI	Confidence Interval
CONCLUDE	Cobitolimod Novel Concept for Left-Sided Ulcerative Colitis Disease Evaluation Study
COVID-19	Coronavirus disease 2019
CSR	Clinical Study Report
DMC	Data Monitoring Committee
EDC	Electronic data capture
FAS	Full Analysis Set
FASM	Full Analysis Set Maintenance
GCS	Glucocorticosteroids
JAK	Janus kinase
MedDRA	Medical Dictionary for Regulatory Activities
NRI	Non-Responder Imputation
ODN	Oligodeoxyribonucleotide
PT	Preferred Term
rINN	Recommended International Nonproprietary Name
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAFM	Safety Analysis Set Maintenance
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TLR9	Toll-like receptor 9
TNFα	Tumour Necrosis Factor (Alpha)
UC	Ulcerative Colitis

5 Ethics

All participating centers have been approved by their Independent Ethics Committee/ Institutional Review Board. A full list of committees is not reported in this abbreviated clinical study report (CSR) but can be requested from the Sponsor.

6 Investigators and Study Administrative Structure

A full list of Investigators and centers is not reported in this abbreviated CSR but can be requested from the Sponsor.

7 Introduction

Ulcerative colitis (UC) is a disease characterised by chronic inflammation of the rectal and colonic mucosa [1-3]. The disease is recurrent, with both active (flares) and inactive stages that differ in pathology, symptoms, and treatment. The underlying cause of UC is not understood, nor is it known what triggers the disease to recur between its inactive and active forms [4].

Current therapy for UC encompasses the treatment of active disease and the maintenance of remission. Treatment of participants with active UC aims to reduce inflammation and promote colonic healing and mucosal recovery. In many cases the disease can be controlled with conventional drugs including 5-aminosalicylic acid (5-ASA)/sulphasalazine [5] and glucocorticoids (GCS) [6]. Left-sided disease, limited to the rectum and the recto-sigmoid or recto-descending area, is often treated with rectal formulations of 5-ASA and GCS. Maintenance treatment with systemic GCS is not advised owing to the risks associated with long-term use and lacking efficacy [7]. For participants who become refractory to GCS and suffer from severe or moderately severe attacks of UC, immunomodulatory agents such as azathioprine (AZA)/6-mercaptopurine (6-MP) and cyclosporine are sometimes used. However, immunomodulators are slow-acting and induction of remission in these participants is often temporary [8]. These treatments are now used less frequently than in the past in view of their side-effect profile and toxicity issues when used long term and at high doses.

Treatment options for UC have rapidly expanded in recent years, and now include multiple biologic agents and the small molecule drug tofacitinib in addition to the non-biologic options [3,9]. However, a significant proportion of participants do not respond to these treatments or lose response to biologics over time. Tumour necrosis factor (alpha) [TNFα] inhibitors carry potential risks associated with their use, and the janus kinase-inhibitor (JAK-inhibitor) tofacitinib has also been associated with serious side effects [10, 11].

There is an enduring unmet need for alternative safe and efficacious treatments with new mechanisms of action.

Cobitolimod (rINN) is a fully synthetic DNA-based 19-mer ODN. The drug functions as an immunomodulatory agent by targeting the TLR9 present inside immune cells or on the surface of epithelial cells. These immune cells (e.g., B cells, macrophages, and plasmacytoid dendritic cells) reside in high abundance on mucosal surfaces, such as colonic and nasal mucosa.

Cobitolimod will be rectally administered at the site of inflammation as a 50 mL enema, placing the drug in close contact with a high number of intended target cells in an area rich in toll-like receptor 9-expressing cells (TLR9-expressing cells). Binding of the TLR9 by cobitolimod triggers the cells to produce anti-inflammatory cytokines, such as IL-10, which are believed to be important for the clinical effect of cobitolimod.

7.1.1 Summary of Findings from Non-clinical Studies with Potential Clinical Relevance

A range of non-clinical safety studies have been conducted with cobitolimod according to good laboratory practice and have shown that cobitolimod is well tolerated with no evidence of systemic or local toxicity.

7.1.2 Summary of Findings from Previous Clinical Studies

Cobitolimod has been assessed in a total of five controlled clinical studies and in one named participant use programme. In total, 424 (in accordance with the latest Drug Safety Update Report) participants with inflammatory bowel disease have received at least one dose of cobitolimod.

Cobitolimod was first assessed for clinical efficacy and safety in a small exploratory placebo-controlled, double-blind study in steroid-resistant/dependent participants on concomitant steroid treatment with active left-sided UC or colonic crohn’s disease (CD). In this study, 11 participants (6 with UC and 5 with CD) were randomised to receive a single rectal administration of 3 mg or 30 mg cobitolimod, or placebo. Clinical (stool frequency and rectal bleeding) and endoscopic evaluation at Week 1 indicated a combined response rate of 71% in the cobitolimod-treated participants and 25% in the placebo group.

The second study randomised 151 participants with mild to moderate active left-sided UC. Participants were treated with either a single rectal dose of cobitolimod (0.3, 3, 30 or 100 mg) or placebo. The primary endpoint was induction of clinical remission at any of the follow-up visits

during the 12-Week study period. Cobitolimod did not show a statistically significant superiority to placebo at any of the four dose levels tested. However, at Week 4, a numerically higher proportion of participants in the 30 mg and 100 mg groups had achieved clinical remission than in the lower dose groups and the placebo group.

The third study evaluated clinical response and safety following a single rectal dose of 30 mg cobitolimod or placebo in 34 participants with active left-sided UC. Clinical response rates did not show a statistically significant difference between cobitolimod and placebo. However, at Week 1, 41.2% of participants in the cobitolimod-treated group compared with 9.1% in the placebo group had a clinical response. Of the Week 1 responders in the cobitolimod group, 85.7% were still responders at Week 4, whereas the Week 1 responders in the placebo group had relapsed by Week 4. In the cobitolimod group, 11.8% and 17.7% of participants were in clinical remission at Week 1 and Week 4, respectively, whereas no participants receiving placebo were in clinical remission at these time points.

The fourth study assessed the efficacy and safety of two single doses of cobitolimod (administered at Week 0 and Week 4) in participants with moderate to severe active treatment refractory UC. A total of 131 participants were treated with cobitolimod 30 mg or placebo applied with a spray catheter during endoscopy. The primary efficacy endpoint was defined as a clinical activity index (CAI) score ≤4 at Week 12. There was no statistically significant difference between cobitolimod and the placebo group in the proportion of participants that achieved the primary endpoint (44.4% vs 46.5% respectively). However, secondary endpoints showed statistically significant effects for symptomatic remission at Weeks 4 and 8, and for registration remission (defined as CAI score of ≤4 and endoscopic Mayo score of 0 or 1) at Week 4 [12].

The fifth clinical study, CSUC-01/16 (CONDUCT), assessed the efficacy and safety of cobitolimod induction treatment with different dose levels and frequencies compared to placebo in participants with moderate to severe active left-sided UC. The primary endpoint was the proportion of participants achieving clinical remission at Week 6, defined as modified Mayo sub-scores of rectal bleeding 0; stool frequency 0 or 1; and endoscopy 0 or 1, excluding physician's global assessment. Out of the randomised participants, 211 received study treatment administered as a standard enema and were included in the efficacy and safety analyses. Significantly more participants achieved clinical remission at Week 6 in the group that received two single doses of 250 mg cobitolimod (at Week 0 and Week 3) than in the placebo group (21.4% vs 6.8% p=0.025). Other cobitolimod dose groups showed no significant difference in

clinical remission versus placebo. Results in several clinically relevant secondary endpoints supported the efficacy of the 2x 250 mg cobitolimod dose [13].

An open-label Phase Ib clinical study (CSUC-02/21) has been completed which evaluated the pharmacokinetics, safety, and tolerability of 500 mg cobitolimod, in participants with moderate to severe active UC. In total, 12 participants were screened, and 8 participants were included and dosed in the study. Administration of cobitolimod enemas resulted in fast absorption of cobitolimod where the maximum plasma concentration was reached between 0.5 and 2 hours after administration. Cobitolimod was safe and well tolerated.

Based on the data from non-clinical studies and six clinical studies, cobitolimod is safe and was well tolerated in the treatment of UC. No safety signals were detected in the clinical studies with cobitolimod.

7.1.3 Early Termination of Study

The independent Data Monitoring Committee (DMC) completed the planned dose selection interim analysis including a safety review and futility assessment in induction study of the phase III programme CONCLUDE, and recommended to terminate the study as cobitolimod was unlikely to meet the primary objective. On 21 Nov 2023, the Sponsor decided to terminate the CONCLUDE CSUC-01/21 study based on the independent DMC advice and recruitment of participants was stopped, and no more participants were dosed. Therefore, an abbreviated CSR is written.

7.2 Summary of Impact of Disruption on the Study

There were no disruptions that impacted the study.

8 Study Objectives and Endpoints

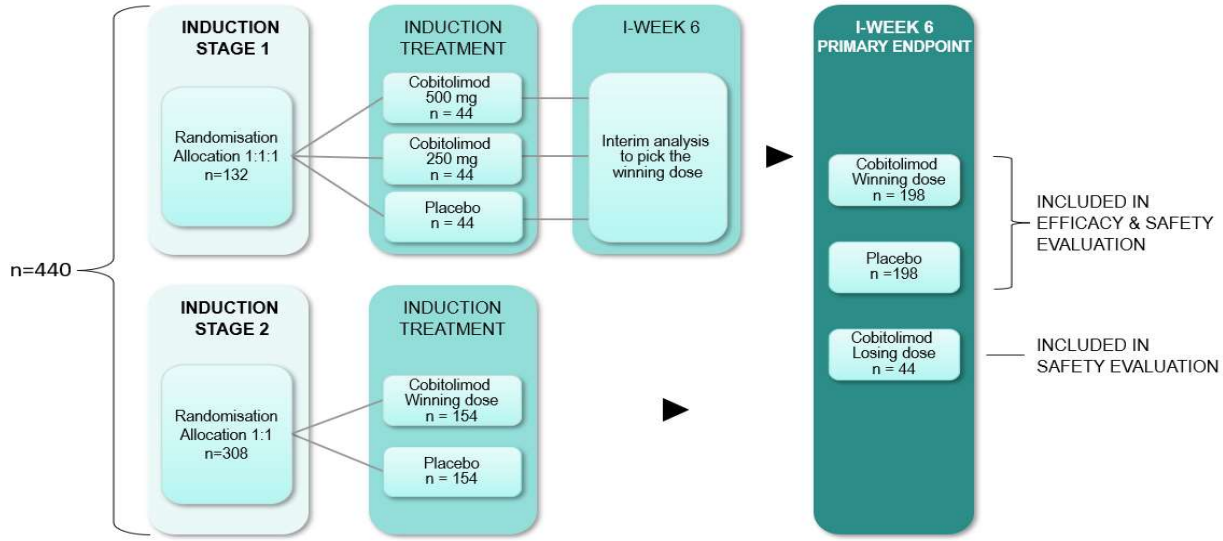
This section is not applicable as this is an abbreviated CSR. For details, please refer to the Study Protocol (Appendix 16.1.1).

9 Investigational Plan

9.1 Overview of Study Design

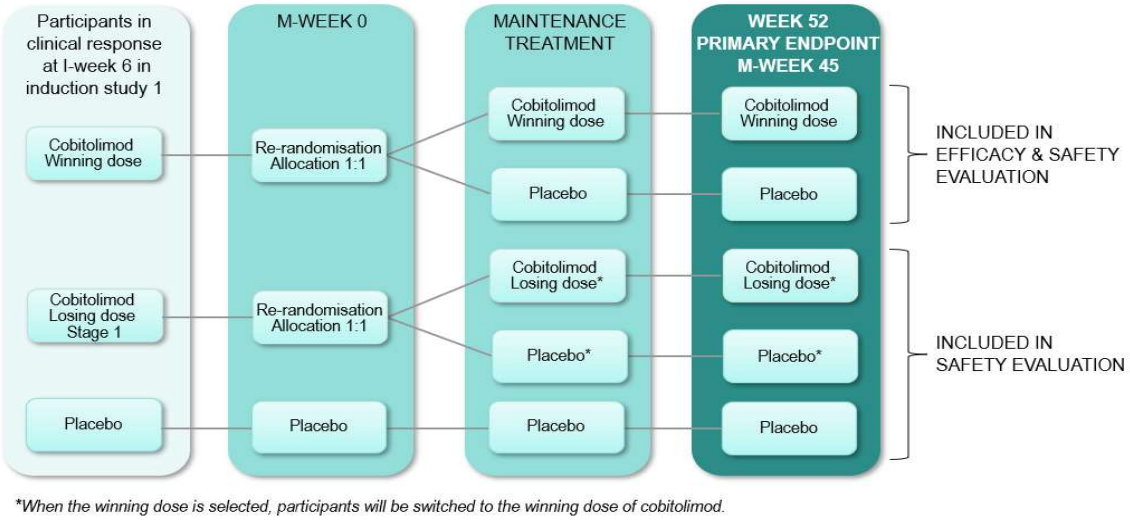
The study design for the induction and maintenance studies is shown in Figure 9-1 and Figure 9-2, respectively. Full details of the study design are given in the Study Protocol (Appendix 16.1.1).

