Supplementary Information

Faecalibacterium prausnitzii *EXL01 for the Maintenance of Steroid-induced Clinical Response or Remission in Patients with Crohn's Disease: a first in human trial*

Perle Guarino-Vignon[1,2], Edouard Louis[3], Hang-Phuong Pham[4], Giovanna Orianne[2,5], Emma Tkacz[1,2], Loic Brot[1,2], Eolia Mazzetti[6], Delphine Sedda[6], Pauline Ruffié[6], Nathalie Rolhion[1,2], Geert D'Haens[7], Benjamin Hadida[6], Philippe Langella[2,5], Harry Sokol[1,2,5]

1. Sorbonne Université, INSERM UMRS-938, Centre de Recherche Saint-Antoine, CRSA, AP-HP, F-75012 Paris, France.
2. Gut, Liver & Microbiome Research (GLIMMER) FHU, F-75012 Paris, France
3. Hepato-Gastroenterology and Digestive Oncology Department, University Hospital CHU of Liège, Liège, Belgium.
4. Parean Biotechnologies, F-35400 Saint-Malo, France
5. Université Paris-Saclay, INRAE, AgroParisTech, Micalis Institute, F-78350 Jouy-en-Josas, France
6. Exeliom Biosciences, F-75012 Paris, France
7. Department of Gastroenterology, Amsterdam University Medical Center, Amsterdam, Netherlands.

Content

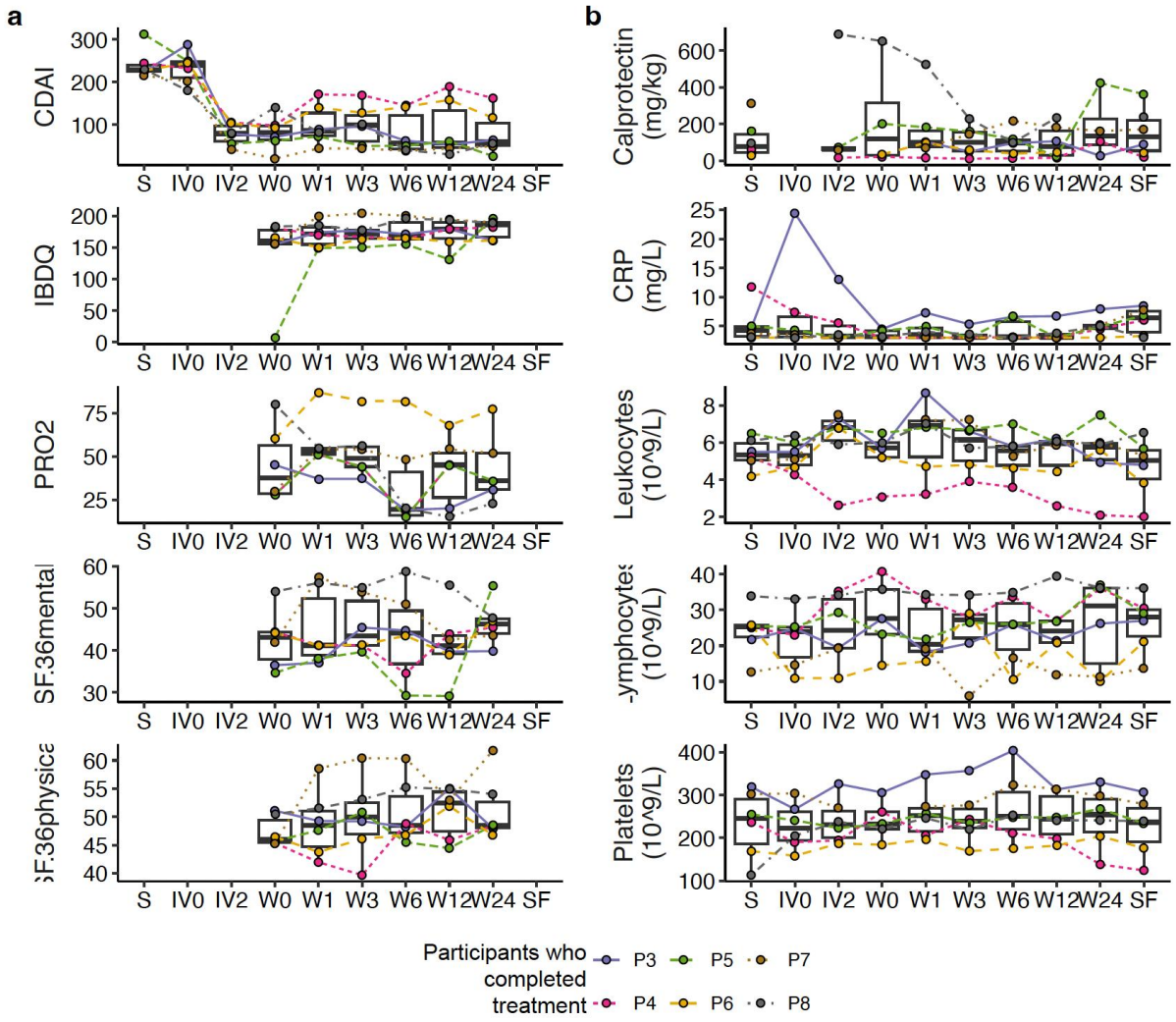
Supplementary Table 1
Supplementary Figure 1-3
Study Protocol
SAP

Supplementary Table

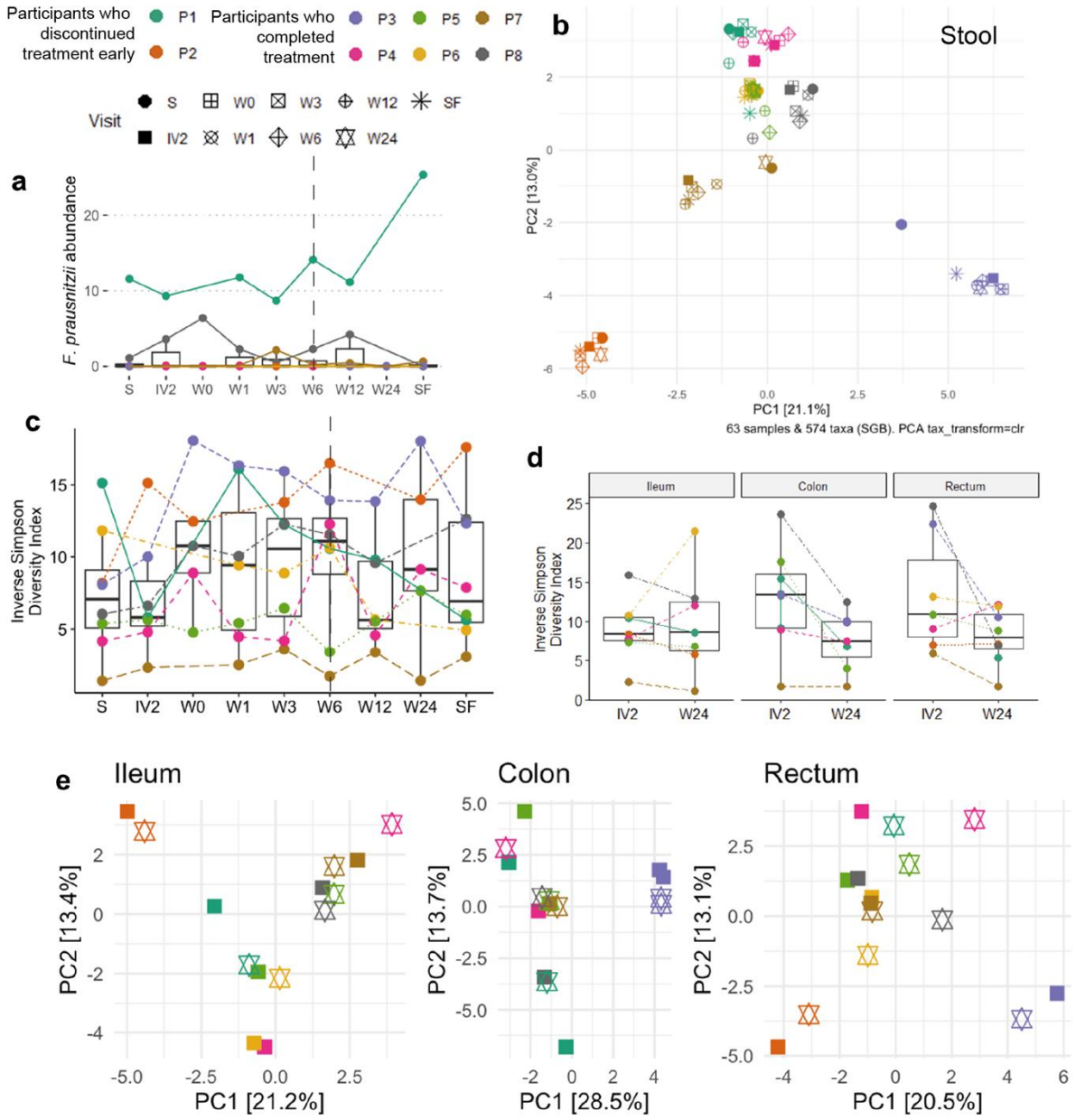
Participant	S	IV2	W0	W1	W3	W6	W12	W24	F	% positive visits (screening and IV2 not included)
P1	-	-	NA	-	-	-	-	NA	-	0% (0/6)
P2	-	-	-	NA	-	+	NA	-	-	20% (1/5)
P3	-	-	-	-	-	-	+	-	+	28,57% (1/5)
P4	-	-	-	+	+	-	-	-	-	28,57% (2/7)
P5	-	-	-	-	-	-	-	-	-	0% (0/7)
P6	-	NA	NA	-	-	-	+	NA	-	20% (1/5)
P7	-	-	NA	-	-	-	+	+	-	33,33% (2/6)
P8	-	-	-	-	-	+	-	NA	-	16,67% (1/6)

Supplementary Table 1: Detection of EXL01 in the feces of the participants

Supplementary Figures

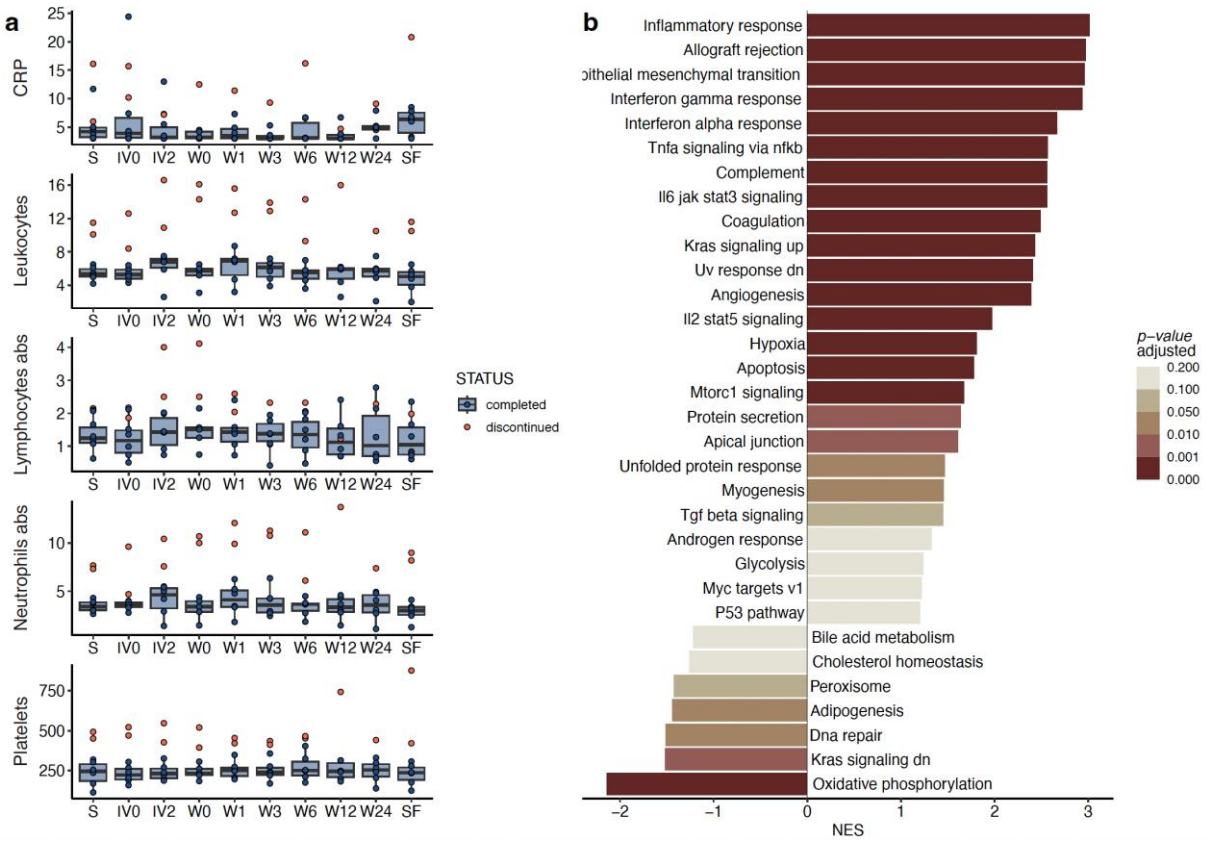


Supplementary Figure 1: Evolution of health scores (a) and biomarkers (b) while taking EXL01 for participants who completed the study (N=6). Boxplots represent the 25%, 50% and 75% quantiles, with upper and lower whiskers showing values within the 1.5 interquartile range. Horizontal segments indicate the mean value for each category. S = Screening, IW = Induction Week, W = Week, SF= Safety Follow-up visit.



Supplementary Figure 2: Stable taxonomical diversity of the stool and intestinal tract microbiome despite detected presence of EXL01 in all participants.

a. *F. prausnitzii* abundance in stool samples. The only Specie Genome Bin (SGB) found across individuals is the SGB15316, while EXL01 belongs to the SGB15332 **b.** Principal Component Analysis (PCA) of the taxonomical (SGB level) diversity of 63 stool microbiomes. **c.** Alpha diversity evolution of stool samples (N=8) calculated using inverse Simpson index. The dashed line indicates the visit participants 1 and 2 were discontinued. **d.** Alpha diversity evolution of biopsy samples (N=8) calculated using inverse Simpson index at the Genus level. **e.** PCA of the taxonomical diversity at Genus-level of the Ileum, colon and rectum microbiome. For b. and e. PCA were calculated using *clr*-transformed relative abundance. S = Screening, IV = Induction Visit, W = Week, SF= Safety Follow-up visit.



Supplementary Figure 3: Relapsing individuals had higher levels of global inflammations at baseline and after corticosteroid treatment a: Levels of markers of the inflammation through the whole study for completed (N=6) and discontinued (N=2) participants. S: Screening, IW: Induction week, W: Week, SF: Safety Follow-up. **b**: Normalized enrichment score (NES) for significantly enriched set of genes (p-val≤0.2 after BH adjustment, HALLMARK database) obtained by the Gene Set Enrichment Analysis (GSEA) comparing the baseline value of discontinued participants to participants who completed the study. Positive NES indicate that the pathways were enriched in discontinued participants compared to the rest, and Negative NEs indicates the opposite. S = Screening, IV = Induction Visit, W = Week, SF= Safety Follow-up visit. Source Data are provided as Supplementary Data 8 for the panel b.

TITLE PAGE

Protocol Title:	A Phase 1 Multicentre, 2-Part, Randomised, Parallel-arm, Placebo-controlled, Partially Double-blind Study to Evaluate the Safety and Target Engagement of EXL01 in the Maintenance of Steroid-induced Clinical Response or Remission in Participants with Mild to Moderate Crohn's Disease
Protocol Number:	EXL01-CD-001
Short Title:	MAINTAIN
Compound:	EXL01
Indication:	Crohn's disease
Study Phase:	1
Regulatory Agency Identifier Numbers:	Eudra Clinical Trial Number: 2021-003432-81 EU Clinical Trial Number: 2022-502241-99 National Clinical Trial Number: NCT05542355
Sponsor:	Exeliom Biosciences, 67 rue des Godrans 21000 Dijon France
Clinical Research Organisation:	Alimentiv Inc., 100 Dundas Street Suite 200 London, Ontario, Canada N6A 5B6
Approval Date (Version):	08-December-2023 (Version 7.1) Previous version(s): 03-August-2023 (Version 7.0) 01-December-2022 (Version 6.0) 31-March-2022 (Version 5.0) 11-February-2022 (Version 4.0) 18-October-2021 (Version 3.0) 05-October-2021 (Version 2.0) 13-July-2021 (Version 1.0)

PROTOCOL APPROVAL PAGE

CLINICAL STUDY PROTOCOL EXL01-CD-001 (MAINTAIN)

A Phase 1 Multicentre, 2-Part, Randomised, Parallel-arm, Placebo-controlled, Partially Double-blind Study to Evaluate the Safety and Target Engagement of EXL01 in the Maintenance of Steroid-induced Clinical Response or Remission in Participants with Mild to Moderate Crohn's Disease.

Protocol Version 7.1: 08-December-2023

PPD [redacted], Date

Chief Executive Officer, Exeliom Biosciences

PPD [redacted] Date

Acting Chief Medical Officer, Exeliom Biosciences

Medical Monitor Contact Information is provided in Section 8.4.2.

INVESTIGATOR AGREEMENT

CLINICAL STUDY PROTOCOL EXL01-CD-001 (MAINTAIN)

A Phase 1 Multicentre, 2-Part, Randomised, Parallel-arm, Placebo-controlled, Partially Double-blind Study to Evaluate the Safety and Target Engagement of EXL01 in the Maintenance of Steroid-induced Clinical Response or Remission in Participants with Mild to Moderate Crohn's Disease.

Protocol Version 7.1: 08-December-2023

I have read the protocol and agree that it contains all necessary details for carrying out this study.

I undertake to conduct this study within the time designated.

I understand that all information concerning the study drug supplied to me by the Sponsor in connection with this study and not previously published is considered confidential information.

The information includes the clinical protocol, the case report form, technical methodology, and basic scientific data provided in the Investigator's Brochure. I agree that documents and other data pertinent to this study are the property of the Sponsor.

Furthermore, I understand that any changes in the protocol must be approved in writing by the Sponsor.

By my signature below, I hereby attest that I have read, understood, and agree to abide by all conditions, instructions, and restrictions contained in the above protocol.

Investigator:

Name and Title	Signature	Date

Name, Address, and Telephone Number of Investigational Site:

PROTOCOL SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Version 7.1	08-December-2023
Version 7.0	03-August-2023
Version 6.0	01-December-2022
Version 5.0	31-March-2022
Version 4.0	11-February-2022
Version 3.0	18-October-2021
Version 2.0	05-October-2021
Original Protocol (Version 1.0)	13-July-2021

Version 7.1 08-December-2023 Summary of Changes:
Overall Rationale for the Amendment: To correct an error in exclusion criterion #11 and to align with the correct wording in the synopsis.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criterion #11	Deletion of "no" from exclusion criterion #11	Correction

TABLE OF CONTENTS

1. Protocol Summary 11
1.1. Synopsis 11
1.2. Schema 15
1.3. Schedule of Activities (SoA) 16
1.3.1. Induction Period 16
1.3.2. Maintenance Period 20
2. Introduction 23
2.1. Study Rationale 23
2.2. Background 23
2.2.1. Disease Background 23
2.2.2. Gut Microbiota 25
2.2.3. Clinical Pharmacology and Toxicology 26
2.2.4. Clinical Experience 27
2.3. Benefit/Risk Assessment 27
3. Objectives and Endpoints 28
4. Study Design 29
4.1. Overall Design 29
4.1.1. Part A 30
4.1.2. Part B 31
4.2. Scientific Rationale for Study Design 31
4.2.1. Rationale for Study Design 31
4.2.2. Rationale for Study Population 32
4.2.3. Rationale for Endpoints 33
4.2.4. Justification for EXL01 Dose Selection, Route of Administration, and Duration of Treatment 34
4.3. Beginning and End of Study Definition 34
4.3.1. Beginning and End of Study Definition 34
4.3.2. Clinical Criteria for Early Study Termination 35
5. Study Population 35
5.1. Inclusion Criteria 35
5.2. Exclusion Criteria 36
5.3. Criteria for Maintenance Period 39
5.4. Lifestyle Considerations 39
5.5. Screen Failures 40
5.5.1. Screen Failure Prior to Induction 40
5.5.2. Failure to Meet Maintenance Period Criteria 40
5.6. Participant Replacement Strategy 40
6. Study Interventions 40
6.1. Study Interventions Administered 41
6.2. Handling, Storage, and Accountability 42
6.3. Measures to Minimise Bias: Randomisation and Blinding 43
6.3.1. Intervention Assignment 43
6.3.2. Blinding and Unblinding Procedure 43
6.4. Study Intervention Compliance 44

6.5. Concomitant Therapies 44
6.5.1. Acceptable Concomitant Medications 45
6.5.2. Prohibited Concomitant Medications 45
6.5.3. Supportive Care and Management of Toxicity 46
6.6. Overdose 46
6.7. Dose Modification or Interruption 47
6.7.1. Corticosteroid Tapering 47
6.7.2. EXL01 and Placebo 47
6.8. Interventions after the End of the Study 48
7. Discontinuation of Study Treatment and Participant Withdrawal From Study 48
7.1. Discontinuation of Study Intervention(s) 48
7.2. Participant Discontinuation/Withdrawal from the Study 49
7.3. Lost to Follow-up 50
8. Study Assessments and Procedures 50
8.1. Administration and General Procedures 50
8.1.1. Informed Consent 51
8.1.2. Screening and Review of Eligibility Criteria 51
8.1.3. Enrolment and Administration of Induction Therapy 51
8.1.4. Administration of Maintenance Therapy 52
8.1.5. Unscheduled Visits 52
8.1.6. Participant Diary 53
8.1.7. Faecal and Blood Sample Collection 53
8.1.8. Calibration of Equipment 53
8.2. Efficacy Assessments 53
8.2.1. Crohn's Disease Activity Index 53
8.2.2. Endoscopy and Biopsy Collection 54
8.2.3. Simple Endoscopic Score for Crohn's Disease 55
8.2.4. Global Histology Activity Score 55
8.2.5. Robarts Histopathology Index 56
8.2.6. Patient-reported Outcomes 57
8.3. Safety Assessments 58
8.3.1. Physical Examinations 58
8.3.2. Vital Signs 59
8.3.3. Electrocardiograms 59
8.3.4. Clinical Safety Laboratory Assessments 59
8.3.5. Pregnancy Testing 60
8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting 60
8.4.1. Method of Detecting AEs and SAEs 60
8.4.2. Procedures for AE and SAE Reporting 60
8.4.3. Regulatory Reporting Requirements for SAE 61
8.4.4. Follow-up of AEs and SAEs 61
8.4.5. Pregnancy 62
8.5. Genetics 63
8.6. Biomarkers 63

8.6.1. Faecal Biomarkers 63
8.6.2. Serum Biomarkers 63
8.6.3. Tissue Biomarkers 63
9. Statistical Considerations 64
9.1. Statistical Hypotheses 64
9.2. Sample Size Determination 64
9.3. Analysis Sets 64
9.4. Statistical Analyses 65
9.4.1. General Considerations 65
9.4.2. Endpoints 66
9.4.3. Time-to-Event Endpoints 66
9.4.4. Safety Endpoints 66
9.4.5. Other Analysis 67
9.5. Interim Analysis 67
10. Supporting Documentation and Operational Considerations 68
10.1. Appendix I: Regulatory, Ethical, and Study Oversight Considerations 68
10.1.1. Regulatory and Ethical Considerations 68
10.1.2. Transparency and Results Disclosure 68
10.1.3. Financial Disclosure 69
10.1.4. Informed Consent Process 69
10.1.5. Data Protection and Confidentiality 69
10.1.6. Independent Data Monitoring Committee 70
10.1.7. Data Quality Assurance 70
10.1.8. Source Documents 71
10.1.9. Study and Site Start and Closure 72
10.1.10. Publication Policy 72
10.2. Appendix II: Contraceptive Guidance and Definitions 74
10.2.1. Women of Childbearing Potential 74
10.2.2. Highly Effective Contraception 75
10.2.3. Contraception and Barrier Requirements for Male Participants 75
10.2.4. Contraception Requirements and Pregnancy Monitoring for WOCBP Participants 76
10.3. Appendix III: Future Biomedical Research Use of Data 77
10.4. Appendix IV: Crohn's Disease Activity Index Sample Worksheet 78
10.5. Appendix V: Clinical Laboratory Tests 79
10.6. Appendix VI: AE and SAE Definitions and Classification 80
10.6.1. Definitions 80
10.6.2. Classification of Adverse Events 82
10.7. Appendix VII: Genetics 85
10.8. Appendix VIII: Protocol Revision History 86
11. References 98

LIST OF FIGURES

Figure 1 MAINTAIN: Two Part (A and B) Study Design 15
Figure 2 MAINTAIN: Part B Study Design 15

LIST OF TABLES

Table 1 Examples of CDAI Eligibility Criteria for Early Phase Clinical Trials 33
Table 2 Overview of Study Interventions to be Administered 42
Table 3 Simple Endoscopic Score for Crohn's Disease 55
Table 4 Global Histologic Disease Activity Score 56
Table 5 Robarts Histopathology Index 57
Table 6 PRO2 Diary Card 58
Table 7 Protocol-Required Safety Laboratory Tests 79
Table 8 Adverse Event Severity Grading 83
Table 9 Adverse Event Causality Assessment 84

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

This list serves as first appearance in text.

ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CFU	colony-forming unit
CGHAS	Colonic Global Histologic Disease Activity Score
CIMS	Central Image Management System
CRF	case report form
CRP	C-reactive protein
CT	computed tomography
DNBS	dinitrobenzene sulfonic acid
ECCO	European Crohn's and Colitis Organisation
ECG	electrocardiogram
ED	early discontinuation
EOT	end of treatment
FMT	faecal microbiota transplant
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GHAS	Global Histologic Disease Activity Score
GI	gastrointestinal
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator Brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IFN	interferon

IGHAS	Ileal Global Histologic Disease Activity Score
IL	interleukin
IRB/IEC	institutional review board / independent ethics committee
IMP	investigational medicinal product
IV	intravenous(ly)
IWRS	interactive web-based response system
JAK	Janus kinase
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NIMP	noninvestigational medicinal product
NOD2	nucleotide-binding oligomerization domain-containing protein
PP	per protocol
PRO2	2-item Patient-Reported Outcome Measure
PTAE	pretreatment adverse event
QoL	quality of life
qPCR	quantitative polymerase chain reaction (assay)
QTL	quality tolerance limits
RHI	Robarts Histopathology Index
SAE	serious adverse event
SAP	Statistical Analysis Plan
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF-36	Short-form Questionnaire (36 items)
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
TCC	total cell count
TEAE	treatment-emergent adverse event
TNBS	trinitrobenzene sulfonic acid
TNF	tumour necrosis factor
UC	ulcerative colitis
ULN	upper limit of normal
WOCBP	woman of childbearing potential

Abbreviations that appear only in figures and tables are defined with the relevant figures and tables.

1. PROTOCOL SUMMARY

1.1. SYNOPSIS

Name of Sponsor/Company:	**Investigational Product:**	**Name of Active Ingredient:**
Exeliom Biosciences	EXL01	EXL01-strain (*Faecalibacterium prausnitzii*)
Protocol Number:	**Date and Version:**	**Study Phase:**
EXL01-CD-001 (MAINTAIN)	Version 7.1: 08-DEC-2023	1

Study Title:

A Phase 1 multicentre, 2-part, randomised, parallel-arm, placebo-controlled, partially double-blind study to evaluate the safety and target engagement of EXL01 in the maintenance of steroid-induced clinical response or remission in participants with mild to moderate Crohn's Disease

Indication:

Maintenance of steroid-induced clinical response/remission in mild to moderate CD

Study Objectives and Endpoints:

In male and female participants aged ≥18 years and <75 years with mild to moderate CD in steroid-induced clinical response or remission:

Objectives	Endpoints
Primary To evaluate the systemic and intestinal safety and tolerability of orally administered EXL01	• AEs • Discontinuing study treatment due to an AE
Secondary To evaluate the proportion of participants in steroid-free clinical remission (CDAI score <150) at Week 24	• CDAI score and use of corticosteroids
To evaluate the proportion of participants in steroid-free clinical remission (CDAI score <150) and mucosal healing (SES-CD <4 with no deep ulcers) at Week 24	• CDAI score • SES-CD • Use of corticosteroids
To evaluate the proportion of participants in steroid-free clinical remission (CDAI score <150) and mucosal healing (SES-CD <4 with no deep ulcers) and normal inflammatory markers (normal CRP and faecal calprotectin <250 mg/kg) at Week 24	• CDAI score • SES-CD score • CRP level • Faecal calprotectin level • Use of corticosteroids
To evaluate the proportion of participants with an endoscopic response (SES-CD score decrease by 50%) at Week 24	• SES-CD score

To compare time to clinical relapse in participants with CD treated with EXL01 to participants treated with placebo (Part B only)	• Time to clinical relapse, defined as the time from first dose of EXL01 or placebo to first documented clinical relapse
To compare the SES-CD and histology of the intestinal mucosa in participants with CD treated with EXL01 to participants treated with placebo (Part B only)	• SES-CD score • GHAS score • RHI score
To compare the evolution of the faecal and mucosa-associated microbiota in participants with CD treated with EXL01 to participants treated with placebo (Part B only)	• 16S sequencing / shotgun metagenomics • *F. prausnitzii* specific qPCR/ddPCR

Study Design:

MAINTAIN is a Phase 1, 2-part, multicentre study to evaluate the safety and preliminary efficacy of the oral administration of EXL01 in the maintenance of corticosteroid-induced clinical response/remission in participants with mild to moderate CD.

This study represents the first oral administration of EXL01 in humans. EXL01 will only be administered to participants who first achieve clinical response or remission following corticosteroid induction therapy.

The study will enrol adult patients with CD and ileal/ileo-colonic involvement diagnosed for at least 3 months, who present with clinically active disease (CDAI score of 180 to 350) and evidence of mucosal inflammation at baseline. To induce remission prior to EXL01 or placebo administration, participants will receive corticosteroids per international guidelines, for at least 3 weeks and a maximum of 7 weeks, until clinical response/remission is observed. Participants not in clinical response/remission within 7 weeks will complete the study without further study treatment. Participants who meet the following criteria after corticosteroid therapy will continue in the study and enter a Maintenance Period:

- Corticosteroid-induced clinical response, defined as CDAI decrease from baseline ≥70, or clinical remission, defined as a CDAI score <150, after a minimum of 3 weeks and maximum of 7 weeks of corticosteroid treatment, and,
- Part B only: A SES-CD score ≥6 (or ≥3 for participants with isolated ileitis), based on a central reading assessment of endoscopy performed upon achievement of clinical response or remission.

The study will be conducted in 2 parts, which differ in the number of participants and procedures for the Maintenance Period:

Part A: This part of the study represents an initial confirmation of safety. In Part A, participants will receive standard of care corticosteroid induction treatment and then participants who meet the Maintenance Period criteria after induction will receive Maintenance Period treatment with open-label oral EXL01 while corticosteroid treatment is progressively tapered over 6 weeks from the start of EXL01 treatment. Part A will be divided into 2 dosing cohorts (A1 and A2). An initial 3 participants will be recruited into Cohort A1 (to target 2 participants with EXL01 exposure). Enrolment into Cohort A2 will only open once data from at least 2 participants, with a minimum of 7 days of EXL01 exposure in Cohort A1 has been collected, reviewed, and determined to show no safety concerns by an Independent Data Monitoring Committee (IDMC). Participants will continue treatment during IDMC review. Cohort A2 will enrol up to 6 participants to target 4 more participants with EXL01 exposure. After 6 weeks of EXL01 treatment in each individual participant, the Investigator will assess safety and tolerability before allowing the participant to continue treatment with EXL01 up to a maximum of 24 weeks or until a study or treatment discontinuation criterion is met. Once a minimum of 6 weeks of EXL01 treatment or follow-up for a target of 6 participants in Part A have been collected, the IDMC will further review the study data.

Part B: A total of 42 participants who meet Maintenance Period criteria will be randomised 2:1 to receive double-blind oral EXL01 or placebo in combination with corticosteroid treatment that is progressively tapered over the first 6 weeks following randomisation. Participants will continue study treatment for up to 24 weeks, or until a

treatment discontinuation criterion is met, whichever comes first. The IDMC will review study data from Part B as outlined in a separate IDMC charter.

Maintenance of corticosteroid-induced remission will be assessed using the CDAI as assessed by the Investigator at Week 24. Endoscopy with mucosal biopsies will be performed at the end of the corticosteroid treatment Induction Period and at the EOT or ED (Week 24 / early termination visit) to determine the SES-CD score. Faecal and blood samples for biomarker assessments will be obtained at Screening, end of the Induction Period, and Weeks 3, 6, 12, and 24. There will also be a remote phone visit at Week 18.

All participants in both Phases will be monitored continuously for safety while on study treatment. AEs will be graded using the NCI-CTCAE Version 5.0.

After the end of EXL01 or placebo study treatment in both Parts A and B, participants will be followed for 30 days for safety monitoring and faecal sampling.

Study Population:

Adult participants with mild to moderate CD are eligible for enrolment. Key inclusion and exclusion criteria are described below. All inclusion and exclusion criteria are provided in Section 5 of the full protocol.

Key Inclusion criteria:

- Has a diagnosis of CD with ileal involvement (ileal only or ileocolonic; L1 or L3 in Montreal classification) for at least 3 months prior to Screening.
- Has a CDAI score >180 and <350.
- Part B only: Has evidence of active mucosal inflammation, meeting at least one of the following criteria:
    - Faecal calprotectin >250 mg/kg performed during routine care of the participant within 4 weeks before Screening and/or at the Screening visit, or
    - Evidence of active ileal inflammation by cross-sectional imaging (CT or MRI) performed during routine care of the participant within 6 months before Screening, or
    - Documentation of ileal inflammation with at least 1 ulceration from an endoscopy performed during routine care of the participant within 12 weeks before Screening.
- Part B only: Has had previous exposure to no more than 3 prior biologic therapies or JAK inhibitors for the treatment of CD including infliximab, ustekinumab, vedolizumab, adalimumab, certolizumab, risankizumab, and upadacitinib.
  Note: For long half-life biologics (eg, IV infliximab, ustekinumab, and IV vedolizumab) there must be at least 6 weeks of washout between the last dose of biologic and start of corticosteroids. If the concentrations of the previous biologic are undetectable, or for biologics with a short half-life (eg, adalimumab, subcutaneous vedolizumab, or subcutaneous infliximab), there must be at least 2 weeks of washout between the last dose of biologic and start of corticosteroids.

Key Exclusion criteria:

- Has stricture with obstructive syndrome <3 months prior to Screening.
- Has stenosis making endoscopic access to the terminal ileum difficult.
- Has received treatment with high dose corticosteroid (≥40 mg prednisone daily) for >5 weeks within 3 months prior to Screening.
- Part B only: Has received more than 3 prior biologic therapies or JAK inhibitors for the treatment of CD
  Note: Prior biologic treatments include infliximab, ustekinumab, vedolizumab, adalimumab, certolizumab, risankizumab, and upadacitinib.
- Has undergone major surgery or significant trauma ≤4 weeks prior to Screening.
- Has had small bowel resection >1 m in total or clinical manifestations of short bowel syndrome.
- Has started or stopped immunosuppressive therapy (thiopurine, methotrexate, tacrolimus, or other classical immunosuppressant) within 3 months prior to Screening.

Number of Participants:

Not all participants will meet the clinical response / remission or endoscopic criteria following corticosteroid induction treatment (30% induction failure assumed), therefore it is expected that approximately 9 participants will

be enrolled in Part A and 58 participants in Part B to achieve the total planned number of evaluable participants for the respective Maintenance Periods, which is a target of 6 participants in Part A and 42 participants in Part B.

Study Interventions:

Induction Period

Induction Period interventions include background standard of care treatment consisting of commercial supply of either oral prednisone 40 mg or budesonide 9 mg once daily for a minimum or 3 weeks and maximum of 7 weeks.

Maintenance Period

Maintenance Period interventions include a corticosteroid tapering regimen over 6 weeks (same product as the Induction Period) combined with either EXL01 or placebo for up to 24 weeks, as follows:

Background Standard of Care	Investigational Medicinal Product
Prednisone: 30 mg for 1 week, 25 mg for 1 week, 20 mg for 1 week, 15 mg for 1 week, 10 mg for 1 week, 5 mg for 1 week and stop OR Budesonide: 6 mg for 3 weeks, 3 mg for 3 weeks, stop Administered orally once daily. In the event of disease flare during tapering, the corticosteroid can be increased to the previous week's level for 1 week before reinitiating the tapering sequence. The dose may only be escalated once, otherwise the participant will be discontinued.	EXL01: Dry matter containing a target dose of 1×10^{10} TCC EXL01 in a size 1 gastro-resistant capsule OR Placebo: Matching gastro-resistant capsule (Part B only) Administered orally once daily on an empty stomach at least 1 hour before or 2 hours after food intake for no more than 24 weeks.

1.2. SCHEMA

Figure 1 MAINTAIN: Two Part (A and B) Study Design

Safety confirmation
n=6, open label EXL01
Duration = 24 weeks
Individual participant safety assessment: Weeks 1, 3, 6, 12, 18, 24

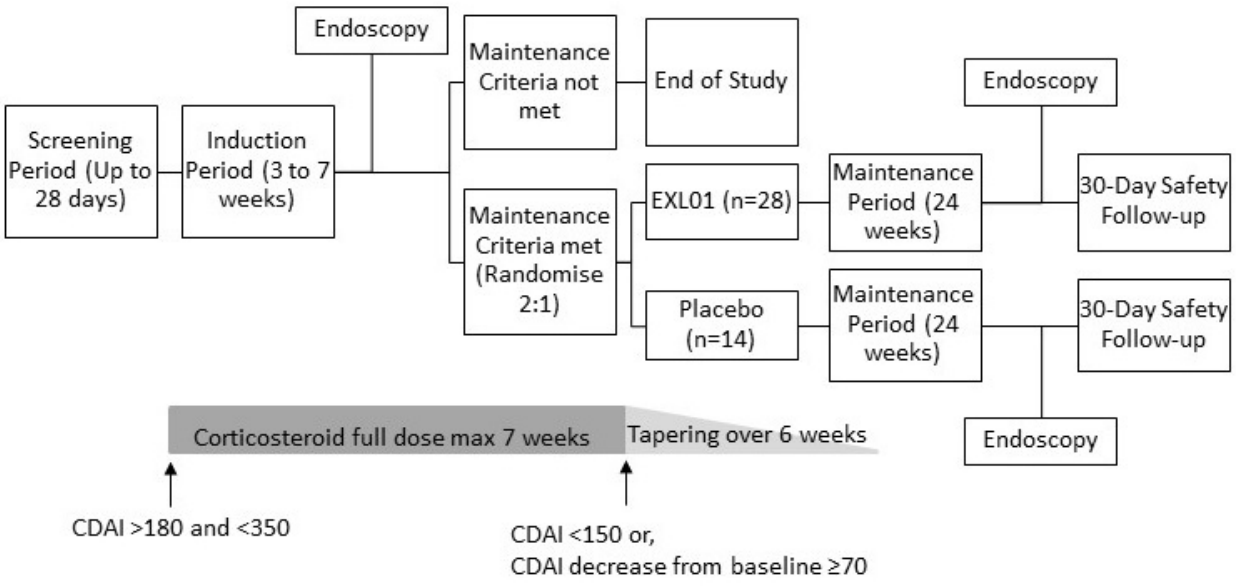
Expanded safety and Go / No-Go efficacy
n= 42, double-blind EXL01 or placebo (2:1 randomisation)
Duration = 24 weeks
Safety assessment: Weeks 1, 3, 6, 12, 18, 24
Efficacy assessment: CDAI, biomarkers, endoscopy

Week 1 data from Cohort A1 reviewed by IDMC before Cohort A2 starts enrolment

Enrollment in Part B to start only after interim analysis of Week 6 data from all participants in Part A is reviewed by IDMC and submission of substantial amendment

Abbreviations: CDAI = Crohn's disease activity index; IDMC = independent data monitoring committee.

Figure 2 MAINTAIN: Part B Study Design



Abbreviations: CDAI = Crohn's disease activity index.

1.3. SCHEDULE OF ACTIVITIES (SOA)

1.3.1. Induction Period

Study Period	**Screening**	**Induction Period**			**End of Study (only for participants that do not meet Maintenance Period criteria)**	**Notes**
Study Visit	**NA**	**1**	**Tcon**	**2**		
Study Week of Induction	**NA**	**0**	**3,4,5,6,7**	**3 to 7**		
Scheduling Window (Days)	**-28 to -1**	**0**	**Q7D (±1)**	**(+7)**		
Administrative Procedures[a]						
Informed consent	X					
Informed consent for future biomedical research (optional)	X					See Appendix III
Inclusion and exclusion criteria	X					
Provide participant identification card	X					
Demographics and medical history	X					Includes substance use: drugs, alcohol
Disease history	X					Disease history to include details of any prior surgeries
Prior medication review	X					Prior medication: review all prior medications for inclusion/exclusion
Concomitant medication review		X	X	X	X	Concomitant medication: Record any ongoing and new medications started within 3 months prior to Screening until the end of study
Dispense/ administration of corticosteroids		X	←	→		To be taken orally as prescribed on outpatient basis
Treatment compliance			X	X		Dose taken, count and compliance (including review of participant diaries) will be calculated and recorded in eCRF
Dispense faecal sampling kits	X*	X				*If participant cannot provide screening faecal sample in the clinic then sample can be collected at home but must be returned to clinic within the screening window

Study Period	**Screening**	**Induction Period**			**End of Study (only for participants that do not meet Maintenance Period criteria)**	**Notes**
Study Visit	**NA**	**1**	**Tcon**	**2**		
Study Week of Induction	**NA**	**0**	**3,4,5,6,7**	**3 to 7**		
Scheduling Window (Days)	**-28 to -1**	**0**	**Q7D (±1)**	**(+7)**		
Dispense/review of participant diaries	X	X	X	X		
Review Maintenance Period criteria				X		To occur after all results from Visit 2 assessment have been reviewed. Only participants that meet Maintenance Period inclusion criteria will continue on to the Maintenance Period
Efficacy Assessments						
CDAI scoring	X†	X‡	X*	X**		† At Screening, patient-reported CDAI items can be based on retrospective recall of participants for preceding week, if no diary data available ‡ At Visit 1, to be based on Screening haematocrit value and participant diary * Review patient-reported CDAI items for potential response / remission at telephone visits ** CDAI to be determined and other eligibility confirmed before endoscopy
Endoscopy				X*		*Scheduling window is +5 days
GI biopsies for qPCR analysis, histology, cytokine, gene expression profiling, and microbiota analysis				X		Tissue samples to be frozen for microbiota analysis (16S, qPCR/ddPCR, shotgun mucosa transcriptomics)
GHAS and RHI scores				X		To be assessed by central reader
SES-CD score				X		To be assessed by central reader
Patient-reported QoL outcomes: SF-36, IBDQ		X		X		To be performed prior to all other assessments in the order listed
Safety Assessments						

Study Period	**Screening**	**Induction Period**			**End of Study (only for participants that do not meet Maintenance Period criteria)**	**Notes**
Study Visit	**NA**	**1**	**Tcon**	**2**		
Study Week of Induction	**NA**	**0**	**3,4,5,6,7**	**3 to 7**		
Scheduling Window (Days)	**-28 to -1**	**0**	**Q7D (±1)**	**(+7)**		
Full physical examination	X				X	To include weight at all scheduled examinations and height at Screening only
Vital signs	X				X	Temperature (oral or tympanic), pulse rate, respiratory rate, and blood pressure; must be measured prior to blood collection
12-lead ECG	X			X		To be read locally
Haematology and biochemistry laboratory assessments	X*	X		X	X	To include liver chemistries, electrolytes, and CRP; see Appendix V *PT/INR to be assessed at screening only
Urinalysis	X	X		X	X	
Faecal parasitology and bacteriology, including *Clostridioides difficile*	X					See Appendix V
Serum pregnancy test (WOCBP only)	X			X		
HIV, Hepatitis B and C screening	X					Documentation of prior negative HIV test within 6 months prior to Screening or negative HBV and HCV test within 4 weeks prior to Screening may be used for eligibility
Pretreatment AE/SAE review		X	X	X	X	
Biomarker Assessments						
Blood for genotyping	X					NOD2 & other major IBD-associated polymorphisms
Serum sample for cytokines		X		X		
Faecal sample for calprotectin and microbiota analysis	X			X		Sample aliquot to be frozen for microbiota analysis (16S, qPCR/ddPCR, shotgun sequencing, and metabolomics)

Study Period	Screening	Induction Period			End of Study (only for participants that do not meet Maintenance Period criteria)	Notes
Study Visit	NA	1	Tcon	2		
Study Week of Induction	NA	0	3,4,5,6,7	3 to 7		
Scheduling Window (Days)	-28 to -1	0	Q7D (±1)	(+7)		

Abbreviations: AE = adverse event; CDAI = Crohn's Disease Activity Index; CRP = C-reactive protein; ddPCR = digital droplet polymerase chain reaction; ECG = electrocardiogram; eCRF = electronic case report form; ED = early discontinuation; EOT = end of treatment; GHAS = Global Histologic Activity Score; GI = gastrointestinal; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IBD = irritable bowel disease; IBDQ = Inflammatory Bowel Disease Questionnaire; NOD2 = Nucleotide-binding oligomerization domain-containing protein 2; PT/INR = prothrombin time/international normalised ratio; Q7D = every 7 days; qPCR = quantitative polymerase chain reaction; QoL = quality of life; RHI = Robarts Histopathology Index; SAE = serious adverse event; SES-CD = Simple Endoscopic Score for Crohn's disease; SF-36 = 36-item Short-Form questionnaire; Tcon = Telephone contact; UNS = unscheduled; WOCBP = women of childbearing potential.

a. In addition to listed procedures, sites must adhere to all local rules and regulations regarding COVID-19, which may include testing for COVID-19. If required, COVID-19 testing will be performed in accordance with local and institutional guidelines and requirements.

1.3.2. Maintenance Period

Study Period	**Maintenance Period**								**30-day Safety Follow-up**	**Notes:** ***Participants who experience disease flare must have a clinic visit within 7 days. Record as UNS visit if outside of a scheduled clinic visit window. If UNS visit is for other reasons, perform only procedures applicable to the reason for visit.**
Study Visit	**3**	**4**	**5**	**6**	**7**	**8 Tcon**	**9**	**UNS***		
Study Week of Maintenance	**0**	**1**	**3**	**6**	**12**	**18**	**24/EOT or ED**	**Any**		
Scheduling Window (Days)	**+5 to +10 from V2**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7 or at ED**	**NA**	**30 days after last dose (±3)**	
Administrative Procedures[a]										
Review Maintenance Period criteria	X									Confirm no change in eligibility status between Visit 2 and Visit 3
Randomisation	X									Only applicable to Part B
Concomitant medication review	X	X	X	X	X	X	X	X	X	Concomitant mediation: Record any changes in medications
Corticosteroid taper	←	—	—	→						To be taken orally as prescribed. Tapering may be 1 week longer if re-escalation is required; refer to Section 6.7.1.
Dispensing of EXL01 or placebo	X		X	X						To be taken orally once daily
Treatment compliance	X	X	X	X	X	X	X	X		Dose taken, count, and compliance (including review of participant diaries) will be calculated and recorded in eCRF on each visit
Dispense faecal sampling kits	X	X	X	X	X		X	X		
Review participant diaries	X	X	X	X	X	X	X	X		

Study Period	**Maintenance Period**								**30-day Safety Follow-up**	**Notes:** ***Participants who experience disease flare must have a clinic visit within 7 days. Record as UNS visit if outside of a scheduled clinic visit window. If UNS visit is for other reasons, perform only procedures applicable to the reason for visit.**
Study Visit	**3**	**4**	**5**	**6**	**7**	**8 Tcon**	**9**	**UNS***		
Study Week of Maintenance	**0**	**1**	**3**	**6**	**12**	**18**	**24/EOT or ED**	**Any**		
Scheduling Window (Days)	**+5 to +10 from V2**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7 or at ED**	**NA**	**30 days after last dose (±3)**	
Efficacy Assessments										
CDAI scoring*	X**	X	X	X	X	X	X	X		*Participants who experience disease flare (CDAI score >70-point increase from baseline of the Maintenance Period for 2 consecutive weeks) must have a clinic visit within 7 days **CDAI score calculation should not include the day of bowel preparation, the day of endoscopy at V2, and the 1 day following endoscopy
Endoscopy							X*			*Scheduling window is ±5 days
GI biopsies for qPCR analysis, histology, cytokine, gene expression profiling, and microbiota analysis							X			Tissue samples to be frozen for microbiota analysis (16S, qPCR/ddPCR, shotgun mucosa transcriptomics)
GHAS and RHI scores							X			To be assessed by a central reader
SES-CD score							X			To be assessed by a central reader
Patient-reported QoL outcomes: SF-36, IBDQ	X	X	X	X	X		X	X		To be performed prior to all other assessments in the order listed
Safety Assessments										
Full physical examination	X	X	X	X	X		X	X	X	To include weight
Vital signs	X	X	X	X	X		X	X	X	Temperature (oral or tympanic), pulse rate, respiratory rate, and blood pressure; must be measured prior to blood collection
12-lead ECG				X*			X			To be read locally; *Part A only

Study Period	**Maintenance Period**								**30-day Safety Follow-up**	**Notes:** ***Participants who experience disease flare must have a clinic visit within 7 days. Record as UNS visit if outside of a scheduled clinic visit window. If UNS visit is for other reasons, perform only procedures applicable to the reason for visit.**
Study Visit	**3**	**4**	**5**	**6**	**7**	**8 Tcon**	**9**	**UNS***		
Study Week of Maintenance	**0**	**1**	**3**	**6**	**12**	**18**	**24/EOT or ED**	**Any**		
Scheduling Window (Days)	**+5 to +10 from V2**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7 or at ED**	**NA**	**30 days after last dose (±3)**	
Haematology and biochemistry laboratory assessments	X	X	X	X	X		X	X	X	To include liver chemistries, electrolytes, and CRP; see Appendix V
Urinalysis		X	X	X	X		X	X	X	
Pregnancy test (WOCBP only)	X		X	X	X		X	X	X	Urine test or serum according to local requirements; more frequent testing (eg, monthly) may be performed as required
AE/SAE review	X	X	X	X	X	X	X	X	X	Record all AEs until 30 days after the last dose of EXL01/placebo
Biomarker Assessments										
Serum sample for cytokines	X	X	X	X	X		X	X		
Faecal sample for calprotectin and microbiota analysis	X	X	X	X	X		X	X	X	Sample aliquot to be frozen for microbiota analysis (16S, qPCR/ddPCR, shotgun sequencing, and metabolomics)

Abbreviations: AE = adverse event; CDAI = Crohn's Disease Activity Index; CRP = C-reactive protein; ddPCR = digital droplet polymerase chain reaction; ECG = electrocardiogram; eCRF = electronic case report form; ED = early discontinuation; EOT = end of treatment; GHAS = Global Histologic Activity Score; GI = gastrointestinal; IBD = irritable bowel disease; IBDQ = Inflammatory Bowel Disease Questionnaire; Q7D = every 7 days; qPCR = quantitative polymerase chain reaction; RHI = Robarts Histopathology Index; SAE = serious adverse event; SES-CD = Simple Endoscopic Score for Crohn's Disease; SF-36 = 36-item Short-Form questionnaire; Tcon = Telephone contact; UNS = unscheduled; WOCBP = women of childbearing potential.

a. In addition to listed procedures, sites must adhere to all local rules and regulations regarding COVID-19, which may include testing for COVID-19. If required, COVID-19 testing will be performed in accordance with local and institutional guidelines and requirements.

2. INTRODUCTION

EXL01 is a live biotherapeutic product, containing an unmodified single-strain of *Faecalibacterium prausnitzii* (herein referred to as EXL01-strain), a commensal bacterium, being developed by Exeliom Biosciences as an oral therapy for CD to prolong the maintenance of remission. EXL01 (finished drug product) is supplied as a gastro-resistant capsule for oral administration and targeted release from the jejunum.

2.1. STUDY RATIONALE

There is no cure for CD. The main aim of treatment is to reduce inflammation – to relieve symptoms by treating flares, put the disease in remission, and maintain remission, as described further in Section 2.2. There is an urgent need to develop new, well-tolerated treatments that maintain remission in patients with CD without the serious side effects associated with some therapies in current use as well as improve QoL and delay surgery. Conventional treatments focus on suppressing the immune response and have not addressed the microbial component. Based on the body of in vitro and in vivo data it is anticipated that delivery of a well-characterised, nonmodified strain of *F. prausnitzii* to the site of inflammation in patients with CD may provide a safe treatment to prolong maintenance of remission. The abundance of *F. prausnitzii* in healthy individuals suggests this approach is safe and may reduce the need for prolonged conventional immunosuppressive therapy. This study will provide safety and preliminary efficacy data for EXL01 in the maintenance of steroid-induced clinical response or remission in participants with mild to moderate CD.