Figure 9-1 Study Design: Induction



Source: Study Protocol (Appendix 16.1.1)

Figure 9-2 Study Design: Maintenance



Source: Study Protocol (Appendix 16.1.1)

9.1.1 Discussion of Study Design

The full phase III programme for cobitolimod in the treatment of moderate to severe UC was intended to include two induction studies (induction study 1 and induction study 2) and one

maintenance study. This CSR (CSUC-01/21 CONCLUDE) covers stage 1 of induction study and the resulting maintenance study. The maintenance study was supposed to include participants from both the induction study 1 and induction study 2.

The rationale for selecting the cobitolimod 250 mg dose in the first induction study in the cobitolimod phase III programme was based on its demonstrated efficacy in the CSUC-01/16 CONDUCT study. However, since the efficacy was demonstrated for the highest dose group in that study, it was possible that a higher dose could provide an improved efficacy. Therefore, an even higher dose of cobitolimod, 500 mg, was explored in humans for the first time as an additional active study arm. The inclusion of the cobitolimod 500 mg dose was justified by previous safety data and toxicology studies. Cobitolimod 500 mg dose had been included in a study with UC participants to describe pharmacokinetics and tolerability.

Induction Study

Induction study was a randomised, double-blind, placebo-controlled, parallel-group, multicentre study, with an adaptive design in two stages that enrolled participants with moderate to severe active left-sided UC who demonstrated an inadequate response to or intolerance of conventional biologics (infliximab, adalimumab, golimumab, vedolizumab, ustekinumab), JAK inhibitors (tofacitinib), or other approved advanced therapy for UC.

Stage 1 explored the efficacy of two different doses of cobitolimod (250 mg and 500 mg, administered twice 3 Weeks apart) with placebo as a control, in order to select the most effective and safe dose. In stage 2, the study was supposed to continue with the winning dose of cobitolimod. The primary objective of the induction study was to confirm a superior efficacy in the selected (winning) dose arm compared to placebo at I-Week 6 (Figure 9-1).

In stage 1, participants were randomly assigned in a 1:1:1 allocation to receive rectal doses of cobitolimod 250 mg, cobitolimod 500 mg, or placebo. After approximately 44 participants were randomised into each arm and had eligible efficacy data for the primary endpoint, an interim analysis was performed. A total of 133 participants (i.e., approximately 30% of the total 440 participant enrollment target in induction study) completed the 6-Week induction study and were included in the induction study interim analysis. The independent DMC completed the planned dose selection interim analysis including a safety review and futility assessment and advised to terminate the study because cobitolimod was unlikely to meet the primary objective upon completion of induction study. The Sponsor decided to terminate the study on 21 Nov 2023 based on the advice from the independent DMC.

Randomisation in the induction study was stratified for concomitant use of GCS treatment at I-Week 0 and previous treatment with biologics or JAK inhibitors.

The screening period consisted of two screening visits (with one exception described below). At the first screening visit, visit 1a, a written informed consent form (including consent for the induction and maintenance study) was signed before any other study procedure was done. The participants were assigned a unique participant identification number and enrolment procedures commenced. At the second screening visit, visit 1b, a full colonoscopy was performed. There was one exception to the schedule. If the participant was already scheduled for an endoscopy and had undergone bowel preparation, visit 1b could be done on the same day as visit 1a provided that informed consent was given before the endoscopy was performed. This was only applicable if bowel preparation was scheduled before study participation was planned for the participant.

Visits during the induction study were performed during the screening period, with approximately 10 days from endoscopy until randomisation, and at I-Week 0 (day 1), I-Week 3, and I-Week 6.

Study intervention was administered rectally using an enema. Participants self-administered the study intervention at the clinic under the supervision of the study staff, to ensure they managed to administer the study intervention appropriately.

All permitted UC-specific medical therapies (e.g., GCS, 5-ASA, AZA/6-MP) were to be maintained at a stable dose throughout the study, except for GCS in participants with clinical response at I-Week 6; in these participants, GCS had to be tapered off from I-Week 6.

Maintenance Study

Participants who demonstrated a clinical response at I-Week 6 after starting induction treatment were eligible for participation in the maintenance study. Clinical response was defined by a decrease in the 3-component Mayo score (rectal bleeding, stool frequency, and endoscopy) of at least two (2) points and at least 35% from I- Week 0 with either a decrease in the rectal bleeding sub-score of at least one (1) point or a rectal bleeding sub-score of 0 or 1.

Participants who were not eligible for the maintenance study, i.e., who did not have clinical response at I-Week 6 or did not fulfill other inclusion criteria for the maintenance study, had their last visit at I-Week 6, three Weeks after the last administration of study intervention.

The maintenance study was to evaluate the efficacy and safety of cobitolimod compared to placebo through 46 Weeks' maintenance therapy, following 6 Weeks of cobitolimod induction therapy (52 Weeks' study treatment in total). Cobitolimod or placebo was administered every 3 Weeks.

Participants who were eligible for the maintenance study were randomly assigned in a 1:1 allocation (re-randomisation) and received rectal administrations of cobitolimod (250 mg or 500 mg) or placebo, administered once every 3 Weeks for up to 46 Weeks. The participants from stage 1 of the induction study, who were randomised to active intervention and entered the maintenance study before the winning dose could be selected, were re-randomised to either the same dose of active intervention as in the induction study or to placebo. Participants with placebo treatment during induction study continued with placebo in the maintenance study.

Randomisation should have been stratified for clinical remission at I-Week 6 and concomitant use of GCS at I-Week 6. However, as the electronic data capture (EDC) system was non-functioning for clinical remission parameter, no participants were stratified for clinical remission status. The study was terminated before the EDC system could be updated to rectify the issue.

After the selection of winning dose, it was planned that the participants that had been enrolled into the maintenance study based on clinical response in the losing dose arm, should be switched to the winning dose in the maintenance study at the next visit to the clinic, with the justification to collect further safety data for the winning dose. These participants would not have been part of the efficacy evaluation in the maintenance study.

Fifty-nine participants were randomised into the maintenance study from the induction study. Participants were scheduled for clinic or virtual visits at M-Weeks 0, 7, 15, 23, 31, 39 and 45 (further described in the schedule of activities of the Study Protocol [Appendix 16.1.1]). Evaluation and follow-up of participants were performed at all visits.

The first maintenance study visit, M-Week 0 occurred when the endoscopy result confirmed clinical response and other inclusion/exclusion had been reviewed. At this visit the re-randomisation occurred and the study intervention was self-administered at the clinic by the participant, supervised by study staff. During all subsequent administration occasions in the maintenance study, the study intervention was self-administered by the participant at home every third Week.

9.1.2 Changes in Study Conduct

There were no changes to the protocol in the conduct of the study.

9.2 Statistical Analysis

Planned analyses were reduced due to early termination of the study. All changes in the planned analyses for the study were implemented by SAP addendum (Appendix 16.1.9).

In the induction study, the primary analysis of the primary endpoint was based on the FAS population and was performed using logistic regression adjusting for randomisation strata GCS use at I-Week 0 and prior use of biologics or JAK-inhibitors.

Key secondary endpoints were analysed using the same principles. The testing procedure was controlled using the overall type I error rate of 0.05 with a two-sided test. Adjustment for multiplicity was done for the key secondary endpoints. No imputation was done except for the principle of non-responder imputation that was used in the analysis of the DMC data set i.e., for the endpoints, clinical remission, endoscopic improvement, and symptomatic remission. Data from participants that exited the study due to the study termination were not imputed as non-responder but excluded from the final efficacy analysis. No formal statistical analysis was done for the maintenance study.

Full details of the original planned analyses are provided in the Study Protocol (Appendix 16.1.1).

9.2.1 Statistical Analysis Plan

The planned analyses, comparisons, statistical tests, and determination of sample size are described in the final version of the SAP (Section 3, version 3.0, dated 03 Oct 2023), SAP addendum (Appendix 16.1.9), and continued in the Study Protocol (Appendix 16.1.1).

9.2.2 Changes in Planned Analyses Prior to Unblinding or Database Lock

All changes in the planned analysis for the study were implemented by SAP addendum as described in Appendix 16.1.9 Documentation of Statistical Methods. Only a subset of outputs was produced due to early termination of the study.

9.2.3 Changes Following Study Unblinding/Database Lock and Post-hoc Analyses

There were no changes in the analysis following study unblinding/database lock and post-hoc analyses.

10 Study Participants

In this CSR, the terms participant and patient are used interchangeably.

10.1 Disposition of Participants

Induction Study

The disposition of participants in the induction study is summarized in (Table 10-1) and are listed in Listing 12.2.1.

A total of 466 participants were screened, out of these, 171 participants were randomised into the induction study. Among the randomised participants, 168 (98.2%) participants received the study intervention, and 142 (83.0%) participants completed the induction study. A total of 29 participants (17 participants discontinued from induction study before I-Week 3 and 12 participants discontinued from induction study at or after I-Week 3 and before I-Week 6) discontinued the study prior to I-Week 6. The most common reason for discontinuation prior to I-Week 6 was study termination by Sponsor (10.5%). Two (1.2%) participants discontinued the study due to treatment-emergent adverse events (TEAEs). For details on participants discontinued due to TEAEs, please refer to Section 11.2.1.5. Participant disposition was similar across treatment groups (Table 10-1).

Table 10-1 Disposition of Participants - Induction Study

	Cobitolimod 250mg n (%)	Cobitolimod 500mg n (%)	Placebo n (%)	Overall n (%)
Patients screened				466
Patients failed screening [1]				268
Reason for failed screening				
Inclusion criteria				241
Exclusion criteria				69
Patients not randomised due to termination of study by sponsor				21
Patients randomised	56 (100)	58 (100)	57 (100)	171 (100)
Patients treated with study intervention	54 (96.4)	57 (98.3)	57 (100)	168 (98.2)

	Cobitolimod 250mg n (%)	Cobitolimod 500mg n (%)	Placebo n (%)	Overall n (%)
Patients randomised not treated with the study intervention	2 (3.6)	1 (1.7)	0	3 (1.8)
Patients discontinued from induction study 1 before I-Week 3	4 (7.1)	7 (12.1)	6 (10.5)	17 (9.9)
Patients discontinued from induction study 1 at or after I-Week 3 and before I-Week 6	3 (5.4)	4 (6.9)	5 (8.8)	12 (7.0)
Reason for discontinuation from induction study before I-Week 6				
Lack of Efficacy	0	2 (3.4)	1 (1.8)	3 (1.8)
Treatment-emergent Adverse Event	1 (1.8)	0	1 (1.8)	2 (1.2)
Withdrawal of Consent	1 (1.8)	2 (3.4)	2 (3.5)	5 (2.9)
Study Terminated by Sponsor	4 (7.1)	7 (12.1)	7 (12.3)	18 (10.5)
Other	1 (1.8)	0	0	1 (0.6)
Patients ongoing in the induction study 1 (I-Week 6)	0	0	0	0
Patients completed the induction study 1 (I-Week 6)	49 (87.5)	47 (81.0)	46 (80.7)	142 (83.0)
Patients in SAF	54 (96.4)	57 (98.3)	57 (100)	168 (98.2)
Patients in FAS	50 (89.3)	50 (86.2)	49 (86.0)	149 (87.1)

n: number of patients with observation; %: percentage of randomised patients in the randomised group with observation.

FAS: Full Analysis Set; SAF: Safety Analysis Set.

[1] Patients failing several Inclusion and/or Exclusion Criteria will be only counted once per group.

Sources: Table 11.1.1.1 and Listing 12.2.1

Maintenance Study

The disposition of participants in the maintenance study is summarized in Table and are listed in Listing 12.2.1.

In the maintenance study, 59 participants were randomised. Among the randomised participants, 58 (98.3%) participants received the study intervention, and 8 (13.6%) participants completed the maintenance study. A total of 51 participants (31 participants discontinued from maintenance study before M-Week 15, 13 participants discontinued at or after M-Week 15 and before M-Week 31, and 7 participants discontinued at or after M-Week 31 and before M-Week 45) discontinued the study prior to M-Week 45. The most common reason for discontinuation prior to M-Week 45 was study termination by Sponsor (67.8%). Three (5.1%) participants discontinued the study due to TEAEs. For details on participants discontinued due to TEAEs, please refer to Section 11.2.1.5. Participant disposition was similar across treatment groups (Table).

Table 10-2 Disposition of Participants - Maintenance Study

	Cobitolimod 250mg (Cobitolimod 250mg) (N=10) n (%)	Cobitolimod 500mg (Cobitolimod 500mg) (N=12) n (%)	Placebo (Cobitolimod 250mg) (N=10) n (%)	Placebo (Cobitolimod 500mg) (N=10) n (%)	Placebo (Placebo) (N=17) n (%)	Overall (N=59) n (%)
Patients randomised to maintenance study	10 (100)	12 (100)	10 (100)	10 (100)	17 (100)	59 (100)
Patients treated with study intervention in maintenance study	10 (100)	12 (100)	10 (100)	10 (100)	16 (94.1)	58 (98.3)
Patients randomised not treated with the study intervention in maintenance study	0	0	0	0	1 (5.9)	1 (1.7)
Patients discontinued from maintenance study before M-Week 15	6 (60.0)	5 (41.7)	6 (60.0)	4 (40.0)	10 (58.8)	31 (52.5)
Patients discontinued at or after M-Week 15 and before M-Week 31	1 (10.0)	4 (33.3)	3 (30.0)	4 (40.0)	1 (5.9)	13 (22.0)
Patients discontinued at or after M-Week 31 and before M-Week 45	1 (10.0)	2 (16.7)	1 (10.0)	1 (10.0)	2 (11.8)	7 (11.9)
Reason for discontinuation from maintenance study before M-Week 45						
Loss of Response confirmed by 3-component Mayo Score	0	0	1 (10.0)	1 (10.0)	0	2 (3.4)
Lack of Efficacy	0	1 (8.3)	0	1 (10.0)	1 (5.9)	3 (5.1)
Treatment-emergent Adverse Event	0	0	1 (10.0)	1 (10.0)	1 (5.9)	3 (5.1)
Withdrawal of Consent	0	0	1 (10.0)	0	1 (5.9)	2 (3.4)
Study Terminated by Sponsor	8 (80.0)	9 (75.0)	7 (70.0)	6 (60.0)	10 (58.8)	40 (67.8)
Other	0	1 (8.3)	0	0	0	1 (1.7)
Patients in FASM	2 (20.0)	3 (25.0)	3 (30.0)	4 (40.0)	6 (35.3)	18 (30.5)
Patients in SAFM	10 (100)	12 (100)	10 (100)	10 (100)	16 (94.1)	58 (98.3)
Patients completed the maintenance study	2 (20.0)	1 (8.3)	0	1 (10.0)	4 (23.5)	8 (13.6)

N: number of patients in the treatment group; n: number of patients with observation; %: percentage of randomised patients in the randomised group with observation.

SAFM: Safety Analysis Set Maintenance; FASM: Full Analysis Set Maintenance.

Treatment group: Before parentheses the dose in maintenance study is shown. In parentheses the dose in induction study is shown.

Sources: Table 11.1.1.2 and Listing 12.2.1

11 Evaluation of Response to Study Intervention

11.1 Efficacy

Summary data for efficacy are provided in Tables 11.1.6.1 to 11.1.6.8 and Listings 12.2.5.1 to 12.2.5.3 and Listing 12.2.7.3. The independent DMC completed the planned dose selection interim analysis including a safety review and assessment for futility in induction study of the phase III programme CONCLUDE and recommended to terminate the study as cobitolimod was unlikely to meet the primary objective of demonstrating clinically relevant and statistically significant efficacy in inducing clinical remission at I-Week 6. On 21 Nov 2023, the Sponsor decided to terminate the CONCLUDE CSUC-01/21 study based on the independent DMC advice and recruitment of participants was stopped, and no more participants were dosed.

11.2 Safety

11.2.1 Adverse Events

11.2.1.1 Brief Summary of Adverse Events

Induction Study

Overall, 52 (31.0%) participants experienced at least one AE with similar distribution among the treatment groups. Overall, 42 (25.0%) participants experienced at least one TEAE, among which, 4 (2.4%) participants had TEAEs which were likely related to the study intervention.

Severe TEAEs and extraintestinal manifestation of inflammatory bowel disease TEAEs were reported by 1 (0.6%) participant each during the induction study. A total of 4 (2.4%) participants discontinued study intervention due to TEAEs and 2 (1.2%) participants discontinued the induction study due to TEAEs. None of the participants discontinued from study intervention or from the induction study due to a drug-related TEAE. Four (2.4%) participants reported serious TEAEs, and all SAEs were considered unlikely related to the study intervention.

The incidence of all AEs reported during the induction study was comparable between the study treatment groups (Table 11-1**Error! Reference source not found.**). The incidence of all AEs is presented by participant in the Listing 12.2.6.1.

Table 11-1 Overview of Adverse Events: Induction Study (Safety Analysis Set)

	Cobitolimod 250mg (N=54) n (%) [E]	Cobitolimod 500mg (N=57) n (%) [E]	Placebo (N=57) n (%) [E]	Overall (N=168) n (%) [E]
Patients with AEs	17 (31.5) [28]	19 (33.3) [42]	16 (28.1) [33]	52 (31.0) [103]
Patients with TEAEs	16 (29.6) [24]	12 (21.1) [28]	14 (24.6) [26]	42 (25.0) [78]
Patients with Severe TEAEs	0	1 (1.8) [1]	0	1 (0.6) [1]
Patients with Extraintestinal Manifestation of Inflammatory Bowel Disease TEAEs	1 (1.9) [1]	0	0	1 (0.6) [1]
Patients with Serious TEAEs	1 (1.9) [1]	1 (1.8) [1]	2 (3.5) [3]	4 (2.4) [5]
Death	0	0	0	0
Life-threatening TEAE	0	0	0	0
Hospitalisation/Prolonged Hospitalisation	1 (1.9) [1]	1 (1.8) [1]	2 (3.5) [3]	4 (2.4) [5]
Disability or Incapacity	0	0	0	0
Congenital Anomaly or Birth Defect	0	0	0	0
Other Medically Important Event	0	0	0	0
TEAEs by Relationship to Study Intervention				
Unlikely Related	15 (27.8) [21]	12 (21.1) [28]	13 (22.8) [24]	40 (23.8) [73]
Likely Related	2 (3.7) [3]	0	2 (3.5) [2]	4 (2.4) [5]
Serious TEAEs by Relationship to Study Intervention				
Unlikely Related	1 (1.9) [1]	1 (1.8) [1]	2 (3.5) [3]	4 (2.4) [5]
Likely Related	0	0	0	0
Patients that have not completed the study intervention due to a TEAE	2 (3.7) [2]	1 (1.8) [1]	1 (1.8) [1]	4 (2.4) [4]
Patients that have not completed the study intervention due to a drug-related TEAE	0	0	0	0
Patients that have not completed the study intervention due to a serious drug-related TEAE	0	0	0	0
Patients that have not completed the study due to a TEAE	1 (1.9) [2]	0	1 (1.8) [1]	2 (1.2) [3]
Patients that have not completed the study due to a drug-related TEAE	0	0	0	0
Patients that have not completed the study due to a serious drug-related TEAE	0	0	0	0
Patients with AEs with outcome equal to "FATAL"	0	0	0	0

E: number of events; N: number of patients in the treatment group; n: number of patients with observation; %: percentage of patients in the group with observation.
AE: adverse event; TEAE: treatment emergent adverse event.
Classification according to Medical Dictionary for Regulatory Activities (MedDRA) version 24.0.
Sources: Table 11.1.8.1.1 and Listing 12.2.6.1

Maintenance Study

Overall, 18 (31.0%) participants experienced at least one TEAE, among which, 1 (1.7%) participant had a TEAE which was likely related to the study intervention.

Severe TEAEs were reported by 2 (3.4%) participants and extraintestinal manifestation of inflammatory bowel disease TEAEs were reported by 1 (1.7%) participant. A total of 3 (5.2%) participants discontinued study intervention due to TEAEs and 3 (5.2%) participants discontinued the maintenance study due to TEAEs. One (1.7%) participant discontinued study intervention and maintenance study due to a drug-related TEAE. Three (5.2%) participants reported serious TEAEs, and all SAEs were unlikely related to the study intervention.

The highest incidence of TEAEs reported during the maintenance study was in the placebo group (Table 11-2). The incidence of all AEs is presented by participant in the Listing 12.2.6.1.

Table 11-2 Overview of Adverse Events: Maintenance Study (Safety Analysis Set)

	Cobitolimod 250mg (Cobitolimod 250mg) (N=10) n (%) [E]	Cobitolimod 500mg (Cobitolimod 500mg) (N=12) n (%) [E]	Placebo (Cobitolimod 250mg) (N=10) n (%) [E]	Placebo (Cobitolimod 500mg) (N=10) n (%) [E]	Placebo (Placebo) (N=16) n (%) [E]	Overall (N=58) n (%) [E]
Patients with TEAEs	2 (20.0) [2]	2 (16.7) [7]	5 (50.0) [8]	4 (40.0) [13]	5 (31.3) [13]	18 (31.0) [43]
Patients with Severe TEAEs	0	1 (8.3) [1]	0	1 (10.0) [2]	0	2 (3.4) [3]
Patients with Extraintestinal Manifestation of Inflammatory Bowel Disease TEAEs	0	0	1 (10.0) [1]	0	0	1 (1.7) [1]
Patients with Serious TEAEs	0	1 (8.3) [1]	0	1 (10.0) [1]	1 (6.3) [1]	3 (5.2) [3]
Death	0	0	0	0	0	0
Life-threatening TEAE	0	0	0	0	0	0
Hospitalisation/Prolonged Hospitalisation	0	1 (8.3) [1]	0	1 (10.0) [1]	1 (6.3) [1]	3 (5.2) [3]
Disability or Incapacity	0	0	0	0	0	0
Congenital Anomaly or Birth Defect	0	0	0	0	0	0
Other Medically Important Event	0	1 (8.3) [1]	0	0	0	1 (1.7) [1]

	Cobitolimod 250mg (Cobitolimod 250mg) (N=10) n (%) [E]	Cobitolimod 500mg (Cobitolimod 500mg) (N=12) n (%) [E]	Placebo (Cobitolimod 250mg) (N=10) n (%) [E]	Placebo (Cobitolimod 500mg) (N=10) n (%) [E]	Placebo (Placebo) (N=16) n (%) [E]	Overall (N=58) n (%) [E]
TEAEs by Relationship to Study Intervention						
Unlikely Related	2 (20.0) [2]	2 (16.7) [7]	4 (40.0) [7]	4 (40.0) [13]	5 (31.3) [13]	17 (29.3) [42]
Likely Related	0	0	1 (10.0) [1]	0	0	1 (1.7) [1]
Serious TEAEs by Relationship to Study Intervention						
Unlikely Related	0	1 (8.3) [1]	0	1 (10.0) [1]	1 (6.3) [1]	3 (5.2) [3]
Likely Related	0	0	0	0	0	0
Patients that have not completed the study intervention due to a TEAE	0	0	1 (10.0) [1]	1 (10.0) [1]	1 (6.3) [1]	3 (5.2) [3]
Patients that have not completed the study intervention due to a drug-related TEAE	0	0	1 (10.0) [1]	0	0	1 (1.7) [1]
Patients that have not completed the study intervention due to a serious drug-related TEAE	0	0	0	0	0	0
Patients that have not completed the study due to a TEAE	0	0	1 (10.0) [1]	1 (10.0) [1]	1 (6.3) [1]	3 (5.2) [3]
Patients that have not completed the study due to a drug-related TEAE	0	0	1 (10.0) [1]	0	0	1 (1.7) [1]
Patients that have not completed the study due to a serious drug-related TEAE	0	0	0	0	0	0
Patients with AEs with outcome equal to "FATAL"	0	0	0	0	0	0

E: number of events; N: number of patients in the treatment group; n: number of patients with observation; %: percentage of patients in the group with observation.