2.2. BACKGROUND

2.2.1. Disease Background

Inflammatory bowel disease results in various degrees of abdominal pain, diarrhoea, and intestinal bleeding. The 2 types of IBD, CD and UC, differ most in the regions of the GI tract where inflammation progresses and the depth of inflammation, and are characterised by an inappropriate and chronic activation of the immune system in the GI tract. IBD is a chronic (ongoing and life-long) condition in which symptoms vary from person to person and range from mild to severe and have a significant impact on QoL. Symptoms change over time, with periods of few or no symptoms (remission) alternating with periods of active symptoms (relapses or ‘flare-ups’). There is no cure for IBD; treatment is directed at reducing inflammation – to relieve symptoms by treating flares, put the disease in remission, and maintain remissions.

Induction of remission

Aside from mild UC, which is usually treated with mesalamine, standard treatment of acute CD flares is administration of systemic corticosteroids, budesonide or prednisone (orally or intravenously), according to disease severity and topography. Once symptoms have subsided, the dose is tapered and finally stopped, other agents are then introduced to maintain remission, as outlined below (1, 2).

If systemic steroid therapy does not induce remission, anti-TNF-α antibodies (infliximab, adalimumab, certolizumab pegol and golimumab), anti-IL-12/23 antibody (ustekinumab), the

anti-integrin antibody, vedolizumab, or JAK inhibitor (tofacitinib for UC only) can be used (1, 2).

Maintenance of remission

ECCO guidelines support the use of thiopurine immunomodulators (azathioprine and mercaptopurine) as effective maintenance therapy for both CD and UC (1, 3). Aminosalicylates can be used for maintenance in UC but are not effective in CD (2). Patients who become steroid-dependent or who have frequent relapses should receive immunosuppressive therapy; the first line of treatment is one of the thiopurine drugs, azathioprine or 6-mercaptopurine. If poorly tolerated, methotrexate is an alternative in CD. If a relapse has been successfully treated with anti-TNF-α antibodies, this treatment can be continued to maintain remission (1, 2, 4).

For each major class of IBD medications (5-aminosalicyclates, immunomodulators, biologic agents and small molecules), used alone or in combination, there is a risk of relapse following reduction or cessation of treatment (3). Treatment costs associated with indefinite maintenance therapy are considerable, and some toxicity of treatment may be due to the prolonged exposure to treatment. On top of the increased risk of serious infection associated with the use of all immunosuppressants, there is also an increased risk of neoplasia (5). Indeed, risks associated with long-term use of thiopurine in patients with IBD include: elevated risk of lymphoproliferative disorders, non-melanoma skin cancers, myeloid disorders, and urinary tract cancers. The use of anti-TNF agents is associated with an increased risk of urinary tract cancers, melanoma and hepatosplenic T-cell lymphoma (3, 5).

Loss of response leads to frequent incomplete control of the disease and a need for frequent changes of therapeutics; intestinal damage accumulates and most patients will ultimately require surgery; 50% of patients with CD undergo surgical treatment (removal of the entire colon and rectum or in others, removal of damaged segments of small bowel) within 10 years of receiving the diagnosis (2). Surgery is however not a cure. Disease typically recurs at the anastomosis or in the segments neighbouring the resected, diseased bowel segment in 10% to 60% of cases. Twenty percent of patients who undergo surgical treatment need surgery again within 5 years (2). Thus, there is a large unmet medical need for new therapies, with fewer side effects, to maintain patients with CD in remission for longer, improve QoL, and delay/avoid the need for invasive surgery.

There is no cure for CD. The main aim of treatment is to reduce inflammation – to relieve symptoms by treating flares putting the disease in remission and maintaining remission. There is an urgent need to develop new well-tolerated treatments that maintain patients with CD in remission without the serious side effects associated with some therapies in current use, improve QoL, and delay surgery. The isolation and manufacturing of a single *F. prausnitzii* strain (EXL01-strain) from a healthy volunteer provides an opportunity to utilise the protective properties of *F. prausnitzii* on gut dysfunction mediated by inflammation. Based on the body of in vitro and in vivo data, it is anticipated that delivery of a well-characterised, nonmodified single strain of *F. prausnitzii* to the site of inflammation in patients with CD may provide a safe treatment to prolong maintenance of remission. The abundance of *F. prausnitzii* in healthy individuals suggests this approach is safe and may reduce the need for prolonged conventional immunosuppressive therapy.

2.2.2. Gut Microbiota

The human gut microbiota is estimated to contain as many as 500 to 1000 different bacterial species, totalling 10^{13} bacterial cells. The gut microbiota concentration increases along the GI tract to reach a maximum in the distal colon (10^{11} bacteria/g of content). It shapes a close relationship with the host in maintaining human health (4, 6). *F. prausnitzii*, a member of the Firmicutes phylum, is the most abundant species in the human intestinal microbiota of healthy adults, represents approximately 5% of the total faecal microbiota in healthy adults (7, 8), which extrapolates to 5×10^{11} bacteria. The abundance and ubiquity of *F. prausnitzii* suggests that it is a major contributor to microbiota functions in healthy individuals and modulation of *F. prausnitzii* populations may be useful for preventive or therapeutic treatments (9).

Alterations or imbalances in the microbial composition in the GI tract have been reported in IBD, notably in CD. Accumulating evidence has revealed a diminished prevalence and abundance of the anti-inflammatory bacterium *F. prausnitzii* in the faecal samples of patients with CD (10); low abundance of *F. prausnitzii* has been associated with higher risk of postoperative endoscopic recurrence (11-13) and higher relapse risk (14, 15). Furthermore, recovery of *F. prausnitzii* counts has been associated with maintenance of remission in patients with UC and CD (15, 16). Based on the lack of specific of blood markers in IBD and the complexity of performing endoscopy/biopsy, the proportion of *F. prausnitzii*, alone or in association with other gut microbiota features, has been proposed as a biomarker of disease activity and predictor of clinical relapse (17, 18). Finally, a high level of *F. prausnitzii* is associated with a better response to treatment (19).

Of note, a high abundance of *F. prausnitzii* has never been associated with any infections or any other diseases in human either in the nonpatient setting or after intervention by FMT for disease.

Anti-inflammatory properties attributed to the *F. prausnitzii* species include (20-22):

- Induction of a tolerogenic cytokine profile on immune cells and particularly antigen presenting cells (dendritic cells, macrophages) and CD4CD8aa+ regulatory T-cells with elevated secretion of the anti-inflammatory cytokine IL-10 and very low secretion of pro-inflammatory cytokines like IL-12 and IFN-γ.
- Butyrate production: Butyrate (a short chain fatty acid) can reduce intestinal mucosa inflammation through inhibiting nuclear factor-κB transcription factor activation, upregulating peroxisome proliferator-activated receptorγ and inhibiting IFN-γ, and promoting Foxp3+ regulatory T-cells.
- Production of the MAM protein which exhibits anti-inflammatory signalling in intestinal epithelial cells.

Furthermore, *F. prausnitzii* cells have been reported to reduce the severity of acute (23-26), chronic (27), and low grade (28) chemically-induced inflammation in murine models.

In murine models of TNBS- and DNBS-induced colitis, intragastric administration of *F. prausnitzii* decreased colitis severity in both severe and moderate chronic colitis models. The lower severity of colitis was associated with down regulation of myeloperoxidase, pro-inflammatory cytokines (IL-12, IL-6, and IFN-γ), and effector T-cell levels (25, 27).

Together, these findings indicate that *F. prausnitzii* has a crucial role in maintaining gut physiology and host well-being. Due to the importance of the microbiota in the development of

IBD, there is increasing interest in the development of microbiota-modulating therapies of which *F. prausnitzii* is an ideal candidate. It is a well-characterised, extremely oxygen sensitive, commensal, anti-inflammatory bacteria that in healthy individuals colonises the area of the GI tract affected by inflammation in CD.

2.2.3. Clinical Pharmacology and Toxicology

EXL01-strain has gone through extensive in vitro and in vivo testing. In vitro studies showed EXL01-strain induced the secretion of the major anti-inflammatory cytokine IL-10 from human PBMCs.

In vivo studies demonstrate that EXL01-strain has anti-inflammatory activities at the macroscopic and histologic levels in acute DNBS-induced colitis in mice and acute TNBS-induced colitis is rats. In addition, models of acute IBS/visceral hypersensitivity, demonstrate administration of EXL01-strain by oral gavage prevents PRS- and NMS-induced visceral hypersensitivity.

In a dose-ranging study in acute TNBS-induced colitis in rats, EXL01-strain demonstrated a strong dose-related anti-inflammatory effect [redacted] at the colonic macroscopic and histologic levels; the percentage improvement ranged from 19% ([redacted]) to 34% ([redacted]) after 11 days of oral administration. Of note, the anti-inflammatory effects of EXL01-strain were higher than those induced by mesalazine (Pentasa®), a benchmark drug used in patients with IBD. Based on results obtained at the colonic macroscopic and histologic levels, the minimum effective dose of EXL01-strain administered daily by oral gavage in rats was [redacted] TCC.

In vitro studies mimicking a) the conditions of PMBC coculture and b) conditions along the rodent GI tract, demonstrate the immunomodulatory properties of EXL01-strain observed in vitro and in vivo are dependent on the presence of morphologically intact bacteria (ie, TCC) and not on cultivable cells (ie, CFU), as enumerated by more traditional plate spread techniques.

The isolation history and taxonomic classification of EXL01-strain, together with a thorough determination of phenotypic and genotypic properties provides reassurance of the safety profile of EXL01. Safety assessments focus on the possible translocation and associated infection potential of EXL01-strain and on its administration in the context of an impaired intestinal barrier or compromised immune system. The risk of emergence and dissemination of antibiotic resistance has been fully evaluated.

In healthy Sprague Dawley rats, EXL01-strain induced no signs of toxicity and no gross findings at necropsy after single oral gavage administration of [redacted] TCC equivalent, approximately equivalent to 150 to 1,000 times the proposed daily clinical dose in humans. A toxicity study of the proposed clinical formulation, using doses of [redacted] TCC (low dose) and [redacted] TCC (high dose) in healthy Beagle dogs is ongoing.

The data from the nonclinical studies support the progression of EXL01 into clinical studies in humans.

Further information on clinical pharmacology and toxicology of EXL01 and EXL01-strain can be found in the IB.

2.2.4. Clinical Experience

The proposed study (MAINTAIN) represents the first oral administration of EXL01 in humans.

There are no reports in the literature of any infections or signs of pathogenicity related to *F. prausnitzii* in healthy individuals, including in immunocompromised patients following FMT, which involves large numbers of mixed bacterial populations.

2.3. BENEFIT/RISK ASSESSMENT

F. prausnitzii is an abundant and ubiquitous member of the normal human gut microbiota. Thus, although the proposed study represents the first oral administration of EXL01-strain to humans, all healthy individuals have substantial exposure to bacteria from the same species in their GI tract. The isolation history and taxonomy, together with a thorough determination of the phenotypic and genotypic properties of EXL01-strain, provides reassurance of the safety profile.

EXL01-strain induced no signs of toxicity in vitro and in vivo tests. In addition, there are no reports in the literature of any infections or signs of pathogenicity related to *F. prausnitzii* in healthy individuals either as a commensal or following FMT as a clinical intervention or in trials.

The proposed oral gastro-resistant formulation will deliver EXL01-strain to the jejunum onwards. Oral administration of EXL01-strain demonstrated anti-inflammatory effects in chemically-induced models of colitis in rodents, suggesting the potential to aid reduction of intestinal inflammation in patients with CD.

Additional safety measures have been incorporated into the proposed study design to provide initial short-term open-label safety data in a small number of participants (n = 6; Part A) before enrolling a larger number (n = 42) into the randomised double-blind, placebo-controlled part of the study (Part B). The Investigator will assess safety and tolerability at each visit before allowing the participant to continue treatment up to a maximum of 24 weeks. Results from Part A of the study will be reviewed by an IDMC and submitted to Regulatory Authorities and Ethics Committee for review and approval as a substantial protocol amendment before Part B is initiated. See Appendix I for more information on protocol amendments. The 2-part design provides reassurance of safety monitoring and provides an initial and meaningful assessment of target engagement (clinical, histological, microbiological, and cytokine biomarkers) while minimising the number of participants exposed.

The overall benefit/risk profile for participants in the proposed study is therefore considered favourable. The observed abundance and ubiquitous nature of *F. prausnitzii* in the GI tract suggest it plays an important role in maintaining human health. The in vivo anti-inflammatory activity of EXL01-strain, along with evidence of diminished quantities in patients with CD, suggests that EXL01 has the potential to provide improvements in duration of remission, symptom control, and QoL in participants with CD, with benefits outweighing the risks.

Participants will be closely monitored to detect AEs during the study and followed appropriately to ensure resolution of AEs. More information on AE reporting is provided in Appendix VI.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of EXL01 may be found in the IB.

3. OBJECTIVES AND ENDPOINTS

In male or female participants aged ≥18 years and <75 years with mild to moderate CD prior to steroid-induced clinical response or remission:

Objectives	Endpoints
Primary To evaluate the systemic and intestinal safety and tolerability of orally administered EXL01	• AEs • Discontinuing study treatment due to an AE
Secondary To evaluate the proportion of participants in steroid-free clinical remission (CDAI score <150) at Week 24	• CDAI score and use of corticosteroids
To evaluate the proportion of participants in steroid-free clinical remission (CDAI score <150) and mucosal healing (SES-CD <4 with no deep ulcers) at Week 24	• CDAI score • SES-CD • Use of corticosteroids
To evaluate the proportion of participants in steroid-free clinical remission (CDAI score <150) and mucosal healing (SES-CD <4 with no deep ulcers) and normal inflammatory markers (normal CRP and faecal calprotectin <250 mg/kg) at Week 24	• CDAI score • SES-CD score • CRP level • Faecal calprotectin level • Use of corticosteroids
To evaluate the proportion of participants with an endoscopic response (SES-CD score decrease by 50%) at Week 24	• SES-CD score
To compare time to clinical relapse in participants with CD treated with EXL01 to participants treated with placebo (Part B only)	• Time to clinical relapse, defined as the time from the first dose of study treatment to first documented clinical relapse
To compare the SES-CD and histology of the intestinal mucosa in participants with CD treated with EXL01 to participants treated with placebo (Part B only)	• SES-CD score • GHAS score • RHI score
To compare the evolution of the faecal- and mucosa-associated microbiota in participants with CD treated with EXL01 to participants treated with placebo (Part B only)	• 16S sequencing / shotgun metagenomics • *F. prausnitzii* specific qPCR/ddPCR
Exploratory To evaluate the health-related quality of life (HRQoL)	• SF-36 score • IBDQ score
To evaluate the mucosa transcriptome in biopsies in participants with CD treated with EXL01 and placebo (Part B only)	• qPCR • RNA Sequencing
To evaluate serum and tissue cytokines at various time points in participants with CD treated with EXL01 and placebo (Part B only)	Serum and tissue cytokine levels including: • TNF-α, IL-10 and sCD14

Objectives	Endpoints
To investigate predictive factors of response to EXL01 (including clinical, biological, endoscopic microbiota, transcriptomic, and genetic)	• CDAI score • SES-CD score • CRP level • Faecal calprotectin level

4. STUDY DESIGN

4.1. OVERALL DESIGN

MAINTAIN is a Phase 1, 2-part study of the oral administration of EXL01 in the maintenance of corticosteroid-induced clinical response/remission in participants with CD. The study will be conducted in 2 parts: Part A will be an open-label evaluation of safety in a small group of participants (n = 6) and, if the results from at least 6 weeks of treatment and follow-up with EXL01 indicate it is safe to initiate the second part, Part B will be a randomised, double-blind, placebo-controlled evaluation conducted in a larger group of participants (n = 42) (Figure 1). To add further assurance of safety, a sentinel approach will be used in Part A for the start of treatment with EXL01, with data reviewed by an IDMC as outlined further in Section 4.1.1 and 10.1.6.

This study represents the first oral administration of EXL01 in humans.

There are no hypotheses being tested. The primary objective is to evaluate the safety of orally administered EXL01 in participants with CD after achieving corticosteroid-induced clinical response/remission. Participants will have mild to moderate CD (defined by CDAI score of >180 to <350) at the start of corticosteroid induction therapy. Secondary and exploratory endpoints are included to provide initial assessments of efficacy and target engagement (clinical, endoscopic, histological, microbiological, and cytokine biomarkers).

Both parts of the study will enrol adult patients with CD and ileal/ileo-colonic involvement diagnosed for at least 3 months, presenting with clinically active disease at baseline. To induce remission, participants will enter an Induction Period and receive a course of corticosteroids until clinical remission (CDAI score <150) or response (CDAI decrease from baseline ≥70) is achieved; corticosteroid therapy will be used for a minimum of 3 weeks and maximum of 7 weeks to assess the induction response. Participants who meet the following criteria after corticosteroid therapy will continue in the study and enter a Maintenance Period:

- Corticosteroid-induced clinical response, defined as CDAI decrease from baseline ≥70, or clinical remission, defined as a CDAI score <150, after a minimum of 3 weeks and maximum of 7 weeks of corticosteroid treatment, and
- Part B only: A SES-CD score ≥6 (or ≥3 for participants with isolated ileitis), based on a central reading assessment of endoscopy performed upon achievement of clinical response or remission.

Participants who do not meet criteria for the Maintenance Period after 7 weeks of corticosteroid induction treatment will complete the study at that time.

Treatment in the Maintenance Period will consist of progressive tapering of corticosteroids according to a standard regimen over 6 weeks in combination with the study treatment (open-label EXL01 in Part A and blinded EXL01 or placebo in Part B) for up to 24 weeks. Participants will not receive EXL01 or placebo during the Induction Period. In the event of new disease flare (defined as a >70-point increase in CDAI from baseline of the Maintenance Period for 2 consecutive weeks), participants will be offered once to re-escalate the corticosteroid dose to the most recent previous dose level for 1 week before restarting tapering. During steroid tapering or re-escalation, the participant will continue to receive EXL01 or placebo. In the event of a second disease flare, or if disease flare/recurrence occurs after corticosteroid tapering has been completed, then the participant will discontinue EXL01 or placebo. Participants that discontinue EXL01 or placebo treatment during the Maintenance Period for any reason, including disease flare, will have an end of treatment visit, move to Safety Follow-up, and be treated according to standard of care.

All participants will be monitored continuously for safety while on the study treatment (EXL01 / placebo). The Medical Monitor will review blinded data at least monthly. AEs will be graded using the NCI-CTCAE Version 5.0. After the end of study treatment (EXL01 / placebo) in both Parts A and B, participants will be followed for 30 days for AE monitoring and faecal sampling.

Details specific to Part A or Part B are described further in the next sections.

4.1.1. Part A

This part of the study is an initial, closely monitored evaluation of safety. Part A will enrol participants with CD who will receive standard of care corticosteroids for induction of remission, until a total of 6 participants meet criteria for the Maintenance Period, as outlined above, and initiate treatment with open-label EXL01. Part A will be divided into 2 dosing cohorts (A1 and A2). An initial 3 participants will be recruited into Cohort A1, to target EXL01 exposure in at least 2 participants. Enrolment into Cohort A2 will only open after the data from at least 2 participants with a minimum of 7 days of EXL01 exposure in Cohort A1 has been collected, reviewed, and show no safety concerns identified by the IDMC. Participants will continue treatment during the IDMC review. Cohort A2 will enrol up to 6 participants, to target 4 more participants with EXL01 exposure. An independent physician (IDMC chair) will review the 7-day exposure data from each participant in Part A and the full IDMC will review data from all participants in Cohort A1 before Cohort A2 is recruited.

After 6 weeks of EXL01 treatment and follow-up in each individual participant, the Investigator will assess safety and tolerability before allowing the participants to continue treatment with EXL01 for up to a maximum of 24 weeks, unless a study or treatment discontinuation criterion is met as outlined in Sections 7.1 and 7.2. Participants will be assessed for safety at the end of Weeks 1, 3, 6, 12, 18, and 24 of maintenance therapy. Efficacy assessments will be performed as outlined for Part B.

A safety interim analysis will be conducted after a minimum of 6 weeks of EXL01 treatment or follow-up data for a target of 6 participants in Part A have been collected. The results of this interim analysis will be reviewed by the IDMC, who may provide recommendations for Part B of the study. The results from Part A, including any potential proposed changes to the protocol based on the results from Part A, will be submitted for approval as a substantial protocol

amendment. Recruitment into Part B will not start until regulatory and ethics approval has been received.

4.1.2. Part B

In Part B, 42 participants who meet Maintenance Period criteria will be randomised 2:1 to receive double-blind treatment with either oral EXL01 or placebo, for up to 24 weeks or until a study discontinuation criterion is met (Figure 2).

In Part B, maintenance of corticosteroid-induced remission will be assessed using the CDAI as assessed by the Investigator at Week 24. Endoscopy and mucosal biopsies will be performed at the end of the Induction Period and at the end of Maintenance Period treatment (Week 24) to determine the SES score. Faecal and blood samples for biomarker assessments will be obtained at Screening, end of the Induction Period, and Weeks 1, 3, 6, 12, and 24. There will be a remote phone visit at Week 18. If participants experience a disease flare or AE at any time between clinic visits, the Investigator will schedule a clinic visit within 7 days for further assessments. If disease flare occurs during the corticosteroid tapering, then participants will be permitted to re-escalate the corticosteroid dose one time, as described further in Section 6.7.1. Participants who experience disease flare after corticosteroid tapering has completed but before Week 24 of the Maintenance Period will discontinue the study treatment (EXL01 or placebo) and undergo end of study procedures.

Data from Part B will be reviewed by the IDMC, as outlined in a separate IDMC charter (see Section 10.1.6).

4.2. SCIENTIFIC RATIONALE FOR STUDY DESIGN

4.2.1. Rationale for Study Design

This is the first study of oral administration of EXL01 and therefore, the study was designed in 2-parts to provide an open-label evaluation of EXL01 in Part A with a small group of participants (n = 6) to ensure safety prior to expanding the size of the study sample in Part B (n = 42). In Part A, the start of each participant's treatment with EXL01 will be staggered based on the natural rate of recruitment of participants with CD across selected study centres and individual variability in timing of response to background corticosteroid treatment. To add further separation between the start of EXL01 treatment among participants in Part A, a sentinel approach will be used, as outlined in Section 4.1.1.

Individual participants will be monitored for safety and treatment discontinuation criteria on an ongoing basis throughout study treatment. An interim safety analysis will be conducted after a minimum of 6 weeks of treatment and follow-up data from a target of 6 participants enrolled in Part A. The results of this interim analysis will be reviewed by the IDMC, who may provide recommendations for Part B of the study. As per the request of a health authority during a scientific advice meeting, the results of the interim safety analysis will be submitted to the Regulatory Authority and IRB/IEC as a substantial amendment. The study would then progress to Part B with a larger, double-blind cohort (n = 42) upon approval of the data by the Regulatory Authority and IRB/IEC. The IDMC will continue to monitor data at regular intervals during Part B.

EXL01 is being developed as a potential maintenance treatment for patients with CD. Therefore, this study design employs a naturalistic approach, in which participants with mild to moderate symptoms first receive a standard of care induction regimen with corticosteroids, until they achieve clinical response or remission based on clearly defined CDAI criteria. Participants who meet criteria for the Maintenance Period will transition to maintenance therapy consisting of open-label EXL01 (in Part A) or blinded EXL01 or placebo (in Part B) in accordance with the disease course of each participant, rather than a predefined schedule. This flexible approach more closely follows the typical continuum of therapy in clinical practice and limits the duration of exposure to corticosteroids where possible. Furthermore, the choice of prednisone or budesonide corticosteroid therapy will be left to Investigator discretion and local prescribing practices to more closely follow real-world clinical practice.

All participants will receive background standard of care active treatment consisting of corticosteroid therapy in the Induction Period with tapering during the Maintenance Period, including participants who are allocated to receive placebo. Part B of the study includes a matched placebo control with blinded and randomised treatment allocation in the Maintenance Period as standard techniques to minimise bias in response evaluations. The use of standard corticosteroid tapering guidelines in combination with the investigational study treatment (EXL01 or placebo) will also limit potential variability between treatment groups.

Participants that do not achieve clinical response or remission within 7 weeks of corticosteroid therapy in the Induction Period, will not be evaluated for therapy with EXL01 and will complete the study at that time. In clinical practice settings, if clinical response or remission is not achieved with corticosteroids within this time frame, alternative therapy is usually indicated, and the participant would not be suitable for EXL01 maintenance therapy. The sample sizes for both parts of the study are based on the evaluable number of subjects that receive EXL01 or placebo, therefore, additional participants may be enrolled in the Induction Period to achieve the stated number of participants who meet Maintenance Period criteria.

4.2.2. Rationale for Study Population

Although Phase 1 studies are typically conducted in healthy volunteers, patients with CD have increased intestinal permeability or mucosal damage leading to a greater risk of commensal bacteria translocation, which could lead to septicaemia (29). Therefore, testing the clinical safety of EXL01 in a healthy study population with a normal intestinal barrier and high abundance of *F. prausnitzii* does not provide a relevant assessment of safety to support further development. This study will assess the safety, and particularly risk of translocation, in a more appropriate target population with impaired intestinal barrier, such as CD. Given the disease under study, nonclinical safety assessments of EXL01 have therefore focused on the possible translocation and associated infection potential of the beneficial intestinal commensal bacterium EXL01-strain in the context of an impaired intestinal barrier or in immunocompromised patients.

EXL01 (or placebo) will be administered as maintenance therapy only to participants who achieve clinical remission or response after corticosteroid induction treatment, however, the study inclusion and exclusion criteria are based on the participant's status at the point of enrolment into the study (ie, prior to the start of corticosteroid induction). CD severity is typically defined based on CDAI score, with scores of 150 to <220 considered mild disease, 220 to <400 moderate disease, and >400 considered severe disease; remission is defined by

consensus guidelines as CDAI <150 (1, 30, 31). In routine clinical practice, corticosteroids are used as induction therapy in patients with a wide range of disease severity, including moderate to severe CD (1). For inclusion into this study, a participant must have CDAI score >180 and <350 prior to starting corticosteroids, which therefore encompasses participants with CD signs and symptoms considered mild to moderate. However, participants with the mildest disease (CDAI between 150 and 180 prior to starting corticosteroids) are not eligible for the study because it reduces the possibility that remission or response criteria for starting EXL01 treatment could be met based on minor clinical variability rather than true clinical response to corticosteroid treatment. The maximum CDAI score has been limited to <350 in order to exclude participants with greater disease severity, who may not have an adequate response with corticosteroid treatment alone and/or who may not be successful in tapering off corticosteroids within the study's tapering guidelines in Section 6.7.1. Participants who enter the Maintenance Period of the study will have a lower CDAI score than defined by inclusion criteria at the time they start EXL01 or placebo because they must be responders (decrease in CDAI score of ≥70) or in remission (CDAI <150). Furthermore, the CDAI criteria in this study for starting corticosteroids and for starting maintenance are in alignment with those for other contemporary early phase clinical trials (Table 1).