AE: adverse event; TEAE: treatment emergent adverse event.

Treatment group: Before parentheses the dose in Maintenance Study is shown. In parentheses the dose in Induction Study is shown.

Classification according to MedDRA version 24.0.

Sources: Table 11.1.8.1.2 and Listing 12.2.6.1

11.2.1.2 Analyses of All Adverse Events

11.2.1.2.1 Frequency of TEAEs by System Organ Class and Preferred Term

Induction Study

The incidence of TEAEs (SOC ≥5%) in participants in any of the treatment groups is summarised in Table 11-3Table 11-3.

Overall, 42 (25.0%) participants experienced at least one TEAE during the study and the incidence of TEAEs reported during the study was similar between treatment groups (Table 11-3).

The most commonly reported AEs (>5% overall) were in the SOCs of infections and infestations (15 participants; 8.9%) and gastrointestinal disorders (12 participants; 7.1%).

The most commonly (>1% overall or >1 participant) experienced TEAEs by PT were headache and colitis ulcerative (7 participants in each; 4.2% in each), COVID-19 (3 participants; 1.8%), nasopharyngitis, pharyngitis, alanine aminotransferase increased, blood creatine phosphokinase increased, pyrexia, and cough (2 participants in each; 1.2% in each).

Table 11-3 Summary of TEAEs by SOC and Preferred Term: Induction Study

System Organ Class Preferred Term	Cobitolimod 250mg (N=54) n (%) [E]	Cobitolimod 500mg (N=57) n (%) [E]	Placebo (N=57) n (%) [E]	Overall (N=168) n (%) [E]
Any TEAE	16 (29.6) [24]	12 (21.1) [28]	14 (24.6) [26]	42 (25.0) [78]
Infections and infestations	3 (5.6) [3]	7 (12.3) [8]	5 (8.8) [8]	15 (8.9) [19]
COVID-19	0	2 (3.5) [2]	1 (1.8) [1]	3 (1.8) [3]
Nasopharyngitis	1 (1.9) [1]	1 (1.8) [1]	0	2 (1.2) [2]
Pharyngitis	1 (1.9) [1]	0	1 (1.8) [1]	2 (1.2) [2]
Herpes simplex	0	0	1 (1.8) [2]	1 (0.6) [2]
Herpes virus infection	1 (1.9) [1]	0	0	1 (0.6) [1]
Hordeolum	0	1 (1.8) [1]	0	1 (0.6) [1]
Influenza	0	0	1 (1.8) [1]	1 (0.6) [1]
Pyelonephritis	0	0	1 (1.8) [1]	1 (0.6) [1]
Respiratory tract infection	0	1 (1.8) [1]	0	1 (0.6) [1]
Respiratory tract infection viral	0	1 (1.8) [1]	0	1 (0.6) [1]
Rhinitis	0	1 (1.8) [1]	0	1 (0.6) [1]
Sinusitis	0	1 (1.8) [1]	0	1 (0.6) [1]
Sinusitis bacterial	0	0	1 (1.8) [1]	1 (0.6) [1]
Viral rhinitis	0	0	1 (1.8) [1]	1 (0.6) [1]

System Organ Class Preferred Term	Cobitolimod 250mg (N=54) n (%) [E]	Cobitolimod 500mg (N=57) n (%) [E]	Placebo (N=57) n (%) [E]	Overall (N=168) n (%) [E]
Gastrointestinal disorders	5 (9.3) [5]	2 (3.5) [3]	5 (8.8) [7]	12 (7.1) [15]
Colitis ulcerative	3 (5.6) [3]	2 (3.5) [2]	2 (3.5) [2]	7 (4.2) [7]
Abdominal pain	0	0	1 (1.8) [1]	1 (0.6) [1]
Diarrhoea	0	0	1 (1.8) [1]	1 (0.6) [1]
Duodenitis	0	0	1 (1.8) [1]	1 (0.6) [1]
Gastrooesophageal reflux disease	1 (1.9) [1]	0	0	1 (0.6) [1]
Haemorrhoids thrombosed	0	0	1 (1.8) [1]	1 (0.6) [1]
Hiatus hernia	0	0	1 (1.8) [1]	1 (0.6) [1]
Nausea	0	1 (1.8) [1]	0	1 (0.6) [1]
Rectal haemorrhage	1 (1.9) [1]	0	0	1 (0.6) [1]
Nervous system disorders	4 (7.4) [4]	2 (3.5) [4]	2 (3.5) [2]	8 (4.8) [10]
Headache	3 (5.6) [3]	2 (3.5) [4]	2 (3.5) [2]	7 (4.2) [9]
Dizziness	1 (1.9) [1]	0	0	1 (0.6) [1]
Investigations	3 (5.6) [3]	4 (7.0) [4]	0	7 (4.2) [7]
Alanine aminotransferase increased	1 (1.9) [1]	1 (1.8) [1]	0	2 (1.2) [2]
Blood creatine phosphokinase increased	1 (1.9) [1]	1 (1.8) [1]	0	2 (1.2) [2]
Blood alkaline phosphatase increased	0	1 (1.8) [1]	0	1 (0.6) [1]
C-reactive protein increased	0	1 (1.8) [1]	0	1 (0.6) [1]
Lymphocyte count decreased	1 (1.9) [1]	0	0	1 (0.6) [1]
General disorders and administration site conditions	2 (3.7) [2]	2 (3.5) [2]	1 (1.8) [1]	5 (3.0) [5]
Pyrexia	1 (1.9) [1]	1 (1.8) [1]	0	2 (1.2) [2]
Cyst	0	0	1 (1.8) [1]	1 (0.6) [1]
Fatigue	0	1 (1.8) [1]	0	1 (0.6) [1]
Oedema peripheral	1 (1.9) [1]	0	0	1 (0.6) [1]
Musculoskeletal and connective tissue disorders	2 (3.7) [2]	2 (3.5) [2]	1 (1.8) [1]	5 (3.0) [5]
Arthralgia	1 (1.9) [1]	0	0	1 (0.6) [1]
Arthritis	1 (1.9) [1]	0	0	1 (0.6) [1]
Back pain	0	1 (1.8) [1]	0	1 (0.6) [1]
Chondropathy	0	1 (1.8) [1]	0	1 (0.6) [1]
Neck pain	0	0	1 (1.8) [1]	1 (0.6) [1]
Injury, poisoning and procedural complications	1 (1.9) [1]	1 (1.8) [1]	1 (1.8) [1]	3 (1.8) [3]
Foot fracture	0	0	1 (1.8) [1]	1 (0.6) [1]
Meniscus injury	0	1 (1.8) [1]	0	1 (0.6) [1]
Overdose	1 (1.9) [1]	0	0	1 (0.6) [1]
Blood and lymphatic system disorders	1 (1.9) [1]	1 (1.8) [1]	0	2 (1.2) [2]

System Organ Class Preferred Term	Cobitolimod 250mg (N=54) n (%) [E]	Cobitolimod 500mg (N=57) n (%) [E]	Placebo (N=57) n (%) [E]	Overall (N=168) n (%) [E]
Anaemia	0	1 (1.8) [1]	0	1 (0.6) [1]
Eosinophilia	1 (1.9) [1]	0	0	1 (0.6) [1]
Metabolism and nutrition disorders	1 (1.9) [1]	1 (1.8) [1]	0	2 (1.2) [2]
Hypokalaemia	1 (1.9) [1]	0	0	1 (0.6) [1]
Iron deficiency	0	1 (1.8) [1]	0	1 (0.6) [1]
Respiratory, thoracic and mediastinal disorders	1 (1.9) [1]	1 (1.8) [1]	0	2 (1.2) [2]
Cough	1 (1.9) [1]	1 (1.8) [1]	0	2 (1.2) [2]
Skin and subcutaneous tissue disorders	0	0	2 (3.5) [2]	2 (1.2) [2]
Hidradenitis	0	0	1 (1.8) [1]	1 (0.6) [1]
Rash maculovesicular	0	0	1 (1.8) [1]	1 (0.6) [1]
Eye disorders	1 (1.9) [1]	0	0	1 (0.6) [1]
Eyelid oedema	1 (1.9) [1]	0	0	1 (0.6) [1]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (1.8) [1]	0	1 (0.6) [1]
Neuroma	0	1 (1.8) [1]	0	1 (0.6) [1]
Psychiatric disorders	0	0	1 (1.8) [1]	1 (0.6) [1]
Anxiety	0	0	1 (1.8) [1]	1 (0.6) [1]
Renal and urinary disorders	0	0	1 (1.8) [3]	1 (0.6) [3]
Nephrolithiasis	0	0	1 (1.8) [1]	1 (0.6) [1]
Renal colic	0	0	1 (1.8) [2]	1 (0.6) [2]

E: number of events; N: number of patients in the treatment group; n: number of patients with observation; %: percentage of patients in the group with observation, COVID-19: coronavirus disease 2019, TEAE: treatment-emergent adverse event.

Classification according to MedDRA version 24.0.

Sources: Table 11.1.8.2.1 and Listing 12.2.6.1

Maintenance Study

The incidence of TEAEs (SOC ≥5%) in participants in any of the treatment groups is summarized in Table 11-4.

Overall, 18 (31.0%) participants experienced at least one TEAE during the study and the highest incidence of TEAEs reported during the study was in the placebo group (Table 11-4).

The most commonly (> 5% overall) affected SOCs were gastrointestinal disorders, infections and infestations (6 participants each; 10.3% each), and musculoskeletal and connective tissue disorders (5 participants; 8.6%) (Table 11-4).

Most commonly (>2% overall or >1 participant) experienced TEAEs by PT were colitis ulcerative (3 participants; 5.2%), arthralgia, back pain, and seasonal allergy (2 participants each; 3.4% each).

Table 11-4 Summary of TEAEs by SOC and Preferred Term: Maintenance Study

System Organ Class Preferred Term	Cobitolimod 250mg (Cobitolimod 250mg) (N=10) n (%) [E]	Cobitolimod 500mg (Cobitolimod 500mg) (N=12) n (%) [E]	Placebo (Cobitolimod 250mg) (N=10) n (%) [E]	Placebo (Cobitolimod 500mg) (N=10) n (%) [E]	Placebo (Placebo) (N=16) n (%) [E]	Overall (N=58) n (%) [E]
Any TEAE	2 (20.0) [2]	2 (16.7) [7]	5 (50.0) [8]	4 (40.0) [13]	5 (31.3) [13]	18 (31.0) [43]
Gastrointestinal disorders	0	1 (8.3) [1]	3 (30.0) [5]	1 (10.0) [5]	1 (6.3) [1]	6 (10.3) [12]
Colitis ulcerative	0	0	2 (20.0) [2]	0	1 (6.3) [1]	3 (5.2) [3]
Abdominal pain	0	0	1 (10.0) [1]	0	0	1 (1.7) [1]
Colitis	0	0	0	1 (10.0) [4]	0	1 (1.7) [4]
Diarrhoea	0	0	1 (10.0) [1]	0	0	1 (1.7) [1]
Enteritis	0	0	1 (10.0) [1]	0	0	1 (1.7) [1]
Oesophagitis	0	0	0	1 (10.0) [1]	0	1 (1.7) [1]
Peritoneal adhesions	0	1 (8.3) [1]	0	0	0	1 (1.7) [1]
Infections and infestations	2 (20.0) [2]	0	0	0	4 (25.0) [6]	6 (10.3) [8]
COVID-19	0	0	0	0	1 (6.3) [1]	1 (1.7) [1]
Conjunctivitis	1 (10.0) [1]	0	0	0	0	1 (1.7) [1]
Influenza	0	0	0	0	1 (6.3) [1]	1 (1.7) [1]
Sinusitis	0	0	0	0	1 (6.3) [1]	1 (1.7) [1]
Upper respiratory tract infection	0	0	0	0	1 (6.3) [3]	1 (1.7) [3]
Viral infection	1 (10.0) [1]	0	0	0	0	1 (1.7) [1]
Musculoskeletal and connective tissue disorders	0	1 (8.3) [1]	1 (10.0) [1]	1 (10.0) [1]	2 (12.5) [4]	5 (8.6) [7]
Arthralgia	0	0	1 (10.0) [1]	1 (10.0) [1]	0	2 (3.4) [2]
Back pain	0	1 (8.3) [1]	0	0	1 (6.3) [1]	2 (3.4) [2]
Hip deformity	0	0	0	0	1 (6.3) [1]	1 (1.7) [1]
Osteopenia	0	0	0	0	1 (6.3) [1]	1 (1.7) [1]