Table 1 Examples of CDAI Eligibility Criteria for Early Phase Clinical Trials

Study Identifier	Phase	Design	Sample Size (n)	CDAI Eligibility
NCT04590508	2a	Randomised	32	Active CD not in remission, CDAI >150
NCT03733314	2a	Randomised	40	Moderate to severe CD at start of study drug, CDAI 220 to 450
NCT03992469	2a	Randomised	28	Severe CD excluded, based on CDAI (specific score cut-off not known)
NCT03167437	1	Nonrandomised	35	Active CD, CDAI 220 to 450
NCT04263831	1/2	Single group assignment	30	Moderate to severe CD, CDAI 220 to 450
NCT04713631	2a	Randomised	40	Mild to moderate CD, CDAI 150 to 450
NCT03185000	2a	Randomised	24	Moderate to severe CD, CDAI ≥220

Source: Clinicaltrials.gov

4.2.3. Rationale for Endpoints

This study has incorporated a number of clinical, endoscopic, and histologic assessments to assess disease activity in the study participants, all of which are standard for assessing disease activity in participants with CD in a clinical trial setting. In addition, the study has included biomarker assessments to investigate potential mechanisms of action and provide further information on the effects of EXL01 on disease activity. All clinical and laboratory procedures in this study are standard and generally accepted for the assessment of safety and efficacy of study participants. Central reading of endoscopy and histology in this study will increase consistency and improve the robustness of study results.

4.2.4. Justification for EXL01 Dose Selection, Route of Administration, and Duration of Treatment

EXL01 will be administered orally once daily at a target dose of 1×10^{10} TCC/day for a total duration of up to 24 weeks.

Oral dosing using a gastro-resistant capsule formulation will target delivery of EXL01 from the jejunum and thus have the potential to exert maximal effect along the full length of the GI tract.

In an in vivo dose-ranging study in acute TNBS-induced colitis in rats, intragastric administration of EXL01-strain was well-tolerate at doses of CCI [redacted] TCC/day. The minimum effective dose was [redacted] CC TCC (see IB). Extrapolating these doses to humans, based on surface area of small intestine in humans and in rats, the equivalent effective dose in humans is CCI [redacted] to CCI [redacted] TCC/day or CCI [redacted] to CCI [redacted] TCC/day depending on the extrapolation factor used (32, 33). The EXL01 dose for this study is within the equivalent therapeutic dose range and is therefore clinically relevant for the purposes of an initial evaluation of safety and preliminary efficacy.

Due to the nature of CD and the anticipated effect of EXL01 as a maintenance treatment, no clinically meaningful data on the safety or efficacy (biomarkers and relapse rates) potential of EXL01 would be generated from a study of short duration. In the maintenance setting, a sufficient length of study is required to evaluate any IMP and provide the opportunity for participants to develop clinically relevant events, including the evolution of biomarkers, endoscopic lesions, and clinical recurrence; no short term surrogates are validated. Furthermore, the study duration should be long enough to evaluate monotherapy with EXL01 following the completion of corticosteroid tapering at the start of maintenance; for this reason, the corticosteroid tapering regimen has been selected to achieve the soonest discontinuation of corticosteroids possible, within current guidelines. For these reasons, a study of short duration ie, <6 months is not expected to provide sufficient information about the safety or efficacy of EXL01 to enable subsequent development of this new therapy.

4.3. BEGINNING AND END OF STUDY DEFINITION

4.3.1. Beginning and End of Study Definition

The study begins when the first participant provides documented informed consent. The overall study ends when the last participant in the study globally completes the last study-related procedure shown in the SoA (Section 1.3), withdraws consent, ends participation due to death, or is lost to follow-up.

In the Induction Period, participants can be considered to have completed the study if they do not meet Maintenance Period criteria and have completed the Induction Period, including the End of Study visit (see Section 1.3.1). Participants who are eligible for the Maintenance Period are considered to have completed the study if they have completed the Maintenance Period as shown in the SoA (Section 1.3.2), including the 30-day Safety Follow-up visit. Participants who do not fulfil these requirements for study completion will be considered prematurely discontinued. Criteria for participants to prematurely discontinue study treatment are outlined in Section 7.1.

4.3.2. Clinical Criteria for Early Study Termination

The study may be terminated early at any time if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the benefit/risk ratio to the study population as a whole is no longer acceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems, or if the number of discontinuations for administrative reasons is too high. Participants will be advised of any updates to the benefit/risk profile of EXL01 that lead to stopping enrolment.

Criteria for early study termination will include:

- The incidence or severity of adverse drug reactions in this or other studies suggest a potential health hazard to participants.
- The Sponsor plans to modify or discontinue development of the study drug.

Ample notification will be provided in the event of Sponsor decision to no longer supply EXL01.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. INCLUSION CRITERIA

A participant will be eligible for inclusion in the study only if they meet all of the following criteria at the start of the Induction Period:

1. Is male or female aged ≥18 years and <75 years at the time of providing documented informed consent.
2. Male participants are eligible if they agree to use contraception and barrier methods as outlined in Appendix II for the duration of the study including at least 1 month after the last dose of EXL01 or placebo.
3. Female participants are eligible if they are not pregnant nor breastfeeding, and at least 1 of the following conditions applies:
   - Not a WOCBP, or
   - A WOCBP who agrees to use a contraceptive method that is highly effective (with a failure rate of <1% per year), or be abstinent from heterosexual intercourse as their preferred method and usual lifestyle as described in Appendix II, for the duration of the study including at least 1 month after the last dose of EXL01 or placebo. The Investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study treatment. A WOCBP must have a negative highly sensitive serum pregnancy test at Screening and before the first dose of corticosteroid.

Note: The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk of inclusion of WOCBP with an early undetected pregnancy.

4. Has a diagnosis of CD with ileal involvement (ileal only or ileocolonic; L1 or L3 in Montreal classification) for at least 3 months prior to Screening.
5. Has a CDAI score >180 and <350.
6. Part B only: Has evidence of active mucosal inflammation, meeting at least one of the following criteria:
   - Faecal calprotectin >250 mg/kg performed during routine care of the participant within 4 weeks before Screening and/or at the Screening visit (Note: Retesting within the Screening window is permitted at Investigator's discretion), or
   - Evidence of active ileal inflammation by cross-sectional imaging (CT or MRI) performed during routine care of the participant within 6 months before Screening, or
   - Documentation of ileal inflammation with at least 1 ulceration from an endoscopy performed during routine care of the participant within 12 weeks before Screening.
7. Part B only: Has had previous exposure to no more than 3 biologic therapies or JAK inhibitors for the treatment of CD including infliximab, ustekinumab, vedolizumab, adalimumab, certolizumab, risankizumab, and upadacitinib.
   Note: For long half-life biologics (eg, IV infliximab, ustekinumab, and IV vedolizumab) there must be at least 6 weeks of washout between the last dose of biologic and start of corticosteroids. If the concentrations of the previous biologic are undetectable, or for biologics with a short half-life (eg, adalimumab, subcutaneous vedolizumab, or subcutaneous infliximab), there must be at least 2 weeks of washout between the last dose of biologic and start of corticosteroids.
8. Has provided documented informed consent for the study. The participant may also provide consent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.
9. Is willing and able to adhere to the study requirements and restrictions listed in the ICF and this protocol.

5.2. EXCLUSION CRITERIA

Participants will be excluded from the study if any of the following criteria apply:

1. Has CDAI ≥350 at Screening.
2. Has evidence of an inflammatory abdominal mass.
3. Has a contraindication to endoscopy or anaesthesia.
4. Has stricture with obstructive syndrome <3 months prior to Screening.

5. Has stenosis making endoscopic access to the terminal ileum difficult.
6. Has a history of resistance to corticosteroids.
7. Has known or suspected contraindications to corticosteroid treatment according to the local prescribing information for prednisone or budesonide not listed in other exclusion criteria.
8. Has difficulties in swallowing.
9. Has received treatment with high dose corticosteroid (≥40 mg prednisone daily) for >5 weeks within 3 months prior to Screening.

   Note: The use of physiological doses of corticosteroids for treatment of adrenal insufficiency is permitted.
10. Is likely to require surgical treatment for CD complication within 6 months after Screening, including active perianal fistula or abscess.
11. Part B only: Has received more than 3 prior biologic therapies or JAK inhibitors for the treatment of CD.

    Note: Prior biologic treatments include infliximab, ustekinumab, vedolizumab, adalimumab, certolizumab, risankizumab, and upadacitinib.
12. Has undergone major surgery or significant trauma ≤4 weeks prior to Screening.

    Note: Participants who had surgery >4 weeks prior to Screening must have recovered adequately from any toxicity and/or complications from the surgery or trauma prior to starting study intervention.
13. Has had small bowel resection >1 m in total or clinical manifestations of short bowel syndrome.
14. Has a current stoma (ileostomy or a colostomy) or had a stoma in the last 6 months or any other intraabdominal surgery within 3 months prior to Screening.
15. Has started or stopped immunosuppressive therapy (thiopurine, methotrexate, tacrolimus, or other classical immunosuppressant) within 3 months prior to Screening.

    Note: Participants that started immunosuppressive therapy >3 months prior to Screening must maintain the same dose throughout the study.
16. Has received FMT within 3 months prior to Screening.
17. Is currently participating in or has participated in a study with an investigational compound or device within 3 months prior to the first dose of study intervention.

    Note: Participants who have entered the follow-up phase of an investigational study may participate so long as it has been at least 3 months since the last dose of the previous investigational agent.

18. Has a known history of or newly diagnosed infection with HIV. Documentation of a prior negative HIV test within 6 months prior to Screening may be used in place of a Screening test.
19. Has a known active HBV (defined as HbsAg reactive) or HCV (defined as HCV RNA [qualitative] is detected) infection. Documentation of negative HBV (HbsAg) and HCV (qualitative HCV RNA) tests within 30 days prior to Screening may be used in place of a Screening test.
20. Has a systemic infection or other serious infection requiring systemic treatment within 30 days prior to Screening.
21. Is likely to require antibiotic treatment in the next 6 weeks.
22. Has a known history or newly diagnosed GI parasitic infection within 3 months prior to Screening.

    Note: Participants must have recovered adequately from the toxicity and/or complications from the treatment prior to starting study intervention.
23. Has a history or current evidence of any condition, laboratory abnormality (as outlined in the following table), or other circumstances that might confound the results of the study or interfere with participation for the full duration of the study, such that it is not in the best interests of the participant to take part in the study.

System	Laboratory Value
Haematologic	
Absolute neutrophil count	$<1.0 \times 10^9$/L
Platelet count	$<100 \times 10^9$/L
Haemoglobin	<8.0 g/dL
Hepatic	
Total bilirubin	>1.5 × ULN Note: Patients with Gilbert's Syndrome or other benign congenital hyperbilirubinemia may be eligible at the Investigator's discretion in consultation with the Sponsor
Alanine aminotransferase	>2.0 × ULN
Aspartate aminotransferase	>2.0 × ULN

Abbreviations: ULN = upper limit of normal.

24. Participant is pregnant or breastfeeding or expecting to conceive during the study.
25. Has a history of hypersensitivity to EXL01 and/or any excipients, which are listed in the IB, to corticosteroids as listed in the local prescribing information, and/or to soybean or soy-containing products.
26. Has a known psychiatric disorder that would interfere with proper cooperation with the requirements of the study.
27. Is a regular user of illicit or recreational drugs or has had a recent history (within the last year) of drug or alcohol abuse or dependence.

28. Is currently committed to an institution by virtue of an order issued either by the judicial or administrative authorities.
29. Is a study-site or sponsor employee directly involved with the study or is an immediate family member of or in a dependent relationship with a study-site or sponsor employee directly involved with the study (eg, spouse, parent / legal guardian, child, sibling).

5.3. CRITERIA FOR MAINTENANCE PERIOD

To continue in the Maintenance Period of the study, participants must meet all of the following criteria at the end of the Induction Period (with a review of Maintenance Period eligibility criteria at Visits 2 and 3):

1. Has corticosteroid-induced clinical remission, defined as CDAI score <150, OR response, defined as CDAI score decrease of ≥70 after a minimum of 3 weeks and maximum of 7 weeks of corticosteroid therapy.
2. Part B only: A SES-CD score ≥6 (or ≥3 for participants with isolated ileitis), based on a central reading assessment of endoscopy performed upon achievement of clinical response or remission.
3. Any new health conditions or medications that began during the Induction Period do not meet any exclusion criteria from Screening.

5.4. LIFESTYLE CONSIDERATIONS

Participants should generally maintain their normal diet (eg, starting/stopping a vegetarian or vegan diet is prohibited during the study) and activities, unless modifications are required to manage an AE such as diarrhoea, nausea, or vomiting. Restrictions for this study include the following:

- Consumption of probiotic food and drinks (manufactured products where probiotic bacteria are added artificially) is prohibited during the study.
- Consumption of prebiotic supplements is prohibited during the study.
- Excessive consumption of alcohol is prohibited during the study; moderate consumption, defined as no more than 1 drink per day for women and no more than 2 drinks per day for men, is permitted.
- Smoking and ingestion of caffeine are prohibited on study visit days within 30 minutes prior to the visit.

Compliance with these lifestyle restrictions will be monitored at each visit and a protocol deviation will be recorded if a participant has not adhered to any of the above restrictions.

5.5. SCREEN FAILURES

5.5.1. Screen Failure Prior to Induction

Screen failures are defined as participants who consent to participate in the clinical study but do not meet eligibility criteria to start the Induction Period as outlined in the study protocol.

A minimal set of screen failure information will be recorded to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in the Induction Period (screen failure) may be rescreened. A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date. Please note that repeating of clinical laboratory assessments during Screening does not constitute rescreening and may be performed at the Investigator's discretion.

5.5.2. Failure to Meet Maintenance Period Criteria

Participants are considered enrolled in the study once they start Induction Period treatment with corticosteroids. Participants that fail to meet criteria for the Maintenance Period by Week 7 of the Induction Period will complete the study at that time and receive no further protocol-specified interventions. Participants who are eligible but do not start the Maintenance Period will be considered prematurely discontinued from the study, as outlined in Section 7.2.

If a participant switches from budesonide to prednisone as a result of corticosteroid failure during the Induction Period, then the participant will be permitted to continue in the study for evaluation of response or remission to the second corticosteroid. In these circumstances, baseline disease assessments will be repeated at the time the second corticosteroid is started and a new Induction Period will begin. The duration of corticosteroid therapy will be a minimum of 3 weeks and maximum of 7 weeks for each corticosteroid initiated during the Induction Period. A participant may not switch from prednisone to budesonide.

5.6. PARTICIPANT REPLACEMENT STRATEGY

The sample size of the study is based on the number of evaluable participants who receive any amount of EXL01 (or placebo) treatment as part of the Maintenance Period. Therefore, enrolment into the study will continue until the target number of evaluable participants start the Maintenance Period of the study in each of Part A and Part B.

Participants who discontinue study treatment during the Maintenance Period (ie, during EXL01 or placebo treatment) will not be replaced.

6. STUDY INTERVENTIONS

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies (study intervention(s) provide by the Sponsor) will be packaged to support enrolment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1. STUDY INTERVENTIONS ADMINISTERED

The study interventions to be used are outlined in Table 2.

In the Induction Period, all participants will receive background standard of care corticosteroids consisting of either prednisone or budesonide based on the Investigator's preference and local prescribing practices. In the Maintenance Period, all participants will begin a corticosteroid tapering regimen and, in Part A, will also receive EXL01, or in Part B, will also receive EXL01 or placebo.

Table 2 Overview of Study Interventions to be Administered

Phase / Treatment Group	Induction Period, Part A and Part B (Background Therapy)	Maintenance Period, Part A and Part B EXL01 Group [a]	Maintenance Period, Part B Placebo Group [a]
Intervention Name	Corticosteroids (prednisone or budesonide)	EXL01	Placebo
Intervention Type	Drug	Drug	Drug
Dose Formulation	As available commercially	Gastro-resistant capsule	Matching gastro-resistant capsule
Unit Dose Strength(s)	As available commercially	1×10^{10} TCC	NA
Dosage Level(s)	Prednisone: 40 mg/day Budesonide: 9 mg/day	1×10^{10} TCC/day	NA
Route of Administration	Oral	Oral	Oral
Treatment Regimen	Once daily for ≥3 to ≤7 weeks	Once daily for up to 24 weeks	Once daily for up to 24 weeks
Use	Background intervention (standard of care)	Experimental	Placebo
IMP and NIMP	NIMP	IMP	IMP
Sourcing	Commercially available	Provided centrally by Sponsor	Provided centrally by Sponsor
Packaging and Labelling	As available commercially	Study Intervention will be provided in boxes containing alu-alu foil blister packages. Each box and blister package will be labelled as required per country requirement	Study Intervention will be provided in boxes containing alu-alu foil blister packages. Each box and blister package will be labelled as required per country requirement

Abbreviations: IMP = investigational medicinal product; NA = not applicable; NIMP = non-investigational medicinal product; TCC = total cell count.

a In addition to EXL01 or placebo treatment, a tapering corticosteroid regimen will be employed during the Maintenance Period, as outlined in Section 6.7.1.

6.2. HANDLING, STORAGE, AND ACCOUNTABILITY

The Investigator or designee must confirm temperature conditions, as specified on the investigational medicinal product labelling, have been maintained during transit for all study drug (EXL01 or placebo) received and any discrepancies are reported and resolved before use of the study drug.

Only participants enrolled in the study may be dispensed the study drug (EXL01 or placebo) and only authorised site staff may supply or administer study drug. All study drug must be stored in a

secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorised site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

All unused and partially used study drug will either be returned to the Sponsor, or if authorised, will be disposed of at the study site upon completion of the study and only after inventoried by the Sponsor or designee. All materials containing the study drug will be disposed of in accordance with governing regulations.

6.3. MEASURES TO MINIMISE BIAS: RANDOMISATION AND BLINDING

6.3.1. Intervention Assignment

After informed consent has been documented and eligibility has been confirmed, each participant will be assigned a unique number at each site.

Part A is not randomised and all participants will receive EXL01.

In Part B, there are 2 intervention arms for the Maintenance Period. Participants who are eligible to begin the Maintenance Period will be assigned randomly in a 2:1 ratio to receive either EXL01 or placebo, respectively, in combination with corticosteroid tapering (background intervention). Randomisation will occur centrally using IWRS. Each participant will be randomised to a study intervention group according to the randomisation schedule and will only be dispensed blinded study drug (EXL01 or placebo) labelled in accordance with the randomisation assignment.

The randomisation list will be stored in the secure study database, inaccessible to blinded study team members, for the duration of the study. A participant's study intervention will only be made known if the Investigator deems unblinding necessary, as described in Section 6.3.2.

6.3.2. Blinding and Unblinding Procedure

Part A of the study is open label; the Sponsor, Investigator, and participant will know the interventions administered.

In Part B, a double-blinding technique will be used for the assignment of EXL01 or placebo; background corticosteroid use is open-label. EXL01 and placebo will be prepared and dispensed in a blinded fashion by a pharmacist or other qualified study site personnel. Instructions for dispensing and preparation of EXL01 and placebo will be provided in a separate manual.

The participant, Investigator, site study personnel, and Sponsor or delegate(s) must remain blinded to the participant's treatment assignment until completion of the study. The blind should be broken only if the participant experiences a medical emergency and knowledge of the blinded treatment assignment is deemed necessary for further management of the participant.

If unblinding is deemed necessary for the safety of the participant, before breaking the blind, the Investigator will contact the Medical Monitor to discuss the need for the unblinding. The

Investigator may break the blind independent of the Medical Monitor if the event is considered an emergency by the Investigator and the code break is necessary for the appropriate medical management of the participant. The Investigator must inform the Medical Monitor within 24 hours.

Emergency unblinding can be performed by the Investigator or delegate by contacting the IWRS in consultation with the Medical Monitor, if time allows.

Individual code breaks by the Investigator will result in discontinuation of the participant from the study. The date and reason for the code break must be documented in the source documents and on the appropriate electronic case report form (eCRF). The Sponsor must be informed as soon as possible.

If required for regulatory reporting purposes or if required by local health authorities, the Sponsor may unblind treatment assignment for serious, unexpected, suspected adverse reactions that are considered by the Investigator or Sponsor to be related to study drug (see Section 8.4.2).

6.4. STUDY INTERVENTION COMPLIANCE

Participants will self-administer study interventions(s) at home. Compliance will be assessed through direct questioning of the participants during visits, review of participant diary entries, and counts of returned packages. Compliance will be checked remotely between visits if electronic methods permit and reviewed at each visit and documented in the source documents and CRF. Any deviation(s) from the prescribed dosage regimen, including any deviation in timing of the dose before or after ingestion of food, should be recorded in the source documents and CRF. If participants are found to not be in compliance with the study intervention regimen, participants will be reminded of the instructions on administration of the intervention. In the event of repeated noncompliance, the participant may be removed from the study as described in Section 7.2.

A record of the quantity of EXL01 or placebo dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, and reason will also be recorded in the CRF.

6.5. CONCOMITANT THERAPIES

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the study.

All treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care except for those that are prohibited, as described in Section 6.5.2. The Investigator should review the local approved prescribing information (eg, Summary of Product Characteristics or Package Insert) for the corticosteroid product that has been prescribed for the participant's Induction Period treatment to ensure that there are no known interactions with any concomitant medication.

Any concomitant medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, intravenous medications, and fluids) that the participant is

receiving at the time of enrolment or receives during the study must be recorded along with the following details:

- Name (include the brand name for over-the-counter medicines, vitamins, and herbal supplements)
- Reason for use
- Dates of administration including start and end dates
- Dosage information, including dose and frequency
- Any changes to dose, frequency, or route

All concomitant medication received within 3 months prior to Screening and up to study completion (which includes 30 days after the last dose of EXL01 or placebo for participants that have any Maintenance Period visits) should be recorded. In the event of an SAE, concomitant medications administered after 30 days after the last dose of study treatment (EXL01 or placebo) should be recorded.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Acceptable Concomitant Medications

Permitted concomitant medications include:

- Oral 5-aminosalicylic acid (maximum 4 g), if started before Screening and maintained at the same dose throughout the study.
- Treatment with chronic immunosuppressants (thiopurine, methotrexate, tacrolimus), if started >3 months before the Screening and maintained at the same dose throughout the study.

Acute treatment for underlying autoimmune disorders (eg, reactive airway disease, rheumatoid arthritis, etc.) with corticosteroid doses >10 mg prednisone daily (or equivalent) for ≤1 week is permitted during the study.

The following therapies are to be avoided during the Screening, Induction, and Maintenance Periods of this study; however, they are not prohibited if, in the assessment of the Investigator, they are required for clinical management:

- Nonsteroidal anti-inflammatories
- Antacids
- Proton-pump inhibitors

6.5.2. Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening, Induction, and Maintenance Periods of this study:

- Any concomitant medication prohibited in the local prescribing information for prednisone or budesonide (during the Induction Period and during corticosteroid tapering only)

- Antibiotics (prohibited during Screening and Induction and to be avoided during Maintenance)
- Systemic treatment for CD not specified in this protocol, including: infliximab, vedolizumab, ustekinumab, adalimumab, golimumab, certolizumab, risankizumab, and upadacitinib
- Opioids
- Investigational agents other than EXL01 or placebo
- Probiotics
- Prebiotic supplements
- Bile acid sequestrants

Participants who, in the assessment of the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from study treatment (EXL01 or placebo), and discontinue the study. If a participant requires antibiotics during the Maintenance Period for clinical management, the Investigator should contact the Medical Monitor to discuss whether continued study treatment is appropriate. The start and stop dates and reasons for use of these medications should be recorded.

6.5.3. Supportive Care and Management of Toxicity

Participants who experience an AE will be provided with appropriate supportive care as deemed necessary by the Investigator.

As outlined in Section 6.7.1, corticosteroids may be re-escalated in the event of a disease flare during corticosteroid tapering. However, in the event of a second disease flare, or if additional rescue therapy for worsening CD is required, the participant must discontinue the study treatment (EXL01 or placebo) and be removed from the study. The rescue medication should be recorded in the eCRF.

6.6. OVERDOSE

For this study, deliberate or accidental administration of any dose of EXL01 or placebo greater than the dose assigned to that individual participant will be considered an overdose. Deliberate or accidental administration of background corticosteroid above the maximum recommended dose according to the reference safety information will be considered as an overdose. Participants should be informed to contact their doctor immediately if they have taken an overdose.

In the case of overdose, clinic staff should be notified immediately, and supportive care is to be given as indicated. If any symptom or sign is judged as a severe disease or disorder, treatment should be given under the Investigator's/treating physician's previous experience.

All cases of overdose (with or without associated AEs) will be documented on an overdose page of the eCRF, to capture this important safety information consistently in the database.

Cases of overdose without manifested signs or symptoms are not considered AEs.

Overdoses will not be considered SAEs unless the outcome of the overdose meets seriousness criteria as defined in Appendix VI.

AEs/SAEs associated with an overdose will be documented and reported according to the procedures in Section 8.4.2.

In the event of an overdose, the Investigator/treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAEs and laboratory abnormalities as per institutional standards of care.
3. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

6.7. DOSE MODIFICATION OR INTERRUPTION

6.7.1. Corticosteroid Tapering

Upon completion of the Induction Period and start of the Maintenance Period, corticosteroid treatment will be progressively tapered according to the predefined schedule recommended by ECCO guidelines 2016, namely:

- Prednisone: 30 mg for 1 week, 25 mg for 1 week, 20 mg for 1 week, 15 mg for 1 week, 10 mg for 1 week, 5 mg for 1 week and stop.

Or

- Budesonide: 6 mg for 3 weeks, 3 mg for 3 weeks, and stop.

In the event of a disease flare during tapering, corticosteroids can be increased to the previous week's level for 1 week before reinitiating the tapering sequence. A disease flare is defined as a >70-point increase in CDAI from baseline (ie, start of Maintenance Period and EXL01 or placebo treatment) for 2 consecutive weeks. During escalation of corticosteroids, the study treatment (EXL01 or placebo) will continue.

If a second disease flare occurs, or an initial disease flare occurs after tapering has completed, the participant will discontinue study treatment (EXL01 or placebo), have an Early Discontinuation visit, enter Safety Follow-up, and be treated according to local standard of care.

6.7.2. EXL01 and Placebo

Modifications of the EXL01 or placebo dose are not permitted.

Temporary interruptions in the protocol-specified EXL01/placebo treatment plan for ≥7 continuous days for management of an AE, administrative, or other reasons require consultation between the Investigator and the Sponsor and written documentation of the

collaborative decision on whether the reason for interruption meets criteria for study treatment discontinuation. The date and number of missed dose(s) must be documented.

6.8. INTERVENTIONS AFTER THE END OF THE STUDY

There is no study-specified intervention following the end of the study. Participants will no longer receive EXL01 or placebo upon completion of the study and the Investigator will inform the participant what their options are for future care and medical management of CD.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT WITHDRAWAL FROM STUDY

If a participant is prematurely discontinued from the study or from study intervention (EXL01, placebo, or corticosteroids), the reason must be documented in the source document and recorded in the eCRF. All EOT procedures will be performed at the time of discontinuation. The participant will be instructed to return all remaining study drug/supplies. If a participant is discontinued due to an SAE, the participant will be followed to the resolution or stabilisation of the event, or if discontinued due to pregnancy, the participant will be followed until outcome of the pregnancy.

7.1. DISCONTINUATION OF STUDY INTERVENTION(S)

A participant should be discontinued from study intervention(s) after discussion with the Investigator and/or the Medical Monitor for any of the following circumstances:

- A female participant who desires to become pregnant at the current time, stops contraception, expels her intrauterine device/implant, or becomes pregnant
- Any evidence indicating the participant no longer meets inclusion/exclusion criteria intended primarily for safety reasons, persistent AEs, or an SAE that in the Investigator's and/or Sponsor's opinion compromises the participant's safety or ability to continue study-specific procedures
- At the discretion of the Investigator and/or Sponsor's opinion where discontinuation is deemed to be in the best interest of the participant
- Participant withdrawal of consent (Investigator will attempt to ascertain reason)
- Protocol violation or persistent lack of adherence to study procedures
- Persistent noncompliance with study drug (EXL01 or placebo)
- Unacceptable toxicity
- Any medical condition or clinically significant abnormal finding(s) (physical, laboratory, vital sign, electrocardiogram, etc.) that may jeopardize the participant's safety if study drug is continued, in the Investigator's and/or Sponsor's opinion
- Any anaphylactoid reaction/allergic reaction (hypersensitivity) with moderate or severe intensity requiring intervention, after the first dose of EXL01 or placebo and judged to be related to study treatment by the Investigator
- Septicaemia or sepsis, at any time after the first dose of EXL01 or placebo, that requires systemic antibiotic treatment

    - Note: any signs or symptoms of potential septicaemia after the first dose of EXL01 or placebo should be thoroughly evaluated by the Investigator
- Severe anaemia requiring a blood transfusion at any time after the first dose of EXL01 or placebo
- A hepatic event or liver test abnormality, where considerations for discontinuation include:
    - ALT or AST >5 x ULN for more than 2 weeks, after the first dose of EXL01 or placebo and judged to be related to study treatment by the Investigator (excluding participants with a known history of Gilbert's syndrome)
    - ALT or AST >3 x ULN and either TBL >2 x ULN or INR >1.5, after the first dose of EXL01 or placebo and judged to be related to study treatment by the Investigator
- Disease flare or worsening disease that requires more than 1 corticosteroid dose increase at any time after the first dose of EXL01 or placebo, or requires an intervention prohibited by the protocol.

The Investigator must determine the primary reason for discontinuation of a study intervention and record this information on the CRF.

Regardless of the reason for discontinuation, participants who discontinue treatment with EXL01 or placebo should have Early Discontinuation and Safety Follow-up Visits as per the SoA (Section 1.3.2) (unless consent is withdrawn).

Participants who discontinue during the Induction Period (prior to the start of EXL01 or placebo) should have an End of Study visit (Section 1.3.1).

7.2. PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

It has been well documented that a higher rate of withdrawal from a study can render a study uninterpretable; therefore, unnecessary withdrawal of participants should be avoided.

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, or compliance reasons.

When discontinuation takes place during the Maintenance Period, if possible, an early discontinuation (ED) visit should be conducted at the time of discontinuation, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study intervention and from the study at that time.

Any AEs that are present at the time of study discontinuation should be followed in accordance with the safety requirements outlined in Section 8.4.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3. LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible (and within the visit window, where one is defined) and counsel the participant on the importance of maintaining the protocol-specified visit schedule.
- In cases in which the participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study as of the last scheduled visit.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Section 1.3). Study procedures are to be performed as outlined in the remainder of this section; any alterations from the planned timing, method, or guidance specified below must be recorded in a protocol deviation log.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Protocol waivers or exemptions are not allowed.

Any urgent safety concerns should be discussed with the Sponsor immediately to determine if the participant should continue or discontinue study intervention.

The Investigator is responsible for ensuring that procedures are conducted by appropriately qualified staff (defined by education, training, and experience). Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

All study-related medical decisions must be made by the Investigator who is a qualified physician.

Any laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

8.1. ADMINISTRATION AND GENERAL PROCEDURES

The study consists of a 28-day Screening period, 3- to 7-week Induction Period (during which the participant receives background treatment with corticosteroids), a 24-week Maintenance Period (during which the participant receives treatment with EXL01 or placebo and tapering off corticosteroids), and a 30-day Safety Follow-up period after completion of EXL01 or placebo.

Participants that do not meet the Maintenance Period criteria (see Section 5.3) will complete the study upon completion of the Induction Period.

All sites must adhere to all local rules and regulations regarding COVID-19, as mandated by applicable health and regulatory authorities, that are in effect during the study. If required, testing for COVID-19 will be performed in accordance with local and institutional guidelines and requirements. Furthermore, COVID-19 mitigation strategies may be implemented in accordance with the applicable local, country, and European COVID-19 guidelines and recommendations.

8.1.1. Informed Consent

Screening procedures may not be performed until informed consent is obtained and documented. However, procedures conducted as part of the participant's routine clinical management (eg, blood count or CT/MRI) and obtained before documentation of informed consent may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA or eligibility criteria.

Participants will be asked for a general informed consent for this study and optional consent for the use of their data and/or samples for future biomedical research. Participants may choose to participate in the study without providing consent for future biomedical research. Requirements for informed consent are provided in further detail in Section 10.1.4 and optional consent for future biomedical research in Appendix III.

Informed consent, including consent for future biomedical research, will be documented in the eCRF.

8.1.2. Screening and Review of Eligibility Criteria

All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a Screening log to record details of all participants screened and to confirm eligibility or record reasons for Screening failure, as applicable.

Screening procedures will include the collection of demographic information (age, gender, and race/ethnicity as described by the participant), medical and surgical history, and baseline disease characteristics. Medical and surgical history must be reviewed by the Investigator or suitably medically qualified designate and will include all relevant surgical and medical history including CD-related complications, other significant conditions or diseases relevant to the disease under study, previous surgeries for CD, and the extent and duration of disease at baseline. Medication history will include medications relevant to the eligibility criteria and any others that were stopped ≤3 months prior to providing informed consent, as described further in Section 6.5.

8.1.3. Enrolment and Administration of Induction Therapy

Participants will be considered enrolled in the study when all Screening procedures are completed, and the participant is deemed to meet all inclusion criteria for the study and none of the exclusion criteria. All enrolled participants will be provided with a participant ID card to identify study participation and provide emergency contact information.

Once enrolled, participants will be prescribed a background regimen of commercially available corticosteroids as treatment for CD, according to local prescribing practices and as described further in Section 6.1. Corticosteroid treatment will be continued daily for a minimum of 3 weeks and maximum of 7 weeks during the Induction Period.

Participants will be contacted weekly starting at Week 3 by telephone to monitor for clinical remission or response. When a participant is suspected to meet CDAI criteria for clinical remission or response, participants will have a study visit to confirm clinical remission / response criteria, undergo endoscopy, and perform other assessments as outlined in the SoA for the Induction Period (Section 1.3.1).

Participants that do not meet CDAI clinical remission or response criteria by Week 7 of the Induction Period, or who meet these criteria but do not meet endoscopy or other criteria for the Maintenance Period (refer to Section 5.3) will have an End of Study visit and complete the study.

8.1.4. Administration of Maintenance Therapy

Participants who meet Maintenance Period criteria (refer to Section 5.3) will continue in the study for Maintenance Period therapy, consisting of:

- Part A: open-label EXL01 (refer to Section 6.1) + corticosteroid tapering (refer to Section 6.7.1)
- Part B: blinded EXL01 or placebo (refer to Section 6.1) + corticosteroid tapering (refer to Section 6.7.1)

In Part B of the study, randomisation may not be performed until the participant is deemed to meet criteria for the Maintenance Period. Randomisation procedures are described further in Section 6.3.1.

Study treatments will be administered on an outpatient basis.

Corticosteroid administration should follow the respective labelling and product instructions. EXL01 and placebo capsules should be administered orally, once daily, on an empty stomach at least 1 hour before or 2 hours after food intake. Participants will be instructed to take their dose at the same time each day, as much as possible, and to avoid missing any doses, even if food has been consumed close to the time of administration.

8.1.5. Unscheduled Visits

Participants will be instructed to contact the study coordinator/Investigator when any significant change in health status occurs. The participant will be asked to return for an unscheduled clinic visit if clinically indicated. At unscheduled visits, at minimum, AEs and concomitant medications will be recorded and results of any study-related procedures deemed appropriate to perform by the Investigator will also be recorded. If the unscheduled visit is to assess a disease flare during the Maintenance Period with potential re-escalation of corticosteroids, then all of the procedures identified for an unscheduled visit in the SoA for the Maintenance Period (Section 1.3.2) should be performed.

If it is determined that the participant should be discontinued from the study at the unscheduled visit, then the ED study procedures will be completed and recorded as an ED visit instead. The

participant will be asked to return for a Safety Follow-up clinic visit 4 weeks after the last dose of study treatment (EXL01 or placebo).

8.1.6. Participant Diary

Each participant will be provided with a diary in which to record their CD symptoms, details of their bowel movements, and administration of study treatments (including time of dose and time of food consumption). Participants will complete the diary entries daily, from Screening until the completion of study treatment (EXL01 or placebo). Study personnel will provide instructions for proper completion of the diary and review the diary entries for compliance and completeness at each study visit, or remotely if technology permits. The study plans to use electronic diaries with paper diaries to be available as a back-up in the event of a problem with the electronic diary.

8.1.7. Faecal and Blood Sample Collection

Participants will be given instructions and supplies for home collection of faecal samples as indicated in the SoA. The date and time of each sample collection will be recorded in the participant diary. Faecal samples will be returned to the study centre, processed, and stored until shipment to a central laboratory for analysis.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will be described in the ICF. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1.8. Calibration of Equipment

The Investigator (or qualified designee) is responsible for ensuring that any device or instrument used for a clinical evaluation/test during the study that provides information about eligibility criteria and/or safety or efficacy parameters is suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration per local procedure must be retained for the Trial Master File.

8.2. EFFICACY ASSESSMENTS

The planned time points for all assessments are provided in the SoAs (Section 1.3).

8.2.1. Crohn's Disease Activity Index

The CDAI consists of 8 items including physical examination items, extraintestinal manifestations, the haematocrit, and patient-reported outcome measures (number of liquid or very soft stools/day, abdominal pain and general well-being), recorded in a participant diary card for the 7 days prior to the clinic visit (refer to Section 8.1.6 and Appendix IV) (30). At Screening the PRO measures may be based on participant recall for the preceding week if no diary data is available. At Visit 1, to avoid delays in reconfirming eligibility, the CDAI score will be based on the haematocrit value obtained at Screening. Each item is multiplied by a weighting factor and summed to give a total CDAI score, ranging from 0 to over 600 points, with higher scores representing more severe disease activity. To avoid confounding the data, the CDAI score

calculation will not include any day in which the participant takes bowel preparation, has an endoscopy, and the day following endoscopy.

During the Induction Period, study personnel will monitor patient-reported CDAI component items by telephone on a weekly basis from Week 3 until Week 7 or when remission/response is confirmed by an in-clinic visit. Corticosteroid-induced remission or response based on CDAI scores can only be confirmed by a clinic visit.

8.2.2. Endoscopy and Biopsy Collection

Participants will undergo endoscopy using standard local procedures. Note: the endoscopy procedure at the end of the Induction Period should be scheduled at least 5 days prior to the planned randomisation visit to allow for central reading, and should only be performed if the latest CDAI score has been reviewed and determined to meet the clinical remission criteria as defined in Section 5.3.

The endoscopy procedure will be recorded with a video capture system (Alimentiv CIMS). Detailed instructions for setting up equipment, capturing, and transmitting endoscopic videos will be provided in a study CIMS manual. Video recordings will be timed to include the biopsy procedures. Endoscopy videos and histopathology images will be marked to identify the segment and will be scored by qualified independent, blinded central readers as described for the relevant assessments below.

During the endoscopies, mucosal biopsies will be obtained from the area with the greatest inflammation in each segment. If ulceration is present, biopsies should be taken from the edge of the largest ulcer. If no ulceration is present, biopsies should be taken from the area of greatest inflammation. If mucosa appears normal, then random biopsies of the segment should be obtained.

Biopsy samples will be collected for histopathology, immunohistochemistry, transcriptomics, cytokine, and microbiota analysis, as follows:

- At the end of the Induction Period (Visit 2), 6 biopsies will be collected from selected segments, as follows: rectum, ileum, and the segment with the most severe inflammation of the left, transverse, and right colonic segments (18 biopsies total). In the selected segments, if ulcers are present, biopsies are to be collected from the edge of ulceration. If no ulcers are present, biopsies are to be collected from the area of worst inflammation, and if no inflammation is visible, biopsies are to be collected randomly from within the segment.
- At the end of the Maintenance Period (Visit 9), biopsies will be taken from the same segments from which biopsies were obtained at Visit 2. Biopsies are to be collected as described above for Visit 2.

Refer to Section 8.6.3 for further information about biopsy sample processing, handling, and analysis.

8.2.3. Simple Endoscopic Score for Crohn's Disease

The SES-CD scores 4 endoscopic items (ulcer size, proportion of ulcerated surface, proportion of the surface area affected by any disease lesion, and stenosis), from 0 to 3, with higher scores representing more severe endoscopic disease activity (34). Each item is scored for the 5 intestinal segments (ileum, right colon, transverse colon, left colon, and rectum) and summed to provide the total item score. The SES-CD score is then calculated as the total sum of the item scores (Table 3). Each participant will have a single SES-CD score per time point provided by a central reader based on consensus scoring rules.

Table 3 Simple Endoscopic Score for Crohn's Disease

Variable	SES-CD Values			
	0	**1**	**2**	**3**
Size of ulcers	None	Aphthous ulcers (0.1 < 0.5 cm)	Large ulcers (> 0.5 – 2 cm)	Very large ulcers (> 2.0 cm)
Ulcerated surface (%)	None	< 10%	10-30%	> 30%
Affected surface (%)	Unaffected segment	< 50%	50-75%	> 75%
Presence of narrowing	None	Single, can be passed	Multiple, can be passed	Cannot be passed

	Ileum	Right colon	Transverse colon	Left colon	Rectum	Total
Presence and size of ulcers (0-3)						
Extent of ulcerated surface (0-3)						
Extent of affected surface (0-3)						
Presence and type of narrowings (0-3)						
					Total SES-CD =	

Source: Daperno M et al. Gastrointest Endosc. 2004.

8.2.4. Global Histology Activity Score

The GHAS is comprised of the extent and/or severity of 7 histologic variables. Four variables (epithelial damage, architectural changes, infiltration of mononuclear cells in the lamina propria, and infiltration of polymorphonuclear cells in the lamina propria) are scored from 0 to 2, and 1 variable (polymorphonuclear cells in epithelium) is scored from 0 to 3 (Table 4) (35). The presence of erosions and/or ulcers, and the presence of granuloma are scored 1 if present, or 0 if absent. Finally, an adjustment for the number of affected biopsies is provided by scoring from 0 (none) to 3 (> 66% of biopsies). The total GHAS is calculated by summing the scores for each histological variable (range: 0 to 16), with higher scores representing more severe disease activity. Disease activity is scored separately for colonic (CGHAS) and ileal (IGHAS) biopsies.

Table 4 Global Histologic Disease Activity Score

Histological Variable	Description	Scores Allowed for Histologic Remission
Epithelial damage	0 normal 1 focal pathology 2 extensive pathology	0
Architectural changes	0 normal 1 moderately disturbed (<50%) 2 severely disturbed (>50%)	0-2
Infiltration of mononuclear cells in the lamina propria	0 normal 1 moderate increase* 2 severe increase**	0-2
Infiltration of polymorphonuclear cells in the lamina propria	0 normal 1 moderate increase* 2 severe increase**	0
Polymorphonuclear cells in epithelium	0 absent 1 in surface epithelium 2 cryptitis 3 crypt abscess	0
Presence of erosion and/or ulcers	0 no 1 yes	0
Presence of granuloma	0 no 1 yes	0-1
Number of biopsy specimens affected	0 none 1 < 33% (1 or 2 of 6) 2 33–66% (3 or 4 of 6) 3 > 66% (5 or 6 of 6)	0-3

Note: *Moderate increase, up to twice the number of cells that can normally be expected; ** Severe increase, more than twice the normal number of cells.
Source: D'Haens GR et al. Gastroenterology. 1998.

GHAS will be assessed by a central reader from biopsy samples collected during the scheduled endoscopies.

8.2.5. Robarts Histopathology Index

The RHI was developed by selecting items from the Geboes score that showed at least moderate intrarater reliability and best predicted scores on a visual analogue scale (36). The RHI was initially developed in patients with UC but also demonstrated treatment differences from placebo in clinical trials of patients with CD (37). The 4 items selected for inclusion include: 1) the extent of chronic inflammatory cell infiltration, 2) neutrophils in the lamina propria, 3) neutrophils in the epithelium, and 4) erosions and ulceration (Table 5). Each item is scored from 0 to 3 and multiplied by a weighting factor and summed to give the overall RHI score, with total scores ranging from 0 (no disease activity) to 33 (severe disease activity).

Table 5 Robarts Histopathology Index

Histological Variable	Grading	Multiplication Factor
Chronic inflammatory infiltrate	0=No increase 1=Mild but unequivocal increase 2=Moderate increase 3=Marked increase	X1
Lamina propria neutrophils	0=None 1=Mild but unequivocal increase 2=Moderate increase 3=Marked increase	X2
Neutrophils in epithelium	0=None 1= < 5% crypts involved 2= < 50% crypts involved 3= > 50% crypts involved	X3
Erosion or ulceration	0=No erosion, ulceration, or granulation tissue 1=Recovering epithelium + adjacent inflammation 1=Probably erosion-focally stripped 2=Unequivocal erosion 3=Ulcer or granulation tissue	X5

Source: Mosli MH et al. Gut. 2017.

RHI scores will be determined by a central reader from biopsy samples collected during the scheduled endoscopies.

8.2.6. Patient-reported Outcomes

SF-36 and IBDQ assessments should be completed at the scheduled times as per the SoA (Section 1.3). The SF-36 and IBDQ will be administered by trained site personnel and completed electronically by the participant in the following order: SF-36 then IBDQ. PRO2 scores will be calculated based on the daily recording of CDAI component items in the participant diary (see Section 8.2.6.1).

It is best practice and strongly recommended that ePROs are administered before AE evaluation and disease status notification.

8.2.6.1. 2-item Patient-reported Outcome Measure

The PRO2 consists of the 2 CDAI component items (see Section 8.2.1): daily stool frequency and abdominal pain (38). For 7 consecutive days, participants record the number of liquid or very soft stools and a rating for abdominal pain (from 0-3) (Table 6). Diary entries are to be completed over the 7 days before a clinic site visit.

Table 6 PRO2 Diary Card

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Number of liquid or very soft stools per day							
Daily abdominal pain rating (0 = none, 1 = mild, 2 = moderate, 3 = severe)							

Source: Khanna, et al. Aliment Pharmacol Ther. 2015.

8.2.6.2. Short-Form Survey (36-Item)

The 36-item short-form survey (SF-36) is a widely used generic health-related quality of life questionnaire consisting of 35 items across 8 health domains (general health, physical functioning, role limitations due to physical problems, role limitations due to emotional problems, bodily pain, vitality, social functioning, and mental health), and an additional item assessing change in health status over the past year (39, 40). Each domain item score is coded, summed, and transformed onto a scale from 0 (worst possible health state) to 100 (best possible health state). The 8 domain scores can be presented as raw scores or calibrated so that the mean = 50 and standard deviation = 10 (norm-based scoring). The domain scores are summarised by 2 component scores – the physical component summary and mental component summary scores, which are also scaled from 0 to 100, but can also be presented as norm-based scores. Version 2.0 of the SF-36 will be used in this study, which incorporates improvements in wording, layout, and response level choices for some questions with improvements in scoring precision (41).

8.2.6.3. Inflammatory Bowel Disease Questionnaire

The IBDQ is a disease-specific QoL instrument for patients with IBD (42). The IBDQ covers 4 dimensions: bowel symptoms (10 items), systemic symptoms (5 items), emotional function (12 items), and social function (5 items). Items are scored on a 7-point Likert scale, for a total global score in the range 32 to 224 (with higher scores indicating better QoL). The IBDQ has been designed to be self-administered and completed in 5 minutes.

8.3. SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA (Section 1.3). Additional visits may be conducted as necessary for any abnormal findings that require medical follow-up.

8.3.1. Physical Examinations

A complete physical examination including height and weight, will be conducted by the Investigator of medically qualified designee as per institutional standards. Height will be recorded at Screening only.

A full physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems.

Clinically significant abnormal findings at Screening should be recorded as medical history. After the first dose of study intervention (start of the Induction Period), new clinically significant abnormal findings should be recorded as pretreatment AEs (during the Induction Period) or AEs (during the Maintenance Period, after start of EXL01 or placebo).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2. Vital Signs

The Investigator or qualified designee will take vital signs as specified in the SoA. Vital signs will consist of body temperature (oral or tympanic), pulse rate, respiratory rate, and blood pressure assessments and will be assessed before blood collection for laboratory tests, in the sitting position with a completely automated device; manual techniques will be used only if an automated device is not available. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones). Smoking and caffeine are prohibited within 30 minutes prior to the measure of blood pressure.

8.3.3. Electrocardiograms

A single 12-lead ECG will be using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT intervals. ECG results will be reviewed and interpreted locally. Clinically significant abnormal findings at Screening should be recorded as medical history and clinically significant abnormal findings of any subsequent ECGs should be recorded as PTAEs or AEs.

8.3.4. Clinical Safety Laboratory Assessments

See Appendix V for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE in the CRF. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

All protocol-required laboratory tests must be conducted in accordance with the laboratory manual.

If laboratory values from tests performed during routine care of the participant (ie, tests not specified by the protocol) require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.3.5. Pregnancy Testing

Pregnancy tests will be performed on WOCBP as defined in Appendix II. A negative serum pregnancy test at Screening, as outlined in Section 5.1, is required to participate in the study.

Pregnancy testing (urine or serum as required by local regulations) will be conducted as scheduled in the SoA (Section 1.3) and corresponds with the time frame for female participant contraception as defined in Appendix II. In the event of a positive pregnancy test during the study, the participant must discontinue the study intervention(s) and undergo end of study procedures as outlined in the SoAs; refer to Section 8.4.5 for instructions to report pregnancy. If a urine pregnancy test result is ambiguous, then a serum pregnancy test must be performed.

Additional serum or urine pregnancy test may be performed, as deemed necessary by the Investigator or required locally, to establish the absence of pregnancy at any time during the study.

8.4. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

8.4.1. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.2. Procedures for AE and SAE Reporting

The Investigator and any medically qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue study treatment or the study. Definitions and classification of AEs and SAEs are provided in Appendix VI.

All AEs and SAEs experienced by the participant from the time of documented informed consent till the Safety Follow-up visit (ie, 30 days after the last dose of study intervention) will be reported. All AEs and SAEs must be recorded in the eCRF. For both serious and nonserious AEs, the Investigator must determine both the severity of the event and the relationship of the event to study drug administration.

Medical occurrences that begin before the start of study interventions (including corticosteroids in the Induction Period) but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section. Medical occurrences that begin before the start of study treatment (EXL01 or placebo) but after starting the Induction Period corticosteroid treatment will be recorded as a PTAE in the CRF.

The Investigator (or designee) is required to complete an SAE form and report it to Alimentiv Safety immediately (without undue delay and no later than within 24 hours) after becoming aware of the event, using the electronic data capture (EDC) system. In the event EDC transmission is not possible, (eg, there are access or system problems), then the Investigator (or

designee) must report the event by faxing or emailing a completed paper SAE form immediately (without undue delay), but no later than 24 hours of awareness of event to:

Clinical Safety Specialist

Alimentiv Inc.

Fax: PPD [redacted]

Email: PPD [redacted]

The initial SAE report should include at a minimum: participant number, a narrative description of the event, and an assessment by the Investigator of the intensity of the event and relationship of the event to study drug. The initial SAE report received from the site should be as complete as possible. A complete follow-up SAE report must be submitted when the information, not available at the time of the initial report, becomes available. The Sponsor (or designee) may request SAE follow-up information.

Investigators are not obliged to actively seek AEs or SAEs after the conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor or designee.

The follow-up period for AEs and SAEs is outlined in Section 8.4.4.

8.4.3. Regulatory Reporting Requirements for SAE

If there are serious, unexpected ADRs (for Europe SUSAR) associated with the use of the study drug during the Maintenance Period, the appropriate regulatory agency(ies) and all participating investigators will be notified on an expedited basis in accordance with local regulatory guidance and requirements.

It is the responsibility of the Investigator to promptly notify the IRB/IEC of all SAE that occur at his or her site.

Investigators will be notified of all SUSARs (7/15 Day Safety Reports) that occur during any clinical studies that are using the investigative compound. Each site is responsible for notifying their IRB/IEC/Central Ethics Committee of these additional SUSARs in accordance with local regulations.

The study centres shall be responsible for reporting any AE/SAE considered to be causally related to corticosteroids directly to the local pharmacovigilance department of the manufacturer.

8.4.4. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs and other reportable safety events, including pregnancy and overdose should be followed until judged to be resolved or stabilised, the participant is lost to follow-up, or until the AE is clearly determined to not be caused by study treatment.

Participants that experience a serious PTAE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline, or there is a satisfactory explanation for the change. Nonserious PTAEs, whether related or unrelated to the study, do not need to be followed for the purposes of the protocol data collection.

8.4.5. Pregnancy

Pregnancy in a study participant, or in the female partner of a male participant, occurring after start of study intervention (after Induction Period) and until the end of the Safety Follow-up period, is considered immediately reportable and must be reported to Alimentiv within 1 working day of awareness.

Pregnancy reports will be submitted by Investigator/clinical site by completing the Pregnancy Form (FRM-035), via fax or email, to Alimentiv Clinical Safety:

Clinical Safety Specialist

Alimentiv Inc.

Fax: PPD

Email: PPD

Female participants who become pregnant will discontinue study drug (EXL01 or placebo). A determination regarding study drug discontinuation will be made for male participants with a partner pregnancy.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Hospitalization for normal delivery of a healthy newborn should not be considered a SAE.