System Organ Class Preferred Term	Cobitolimod 250mg (Cobitolimod 250mg) (N=10) n (%) [E]	Cobitolimod 500mg (Cobitolimod 500mg) (N=12) n (%) [E]	Placebo (Cobitolimod 250mg) (N=10) n (%) [E]	Placebo (Cobitolimod 500mg) (N=10) n (%) [E]	Placebo (Placebo) (N=16) n (%) [E]	Overall (N=58) n (%) [E]
Spinal pain	0	0	0	0	1 (6.3) [1]	1 (1.7) [1]
Immune system disorders	0	1 (8.3) [1]	0	0	1 (6.3) [1]	2 (3.4) [2]
Seasonal allergy	0	1 (8.3) [1]	0	0	1 (6.3) [1]	2 (3.4) [2]
Nervous system disorders	0	0	0	2 (20.0) [2]	0	2 (3.4) [2]
Headache	0	0	0	1 (10.0) [1]	0	1 (1.7) [1]
Syncope	0	0	0	1 (10.0) [1]	0	1 (1.7) [1]
Respiratory, thoracic and mediastinal disorders	0	1 (8.3) [3]	0	1 (10.0) [1]	0	2 (3.4) [4]
Rhinitis allergic	0	1 (8.3) [3]	0	0	0	1 (1.7) [3]
Rhinorrhoea	0	0	0	1 (10.0) [1]	0	1 (1.7) [1]
Skin and subcutaneous tissue disorders	0	0	1 (10.0) [1]	1 (10.0) [1]	0	2 (3.4) [2]
Onychomadesis	0	0	0	1 (10.0) [1]	0	1 (1.7) [1]
Pruritus	0	0	1 (10.0) [1]	0	0	1 (1.7) [1]
Ear and labyrinth disorders	0	0	0	1 (10.0) [1]	0	1 (1.7) [1]
Vertigo	0	0	0	1 (10.0) [1]	0	1 (1.7) [1]
Endocrine disorders	0	0	1 (10.0) [1]	0	0	1 (1.7) [1]
Hyperthyroidism	0	0	1 (10.0) [1]	0	0	1 (1.7) [1]
Investigations	0	0	0	1 (10.0) [2]	0	1 (1.7) [2]
Blood creatine phosphokinase increased	0	0	0	1 (10.0) [1]	0	1 (1.7) [1]
C-reactive protein increased	0	0	0	1 (10.0) [1]	0	1 (1.7) [1]
Metabolism and nutrition disorders	0	1 (8.3) [1]	0	0	0	1 (1.7) [1]
Hypokalaemia	0	1 (8.3) [1]	0	0	0	1 (1.7) [1]
Renal and urinary disorders	0	0	0	0	1 (6.3) [1]	1 (1.7) [1]

System Organ Class Preferred Term	Cobitolimod 250mg (Cobitolimod 250mg) (N=10) n (%) [E]	Cobitolimod 500mg (Cobitolimod 500mg) (N=12) n (%) [E]	Placebo (Cobitolimod 250mg) (N=10) n (%) [E]	Placebo (Cobitolimod 500mg) (N=10) n (%) [E]	Placebo (Placebo) (N=16) n (%) [E]	Overall (N=58) n (%) [E]
Dysuria	0	0	0	0	1 (6.3) [1]	1 (1.7) [1]

E: number of events; N: number of patients in the treatment group; n: number of patients with observation; %: percentage of patients in the group with observation, COVID-19: coronavirus disease 2019,
TEAE: treatment-emergent adverse event.

Treatment group: Before parentheses the dose in Maintenance Study is shown. In parentheses the dose in Induction Study is shown.

Classification according to MedDRA version 24.0.

Sources: Table 11.1.8.2.2 and Listing 12.2.6.1

11.2.1.2.2 TEAEs by Severity

Induction Study

Overall, most of the participants experienced mild TEAEs (30 participants; 17.9%). Moderate and severe TEAEs were reported in 19 (11.3%) participants and 1 (0.6%) participant (Table 11.1.8.5.1).

The most commonly reported TEAE of moderate intensity was colitis ulcerative (7 participants; 4.2%). The TEAE of meniscus injury was severe in intensity and was reported in the cobitolimod 500 mg treatment group. The event was an SAE, considered unlikely related to study intervention, and was reported as resolved. For further information on SAEs, please refer to Section 11.2.1.4.

The severity of TEAEs was comparable across the treatment groups.

Maintenance Study

Overall, most of the participants experienced mild TEAEs (16 participants; 27.6%). For 5 (8.6%) participants, the TEAEs reported were moderate in intensity, and for 2 (3.4%) participants, the TEAEs reported were severe in intensity (Table 11.1.8.5.2).

The TEAE of peritoneal adhesions was severe in intensity and was reported in the cobitolimod 500 mg treatment group. Another TEAE of colitis was severe in intensity and was reported in the placebo treatment group. Both the TEAEs were SAEs, considered unlikely related to study intervention, and were reported as resolved. For further information on SAEs, please refer to Section 11.2.1.4.

11.2.1.2.3 Treatment-related TEAEs

Induction Study

The incidence of TEAEs related to study intervention by SOC and PT is summarized in Table 11-5 and all TEAEs, by participant, including relatedness with the study intervention, are listed in Listing 12.2.6.1.

Overall, 4 (2.4%) participants had TEAEs related to study intervention. All the related TEAEs were considered mild in intensity, reported as resolved, and had no action taken with the study intervention due to these TEAEs. No trend was observed across treatment groups.

One (0.6%) participant reported a treatment-related TEAE of overdose in cobitolimod 250 mg treatment group on Study Day 1. On the same day, the participant experienced paraesthesia, a mild event assessed as unlikely related to study intervention. No action was taken with the study intervention. The event of overdose resolved on the date of onset, while the event of paraesthesia did not resolve. Other TEAEs reported for this participant were dizziness and rectal hemorrhage during the study.

Table 11-5 Summary of TEAEs Related to Study Intervention by SOC and PT: Induction Study

System Organ Class Preferred Term	Cobitolimod 250mg (N=54) n (%) [E]	Cobitolimod 500mg (N=57) n (%) [E]	Placebo (N=57) n (%) [E]	Overall (N=168) n (%) [E]
Any TEAE Related to Study Intervention	2 (3.7) [3]	0	2 (3.5) [2]	4 (2.4) [5]
Gastrointestinal disorders	0	0	2 (3.5) [2]	2 (1.2) [2]
Abdominal pain	0	0	1 (1.8) [1]	1 (0.6) [1]
Diarrhoea	0	0	1 (1.8) [1]	1 (0.6) [1]
Eye disorders	1 (1.9) [1]	0	0	1 (0.6) [1]
Eyelid oedema	1 (1.9) [1]	0	0	1 (0.6) [1]
General disorders and administration site conditions	1 (1.9) [1]	0	0	1 (0.6) [1]
Oedema peripheral	1 (1.9) [1]	0	0	1 (0.6) [1]
Injury, poisoning and procedural complications	1 (1.9) [1]	0	0	1 (0.6) [1]
Overdose	1 (1.9) [1]	0	0	1 (0.6) [1]

E: number of events; N: number of patients in the treatment group; n: number of patients with observation; %: percentage of patients in the group with observation, TEAE: treatment-emergent adverse event.
Classification according to MedDRA version 24.0.
Sources: Table 11.1.8.4.1 and Listing 12.2.6.1

Maintenance Study

The incidence of TEAEs related to study intervention by SOC and PT is summarized in Table 11-6 and all TEAEs, by participant, including relatedness with the study intervention, are listed in Listing 12.2.6.1.

One (1.7%) participant had a TEAE of colitis ulcerative related to study intervention in the placebo treatment group. The event was considered mild in intensity, was reported as resolved, and led to the discontinuation of study intervention.

Table 11-6 Summary of TEAEs Related to Study Intervention by SOC and PT: Maintenance Study

System Organ Class Preferred Term	Cobitolimod 250mg (Cobitolimod 250mg) (N=10) n (%) [E]	Cobitolimod 500mg (Cobitolimod 500mg) (N=12) n (%) [E]	Placebo (Cobitolimod 250mg) (N=10) n (%) [E]	Placebo (Cobitolimod 500mg) (N=10) n (%) [E]	Placebo (Placebo) (N=16) n (%) [E]	Overall (N=58) n (%) [E]
Any TEAE Related to Study Intervention	0	0	1 (10.0) [1]	0	0	1 (1.7) [1]
Gastrointestinal disorders	0	0	1 (10.0) [1]	0	0	1 (1.7) [1]
Colitis ulcerative	0	0	1 (10.0) [1]	0	0	1 (1.7) [1]

E: number of events; N: number of patients in the treatment group; n: number of patients with observation; %: percentage of patients in the group with observation, TEAE: treatment-emergent adverse event.
Treatment group: Before parentheses the dose in Maintenance Study is shown. In parentheses the dose in Induction Study is shown.
Classification according to MedDRA version 24.0.
Sources: Table 11.1.8.4.2 and Listing 12.2.6.1

Analyses of all AEs are detailed from Listing 12.2.6.1 to Listing 12.2.6.4.

11.2.1.3 Deaths

Induction Study

No deaths were reported during the induction study (Table 11.1.8.9.1 and Listing 12.2.6.2).

Maintenance Study

No deaths were reported during the maintenance study (Table 11.1.8.9.2 and Listing 12.2.6.2).

11.2.1.4 Serious Adverse Events

Induction Study

Overall, 4 (2.4%) participants reported 5 serious TEAEs during the induction study (Table 11-7).

The serious TEAE of colitis ulcerative was reported in cobitolimod 250 mg treatment group and the serious TEAE of meniscus injury was reported in cobitolimod 500 mg treatment group. The serious TEAEs of pyelonephritis, nephrolithiasis, and renal colic were reported in the placebo treatment group. All the serious TEAEs were considered moderate in intensity except the serious TEAE of meniscus injury which was considered severe in intensity. The serious TEAEs were unlikely related to the study intervention, were reported as resolved, and no action was taken with the study intervention due to these serious TEAEs. None of the participants discontinued the study due to the serious TEAEs.

Serious TEAEs for the induction study are summarised by SOC and PT in Table 11-7 and listed by participant in Listing 12.2.6.3.

Individual participant narratives are detailed in Section 14.3.3.

Table 11-7 Summary of SAEs by SOC and PT: Induction Study

System Organ Class Preferred Term	Cobitolimod 250mg (N=54) n (%) [E]	Cobitolimod 500mg (N=57) n (%) [E]	Placebo (N=57) n (%) [E]	Overall (N=168) n (%) [E]
Any Serious TEAE	1 (1.9) [1]	1 (1.8) [1]	2 (3.5) [3]	4 (2.4) [5]
Gastrointestinal disorders	1 (1.9) [1]	0	0	1 (0.6) [1]
Colitis ulcerative	1 (1.9) [1]	0	0	1 (0.6) [1]
Infections and infestations	0	0	1 (1.8) [1]	1 (0.6) [1]
Pyelonephritis	0	0	1 (1.8) [1]	1 (0.6) [1]
Injury, poisoning and procedural complications	0	1 (1.8) [1]	0	1 (0.6) [1]
Meniscus injury	0	1 (1.8) [1]	0	1 (0.6) [1]
Renal and urinary disorders	0	0	1 (1.8) [2]	1 (0.6) [2]
Nephrolithiasis	0	0	1 (1.8) [1]	1 (0.6) [1]
Renal colic	0	0	1 (1.8) [1]	1 (0.6) [1]

E: number of events; N: number of patients in the treatment group; n: number of patients with observation; %: percentage of patients in the group with observation, TEAE: treatment-emergent adverse event.
Classification according to MedDRA version 24.0.
Sources: Table 11.1.8.3.1 and Listing 12.2.6.3

Maintenance Study

Overall, 3 (5.2%) participants reported serious TEAEs during the maintenance study (Table 11-8).