The Investigator (or designee) must follow-up and document the course and outcome of all pregnancies even if the participant was discontinued from the study or the study has ended. Details of the outcome of the pregnancy (eg, full-term delivery, stillbirth, congenital anomaly, miscarriage) will be collected and reported within 30 days of awareness.

Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as per Section 8.4.2.

Elective abortions without complications should not be handled as AEs unless they were therapeutic abortions. The medical reason (example mental health or foetal disease) for an elective termination of pregnancy will be reported as an AE or SAE. Prenatal testing showing foetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE.

Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported as described in Section 8.4.2. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

8.5. GENETICS

A blood sample for DNA isolation and genotyping of major IBD-associated polymorphisms, including NOD2, will be collected from participants during Screening. The genotype assessment will support exploratory analyses of the study in examining potential factors that may be predictive of treatment response.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix VII for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples will be provided in the laboratory manual.

8.6. BIOMARKERS

8.6.1. Faecal Biomarkers

Participants will be provided with home sample kits for faecal collection as described in Section 8.1.7. These samples will be analysed by a central laboratory to evaluate faecal calprotectin levels and microbiota analysis according to the schedule outlined in the SoA (Section 1.3). Instructions for processing, storage, and shipment of samples will be provided in the laboratory manual.

8.6.2. Serum Biomarkers

Serum samples for the assessment of serum cytokines will be collected according to the schedule outlined in the SoA (Section 1.3). Instructions for processing, storage, and shipment of samples will be provided in the laboratory manual.

8.6.3. Tissue Biomarkers

Instructions for obtaining mucosal biopsy during the endoscopy procedure are provided in Section 8.2.2. Biopsy samples will be handled as follows after each endoscopy procedure:

1. 2 biopsies will be fixed in formalin and stored in ethanol for histopathological and immunohistochemical analyses.
2. 1 biopsy will be snap frozen for multiplex cytokine analysis.
3. 1 biopsy will be stored in a cryovial with RNA stabilisation buffer for RNA analysis.
4. 2 biopsies will be snap frozen for microbiota analysis.

Samples will be processed at the study site, and then shipped to the central laboratory. Sample processing, handling, and shipping information will be defined in the central laboratory manual and biopsy instruction card.

Further details for tissue biomarker and microbiota analyses will be provided in a separate Translational Medicine Plan.

9. STATISTICAL CONSIDERATIONS

9.1. STATISTICAL HYPOTHESES

This is a hypothesis-generating study and only descriptive analyses are planned. No formal statistical tests are planned.

9.2. SAMPLE SIZE DETERMINATION

Part A of the study plans for a target of 6 participants to receive maintenance treatment with EXL01 and Part B of the study plans for a target of 42 participants to receive maintenance treatment with EXL01 or placebo. This number of evaluable participants is based on clinical and scientific judgement to meet the objectives of the study. As this is a Phase 1, proof-of-concept study, a formal sample size calculation was not performed.

Not all participants will meet the clinical response / remission or endoscopic criteria following corticosteroid induction treatment (30% induction failure assumed), therefore it is expected that approximately 9 participants will be enrolled in Part A and 58 participants in Part B to achieve the total planned number of evaluable participants for the respective Maintenance Periods, which is 6 participants in Part A and 42 participants in Part B.

9.3. ANALYSIS SETS

All participants who provide documented informed consent for study participation, including Screening failures, will be accounted for and tabulated in the participant disposition. No statistical analysis will be based on all enrolled patients.

Participants from both Parts A and B will count towards the analysis sets. For purposes of analysis, the following analysis sets are defined in accordance with ICH E9:

Participant analysis set	**Description**
Induction Safety (iSAF)	All screened participants who receive at least 1 dose of corticosteroids as part of the Induction Period.
Maintenance Safety (mSAF)	All enrolled or randomised participants who received at least 1 dose of EXL01 or placebo. Regardless of treatment administration error, these participants will be analysed according to the intervention they actually received.
Modified Intent to Treat (mITT)	All enrolled or randomised participants who received at least 1 dose of EXL01 or placebo. Regardless of treatment administration error, these participants will be analysed according to the intervention they were intended to receive.

Participant analysis set	Description
Per Protocol (PP)	All mITT participants who do not have any major deviations from protocol and complete all Week 24/EOT assessments. Major protocol deviations will be defined in the SAP
Maintenance 6-week Completer	All participants who complete up to 6 weeks of treatment or follow up in the Maintenance Period and receive at least 1 dose of EXL01 in Part A.
Maintenance Long-term	All participants that have data available beyond Week 6 in the Maintenance Period.

9.4. STATISTICAL ANALYSES

The SAP will be finalized prior to the completion of Part A. Amendments to the analysis plan that apply to Part B (if applicable) will be finalized prior to final unblinding at the end of Part B. The plan will include a more technical and detailed description of the statistical analyses listed in this section. This section is a summary of the planned statistical analyses of the most important endpoints. Treatment allocation of participants in the blinded, randomised portion of the study will be held exclusively by unblinded team members and only released when final database lock has been established.

9.4.1. General Considerations

All available efficacy and safety data collected for the study will be included in data listings and/or summary tables. No imputation of missing efficacy or safety data will be performed. If a baseline value is missing, no change from baseline will be calculated. All study data will undergo several data quality checks prior to database lock as outlined in Section 10.1.7. However, if a spurious value(s) deemed of sufficient importance to the safety or efficacy conclusions is discovered after database lock and the correct value(s) can be ascertained, the database will be unlocked, and the spurious value(s) corrected. If the correct value(s) cannot be ascertained or is deemed inconsequential to the safety or efficacy conclusions, the value(s) will be excluded, and an explanation of the action taken with a justification for the action documented in the clinical study report.

In general, continuous variables, including baseline characteristics, will be summarised by reporting the number of observations, mean, standard deviation, median, minimum, and maximum. Continuous variables with baseline values will be reported both as observed and with changes from baseline. Categorical/discrete variables will be summarised using frequency distributions showing the number and percentage of participants within a category. Time-to-event data will be summarised using the Kaplan-Meier method, as appropriate.

Where applicable, 2 baselines will be defined for this study. Induction baseline will be the measurement taken at or closest to Screening, but prior to the start of induction treatment. Maintenance baseline will be the measurement taken at or closest to study Visit 3, but prior to

the start of maintenance treatment. “Steroid-free” will be defined as no use of corticosteroids on the day of evaluation.

Safety endpoints will be evaluated by pooling participants in Parts A and B; however, efficacy endpoints will be analysed separately. The Induction and Maintenance Periods will be analysed separately.

9.4.2. Endpoints

Efficacy, QoL, and biomarker objectives and endpoints are stated in Section 3. These variables will be summarised descriptively using the mITT population by treatment group (for Part B). All efficacy variables will be summarised descriptively by time point with appropriate statistics for categorical or continuous variables, as applicable.

PP analyses will be performed on secondary efficacy endpoints as described in the SAP.

9.4.3. Time-to-Event Endpoints

Time to clinical relapse (disease flare), defined as the time from the first dose of study treatment to first documented clinical relapse, will be analysed with Kaplan-Meier methods using the mITT population.

9.4.4. Safety Endpoints

All safety analyses will be performed using the applicable Safety Population (iSAF or mSAF).

Safety variables, as stated in Section 3, will be summarised descriptively by treatment group with appropriate statistics.

All AEs will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA) current version dictionary. TEAEs will be presented by System Organ Class, Preferred Term unless stated otherwise. The frequencies of TEAEs will be presented including number and percentages of participants having experienced an event and the total number of events.

AEs including SAEs are reported from the date of documented informed consent to participation in the study and until the end of study participation. SAEs reported outside the required reporting window are only entered into the safety database and will be described separately in the report.

All AEs will be listed. The TEAEs will be presented using summary tables including:

- AEs, in total and sorted by frequency
- AEs by relationship
- AEs by CTCAE Grade and maximum CTCAE Grade
- SAEs, in total, and by relationship
- AEs leading to withdrawal from treatment
- AEs leading to study drug-interruption or dose reduction

- Fatal AEs

If a participant experienced more than 2 AEs for a given preferred term, severity is defined as the severity of the most severe event and relationship to study drug is the relationship of the most related event.

Safety laboratory tests including haematology, chemistry, and coagulation parameters will be graded using CTCAE v5.0 if applicable. Change from baseline in CTCAE grade will be summarised.

Additional safety analyses may be performed to enumerate rates of toxicities more clearly and to further define the safety profile of EXL01.

9.4.5. Other Analysis

The exploratory transcriptomic, microbiota, and cytokine analyses to assess target engagement and mechanisms of action of EXL01 will be described in a separate Translational Analysis Plan.

Any planned subgroup analysis will be described in the SAP.

9.5. INTERIM ANALYSIS

A safety interim analysis will take place after the participants in Part A have entered the Maintenance Period and have a minimum of 6 weeks of EXL01 treatment or follow-up data available. Results of the safety interim analysis will be reviewed by the IDMC as outlined in Sections 4.1.1 and 10.1.6, and submitted to the appropriate regulatory and ethics committees as a substantial amendment.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. APPENDIX I: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, and all other applicable local regulations

10.1.2. Transparency and Results Disclosure

The Sponsor will register this trial on an appropriate, publicly accessible protocol registry before the start of the study. The Sponsor will comply with publication rules in accordance with local regulations. A lay summary of the clinical trial results will also be posted for public access in a timely manner upon completion of the study and will not exceed 1 year after study completion.

The Investigator acknowledges that the statutory obligations under EMA CT Directive or Regulation, as applicable, or other locally mandated registries, are that of the Sponsor or

designee and agrees not to submit any information about this study or its results to those registries.

10.1.3. Financial Disclosure

Investigators and subinvestigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. This will include consent to transmit such information to countries outside the EU and notice from the Sponsor that such countries may not have laws protecting personal data. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.4. Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements, where applicable, of local regulations, ICH guidelines, local data protection requirements, and the IRB/IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant.

The ICF will contain a separate section or separate consent that addresses the use of remaining mandatory samples for optional future research (see Appendix III). The Investigator or authorised designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature or check box will be required to document a participant's agreement to allow any remaining specimens to be used for future research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.5. Data Protection and Confidentiality

The Sponsor or designee will conduct this study in compliance with all applicable data protection regulations, including the EU GDPR.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be

explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

By signing this protocol, the Investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations. The Investigator further agrees that any information furnished to the Investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB/IEC or similar or expert committee; affiliated institutions and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the Investigator, except to the extent that it is included in a publication as provided in the publications section of this protocol. In the event of a data security breach, notification to the supervisory authority and to the trial participant will be managed as applicable and in accordance with Articles 33 and 34 of the EU GDPR.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The Sponsor is required to record the names and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory review upon request by those agencies.

10.1.6. Independent Data Monitoring Committee

An IDMC will monitor the interim data from this study. The voting members of the committee will be external to the Sponsor. The members of the IDMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The IDMC will make recommendations to the Sponsor regarding steps to ensure both participant safety and the continued ethical integrity of the study. The IDMC will review study data as outlined in the study design (Section 4), consider the overall benefit and risk to study participants and recommend to the sponsor whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities and governance, including roles and responsibilities of members of the IDMC and the procedures to be followed will be described in the IDMC charter.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded in a printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Guidelines.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, regulatory agency inspections, and provide direct access to source data documents.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Study documentation will be promptly and fully disclosed to the Sponsor or designee by the Investigator upon request and shall also be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authority. The Investigator agrees to promptly undertake any reasonable steps that are requested by the Sponsor or designee or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and CRFs.

QTLs will be predefined in the QTL Management Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarised in the clinical study report.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Risk Management Plan, Monitoring Plan, and/or Communications Plan.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organisations).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the Investigator’s site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the Monitoring Plan.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

The first visit by the first participant is considered the start of recruitment and the last participant enrolled is considered the end of recruitment.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
- Total number of participants included earlier than expected
- If the positive opinion or complete approval of the local regulatory authority or IEC/IRB is revoked
- If the local insurance coverage is no longer sufficient for the study

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

The results of this study may be published or presented at scientific meetings. If publication activity is not directed by the Sponsor, the Investigator agrees to submit all manuscripts or

abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. APPENDIX II: CONTRACEPTIVE GUIDANCE AND DEFINITIONS

10.2.1. Women of Childbearing Potential

A woman is considered a WOCBP following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study treatment, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with one of the following:

    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

    Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, a single FSH measurement (>40 IU/L or mIU/mL) is required.

Females on HRT and whose menopausal status is in doubt will be required to use one of the highly effective, nonestrogen hormonal contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.2.2. Highly Effective Contraception

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of < 1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a to medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent *Failure rate of < 1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – Oral – Intravaginal – Transdermal – Injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] – Oral – Injectable
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant)*
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction)

10.2.3. Contraception and Barrier Requirements for Male Participants

Male participants are eligible to participate if they agree to the following during the study intervention period including for at least 30 days after the last dose of EXL01 or placebo:

- Refrain from donating sperm
- Use one of the following contraception methods:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

OR

- Must agree to:
  - Use a male condom with female partner and should also be advised of the benefit for a female partner who is a WOCBP to use a highly effective method of contraception (as defined and listed in Section 10.2.2) as a condom may break or leak when having sexual intercourse who is not currently pregnant.
  - Use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

10.2.4. Contraception Requirements and Pregnancy Monitoring for WOCBP Participants

A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:

- Is not a WOCBP

OR

- Is a WOCBP and using a contraceptive method that is highly effective (as defined and listed in Section 10.2.2) during the study intervention period including for at least 30 days after the last dose of EXL01 or placebo. The Investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test (serum) at Screening and before the first dose of study intervention at Visit 2.
- Additional requirements for pregnancy testing of WOCBP during and after study intervention are located in Section 8.3.5.
- The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

10.3. APPENDIX III: FUTURE BIOMEDICAL RESEARCH USE OF DATA

After the study is completed, the de-identified, archived data will be transmitted to and stored in an electronic format by the Sponsor, for use by other researchers including those outside of the study. Permission to transmit data to the Sponsor for future biomedical research will be included in the informed consent process at the start of the study.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples (ie, residual from biological samples collected for the purposes of this study) will be stored at a central laboratory (repository) chosen by the Sponsor with the same goal as the sharing of data with future researchers. Any samples for which consent for future biomedical research cannot be verified will be destroyed. These samples could be used to research the causes of CD, its complications, and other conditions for which individuals with CD are at increased risk, and to improve treatment. Samples will be stored de-identified and unlinked from the participant's study data so that any identifying characteristics cannot be deciphered except by the Sponsor. Samples will be stored in the designated repository for up to 20 years from the end of the study.

During the conduct of the study, an individual participant can choose to withdraw consent to have their data or biological specimens used for future research. Participants may withdraw consent at any time by contacting the study Investigator.

- If the medical records for the study are available, the Investigator will contact the Sponsor. The participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the Investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the Investigator to inform participants of the completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request is received by the Sponsor will continue as outlined in the original consent; no new analyses would be generated after the request is received.
- If the medical records of the participant are no longer available (eg, if the Investigator is no longer required by regulatory authorities to retain the study records) or specimens have been completely anonymised, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

When the study is completed, access to study data and/or samples will be provided through requests to the Sponsor.

No information obtained from future biomedical research will be reported to the participant, family, or physicians. If important research findings are discovered, the results may be published, presented at scientific meetings, and/or provided on a public website to rapidly report this information to doctors and the public. Participants will not be identified by name in any published reports about the future biomedical research or in any other scientific publication or presentation.

10.4. APPENDIX IV: CROHN'S DISEASE ACTIVITY INDEX SAMPLE WORKSHEET

DAY	-7	-6	-5	-4	-3	-2	-1	7 day total	
1. Number of liquid or very soft stools									X 2 =
2. Abdominal Pain (0=none, 1=mild, 2=moderate, 3=severe)									X 5 =
3. General well-being (0=generally well, 1=slightly under par, 2=poor, 3=very poor, 4=terrible)									X 7 =

4. Symptoms or findings presumed related to Crohn's Disease (check ALL that apply)

- ☐ Arthritis or arthralgia
- ☐ Skin or mouth lesions
- ☐ Iritis or uveitis
- ☐ Anal fissure, fistula or perirectal abscess
- ☐ Other bowel-related fistula
- ☐ Febrile episode exceeding 100° F (37.8° C) during past week

Total checked boxes ____ X 20 = ____

5. Taking Lomotil or opiates for diarrhoea — no = 0, yes = 1 ____ X 30 = ____

6. Abdominal mass — absent = 0, questionable = 2, present = 5 ____ X10 = ____

7. Haematocrit (Rounded to a whole number)

Males 47 - ____
or = ____ X 6 = ____
Females 42 - ____
If negative, enter 0

8. Body Weight Calculation

Standard Weight ____ kg
minus Actual Weight ____ kg
= ____ ÷ Standard Weight = ____ X 100 = ____ *
Rounded to whole number

*Add (underweight) or subtract (overweight)

TOTAL CDAI = ____
If negative, enter 0

Source: Best WR et al. Gastroenterology 1976;70:439-44.

10.5. APPENDIX V: CLINICAL LABORATORY TESTS

The tests detailed in Table 7 will be performed by the central laboratory, unless indicated otherwise. For further information about central laboratory tests, including sample processing, storage, and shipment, please refer to the laboratory manual.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2, respectively.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations (such as tests for COVID-19) to ensure participant safety.

Table 7 Protocol-Required Safety Laboratory Tests

Laboratory Tests	Parameters			
Haematology	Platelet count RBC count Haemoglobin Haematocrit	RBC indices: MCV MCH %Reticulocytes	WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry	Blood urea nitrogen (BUN)	Potassium	AST/ SGOT	Total and direct bilirubin
	Creatinine	Sodium	ALT/ SGPT	Total protein
	Glucose	Calcium	Alkaline phosphatase	
Other	CRP			
Routine urinalysis	Specific gravity pH, glucose, protein, blood, ketones, by dipstick Microscopic examination (if blood or protein is abnormal)			
Faecal analysis	*Clostridioides difficile* Parasitology (microscopic) and bacteriology (*Salmonella*, *Shigella*, *Yesrinia*, *Campylobacter*, *Escherichia coli*) analysis			
Pregnancy testing	Highly sensitive serum hCG pregnancy test at Screening and end of Induction Period (as needed for WOCBP) Urine or serum pregnancy test throughout the remainder of the study [a]			
Other Screening Tests	Serology (HIV antibody, HBsAg, and hepatitis C virus antibody) Coagulation (PT/INR)			

Abbreviations: ALT, alanine aminotransferase; AST = aspartate aminotransferase; BUN, blood urea nitrogen; CRP = C-reactive protein; HBsAg = hepatitis B serum antigen; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; MCH = mean corpuscular haemoglobin; MCV = mean corpuscular volume; PT/INR = prothrombin time/international normalised ratio; RBC = red blood cell count; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cell count; WOCBP = women of childbearing potential.

a As required by local requirements. Urine pregnancy tests may be performed locally.

Investigators (or medically qualified designee) must document their review of each laboratory safety report.

10.6. APPENDIX VI: AE AND SAE DEFINITIONS AND CLASSIFICATION

10.6.1. Definitions

10.6.1.1. Adverse Event

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. An AE can therefore be any unfavourable or unintended sign (eg, including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product. An AE may be a new illness, worsening of a sign or symptom of a condition, or an effect of the study medication, including the comparator.

Note: for purposes of AE definition, study intervention includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events That Meet the AE Definition

- Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgement of the Investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study drug administration.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. Refer to Section 6.6.

Events that do NOT Meet the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments.

However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfil the definition.

- "Pregnancy" per se will not be reported as an AE or SAE. This will be recorded in separately. However, any complications or related untoward medical occurrence or abnormal outcome will be reported as an AE or SAE. Refer to Section 8.4.5.
- Medical or surgical procedure (eg, endoscopy, appendectomy), rather, the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.6.1.2. Pretreatment Adverse Event

A PTAE is defined as any untoward medical occurrence in a clinical study participant who has provided documented informed consent to participate in a study that occurs prior to administration of EXL01 or placebo; it does not necessarily have to have a causal relationship with study participation.

Collection of PTAEs will commence from the time informed consent to participate in the study is documented and continue until the participant is first administered study medication (EXL01 or placebo). For participants who discontinue prior to study medication (EXL01 or placebo) administration, PTAEs will be collected until the participant discontinues study participation.

10.6.1.3. Adverse Drug Reaction

Adverse drug reactions (ADRs) are all noxious and unintended responses to a medicinal product related to any dose. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, ie, the relationship cannot be ruled out.

10.6.1.4. Unexpected Adverse Drug Reaction

An unexpected ADR is an ADR, the nature and severity of which is not consistent with the applicable product information, eg, the IB.

10.6.1.5. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening, ie, the participant was at immediate risk of death at the time of the event; it does not include any event that hypothetically might have caused death if it had occurred in a more severe form
- Requires inpatient hospitalization or prolongation of existing hospitalization.

  - Hospitalizations and/or surgical procedures that are scheduled to occur during the study period, for an illness or disease that existed before participant enrolment in the study, will not be considered AEs provided the pre-existing condition did not deteriorate (eg, surgery performed earlier than the planned date).
  - Hospitalization signifies that the participant was admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or intervention that would not have been appropriate in the physician's office or outpatient setting.
  - Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious.
  - When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

- Results in persistent or significant disability/incapacity.

  The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate. In other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention, such as study drug discontinuation, to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

All AEs that do not meet any of the criteria for serious, will be regarded as nonserious AEs.

10.6.2. Classification of Adverse Events

10.6.2.1. Severity

The severity of AEs will be graded according to the NCI-CTCAE version 5.0 (27 November 2017). The general categories for each grade are presented in Table 8.

Table 8 Adverse Event Severity Grading

Grade	Severity	Alternate Description
1	Mild (apply event-specific NCI-CTCAE grading criteria)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate (apply event-specific NCI-CTCAE grading criteria)	Minimal; local or noninvasive intervention indicated; limiting age appropriate instrumental ADL
3	Severe (apply event-specific NCI-CTCAE grading criteria)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
4	Very severe, life-threatening, or disabling (apply event-specific NCI-CTCAE grading criteria)	Life-threatening consequences; urgent intervention indicated
5	Death related to AE	Death related to AE

Abbreviations: AE, adverse event; ADL, activities of daily living; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Instrumental ADL refers to preparing meals, shopping for groceries, or clothes, using the telephone, managing money, etc. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The term “severe” is used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as “serious,” which is based on participant/event outcome or action criteria usually associated with events that pose a threat to a participant’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

10.6.2.2. Assessment of Causality

The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.

The Investigator will use clinical judgement to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.

The Investigator will also consult the Investigator’s Brochure and/or Product Information, for marketed products, in his/her assessment.

For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

The relationship of the AE to study treatment (study drug) will be assessed by the Investigator to be not related, unlikely, possible, probable, or definite, as follows (Table 9):

Table 9 Adverse Event Causality Assessment

Not related	No relationship between the AE and the administration of study treatment, judged clearly and incontrovertibly due to extraneous causes such as concomitant medication(s) or the participant's clinical state.
Unlikely	The AE is more likely due to an alternative explanation such as concomitant medication(s), concomitant disease(s) and/or the time relationship suggests that a causal relationship is unlikely.
Possible	The AE might be due to the administration of study treatment. An alternative explanation such as concomitant medication(s) or concomitant disease(s) is inconclusive. The time relationship is reasonable therefore the causal relationship cannot be excluded.
Probable	The AE might be due to the administration of study treatment. An alternative explanation such as concomitant medication(s) or concomitant disease(s) is less likely. The time relationship is suggestive, ie, it is confirmed by de-challenge.
Definite	The AE is a possible ADR and cannot be reasonably explained by an alternative explanation such as concomitant medication(s) or concomitant disease(s). The time relationship is very suggestive, ie, it is confirmed by dechallenge and rechallenge.

For the purposes of safety analyses, all AEs classified with a relationship to study treatment administration of possible, probable, or definite will be considered treatment-related events.

There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor or designee. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or designee.**

The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.7. APPENDIX VII: GENETICS

Use/Analysis of DNA/RNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact intervention absorption, distribution, metabolism, and excretion; mechanism of action of the intervention; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- Planned genetic analysis samples will not be collected at the site if there is a local law or regulation prohibiting collection, or if the IEC does not approve the collection of samples for these purposes. Alternatively, the protocol-specified sample for this purpose may be collected and used instead for other types of future biomedical research if participant consent has been provided for such use.
- For this study, DNA samples will be analysed for NOD2 and other major IBD-associated polymorphisms and RNA samples from colonic tissue will be used to evaluate change in gene expression following treatment. Leftover extracted DNA and RNA will be stored for future biomedical research, as outlined in Appendix III, if the participant provides documented informed consent for future biomedical research.
- Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data, or as part of future biomedical research related to EXL01 or CD and related diseases if consent to future biomedical research has been provided, as outlined in Appendix III. For example, they may be used to develop tests/assays including diagnostic tests related to EXL01 or CD. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- The samples may be analysed as part of a multistudy assessment of genetic factors involved in the response to EXL01 or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The Sponsor will store the DNA and RNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on EXL01 continues but no longer than local requirements permit.

10.8. APPENDIX VIII: PROTOCOL REVISION HISTORY

DOCUMENT HISTORY	
Document	**Date**
Version 7.1	08-December-2023
Version 7.0	03-August-2023
Version 6.0	01-December-2022
Version 5.0	31-March-2022
Version 4.0	11-February-2022
Version 3.0	18-October-2021
Version 2.0	05-October-2021
Original Protocol (Version 1.0)	13-July-2021

The Summary of Changes Table for the current protocol version is located directly before the Table of Contents (TOC). The Summary of Changes Table(s) for previous revision(s) of the protocol are located directly below.