The serious TEAE of peritoneal adhesions was reported in cobitolimod 500 mg treatment group and the serious TEAE of colitis was reported in the placebo treatment group. Both serious TEAEs were considered severe in intensity, unlikely related to the study intervention, and were reported as resolved. No action was taken with the study intervention due to these serious TEAEs. The unlikely related TEAE of colitis ulcerative reported in the placebo treatment group was moderate in intensity, reported as not resolved, and it led to the discontinuation of the participant from study intervention and the study.

Serious TEAEs for the maintenance study are summarised by SOC and PT in Table 11-8 and listed by participant in Listing 12.2.6.3.

Individual participant narratives are detailed in Section 14.3.3.

Table 11-8 Summary of SAEs by SOC and PT: Maintenance Study

System Organ Class Preferred Term	Cobitolimod 250mg (Cobitolimod 250mg) (N=10) n (%) [E]	Cobitolimod 500mg (Cobitolimod 500mg) (N=12) n (%) [E]	Placebo (Cobitolimod 250mg) (N=10) n (%) [E]	Placebo (Cobitolimod 500mg) (N=10) n (%) [E]	Placebo (Placebo) (N=16) n (%) [E]	Overall (N=58) n (%) [E]
Any Serious TEAE	0	1 (8.3) [1]	0	1 (10.0) [1]	1 (6.3) [1]	3 (5.2) [3]
Gastrointestinal disorders	0	1 (8.3) [1]	0	1 (10.0) [1]	1 (6.3) [1]	3 (5.2) [3]
Colitis	0	0	0	1 (10.0) [1]	0	1 (1.7) [1]
Colitis ulcerative	0	0	0	0	1 (6.3) [1]	1 (1.7) [1]
Peritoneal adhesions	0	1 (8.3) [1]	0	0	0	1 (1.7) [1]

E: number of events; N: number of patients in the treatment group; n: number of patients with observation; %: percentage of patients in the group with observation, TEAE: treatment-emergent adverse event.

Treatment group: Before parentheses the dose in Maintenance Study is shown. In parentheses the dose in Induction Study is shown.

Classification according to MedDRA version 24.0.

Sources: Table 11.1.8.3.2 and Listing 12.2.6.3

11.2.1.5 Discontinuations Due to Adverse Events

Induction Study

Overall, 4 (2.4%) participants had TEAEs leading to discontinuation from study intervention (Table 11-9). None of these TEAEs were assessed as related to study intervention (Table 11.1.8.8.1).

Summary of TEAEs leading to discontinuation from study intervention is presented in Table 11.1.8.7.1, and a summary of TEAEs related to study intervention leading to discontinuation from study intervention is presented in Table 11.1.8.8.1. TEAEs leading to discontinuation from the study intervention and from the study are listed in Listing 12.2.6.4.

Table 11-9 Summary of AEDCs by SOC and PT: Induction Study

System Organ Class Preferred Term	Cobitolimod 250mg (N=54) n (%) [E]	Cobitolimod 500mg (N=57) n (%) [E]	Placebo (N=57) n (%) [E]	Overall (N=168) n (%) [E]
Any TEAE Leading to Discontinuation from Study Intervention	2 (3.7) [2]	1 (1.8) [1]	1 (1.8) [1]	4 (2.4) [4]
Gastrointestinal disorders	2 (3.7) [2]	1 (1.8) [1]	0	3 (1.8) [3]
Colitis ulcerative*	2 (3.7) [2]	1 (1.8) [1]	0	3 (1.8) [3]
Skin and subcutaneous tissue disorders	0	0	1 (1.8) [1]	1 (0.6) [1]
Rash maculovesicular**	0	0	1 (1.8) [1]	1 (0.6) [1]

E: number of events; N: number of patients in the treatment group; n: number of patients with observation; %: percentage of patients in the group with observation, TEAE: treatment-emergent adverse event.

Classification according to MedDRA version 24.0.

*One participant in the cobitolimod 250 mg treatment group discontinued the study.

**This participant discontinued the study.

Sources: Table 11.1.8.7.1 and Listing 12.2.6.4

Maintenance Study

Overall, 3 (5.2%) participants experienced TEAEs leading to discontinuation from study intervention (Table 11-10), all reported under the SOC of gastrointestinal disorders. Among these, 1 (1.7%) participant had study drug-related colitis ulcerative (Table 11.1.8.8.2).

Summary of TEAEs leading to discontinuation from study intervention is presented in Table 11.1.8.7.2, and a summary of TEAEs related to study intervention leading to discontinuation from study intervention is presented in Table 11.1.8.8.2. TEAEs leading to discontinuation from the study intervention and study are listed in Listing 12.2.6.4.

Table 11-10 Summary of AEDCs by SOC and PT: Maintenance Study

System Organ Class Preferred Term	Cobitolimod 250mg (Cobitolimod 250mg) (N=10) n (%) [E]	Cobitolimod 500mg (Cobitolimod 500mg) (N=12) n (%) [E]	Placebo (Cobitolimod 250mg) (N=10) n (%) [E]	Placebo (Cobitolimod 500mg) (N=10) n (%) [E]	Placebo (Placebo) (N=16) n (%) [E]	Overall (N=58) n (%) [E]
Any TEAE Leading to Discontinuation from Study Intervention	0	0	1 (10.0) [1]	1 (10.0) [1]	1 (6.3) [1]	3 (5.2) [3]
Gastrointestinal disorders*	0	0	1 (10.0) [1]	1 (10.0) [1]	1 (6.3) [1]	3 (5.2) [3]
Colitis ulcerative	0	0	1 (10.0) [1]	0	1 (6.3) [1]	2 (3.4) [2]
Colitis	0	0	0	1 (10.0) [1]	0	1 (1.7) [1]

E: number of events; N: number of patients in the treatment group; n: number of patients with observation; %: percentage of patients in the group with observation, TEAE: treatment-emergent adverse event.

Treatment group: Before parentheses the dose in Maintenance Study is shown. In parentheses the dose in Induction Study is shown.

Classification according to MedDRA version 24.0.

*All participants discontinued the study.

Sources: Table 11.1.8.7.2 and Listing 12.2.6.4

11.2.2 Clinical Laboratory Evaluation

11.2.2.1 Laboratory Values Over Time

11.2.2.1.1 Hematology

Induction Study

A summary of hematology measured values and changes from Baseline is presented in Table 11.1.9.1.1. Individual values for hematology are provided by participant in Listing 12.2.7.1.

No clinically meaningful trends were observed in changes from Baseline in hematology parameters.

Maintenance Study

A summary of hematology measured values and changes from Baseline is presented in Table 11.1.9.1.2. Individual values for hematology are provided by participant in Listing 12.2.7.1.

No clinically meaningful trends were observed in changes from Baseline in hematology parameters.

11.2.2.1.2 Biochemistry

Induction Study

A summary of blood biochemistry measured values and changes from Baseline is presented in Table 11.1.9.2.1. Individual values for biochemistry are provided by participant in Listing 12.2.7.2.

No clinically meaningful trends were observed in changes from Baseline in biochemistry parameters.

Maintenance Study

A summary of blood biochemistry measured values and changes from Baseline is presented in Table 11.1.9.2.2. Individual values for biochemistry are provided by participant in Listing 12.2.7.2.

No clinically meaningful trends were observed in changes from Baseline in biochemistry parameters.

11.2.2.1.3 Histology

Induction Study

A summary of histological parameters and changes from Baseline is presented in Table 11.1.9.4.1. Individual values for histology are provided by participant in Listing 12.2.7.4. The Robarts Histologic Index was used to score inflammation in the mucosa. This is defined below (Table 11-11):

Table 11-11 Robarts Histologic Index

Chronic inflammatory infiltrate	Lamina propria neutrophils	Neutrophils in epithelium	Erosion or ulceration
0 = No increase	0 = None	0 = None	0 = No erosion, ulceration, or granulation
1 = Mild but unequivocal increase	1 = Mild but unequivocal increase	1 = <5% crypts involved	1 = recovering epithelium + adjacent inflammation
2 = Moderate increase	2 = Moderate increase	2 = <50% crypts involved	2 = unequivocal erosion
3 = Marked increase	3 = Marked increase	3 = >50% crypts involved	3 = ulcer or granulation tissue

Source: Study Protocol (Appendix 16.1.1)

Changes from Baseline [mean (SD)] at I-Week 6 in Robarts Histological Index were -0.9 (3.65) in cobitolimod 250 mg treatment group, -1.5 (3.29) in cobitolimod 500 mg treatment group, and -0.5 (3.33) in placebo group.

Maintenance Study

A summary of histological parameters and changes from Baseline is presented in Table 11.1.9.4.2. Individual values for histology are provided by participant in Listing 12.2.7.4.

11.2.2.2 Clinically Meaningful Laboratory Abnormalities

Induction Study

The following laboratory investigations reported in the table of summary of TEAEs by SOC and PT were reported as AEs:

Alanine aminotransferase increased

Overall, 2 participants reported the AE of alanine aminotransferase increased. Of these, 1 event was reported in cobitolimod 250 mg group and 1 was reported in cobitolimod 500 mg group.

Blood creatine phosphokinase increased

Overall, 2 participants reported the AE of blood creatine phosphokinase increased. Of these, 1 event was reported in cobitolimod 250 mg group and 1 was reported in cobitolimod 500 mg group.

Blood alkaline phosphatase increased

Overall, 1 participant reported the AE of blood alkaline phosphatase increased in cobitolimod 500 mg group.

C-reactive protein increased

Overall, 1 participant reported the AE of C-reactive protein increased in cobitolimod 500 mg group.

Lymphocyte count decreased

Overall, 1 participant reported the AE of lymphocyte count decreased in cobitolimod 250 mg group.

Anaemia

Overall, 1 participant reported the AE of anaemia in cobitolimod 500 mg group.

Eosinophilia

Overall, 1 participant reported the AE of eosinophilia in cobitolimod 250 mg group.

Hypokalaemia

Overall, 1 participant reported the AE of hypokalaemia in cobitolimod 250 mg group.

Iron Deficiency

Overall, 1 participant reported the AE of iron deficiency in cobitolimod 500 mg group.

For a summary of clinically meaningful laboratory abnormalities, refer to Table 11.1.8.2.1.

Maintenance Study

The following laboratory investigations reported in the table of summary of TEAEs by SOC and PT were reported as AEs:

Blood creatine phosphokinase increased

Overall, 1 participant reported the AE of blood creatine phosphokinase increased in placebo treatment group.

C-reactive protein increased

Overall, 1 participant reported the AE of C-reactive protein increased in placebo treatment group.

Hypokalaemia

Overall, 1 participant reported the AE of hypokalaemia in cobitolimod 500 mg group.

For a summary of clinically meaningful laboratory abnormalities, refer to Table 11.1.8.2.2.

11.2.2.3 Vital Signs

Induction Study

Summary of vital signs and changes from Baseline is presented in Table 11.1.9.5.1. Individual values for vital signs are provided by participant in Listing 12.2.7.6.

No clinically meaningful trends were observed in changes from Baseline in vital signs parameters.

Maintenance Study

Summary of vital signs and changes from Baseline is presented in Table 11.1.9.5.2. Individual values for vital signs are provided by participant in Listing 12.2.7.6.

No clinically meaningful trends were observed in changes from Baseline in vital signs parameters.

11.2.2.4 Physical Examination Findings

Summary of physical examination abnormalities are summarised in Listing 12.2.7.7.

11.3 Summary of Evaluation of Response to Study Intervention

Induction Study

Primary efficacy endpoint analysis:

- The primary endpoint of clinical remission at I-Week 6 was observed in 4 (8.0%) participants in the cobitolimod 250 mg group, 3 (6.0%) participants in the cobitolimod 500 mg group, and 3 (6.1%) participants in the placebo group (Table 11-12).

- There was no statistically significant difference in the proportion of participants achieving clinical remission between cobitolimod 250 mg and placebo treatment groups. Also, there was no statistically significant difference in the proportion of participants achieving clinical remission between cobitolimod 500 mg and placebo treatment groups. The risk difference (standard error) for cobitolimod vs placebo (adjusted for stratification factors) was 2.0% (5.10%) in the cobitolimod 250 mg treatment group and -0.2% (4.76%) in the cobitolimod 500 mg treatment group. Thus, the primary objective for this study was not met.

Table 11-12 Analysis of Clinical Remission at I-Week 6 - NRI Imputation Method (Full Analysis Set)

	Statistical Parameter	Cobitolimod 250mg (N=50)	Cobitolimod 500mg (N=50)	Placebo (N=49)	Overall (N=149)
Clinical Remission [1]					
Yes	n (%)	4 (8.0)	3 (6.0)	3 (6.1)	10 (6.7)
No	n (%)	44 (88.0)	41 (82.0)	42 (85.7)	127 (85.2)
Missing/NRI	n (%)	2 (4.0)	6 (12.0)	4 (8.2)	12 (8.1)
Cobitolimod vs Placebo [2] (no adjustment)	Risk Difference (SE)	1.9 (5.14)	-0.1 (4.80)		
	95% CI	-8.20, 11.96	-9.52, 9.28		
	p-value	0.715	0.980		
Cobitolimod vs Placebo [3] (adjusted for stratification factors)	Risk Difference (SE)	2.0 (5.10)	-0.2 (4.76)		
	95% CI	-8.04, 11.94	-9.56, 9.09		
	p-value	0.702	0.961		

N: number of patients in the treatment group; n: number of patients with observation; %: percentage of patients in the group with observation; CI: confidence interval; NRI: Non-Responder Imputation; SE: standard error.

[1] Observed frequencies.

[2] Cobitolimod vs Placebo, risk difference using "Covariate-adjusted difference in proportions from clinical trials using logistic regression" (M. Ge et al., 2011).

[3] Cobitolimod vs Placebo, risk difference adjusted for stratification factors (concomitant glucocorticosteroids (GCS) treatment and Janus kinase (JAK)-inhibitors) using "Covariate-adjusted difference in proportions from clinical trials using logistic regression" (M. Ge et al., 2011).

Sources: Table 11.1.6.1 and Listing 12.2.5.2

Key secondary efficacy endpoint analysis:

- There was no statistically significant difference in the proportion of participants who achieved endoscopic improvement at I-Week 6 between cobitolimod 250 mg and placebo treatment groups (Table 11-13).
- There was no statistically significant difference in the proportion of participants who achieved endoscopic improvement at I-Week 6 between cobitolimod 500 mg and placebo treatment groups (Table 11-13).
- There was no statistically significant difference in the proportion of participants who achieved symptomatic remission at I-Week 6 between cobitolimod 250 mg and placebo treatment groups (Table 11-14).
- There was no statistically significant difference in the proportion of participants who achieved symptomatic remission between cobitolimod 500 mg and placebo treatment groups (Table 11-14).

Table 11-13 Analysis of Endoscopic Improvement at I-Week 6 - NRI Imputation (Full Analysis Set)

	Statistical Parameter	Cobitolimod 250mg (N=50)	Cobitolimod 500mg (N=50)	Placebo (N=49)	Overall (N=149)
Endoscopic Improvement [1]					
Yes	n (%)	8 (16.0)	6 (12.0)	9 (18.4)	23 (15.4)
No	n (%)	41 (82.0)	38 (76.0)	36 (73.5)	115 (77.2)
Missing/NRI	n (%)	1 (2.0)	6 (12.0)	4 (8.2)	11 (7.4)
Cobitolimod vs Placebo [2] (no adjustment)	Risk Difference (SE)	-2.4 (7.58)	-6.4 (7.19)		
	95% CI	-17.23, 12.49	-20.46, 7.73		
	p-value	0.755	0.376		
Cobitolimod vs Placebo [3] (adjusted for stratification factors)	Risk Difference (SE)	-2.4 (7.55)	-6.5 (7.12)		

	Statistical Parameter	Cobitolimod 250mg (N=50)	Cobitolimod 500mg (N=50)	Placebo (N=49)	Overall (N=149)
	95% CI	-17.18, 12.42	-20.41, 7.49		
	p-value	0.752	0.364		

N: number of patients in the treatment group; n: number of patients with observation; %: percentage of patients in the group with observation; CI: confidence interval, NRI: Non-Responder Imputation; SE: standard error.

[1] Observed frequencies.

[2] Cobitolimod vs Placebo, risk difference using "Covariate-adjusted difference in proportions from clinical trials using logistic regression" (M. Ge et al., 2011).

[3] Cobitolimod vs Placebo, risk difference adjusted for stratification factors (concomitant glucocorticosteroids (GCS) treatment and Janus Kinase (JAK)-inhibitors) using "Covariate-adjusted difference in proportions from clinical trials using logistic regression" (M. Ge et al., 2011).

Sources: Table 11.1.6.2 and Listing 12.2.5.2

Table 11-14 Analysis of Symptomatic Remission at I-Week 6 - NRI Imputation (Full Analysis Set)

	Statistical Parameter	Cobitolimod 250mg (N=50)	Cobitolimod 500mg (N=50)	Placebo (N=49)	Overall (N=149)
Symptomatic Remission [1]					
Yes	n (%)	10 (20.0)	13 (26.0)	8 (16.3)	31 (20.8)
No	n (%)	35 (70.0)	31 (62.0)	34 (69.4)	100 (67.1)
Missing/NRI	n (%)	5 (10.0)	6 (12.0)	7 (14.3)	18 (12.1)
Cobitolimod vs Placebo [2] (no adjustment)	Risk Difference (SE)	3.7 (7.74)	9.7 (8.15)		
	95% CI	-11.49, 18.84	-6.29, 25.64		
	p-value	0.635	0.235		
Cobitolimod vs Placebo [3] (adjusted for stratification factors)	Risk Difference (SE)	3.6 (7.61)	9.4 (8.08)		
	95% CI	-11.36, 18.49	-6.42, 25.28		
	p-value	0.640	0.244		

N: number of patients in the treatment group; n: number of patients with observation; %: percentage of patients in the group with observation; CI: confidence interval; NRI: Non-Responder Imputation; SE: standard error.

[1] Observed frequencies.

[2] Cobitolimod vs Placebo, risk difference using "Covariate-adjusted difference in proportions from clinical trials using logistic regression" (M. Ge et al., 2011).

[3] Cobitolimod vs Placebo, risk difference adjusted for stratification factors (concomitant glucocorticosteroids (GCS) treatment and Janus Kinase (JAK)-inhibitors) using "Covariate-adjusted difference in proportions from clinical trials using logistic regression" (M. Ge et al., 2011).

Sources: Table 11.1.6.3 and Listing 12.2.5.2

A summary of other efficacy results (clinical response at I-Week 6; absence of rectal bleeding at I-Week 6; histologic improvement at I-Week 6; histologic remission at I-Week 6; and normalization of faecal calprotectin at I-Week 6) is provided in Table 11-15; Results and Change from Baseline in induction study in 3-component Mayo Score is provided in Table 11-16; Results and Change from Baseline (Logarithmic Scale) in induction study in Faecal Calprotectin (mg/kg) is provided in Table 11-17; Stool Frequency Sub-score, Results and Change from Baseline: induction study in Table 11-18; and Rectal Bleeding Sub-score, Results and Change from Baseline: induction study in Table 11-19.

Table 11-15 Summary of Other Efficacy Results Induction Study at I-Week 6 - Observed Frequencies (Full Analysis Set)

	Statistical Parameter	Cobitolimod 250mg (N=50)	Cobitolimod 500mg (N=50)	Placebo (N=49)	Overall (N=149)
Clinical Response					
Yes	n (%)	19 (38.0)	16 (32.0)	16 (32.7)	51 (34.2)
No	n (%)	25 (50.0)	28 (56.0)	25 (51.0)	78 (52.3)
Missing	n (%)	6 (12.0)	6 (12.0)	8 (16.3)	20 (13.4)
Absence of Rectal Bleeding					
Yes	n (%)	18 (36.0)	17 (34.0)	14 (28.6)	49 (32.9)
No	n (%)	27 (54.0)	27 (54.0)	28 (57.1)	82 (55.0)
Missing	n (%)	5 (10.0)	6 (12.0)	7 (14.3)	18 (12.1)
Histologic Improvement					
Yes	n (%)	3 (6.0)	3 (6.0)	2 (4.1)	8 (5.4)
No	n (%)	45 (90.0)	38 (76.0)	41 (83.7)	124 (83.2)
Missing	n (%)	2 (4.0)	9 (18.0)	6 (12.2)	17 (11.4)
Histologic Remission					
Yes	n (%)	14 (28.0)	14 (28.0)	14 (28.6)	42 (28.2)
No	n (%)	34 (68.0)	27 (54.0)	29 (59.2)	90 (60.4)
Missing	n (%)	2 (4.0)	9 (18.0)	6 (12.2)	17 (11.4)
Normalization of Faecal Calprotectin*					
Yes	n (%)	9 (18.0)	11 (22.0)	11 (22.4)	31 (20.8)
No	n (%)	35 (70.0)	29 (58.0)	31 (63.3)	95 (63.8)

	Statistical Parameter	Cobitolimod 250mg (N=50)	Cobitolimod 500mg (N=50)	Placebo (N=49)	Overall (N=149)
Missing	n (%)	6 (12.0)	10 (20.0)	7 (14.3)	23 (15.4)

N: number of patients in the treatment group; n: number of patients with observation; %: percentage of patients in the group with observation.

*This is an exploratory endpoint.

Sources: Table 11.1.6.4 and Listings 12.2.5.2, 12.2.7.3, 12.2.7.4

Table 11-16 3-component Mayo Score, Results and Change from Baseline: Induction Study (Full Analysis Set)

Visit	Statistical Parameter	Cobitolimod 250mg (N=50)	Cobitolimod 500mg (N=50)	Placebo (N=49)	Overall (N=149)
Baseline [1]	n	49	50	47	146
	Mean	6.9	6.6	6.7	6.7
	SD	1.21	1.24	1.16	1.20
	Median	7.0	7.0	7.0	7.0
	Min, Max	4, 9	2, 9	4, 9	2, 9
Visit 4a - I-Week 6: Actual Value	n	45	43	42	130
	Mean	4.8	4.8	4.9	4.8
	SD	1.98	2.13	2.06	2.04
	Median	5.0	5.0	5.0	5.0
	Min, Max	1, 8	0, 8	0, 8	0, 8
Visit 4a - I-Week 6: Change from Baseline	n	44	43	41	128
	Mean	-2.0	-1.7	-1.8	-1.8
	SD	2.06	2.47	1.84	2.13
	Median	-2.0	-2.0	-2.0	-2.0
	Min, Max	-7, 3	-8, 4	-7, 1	-8, 4

N: number of patients in the treatment group; n: number of patients with observation; SD: standard deviation, min: minimum, max: maximum.

[1] Baseline scores for stool frequency and rectal bleeding is derived based on data from seven days prior to Visit 2 - I-Week 0.