Version 7.0 (03-August-2023) Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 4.1 Overall Design 4.2.1 Rationale for Study Design 5.3 Criterion for Maintenance Period #2	Maintenance criterion #2: A minimum SES-CD score was removed for Part A and decreased to 6 points for ileocolonic CD and 3 points for isolated ileitis for Part B	Part A: Presence of inflammation is not required for the initial safety assessment in Part A Part B: To avoid including participants who may not have had an adequate endoscopic response with corticosteroid therapy alone and/or who may not be successful in tapering off corticosteroids within the tapering guidelines

1.1 Synopsis 5.1 Inclusion Criterion #6	Inclusion criterion #6 was removed from Part A and updated for Part B to: a) include routine faecal calprotectin assessments done within 4 weeks prior to Screening to assess eligibility, b) increase the window for cross-sectional imaging from 4 weeks to 6 months before Screening, and c) decrease the extent of ulceration required on endoscopy	Part A: Presence of inflammation is not required for the initial safety assessment in Part A Part B: To ensure eligibility is based on routine results available at Screening, and to align more closely with standard practice for the study population without putting additional burden on participants
1.1 Synopsis 5.1 Inclusion Criterion #7 5.2 Exclusion Criterion #11 6.5.2 Prohibited Concomitant Medications	Inclusion criterion #7 and exclusion criterion #11 were removed from Part A. For both criteria for Part B: The maximum number of previous biologics or JAK inhibitors that participants could have been exposed to was increased to no more than 3 prior therapies and risankizumab and upadacitinib therapies were added	Part A: Prior biologic exposure does not impact the initial safety assessment Part B: Many patients have been exposed to ≥ 1 biologic or JAK inhibitor, and thus, the maximum number of prior therapies was increased to be more representative of the patient population while minimizing the impact on detecting an efficacy signal Risankizumab and upadacitinib have recently been approved for the treatment of CD
1.2 Schema Figure 2 1.3.1 Schedule of Activities (SoA) Induction Period 8.1 Administration and General Procedures	The Screening window was increased to 28 days	To allow for greater flexibility in completing screening procedures by sites and to ensure results are available before Visit 1

1.3.1 SoA Induction Period 8.2.1 Crohn's Disease Activity Index	Text was added to Section 8.2.1 and notes to the SoA CDAI scoring row for collecting CDAI patient-reported items based on participant recall at Screening and for calculating the CDAI score at Visit 1	To clarify that patient-reported items can be based on participant recall at Screening, if diary data is not available as diary completion for some participants may not start until screening procedures are complete CDAI score calculation at Visit 1 was clarified to avoid delays in reconfirming eligibility
4.3.1 Beginning and End of Study Definition	Deletion of "overall" from the study start definition	To allow the study start definition to apply globally, as well as at the country-level
5.5.1 Screen Failure Prior to Induction	Text was added that repeat clinical laboratory assessments at Screening could be performed at Investigator's discretion	Clarification
10.1.9 Study and Site Start and Closure	Definition for first act of recruitment was updated and a definition for the end of recruitment was added	Clarification of first act of recruitment and study start per country and alignment with EU CTR requirements
Throughout	Correction of inconsistencies and minor editorial changes	Minor updates and corrections for internal consistency and clarification

Version 6.0 (01-December-2022) Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale
Title Page	EU Clinical Trial and National Clinical Trial numbers were added	Preparation for EU CTR transition
1.1 Synopsis 2 Introduction	Deletion of *Faecalibacterium prausnitzii* strain identifier	Removal of company confidential information in preparation for EU CTR submission

1.1 Synopsis 4.1.1 Overall Design – Part A 4.2.1 Rationale for Study Design 9.2 Sample Size Determination	Timing of Part A interim analysis amended from "all" to "a target of" 6 patients with 6 weeks of EXL01 exposure or follow-up	Clarification/alignment with Section 5.6
1.1 Synopsis 5.1 Inclusion Criteria 5.2 Exclusion Criteria	Inclusion criterion #7 – updated to increase permitted prior biologics exposure in Part A from no more than 1 to no more than 3 and updated the required washout period from last dose of a biologic to provide details for long half-life and short half-life biologics Exclusion criterion #11 – aligned with inclusion criterion #7	Prior biologic exposure is a measure of refractoriness to therapy and does not impact the initial assessment of EXL01 safety in Part A of the study. To provide further clarification of the washout periods for prior biologic therapy
1.3.1 Schedule of Assessments (SoA) – Induction Period 8.2.2 Endoscopy and Biopsy Collection	CDAI scoring row: Note added that the score is to be determined before endoscopy and at Visit 2 Endoscopy row: the time scheduling window for endoscopy was reduced to +5 days	To ensure the CDAI eligibility criterion is met before endoscopy is performed and that Visit 2 endoscopy results will be available in a timely fashion to assess Maintenance eligibility
1.3.1 SoA – Induction Period 10.5 Appendix V: Table 7	Addition of coagulation tests (Prothrombin time/international normalised ratio) at screening	Clarification - to align with current sampling
1.3.1 SoA – Induction Period 1.3.2 SoA – Maintenance Period 8.6.2 Serum Biomarkers	Blood sample changed to serum sample for cytokine analysis	To clarify the sample type required for analysis

1.3.1 SoA – Induction Period 1.3.2 SoA – Maintenance Period 5.3 Criteria for Maintenance Period	Review of Maintenance Period criteria to take place at the end of Visit 2 and no change in eligibility to be confirmed at Visit 3	To ensure eligibility criteria are met before continuing in Maintenance Period
1.3.1 SoA – Induction Period 1.3.2 SoA – Maintenance Period 8.3.2 Vital Signs	Clarification that vital signs should be assessed before blood collection and that body temperature can also be measured tympanically	Clarification of procedures for assessing vital signs
1.3.2 SoA – Maintenance Period 8.2.1 Crohn's Disease Activity Index	Visit 3: Scheduling window increased from +5 to 7 days to +5 to 10 days SoA CDAI Scoring row: Note added that CDAI score calculation is not to include the day of bowel preparation, the day of endoscopy at Visit 2, or the 1 day after endoscopy Endoscopy row: scheduling window reduced to ±5 days Section 8.2.1: Sentence added of what days to exclude from CDAI score calculation	To increase the flexibility in scheduling Visit 3, to avoid including days in the CDAI calculation where bowel preparation and endoscopy would affect patient-reported items, and to clarify that the time window for endoscopy is shorter than for other procedures
4.2.1 Rationale for Study Design	Updated to reflect that in Part A, recruitment will be across a "few" selected study centres	To reflect an increase in the number of sites expected to participate in Part A
4.3.2 Clinical criteria for Early Study Termination	Addition of a statement that participants will be notified of any changes to the benefit/risk profile that lead to stopping enrolment	To ensure participants are to be informed of any updates to the benefits/risk profile

5.1 Inclusion Criteria 10.2.4 Contraception Requirements and Pregnancy Monitoring for WOCBP Participants Contraception	Addition of text that a negative serum pregnancy test is required at screening prior to first dose of "corticosteroid" and at the end of the Induction Period (Visit 2) prior to the first dose of study intervention	Clarification that negative serum pregnancy tests are required at both Visits 2 and 3 for study participation
5.2 Exclusion Criteria 6.5.2 Prohibited Concomitant Medications	Exclusion criterion #7 – updated to: "known or suspected contraindications to corticosteroids according to the local prescribing information for prednisone or budesonide not listed in other exclusion criteria" Exclusion criterion #25 – updated to include hypersensitivity to "corticosteroids as listed in local prescribing information and/or soybeans or soy-containing products". Section 6.5.2 - New prohibited concomitant medications: "Any concomitant medication prohibited in the local prescribing information for prednisone or budesonide (during the Induction Period and during corticosteroid tapering only)"	To ensure local prescribing information for corticosteroids is followed and to align with information in Investigator's Brochure
5.4 Lifestyle Considerations	Addition of "Starting or stopping a vegetarian or vegan diet during the study is prohibited"	Clarification of expectations for normal diet maintenance
5.5.2 Failure to Meet Maintenance Period Criteria	Revised to indicate that participants can switch from budesonide to prednisone but not from prednisone to budesonide	Clarification - To align with current prescribing practices
6.3.1 Intervention Assignment	Addition of details regarding where the randomisation list will be stored	Clarification

8.2.2 Endoscopy and Biopsy Collection	Reduced the total number of segments from which biopsies will be obtained and clarified sites for biopsy collection	To reduce the number of biopsies and provide further instruction on biopsy collection
8.4.2 Procedures for AE and SAE Reporting	SAE reporting was updated to "immediately (without undue delay and no later than within 24 hours)"	To ensure SAEs are reported promptly
9.3 Analysis Sets 9.4.2 Endpoints	Definition of the PP analysis set was simplified, and text removed that the PP analyses will be performed on primary and secondary endpoints and text added to Section 9.4.2 that PP analyses will be described in the SAP "Part A Safety" analysis set was replaced with "Maintenance 6-week Completer" and "Maintenance Long-term" analysis sets	To simplify the PP analysis set definition and provide direction on where the PP analyses will be described Replacement of the "Part A Safety" analysis set with 2 specific Part A analysis sets
9.4.1 General Considerations	Addition of text describing the handling of spurious data	Preparation for EU CTR transition
9.4.3 Time-to-Event Endpoints	Addition of definition for clinical relapse	To clarify the definition of clinical relapse
10.1.2 Transparency and Results Disclosure	Addition of text that the sponsor will comply with publication rules in accordance with local regulations and publicly post a lay summary of results within 1 year after study completion. Addition of text clarifying the Investigator obligations under the CT regulation	Clarification of Sponsor's responsibilities regarding publication rules and dissemination of study results and the Investigator's obligations under EMA CT regulation
10.1.5 Data Protection and Confidentiality	Addition of instructions on what to do in case of a data security breach	To comply with EU regulation 536/2014 Annex I section D17 and preparation for EU CTR transition
10.7 Appendix VII: Genetics	Addition of RNA analysis	To align with Section 8.6.3

Throughout	Correction of inconsistencies and errors and minor editorial changes	Minor updates and corrections for internal consistency

Version 5.0 (31-March-2022) Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale
Throughout	The study title is modified to add "partially" double-blind.	To more closely reflect the study design which includes both an open-label part (Part A) and double-blinded part (Part B).
1.1 Synopsis 3 Objective and Endpoints 5.1 Inclusion Criteria	Correction of units for faecal calprotectin.	Typographical error.

Version 4.0 (11-February-2022) Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 4.1 Overall Design 4.1.1 Part A 4.2.1 Rationale for Study Design	Part A will be divided into 2 dosing cohorts (A1 and A2). An initial 3 participants will be recruited into Cohort A1. Enrolment into Cohort A2 will only open once data from at least 2 participants, with a minimum of 7 days of EXL01 exposure in Cohort A1 has been reviewed by an IDMC.	To permit early review of safety data following EXL01 exposure in a limited number of participants in Part A

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 2.3 Benefit/Risk Assessment 4.1 Overall Design 4.1.2 Part B 4.2.1 Rationale for Study Design 9.5 Interim Analysis 10.1.6 Independent Data Monitoring Committee	An IDMC will review study data from both Part A and B, as outlined in a separate IDMC charter, which includes at minimum: • At least 2 participants in Cohort A1 have completed at least 7 days of EXL01 treatment in Part A • After 6 participants in Part A have completed at least 6 weeks of EXL01 treatment or follow-up	To add further oversight for monitoring participant safety and include independent experts in review of the study data
1.3 Schedule of Activities (SoA) Appendix V: Clinical Laboratory Tests	Confirmation that CRP is included with the haematology and biochemistry laboratory assessments planned for this study	CRP measurements support assessment of the secondary objectives, as stated in Section 3
5.4 Lifestyle Considerations 6.5.2 Prohibited Concomitant Medications	Prebiotic supplements are prohibited during the study, in addition to probiotic food and drinks	Clarification
6.3.2 Blinding and Unblinding Procedure	Deletion of reference to unblinded pharmacist	Correction; study treatments will be dispensed by a blinded pharmacist
6.5 Concomitant Therapies	When an additional concomitant medication is being considered, Investigators should be directed to review the local approved prescribing information for the corticosteroid product that has been prescribed for the participant's Induction Period treatment	To confirm that there are no known drug interactions
Throughout	Correction of typographical and editorial errors	Corrections

Version 3.0 (18-October-2021) Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA)	Addition of option to dispense a faecal sampling kit at Screening	Permits home sample collection if required
1.3 Schedule of Activities (SoA) Appendix V: Clinical Laboratory Tests	Removal of routine faecal analysis for occult blood	Simplifies the protocol

Version 2.0 (05-October-2021) Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Addition of key inclusion and exclusion criteria from Sections 5.1 and 5.2 to the synopsis	Clarity
1.3 Schedule of Activities 8.1 Administration and General Procedures Appendix V: Clinical Laboratory Tests	Addition of wording to confirm that all sites must adhere to all local COVID-19 rules and regulations, such as COVID-19 testing	Ensures that applicable local COVID-related rules and regulations are followed during this study
1.3 Schedule of Activities 8.2.6 Faecal Scoring (Bristol Stool Form Score) 11 References	Removal of Bristol Stool Form Score from the study; section removed with protocol section numbering and reference list updated accordingly	Simplification of data collection
1.3 Schedule of Activities Appendix V: Clinical Laboratory Tests	Faecal testing for parasites and bacteria, including *Clostridioides difficile,* will only be performed at Screening	Simplifies and standardises the test procedures
1.3 Schedule of Activities	Modification of EXL01 / placebo dispensing schedule	Reduces total amount of study drug provided to participants at earlier visits

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities 4.1 Overall Design 6.7.1 Corticosteroid Tapering	Modification of disease flare definition to be only >70-point increase in CDAI from baseline of the Maintenance Period (removal of 'or CDAI >250') for 2 consecutive weeks	Simplifies and clarifies definition
1.3 Schedule of Assessments	Addition of blood sample to assess haematology and biochemistry results to Study Visit 3 (baseline visit for Maintenance Period)	Aligns with assessment of CDAI at the baseline for Maintenance Period
5.2 Exclusion criteria	Addition of a new exclusion criterion for participants who are currently committed to an institution by virtue of an order issued either by the judicial or administrative authorities	Avoids conflict of interest or coercion
5.2 Exclusion criteria	Addition of a new exclusion criterion for participants who are study-site or sponsor employees or an immediate family member of or is in a dependent relationship with a study-site or sponsor employee	Avoids conflict of interest or coercion
5.4 Lifestyle Considerations	Use of probiotic food and drinks and excessive consumption of alcohol will be prohibited during the study	Probiotics and excessive alcohol intake may affect the study drug
6.4 Study Intervention Compliance	Removal of guidance for monitoring compliance of study interventions administered at the study site	All study interventions will be self-administered at home therefore this is not applicable to this study
10.1.4 Informed Consent	Removal of reference to a participant's legally authorised representative	Participants who are unable to provide consent for themselves are not eligible for the study

Section # and Name	Description of Change	Brief Rationale
10.1.8 Study and Site Start and Closure	Expansion of the list of reasons for study termination at a site to include: if the positive opinion or complete approval of the regulatory authority or IEC/IRB is revoked, and, if the insurance coverage is no longer sufficient	Confirms these are additional reasons that would prompt termination of the study at a site
Throughout	Correction of inconsistencies and minor editorial changes	Minor updates and corrections for internal consistency

11. REFERENCES

1. Torres J, Bonovas S, Doherty G, et al. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. J Crohns Colitis. 2020;14(1):4-22.
2. Wehkamp J, Gotz M, Herrlinger K, et al. Inflammatory Bowel Disease. Dtsch Arztebl Int. 2016;113(5):72-82.
3. Doherty G, Katsanos KH, Burisch J, et al. European Crohn's and Colitis Organisation Topical Review on Treatment Withdrawal ['Exit Strategies'] in Inflammatory Bowel Disease. Journal of Crohn's & colitis. 2018;12(1):17-31.
4. Eckburg PB, Bik EM, Bernstein CN, et al. Diversity of the human intestinal microbial flora. Science. 2005;308(5728):1635-8.
5. Beaugerie L, Rahier JF, Kirchgesner J. Predicting, preventing, and managing treatment-related complications in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2020;18(6):1324-35 e2.
6. Sekirov I, Russell SL, Antunes LC, et al. Gut microbiota in health and disease. Physiol Rev. 2010;90(3):859-904.
7. Hold GL, Schwiertz A, Aminov RI, et al. Oligonucleotide probes that detect quantitatively significant groups of butyrate-producing bacteria in human feces. Appl Environ Microbiol. 2003;69(7):4320-4.
8. Qin J, Li R, Raes J, et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature. 2010;464(7285):59-65.
9. Miquel S, Martin R, Bridonneau C, et al. Ecology and metabolism of the beneficial intestinal commensal bacterium Faecalibacterium prausnitzii. Gut Microbes. 2014;5(2):146-51.
10. Miquel S, Martin R, Rossi O, et al. Faecalibacterium prausnitzii and human intestinal health. Curr Opin Microbiol. 2013;16(3):255-61.
11. Mondot S, Lepage P, Seksik P, et al. Structural robustness of the gut mucosal microbiota is associated with Crohn's disease remission after surgery. Gut. 2016;65(6):954-62.
12. Sokol H, Lay C, Seksik P, et al. Analysis of bacterial bowel communities of IBD patients: what has it revealed? Inflamm Bowel Dis. 2008;14(6):858-67.
13. Wright EK, Kamm MA, Wagner J, et al. Microbial factors associated with postoperative Crohn's disease recurrence. J Crohns Colitis. 2017;11(2):191-203.
14. Busquets D, Mas-de-Xaxars T, Lopez-Siles M, et al. Anti-tumour necrosis factor treatment with adalimumab induces changes in the microbiota of Crohn's disease. J Crohns Colitis. 2015;9(10):899-906.
15. Rajca S, Grondin V, Louis E, et al. Alterations in the intestinal microbiome (dysbiosis) as a predictor of relapse after infliximab withdrawal in Crohn's disease. Inflamm Bowel Dis. 2014;20(6):978-86.
16. Varela E, Manichanh C, Gallart M, et al. Colonisation by Faecalibacterium prausnitzii and maintenance of clinical remission in patients with ulcerative colitis. Aliment Pharmacol Ther. 2013;38(2):151-61.
17. Marlicz W, Skonieczna-Zydecka K, Dabos KJ, et al. Emerging concepts in non-invasive monitoring of Crohn's disease. Therap Adv Gastroenterol. 2018;11:1756284818769076.
18. Pascal V, Pozuelo M, Borruel N, et al. A microbial signature for Crohn's disease. Gut. 2017;66(5):813-22.

19. Magnusson MK, Strid H, Sapnara M, et al. Anti-TNF therapy response in patients with ulcerative colitis is associated with colonic antimicrobial peptide expression and microbiota composition. J Crohns Colitis. 2016;10(8):943-52.
20. Godefroy E, Alameddine J, Montassier E, et al. Expression of CCR6 and CXCR6 by Gut-Derived CD4(+)/CD8alpha(+) T-Regulatory Cells, Which Are Decreased in Blood Samples From Patients With Inflammatory Bowel Diseases. Gastroenterology. 2018;155(4):1205-17.
21. Lopez-Siles M, Duncan SH, Garcia-Gil LJ, et al. Faecalibacterium prausnitzii: from microbiology to diagnostics and prognostics. ISME J. 2017;11(4):841-52.
22. Sarrabayrouse G, Bossard C, Chauvin JM, et al. CD4CD8alphaalpha lymphocytes, a novel human regulatory T cell subset induced by colonic bacteria and deficient in patients with inflammatory bowel disease. PLoS Biol. 2014;12(4):e1001833.
23. Huang XL, Zhang X, Fei XY, et al. Faecalibacterium prausnitzii supernatant ameliorates dextran sulfate sodium induced colitis by regulating Th17 cell differentiation. World J Gastroenterol. 2016;22(22):5201-10.
24. Qiu X, Zhang M, Yang X, et al. Faecalibacterium prausnitzii upregulates regulatory T cells and anti-inflammatory cytokines in treating TNBS-induced colitis. J Crohns Colitis. 2013;7(11):e558-68.
25. Sokol H, Pigneur B, Watterlot L, et al. Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. Proc Natl Acad Sci U S A. 2008;105(43):16731-6.
26. Zhang M, Qiu X, Zhang H, et al. Faecalibacterium prausnitzii inhibits interleukin-17 to ameliorate colorectal colitis in rats. PLoS One. 2014;9(10):e109146.
27. Martin R, Chain F, Miquel S, et al. The commensal bacterium Faecalibacterium prausnitzii is protective in DNBS-induced chronic moderate and severe colitis models. Inflamm Bowel Dis. 2014;20(3):417-30.
28. Martin R, Miquel S, Benevides L, et al. Functional Characterization of Novel Faecalibacterium prausnitzii Strains Isolated from Healthy Volunteers: A Step Forward in the Use of F. prausnitzii as a Next-Generation Probiotic. Front Microbiol. 2017;8:1226.
29. Munkholm P, Langholz E, Hollander D, et al. Intestinal permeability in patients with Crohn's disease and ulcerative colitis and their first degree relatives. Gut. 1994;35(1):68-72.
30. Best WR, Becktel JM, Singleton JW, et al. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology. 1976;70(3):439-44.
31. Sturm A, Maaser C, Calabrese E, et al. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 2: IBD scores and general principles and technical aspects. J Crohns Colitis. 2019;13(3):273-84.
32. DeSesso JM, Jacobson CF. Anatomical and physiological parameters affecting gastrointestinal absorption in humans and rats. Food Chem Toxicol. 2001;39(3):209-28.
33. Helander HF, Fandriks L. Surface area of the digestive tract - revisited. Scand J Gastroenterol. 2014;49(6):681-9.
34. Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointestinal endoscopy. 2004;60(4):505-12.
35. D'Haens GR, Geboes K, Peeters M, et al. Early lesions of recurrent Crohn's disease caused by infusion of intestinal contents in excluded ileum. Gastroenterology. 1998;114(2):262-7.

36. Mosli MH, Parker CE, Nelson SA, et al. Histologic scoring indices for evaluation of disease activity in ulcerative colitis. The Cochrane database of systematic reviews. 2017;5:Cd011256.
37. Feagan BG, Sandborn WJ, Danese S, et al. Ozanimod induction therapy for patients with moderate to severe Crohn's disease: a single-arm, phase 2, prospective observer-blinded endpoint study. The lancet Gastroenterology & hepatology. 2020;5(9):819-28.
38. Khanna R, Zou G, D'Haens G, et al. A retrospective analysis: the development of patient reported outcome measures for the assessment of Crohn's disease activity. Alimentary pharmacology & therapeutics. 2015;41(1):77-86.
39. Garratt AM, Ruta DA, Abdalla MI, et al. The SF36 health survey questionnaire: an outcome measure suitable for routine use within the NHS? BMJ (Clinical research ed). 1993;306(6890):1440-4.
40. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Medical care. 1992;30(6):473-83.
41. Jenkinson C, Stewart-Brown S, Petersen S, et al. Assessment of the SF-36 version 2 in the United Kingdom. J Epidemiol Community Health. 1999;53(1):46-50.
42. Guyatt G, Mitchell A, Irvine EJ, et al. A new measure of health status for clinical trials in inflammatory bowel disease. Gastroenterology. 1989;96(3):804-10.

A Phase 1 Multicentre, 2-Part, Randomised, Parallel-arm, Placebo-controlled, Partially Double-blind Study to Evaluate the Safety and Target Engagement of EXL01 in the Maintenance of Steroid-induced Clinical Response or Remission in Participants with Mild to Moderate Crohn's Disease

STATISTICAL ANALYSIS PLAN

Version 02
31 October 2024

Protocol No.:	EXL01-CD-001 (MAINTAIN)
SAP Version/Date:	02 / 31 October 2024
Development Phase:	1
Sponsor:	Exeliom Biosciences 67 Rue des Godrans 21000 Dijon, France
Clinical Research Organization:	Alimentiv Inc. 100 Dundas Street, Suite 200 London, Ontario, Canada N6A 5B6

APPROVAL PAGE

A Phase 1 Multicentre, 2-Part, Randomised, Parallel-arm, Placebo-controlled, Partially Double-blind Study to Evaluate the Safety and Target Engagement of EXL01 in the Maintenance of Steroid-induced Clinical Response or Remission in Participants with Mild to Moderate Crohn's Disease

STATISTICAL ANALYSIS PLAN

Version/Date: 02 / 31 October 2024

Name	Position	Signature/Date
[1] PPD	Manager, Statistics Alimentiv Inc.	
[2] PPD	Senior Statistician, Statistics Alimentiv Inc.	
[2] PPD	Acting Chief Medical Officer, Exeliom Biosciences	
[3] PPD	Chief Executive Officer, Exeliom Biosciences	

[1] Author, signs for correctness and completeness

[2] Reviewer, signs for correctness and completeness

[3] Approver, signs for the release of this document

TABLE OF CONTENTS

STATISTICAL ANALYSIS PLAN 1
APPROVAL PAGE 2
TABLE OF CONTENTS 3
DEFINITIONS / ABBREVIATIONS 7
1 INTRODUCTION 8
2 STUDY OBJECTIVES 9
3 STUDY DESIGN 10
3.1 Summary Of Study Design 10
3.1.1 Part A 11
3.1.2 Part B 12
3.2 Determination Of Sample Size 12
3.3 Randomisation And Blinding 12
3.3.1 Randomisation Procedure 12
3.3.2 Blinding and Unblinding Procedure 12
4 GENERAL CONSIDERATIONS FOR DATA ANALYSIS 12
4.1 Reporting Conventions 12
4.2 Analysis Sets 13
4.2.1 Induction Safety (iSAF) 14
4.2.2 Maintenance Safety (mSAF) 14
4.2.3 Modified Intent to Treat (mITT) 14
4.2.4 Per Protocol (PP) 14
4.3 Handling Of Missing Data 14
5 PARTICIPANT CHARACTERISTICS 15
5.1 Participant Disposition 15
5.2 Demographic And Baseline Disease Characteristics 16
5.3 Prior And Concomitant Medication 16
5.4 Medical And Surgical History 17
5.5 Protocol Deviations 17
5.6 Treatment Exposure 18

5.6.1 DURATION OF EXPOSURE 18
5.6.2 COMPLIANCE 18
6 EFFICACY ANALYSES 19
6.1 DERIVATION OF EFFICACY ANALYSES 19
6.1.1 CROHN'S DISEASE ACTIVITY INDEX 19
6.1.2 SIMPLE ENDOSCOPIC SCORE FOR CROHN'S DISEASE 19
6.1.3 GLOBAL HISTOLOGY ACTIVITY SCORE 19
6.1.4 ROBARTS HISTOPATHOLOGY INDEX 20
6.2 EFFICACY ENDPOINTS 20
6.2.1 BINARY EFFICACY ENDPOINTS 20
6.2.2 CONTINUOUS EFFICACY ENDPOINTS 20
6.2.3 MULTIPLICITY 21
7 SAFETY ANALYSES 21
7.1 DEFINITIONS 21
7.1.1 PRETREATMENT ADVERSE EVENTS 21
7.1.2 TREATMENT-EMERGENT ADVERSE EVENTS 22
7.1.3 SERIOUS ADVERSE EVENTS 22
7.2 CLASSIFICATION OF ADVERSE EVENTS 22
7.2.1 SEVERITY 22
7.2.2 ASSESSMENT OF CAUSALITY 22
7.2.3 INCOMPLETE DATES 22
7.3 SUMMARIES OF ADVERSE EVENTS 23
7.4 PHYSICAL EXAMINATION 23
7.5 VITAL SIGNS 24
7.6 CLINICAL LABORATORY TESTS 24
7.7 ELECTROCARDIOGRAMS 24
7.8 LIVER SAFETY MONITORING – HY'S LAW CASES 24
8 OTHER ANALYSES 25
8.1 TIME TO EVENT ANALYSIS 25
8.2 HEALTH-RELATED QUALITY OF LIFE ANALYSIS 25

8.2.1 INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE 25
8.2.2 SF-36 27
8.2.3 2-ITEM PATIENT-REPORTED OUTCOME MEASURE 28
8.3 BIOMARKER ANALYSIS 28
9 INTERIM ANALYSIS 28
10 SUMMARY OF CHANGES 28
10.1 SUMMARY OF CHANGES BETWEEN THE PROTOCOL AND SAP 28
10.2 SUMMARY OF CHANGES FROM PREVIOUS SAP 29
11 SAP REVISION HISTORY 29
12 REFERENCES 30

LIST OF APPENDICES

APPENDIX 1: Simple Endoscopic Score for Crohn's Disease 31
APPENDIX 2: Global Histologic Disease Activity Score 32
APPENDIX 3: Robarts Histopathology Index 33
APPENDIX 4: Inflammatory Bowel Disease Questionnaire 34

LIST OF TABLES

Table 1 Objectives and Endpoints 9
Table 2 Definition of Binary Efficacy Endpoints 20
Table 3 Definition of Continuous Efficacy Endpoints 21
Table 4 Adverse Event Severity Grading 22
Table 5 IBDQ Missing Data Instructions 27
Table 6 Definition of Biomarker Endpoints 28

LIST OF FIGURES

Figure 1 MAINTAIN: 2-Part (Open-label Part A and Blinded Part B) Study Design 11
Figure 2 MAINTAIN: Overall Study Design – Induction and Maintenance (Part B) Periods..... 11

DEFINITIONS / ABBREVIATIONS

ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BMI	body mass index
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
eCRF	electronic case report form
CRP	C-reactive protein
ECG	electrocardiogram
EOT	end of treatment
GCP	Good Clinical Practice
GHAS	Global Histologic Disease Activity Score
HRQoL	Health-related Quality of Life
IBDQ	Inflammatory Bowel Disease Questionnaire
IDMC	Independent Data Monitoring Committee
IEC	independent ethics committee
IRB	institutional review board
IRT	Interactive Response Technology
MedDRA	Medical Dictionary for Regulatory Activities
MLT	Maintenance Long-Term
MC	Maintenance 6 week Completer
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
PP	per protocol
PRO2	2-item patient-reported outcome measure
PT	Preferred Term
PTAE	pretreatment adverse event
qPCR	quantitative polymerase chain reaction (assay)
RHI	Robarts Histopathology Index
SAE	serious adverse event
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF-36	Short-form Questionnaire (36 items)
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
UC	ulcerative colitis
ULN	upper limit of normal

1 INTRODUCTION

This statistical analysis plan (SAP) describes in detail the statistical analysis to be completed for the EXL01-CD-001 (MAINTAIN) study. This SAP is based on the EXL01-CD-001 study protocol and the electronic case report form (eCRF).