Sources: Table 11.1.6.5 and Listing 12.2.5.1

Table 11-17 Faecal Calprotectin (mg/kg), Results and Change from Baseline (Logarithmic Scale): Induction Study (Full Analysis Set)

Visit	Statistical Parameter	Cobitolimod 250mg (N=50)	Cobitolimod 500mg (N=50)	Placebo (N=49)	Overall (N=149)
Baseline [1]	n	50	49	49	148

Visit	Statistical Parameter	Cobitolimod 250mg (N=50)	Cobitolimod 500mg (N=50)	Placebo (N=49)	Overall (N=149)
	Mean	7.159	6.615	7.344	7.040
	SD	1.4209	1.3798	1.2789	1.3873
	Median	7.500	6.724	7.393	7.105
	Min, Max	4.12, 10.06	2.93, 10.17	4.26, 10.18	2.93, 10.18
Visit 3 - I-Week 3: Actual Value	n	48	47	43	138
	Mean	6.923	6.418	7.012	6.779
	SD	1.3509	1.5269	1.4790	1.4658
	Median	7.236	6.450	7.377	7.042
	Min, Max	3.99, 10.09	2.73, 9.36	3.85, 9.20	2.73, 10.09
Visit 3 - I-Week 3: Change from Baseline	n	48	46	43	137
	Mean	-0.268	-0.152	-0.312	-0.243
	SD	1.5205	1.7880	1.4324	1.5795
	Median	-0.293	-0.170	-0.318	-0.260
	Min, Max	-5.23, 2.57	-3.15, 6.00	-3.43, 2.67	-5.23, 6.00
Visit 4a - I-Week 6: Actual Value	n	42	39	42	123
	Mean	6.899	6.635	6.724	6.755
	SD	1.4595	1.5248	1.6653	1.5441
	Median	7.042	6.540	6.544	6.800
	Min, Max	2.99, 9.69	3.66, 9.94	2.86, 10.00	2.86, 10.00
Visit 4a - I-Week 6: Change from Baseline	n	42	39	42	123
	Mean	-0.381	-0.042	-0.632	-0.359
	SD	1.7081	1.8366	1.5292	1.6956
	Median	-0.343	-0.341	-0.837	-0.475
	Min, Max	-4.46, 2.64	-3.80, 3.88	-4.94, 3.07	-4.94, 3.88

N: number of patients in the treatment group; n: number of patients with observation; SD: standard deviation, min: minimum, max: maximum.
[1] Baseline is defined as the last non-missing measurement recorded before first dose of study drug administration in the induction study.
Sources: Table 11.1.6.8 and Listing 12.2.7.3

Table 11-18 Stool Frequency Sub-score, Results and Change from Baseline: Induction Study (Full Analysis Set)

Visit	Statistical Parameter	Cobitolimod 250mg (N=50)	Cobitolimod 500mg (N=50)	Placebo (N=49)	Overall (N=149)
Baseline [1]	n	49	50	47	146
	Mean	2.6	2.3	2.4	2.5
	SD	0.58	0.72	0.72	0.68
	Median	3.0	2.0	3.0	3.0
	Min, Max	1, 3	0, 3	1, 3	0, 3
Visit 4a - I-Week 6: Actual Value	n	45	43	42	130
	Mean	1.7	1.7	1.9	1.7
	SD	0.98	1.00	0.98	0.98
	Median	2.0	2.0	2.0	2.0
	Min, Max	0, 3	0, 3	0, 3	0, 3
Visit 4a - I-Week 6: Change from Baseline	n	44	43	41	128
	Mean	-0.9	-0.7	-0.5	-0.7
	SD	0.95	1.21	0.81	1.01
	Median	-1.0	-1.0	0.0	-1.0
	Min, Max	-3, 1	-3, 2	-3, 1	-3, 2

N: number of patients in the treatment group; n: number of patients with observation; SD: standard deviation; min: minimum, max: maximum.

[1] Baseline scores for stool frequency is derived based on data from seven days prior to Visit 2 - I-Week 0.

Sources: Table 11.1.6.7 and Listing 12.2.5.1

Table 11-19 Rectal Bleeding Sub-score, Results and Change from Baseline: Induction Study (Full Analysis Set)

Visit	Statistical Parameter	Cobitolimod 250mg (N=50)	Cobitolimod 500mg (N=50)	Placebo (N=49)	Overall (N=149)
Baseline [1]	n	49	50	47	146
	Mean	1.7	1.8	1.7	1.7
	SD	0.66	0.66	0.57	0.63
	Median	2.0	2.0	2.0	2.0
	Min, Max	0, 3	0, 3	0, 3	0, 3
Visit 4a - I-Week 6: Actual Value	n	45	44	42	131
	Mean	0.8	1.1	1.0	1.0
	SD	0.78	0.99	0.84	0.88
	Median	1.0	1.0	1.0	1.0
	Min, Max	0, 2	0, 3	0, 3	0, 3
Visit 4a - I-Week 6: Change from Baseline	n	44	44	41	129
	Mean	-0.9	-0.7	-0.8	-0.8
	SD	1.05	1.06	0.85	0.99
	Median	-1.0	-0.5	-1.0	-1.0
	Min, Max	-2, 2	-3, 2	-2, 1	-3, 2

N: number of patients in the treatment group; n: number of patients with observation; SD: standard deviation; min: minimum, max: maximum.

[1] Baseline scores for stool frequency and rectal bleeding was derived based on data from seven days prior to Visit 2- I-Week 0.

Sources: Table 11.1.6.6 and Listing 12.2.5.1

Maintenance Study

No formal statistical analysis was done for the maintenance study. However, the data of the participants in Full Analysis Set maintenance (FASM) are presented in Listing 12.2.5.3. (Refer to Sections 9.2.2 and 9.2.3) and Appendix 16.1.9.

12 Discussion

This was a randomised double-blind placebo-controlled phase III clinical study which was conducted to evaluate the efficacy and safety of cobitolimod as an induction and maintenance therapy in participants with moderate to severe active left-sided UC. A total of 466 participants were screened, of these, 171 participants were randomised into the induction study. Among the randomised participants, 142 (83%) participants completed the induction study. In the maintenance study, 59 participants were randomised. Among the randomised participants, 8 (13.6%) participants completed the maintenance study. The most common reason for discontinuation from study was study termination by Sponsor (10.5% in the induction study and

67.8% in the maintenance study). The independent DMC advised that cobitolimod was unlikely to meet the primary objective upon completion of induction Study based on the planned dose selection interim analysis which included a safety review and a futility assessment based on the primary endpoint “clinical remission” at I-Week 6, and further recommended to terminate the study. The Sponsor’s decision to terminate the study was not based on safety concerns.

13 Conclusions

- The independent DMC completed the planned dose selection interim analysis including a safety review and futility assessment in induction study of the phase III programme CONCLUDE, and recommended to terminate the study as cobitolimod was unlikely to meet the primary objective of demonstrating clinically relevant and statistically significant efficacy in inducing clinical remission upon completion of induction study. The advice to stop the study was not based on safety concerns. The study was stopped by the Sponsor on 21 Nov 2023.

- In the induction study, overall, 52 (31.0%) participants experienced at least one AE with similar distribution among the treatment groups. Overall, 42 (25.0%) participants experienced TEAEs, and 4 (2.4%) participants had TEAEs which were likely related to the study intervention. Four (2.4%) participants reported serious TEAEs, all of which were unlikely related to the study intervention. A total of 4 (2.4%) participants discontinued the study intervention due to TEAEs and 2 (1.2%) participants discontinued the induction study due to TEAEs.

- In the maintenance study, overall, 18 (31.0%) participants experienced at least one TEAE. The highest incidence of TEAEs reported during the maintenance study was in the placebo group. One (1.7%) participant had a TEAE which was likely related to the study intervention. Three (5.2%) participants reported serious TEAEs, all of which were unlikely related to the study intervention. A total of 3 (5.2%) participants discontinued the study intervention followed by discontinuation of maintenance study.

- Cobitolimod at doses of 250 mg and 500 mg was well tolerated in the treatment of moderate to severe active UC and no safety concerns were observed during the study.

14 Tables and Figures

Note: All summary tables are numbered as 11.1.x.x.x and are the final versions.

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14.2 Efficacy Data

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- Table 11.1.6.2 Analysis of Endoscopic Improvement at I-Week 6 - NRI Imputation (Full Analysis Set)
- Table 11.1.6.3 Analysis of Symptomatic Remission at I-Week 6 - NRI Imputation (Full Analysis Set)
- Table 11.1.6.4 Efficacy Endpoints Induction Study: Number and Proportion of Patients at I-Week 6 – Observed Frequencies (Full Analysis Set)
- Table 11.1.6.5 3-component Mayo Score, Results and Change from Baseline: Induction Study (Full Analysis Set)
- Table 11.1.6.6 Rectal Bleeding Subscore, Results and Change from Baseline: Induction Study (Full Analysis Set)
- Table 11.1.6.7 Stool Frequency Subscore, Results and Change from Baseline: Induction Study (Full Analysis Set)
- Table 11.1.6.8 Faecal Calprotectin (mg/kg), Results and Change from Baseline (Logarithmic Scale): Induction Study (Full Analysis Set)

14.3 Safety Data

14.3.1 Displays of Adverse Events

- Table 11.1.8.1.1 Overview of Adverse Events: Induction Study (Safety Analysis Set)
- Table 11.1.8.1.2 Overview of Adverse Events: Maintenance Study (Safety Analysis Set Maintenance)
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- Table 11.1.8.4.1 Summary of Treatment-Emergent Adverse Events Related to Study Intervention Medication by System Organ Class and Preferred Term:
- Induction Study (Safety Analysis Set)
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- Table 11.1.8.6.2 Summary of Treatment-Emergent Adverse Events Related to Study Intervention by Severity, System Organ Class and Preferred Term: Maintenance Study (Safety Analysis Set Maintenance)
- Table 11.1.8.7.1 Summary of Treatment-Emergent Adverse Events Leading to Discontinuation from Study Intervention by System Organ Class and Preferred Term: Induction Study (Safety Analysis Set)
- Table 11.1.8.7.2 Summary of Treatment-Emergent Adverse Events Leading to Discontinuation from Study Intervention by System Organ Class and Preferred Term: Maintenance Study (Safety Analysis Set Maintenance)
- Table 11.1.8.8.1 Summary of Treatment-Emergent Adverse Events Related to Study Intervention Leading to Discontinuation from Study Intervention by System Organ Class and Preferred Term: Induction Study (Safety Analysis Set)

14.3.2 Listing of Deaths, Other Serious, and Clinically Meaningful Adverse Events

- Table 11.1.8.3.1 Summary of Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term: Induction Study (Safety Analysis Set)
- Table 11.1.8.3.2 Summary of Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term: Maintenance Study (Safety Analysis Set Maintenance)
- Table 11.1.8.9.1 Summary of Fatal Adverse Events by System Organ Class and Preferred Term: Induction Study (Safety Analysis Set)
- Table 11.1.8.9.2 Summary of Fatal Adverse Events by System Organ Class and Preferred Term: Maintenance Study (Safety Analysis Set Maintenance)

14.3.3 Narratives of Deaths, Other Serious Adverse Events, and Certain Other Clinically Meaningful Adverse Events

The narratives of serious adverse events are provided as a separate file.

14.3.4 Other Data

- Table 11.1.7.1 Treatment Compliance: Induction Study (Safety Analysis Set)
- Table 11.1.7.2 Treatment Compliance: Maintenance Study (Safety Analysis Set Maintenance)
- Table 11.1.9.1.1 Hematology, Results and Change from Baseline: Induction Study (Safety Analysis Set)
- Table 11.1.9.1.2 Hematology, Results and Change from Baseline: Maintenance Study (Safety Analysis Set Maintenance)
- Table 11.1.9.2.1 Biochemistry, Results and Change from Baseline: Induction Study (Safety Analysis Set)
- Table 11.1.9.2.2 Biochemistry, Results and Change from Baseline: Maintenance Study (Safety Analysis Set Maintenance)
- Table 11.1.9.3.1 Faecal Calprotectin, Results and Change from Baseline: Induction Study (Safety Analysis Set)
- Table 11.1.9.3.2 Faecal Calprotectin, Results and Change from Baseline: Maintenance Study (Safety Analysis Set Maintenance)
- Table 11.1.9.4.1 Histology, Results and Change from Baseline: Induction Study (Safety Analysis Set)
- Table 11.1.9.4.2 Histology, Results and Change from Baseline: Maintenance Study (Safety Analysis Set Maintenance)
- Table 11.1.9.5.1 Vital Signs, Results and Change from Baseline: Induction Study (Safety Analysis Set)
- Table 11.1.9.5.2 Vital Signs, Results and Change from Baseline: Maintenance Study (Safety Analysis Set Maintenance)

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16 Appendices

16.1 Study Information

- 16.1.1 Protocol and Protocol Amendments
- 16.1.2 Sample Case Report Form
- 16.1.5 Signature of Sponsor's Responsible Medical Officer
- 16.1.9 Documentation of Statistical Methods

16.2 Patient Data Listings

Note: All listings are numbered as 12.2.x.x and are the final versions.

16.3 Case Report Forms

16.4 Individual Patient Data Listings