MAINTAIN is a Phase 1, 2-part study to evaluate the safety and target engagement of the oral administration of EXL01 in the maintenance of corticosteroid-induced clinical response or remission in participants with mild to moderate Crohn's disease (CD). The study was to be conducted in 2 parts, to include an interim analysis with data reviewed by an Independent Data Monitoring Committee (IDMC). Part A is an open-label evaluation of safety in a small group of participants (n = 6) and Part B is a randomised, double-blind, placebo-controlled evaluation in a larger group of participants (n = 42). The study was prematurely terminated due to low recruitment at the end of Part A; Part B was not started.

To add assurance of safety, a sentinel approach was used in Part A for the start of treatment with EXL01, with data reviewed by an IDMC. The safety interim analysis was conducted when a minimum of 6 weeks of EXL01 treatment or follow-up data for a target of 6 participants in Part A had been collected. The statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) for the safety interim analysis are described in SAP Version 1.0, dated 12-DEC-2022. This SAP V2.0 describes the statistical analysis methods and data presentations to be used in TFLs for the final analysis of Part A only for the clinical study report (CSR).

A full database lock will occur after all participants included have completed their last visit, or have an early termination, all outstanding data queries have been resolved or adjudicated as unresolvable, and data have been cleaned and finalised.

The SAP and any amendments will be finalised prior final database lock for the final analysis. The TFLs to be included in both the interim analysis and final analysis are outlined and described in a supplementary document. Further details for the exploratory tissue biomarker and microbiota analyses will be provided in a separate Translational Analysis Plan.

2 STUDY OBJECTIVES

The protocol defined primary, secondary, and exploratory objectives and endpoints are listed in Table 1.

Table 1 Objectives and Endpoints

Objectives	Endpoints
Primary Objective	**Primary Endpoints**
To evaluate the systemic and intestinal safety and tolerability of orally administered EXL01	• AEs • Discontinuing study treatment due to an AE
Secondary Objectives	**Secondary Endpoints**
To evaluate the proportion of participants in steroid-free clinical remission (CDAI score <150) at Week 24	• CDAI score and use of corticosteroids
To evaluate the proportion of participants in steroid-free clinical remission (CDAI score <150) and mucosal healing (SES-CD < 4 with no deep ulcers) at Week 24	• CDAI score • SES-CD score • Use of corticosteroids
To evaluate the proportion of participants in steroid-free clinical remission (CDAI score <150) and mucosal healing (SES-CD <4 with no deep ulcers) and normal inflammatory markers (normal CRP and faecal calprotectin <250 mg/kg) at Week 24	• CDAI score • SES-CD score • CRP level • Faecal calprotectin level • Use of corticosteroids
To evaluate the proportion of participants with an endoscopic response (SES-CD score decrease by 50%) at Week 24	• SES-CD score
To compare time to clinical relapse in participants with CD treated with EXL01 to participants treated with placebo (Part B only[a])	• Time to clinical relapse, defined as the time from the first dose of study treatment to first documented clinical relapse
To compare the SES-CD and histology of the intestinal mucosa in participants with CD treated with EXL01 to participants treated with placebo (Part B only[a])	• SES-CD score • GHAS score • RHI score
To compare the evolution of the faecal- and mucosa-associated- microbiota in participants with CD treated with EXL01 to participants treated with placebo[a]	• 16S sequencing / shotgun metagenomics • F. prausnitzii specific qPCR/ddPCR
Exploratory Objectives	**Exploratory Endpoints**
To evaluate the health-related quality of life (HRQoL)	• SF-36 score • IBDQ score
To evaluate the mucosa transcriptome in biopsies in participants with CD treated with EXL01 and placebo[a]	• qPCR • RNA Sequencing
To evaluate serum and tissue cytokines at various time points in participants with CD treated with EXL01 and placebo[a]	• Serum and tissue cytokine levels including: • TNFα, IL10 and sCD14
To investigate predictive factors of response to EXL01 (including clinical, biological, endoscopic microbiota, transcriptomic, and genetic)	• CDAI score • SES-CD score • CRP level • Faecal calprotectin level

a. Part B was not started; no statistical comparisons will be conducted. Only descriptive statistics will be provided for each endpoint parameter.

Abbreviations: AE, adverse event; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; ddPCR, droplet digital polymerase chain reaction; IBDQ, Inflammatory Bowel Disease Questionnaire; IL-10, interleukin-10; GHAS, Global Histologic Disease Activity Score; qPCR, quantitative polymerase chain reaction; RHI, Robarts Histopathology Index; RNA, ribonucleic acid; sCD14, soluble CD14; SES-CD, Simple

Endoscopic Score for Crohn's Disease; SF-36, Short-form Questionnaire (36 items); TNF-α, tumor necrosis factor.

3 STUDY DESIGN

3.1 SUMMARY OF STUDY DESIGN

MAINTAIN is a Phase 1, 2-part, multicentre study to evaluate the safety and preliminary efficacy of the oral administration of EXL01 in the maintenance of corticosteroid-induced clinical response/remission in participants with mild to moderate CD. The study will enroll adult patients with CD and ileal/ileo-colonic involvement diagnosed for at least 3 months, who present with clinically active disease (CDAI score of 180 to 350) and evidence of mucosal inflammation at baseline. To induce remission prior to study treatment, participants will receive corticosteroids per international guidelines, for at least 3 weeks and a maximum of 7 weeks, until clinical response/remission is observed. Participants who meet the following clinical and endoscopic criteria after corticosteroid therapy will continue in the study and enter the Maintenance Period:

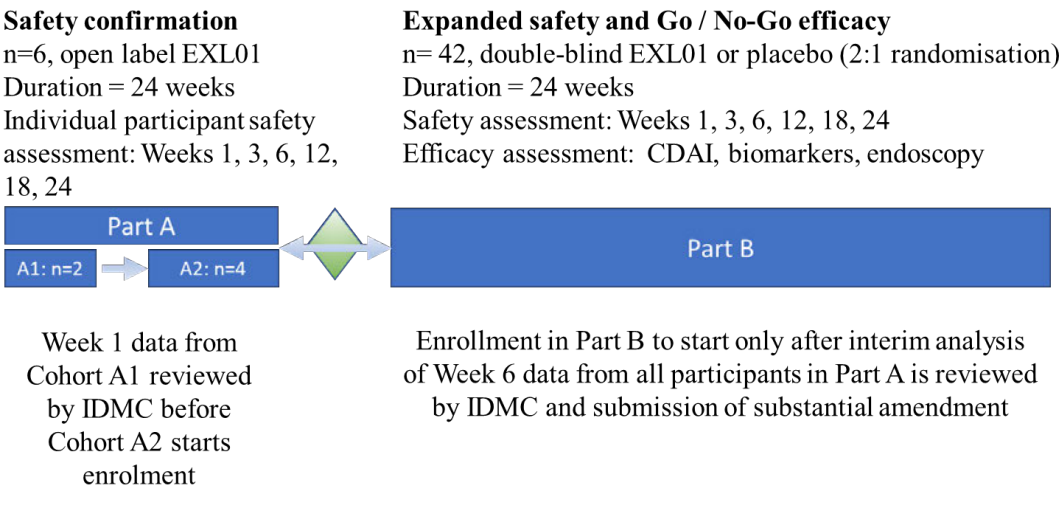
- Corticosteroid induced clinical response, defined as CDAI decrease from baseline ≥70, or clinical remission, defined as a CDAI score <150, after a minimum of 3 weeks and maximum of 7 weeks of corticosteroid treatment, and
- SES-CD score ≥7 (or ≥4 for participants with isolated ileitis), based on a central reading assessment of endoscopy performed upon achievement of clinical response or remission.

Participants who do not meet criteria for the Maintenance Period after 7 weeks of corticosteroid induction treatment will complete the study at that time.

A safety interim analysis will be conducted when a minimum of 6 weeks of EXL01 treatment or follow-up data for a target of 6 participants in Part A have been collected. Results from the interim analysis of Part A will be reviewed by the IDMC and submitted as a substantial protocol amendment before Part B is initiated. Part B will not start until regulatory and ethics approval has been received. The study was terminated early due to low recruitment into Part A and not based on safety of efficacy concerns. The study was closed at the end of Part A; Part B was not started.

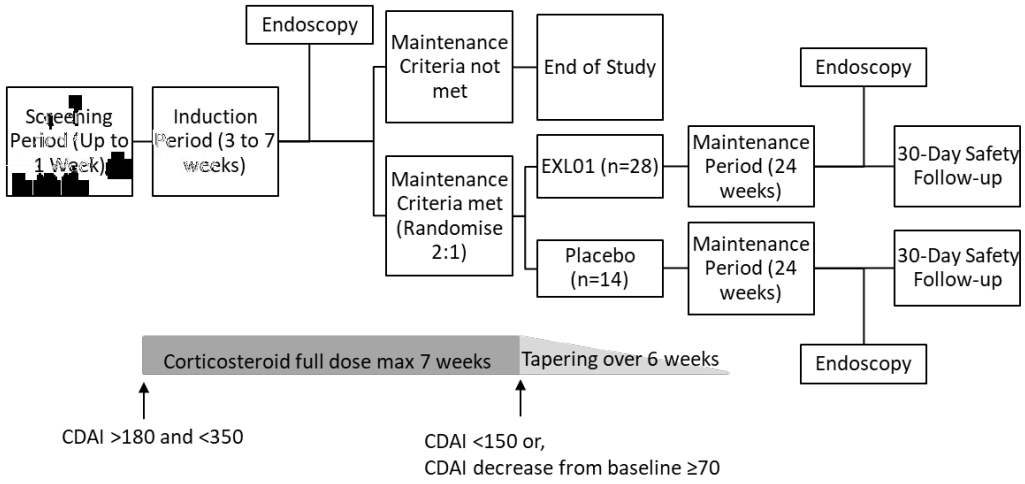
Treatment in the Maintenance Period will consist of progressive tapering of corticosteroids according to a standard regimen over 6 weeks in combination with the study treatment (open-label EXL01 in Part A, and blinded EXL01 or placebo in Part B) for up to 24 weeks. Participants will not receive EXL01 or placebo during the corticosteroid Induction Period. Part A is an open-label evaluation of safety in a small group of participants (n = 6).

Figure 1 MAINTAIN: 2-Part (Open-label Part A and Blinded Part B) Study Design



Abbreviations: CDAI, Crohn's Disease Activity Index; IDMC, independent data monitoring committee.

Figure 2 MAINTAIN: Overall Study Design – Induction and Maintenance (Part B) Periods



The study was closed at the end of Part A; Part B was not started.

Abbreviations: CDAI, Crohn's Disease Activity Index.

3.1.1 PART A

Part A will be divided into 2 dosing cohorts (A1 and A2).

- An initial 3 participants will be recruited into Cohort A1, to target EXL01 exposure in at least 2 participants.
- Cohort A2 will enrol up to 6 participants, to target 4 more participants with EXL01 exposure.

- Enrolment into Cohort A2 will only open after the data from at least 2 participants with a minimum of 7 days of EXL01 exposure in Cohort A1 has been collected, reviewed, and show no safety concerns identified by the IDMC. Participants will continue treatment during the IDMC review.

An independent physician (IDMC chair) will review the 7-day exposure data from each participant in Part A and the full IDMC will review data from all participants in Cohort A1 before Cohort A2 is recruited. After 6 weeks of EXL01 treatment and follow-up in each individual participant, the investigator will assess safety and tolerability before allowing the participants to continue treatment with EXL01 for up to a maximum of 24 weeks, unless a study or treatment discontinuation criterion is met. Participants will be assessed for safety at the end of Weeks 1, 3, 6, 12, 18, and 24 of maintenance therapy.

A safety interim analysis will be conducted after a minimum of 6 weeks of EXL01 treatment or follow-up data for a target of 6 participants in Part A have been collected. The results of this interim analysis will be reviewed by the IDMC, who may provide recommendations for Part B of the study. Recruitment into Part B will not start until regulatory and ethics approval has been received. The study was closed at the end of Part A; Part B was not started.

3.1.2 PART B

In Part B, 42 participants who meet Maintenance Period criteria were to be randomised 2:1 to receive double-blind treatment with either oral EXL01 or placebo, for up to 24 weeks or until a study discontinuation criterion is met (Figure 2). Full details are provided in the Protocol.

3.2 DETERMINATION OF SAMPLE SIZE

No formal sample size calculation was completed for this study. The number of evaluable participants is based on clinical and scientific judgment to meet the objectives of this study.

3.3 RANDOMISATION AND BLINDING

3.3.1 RANDOMISATION PROCEDURE

Part A is not randomised; all participants receive EXL01.

3.3.2 BLINDING AND UNBLINDING PROCEDURE

Part A of the study is open-label; the Sponsor, Investigator, and participant know the interventions administered.

4 GENERAL CONSIDERATIONS FOR DATA ANALYSIS

4.1 REPORTING CONVENTIONS

The summary tables and by-participant listings will be prepared using the following conventions:

- Unless otherwise specified, the baseline value is defined as the last nonmissing assessment before the first dose of study treatment in that study period.
- If the date of interest occurs on or after the first dose/enrollment, the study day will be calculated as (date of interest – date of first dose/enrollment) + 1.

- If the date of interest occurred prior to the first dose/enrollment, then study day will be calculated as (date of interest – date of first dose/enrollment).
- Categorical data will be summarized in terms of frequency counts and percentages.
- Continuous variables will be summarized by treatment group using descriptive statistics (the number of participants [n], mean, median, standard deviation [SD], minimum and maximum [Min, Max]) of the values at each visit and the change from baseline to each visit.
- All mean and median values will be formatted to one more decimal place than the measured values. SD values will be formatted to two more decimal places than the measured value. Min and Max will be formatted to the same number of decimal places as the measured value. The maximum number of decimal places reported shall be four for any summary statistic.
- All percentages will be rounded to one decimal place. The frequency and percentage of responses will be presented in the form XX (XX.X), where the percentage is in the parentheses.
- Change from baseline is calculated as a post-baseline value minus the baseline value in that study period.
- All laboratory data will be reported using standard international units.
- All analysis and summary tables will include the analysis population sample size (i.e., number of participants) in the column headings.
- By-participant listings will be presented for all participants in the relevant analysis sets, and sorted by treatment allocation, study site (if applicable), Participant ID, date, and visit. Numeric data will be listed to the same number of decimal places as recorded on the eCRF or other data source. Data collected on log forms, such as AEs, will be presented in chronological order by participant ID. Age, sex, race, and ethnicity will be included in the listing, as space permits.
- SAS® Software version 9.4 (SAS Institute Inc., Cary, NC, USA.) is to be used for all analyses including TFLs.
- Partial dates will be imputed as follows:
    - If day and month is missing but year is present, the 1st of July of the noted year will be used.
    - If day is missing but year and month are present, the 15th of the noted month and year will be used.
- Medical Dictionary for Regulatory Activities (MedDRA) (version 25.0 or newer) will be used to code adverse events (AEs) and medical history, World Health Organization (WHO) Drug Dictionary version March 2022 or newer will be used for medication coding.

4.2 ANALYSIS SETS

The analysis sets used in the safety interim analysis are described in SAP Version 1.0, dated 12-DEC-2022. The analysis sets described below will be used in the final analysis.

4.2.1 INDUCTION SAFETY (iSAF)

The induction safety analysis set (iSAF) is defined as all screened participants who receive at least 1 dose of corticosteroids as part of the Induction Period.

4.2.2 MAINTENANCE SAFETY (mSAF)

The maintenance safety analysis set (mSAF) is defined as all enrolled or randomised participants who receive at least 1 dose of EXL01 or placebo. Participants will be analysed according to the actual treatment received.

4.2.3 Modified Intent to Treat (mITT)

The mITT analysis set is defined as all enrolled or randomised participants who receive at least 1 dose of EXL01 or placebo. Participants will be analysed according to the treatment they were originally assigned, regardless of what treatment they receive. As the mITT and the mSAF are defined the same way, only the mSAF analysis set will be used in final analysis of Part A; mITT was meant to be used in Part B.

4.2.4 PER PROTOCOL (PP)

The per protocol (PP) analysis set is defined as all mITT participants who do not have any major deviations from protocol and complete all Week 24/EOT assessments associated with the secondary endpoints. PP analyses will be performed on the secondary efficacy endpoints.

4.3 HANDLING OF MISSING DATA

All reasonable efforts will be made to obtain complete data for all participants.

In general, missing data will not be imputed unless methods for handling missing data are specified. No imputation of missing efficacy or safety data will be performed. If baseline values are missing for a particular variable, then the change from baseline and percent change from baseline will not be calculated. The handling of missing or incomplete dates for prior and concomitant medications is described in Sections 5.3, and for AE onset is described in Section 7.2.3.

Where applicable, 2 baselines will be defined for this study. Induction Baseline will be the measurement taken at or closest to Screening, but prior to the start of corticosteroid induction treatment. Maintenance Baseline will be the measurement taken at or closest to Visit 3 (Week 0), but prior to the start of maintenance treatment. “Steroid-free” will be defined as no use of corticosteroids on the day of baseline assessment.

If multiple valid, nonmissing, continuous measurements or visits (regardless if scheduled or unscheduled) occur within a single analysis time point, records will be chosen based on the following rules if a single value is needed:

- For baseline, the value will be the last nonmissing value prior to the first dosing of study drug. If multiple measurements occur on the same day, the last nonmissing value prior to the time of first dosing of study drug will be considered as the baseline value. If these multiple measurements occur at the same time or the time is not available, the average of these measurements will be considered the baseline value.

- For post-baseline values:
  a. The record closest to the nominal day for that visit will be selected.
  b. If there are 2 records that are equidistant from the nominal day, the later record will be selected.
  c. If there is more than 1 record on the selected day, the average will be taken.

If multiple valid, non-missing, categorical observations exist for one visit, records will be selected as follow:

- For baseline, the last available record prior to the first dose of study drug will be selected. If there are multiple records at the same time or no time recorded on the same day, the worst value will be selected unless otherwise specified.
- For post-baseline values:
  a. The record closed to the nominal day for that visit will be selected.
  b. If there are 2 records that are equidistant from the nominal day, the later record will be selected.
  c. If there is more than 1 record on the selected day, the value with the highest degree of severity will be used.

5 PARTICIPANT CHARACTERISTICS

5.1 PARTICIPANT DISPOSITION

Participants screened and participants screen failed will be summarized overall.

The frequency and percentage of all participants in the following disposition categories will be summarized by treatment group and overall:

- Participants enrolled
- Participants enrolled who received study drug
- Participants enrolled who did not receive study drug
- Participants included in each analysis set (see Section 4.2)
- Participants who completed the study
- Participants who prematurely discontinued study drug
- Participants who prematurely discontinued from the study

The reasons for premature discontinuation of study drug and premature discontinuation from the study will be included in the summary table.

The denominator for the percentage calculation will be the total number of participants in the applicable Safety Population (iSAF or mSAF) corresponding to that column.

Listings of participants will be provided for the following categories by Participant ID number in ascending order:

- Individual reasons for screen failure
- Individual reasons for premature study discontinuation

5.2 DEMOGRAPHIC AND BASELINE DISEASE CHARACTERISTICS

Demographic and baseline disease values will be summarized by descriptive statistics by treatment group and overall for the Induction and Maintenance Periods for applicable Safety Population (iSAF or mSAF).

Participant demographic variables will include:

- Age (years)
- Sex (male, female)
- Race (Asian, Black or African American, White)
- Ethnicity (Hispanic/Latino, Not Hispanic/Latino)
- Body measurements (height, weight [kg], and BMI [kg/m^2])
- Baseline smoking status (never, former, current)

Age is calculated using the formula listed below:

$$Age\ (years)\text{: }Date\ of\ first\ dose\ of\ study\ drug\ -\ date\ of\ birth$$

BMI will be calculated from height and weight measurements collected at screening using the following formula:

$$BMI = Weight\ (kg) / [Height\ (m)]^2$$

Baseline disease variables will include:

- Duration and extent of CD
- Baseline values of the CDAI, SES-CD
- History of intestinal resection for CD [yes, no]

A by-participant demographic and baseline characteristics listing will be provided by participant ID number in ascending order.

5.3 PRIOR AND CONCOMITANT MEDICATION

Prior medications are defined as medications that started and stopped before the first dosing date. If the stop date is unknown or incomplete and the medications cannot be considered as stopped prior to first dosing date then the medications will be considered as concomitant medications (e.g., partial stop date is June 2021, first dosing date is 15 June 2021, medication will be considered as concomitant).

Concomitant medications are defined as medications with a start date prior to or on the first dosing date and continued after the first dosing date. Medications with an onset date later than 30 days after the last dose of EXL01 will not be considered as a concomitant medication. If the start date of a medication is incomplete or missing, the medication will be considered a concomitant

medication, unless the incomplete start date (month and/or year) or the stop date (complete or incomplete) clearly indicate that the medication stopped prior to first dosing date or later than 30 days after the last dosing date. Medication with completely missing start and stop dates will be considered concomitant medication.

Prior and concomitant medications, and prior biological therapy, will be classified into anatomical therapeutic chemical (ATC) drug classes using the World Health Organization (WHO) Drug Dictionary (version B3 Mar 2022 or newer).

Summary of prior and concomitant medications will include the frequency and percentage of participants by ATC Classification Level 2 and Preferred Term (PT).

- A participant will be counted only once within a given drug class and within a given drug name, even if they received the same medication at different times.
- If any prior or concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes.
- The summary tables will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used.
- In case any specific medication does not have ATC classification level 2 coded term, it will be summarized under "Unavailable ATC classification" category.

Prior medications and biologics will be summarized for the iSAF analysis set and concomitant medications will be summarized for either the iSAF and mSAF analysis sets, unless they are different. No formal statistical testing is planned.

All prior and concomitant medications, and prior biologic therapy, will be provided in a by-participant listing by treatment group.

5.4 MEDICAL AND SURGICAL HISTORY

Medical and surgical history will include all relevant surgical and medical history including CD-related complications, other significant conditions, or diseases relevant to the disease under study, previous surgeries for CD, and the extent and duration at baseline.

Medical history will be coded using the most current available version of MedDRA (version 25.0 March 2022 or newer) and will be summarised by System Organ Class (SOC) and PT, unless stated otherwise.

By-participant listings will be provided for those participants with any medical/surgical history for the applicable Safety Population (iSAF or mSAF). No formal statistical testing is planned.

5.5 PROTOCOL DEVIATIONS

Review of all protocol deviations, including COVID-19-related deviations, will be performed on an ongoing basis during the conduct of the study. Protocol deviations will be summarized by type in each treatment group and overall. The frequency and percentage of participants with protocol deviations will be summarized as major/minor (as defined by Good Clinical Practice [GCP]) for the Induction and Maintenance periods. A major deviation is a change from the protocol, pharmacy

manual, or lab manual that may adversely affect the rights, safety, or well-being of the participants, and/or the quality and integrity of data. These are serious findings that are direct violations of GCP principles. The protocol deviation list will be finalised before the database lock and a by-participant listing will be provided for those participants with any protocol deviations.

5.6 TREATMENT EXPOSURE

5.6.1 DURATION OF EXPOSURE

Total duration of exposure to study treatment or corticosteroids is defined as the date of the last dosing date minus the date of the first dosing date plus 1. The total duration of exposure and median duration of exposure to study treatment or corticosteroids will be summarized using descriptive statistics for both parts of the study. Summaries will be provided for the applicable Safety Population (iSAF or mSAF) and included in the Part A interim analysis. For the Part A interim analysis, the number of participants who received more than 6 weeks of EXL01 will also be summarised. Descriptive statistics for exposure along with the frequency and percentage of participants belonging to exposure categories (e.g., > 0 weeks, 6 weeks, > 6 weeks, ≥ 12 weeks, ≥ 18 weeks, 24 weeks) will be provided by treatment group.

5.6.2 COMPLIANCE

Compliance with both corticosteroids and study treatment will be assessed through direct questioning of the participants during visits, review of participant diary entries, and counts of returned packages. In the event of repeated noncompliance, a participant may be removed from the study. A record of the quantity of EXL01 or placebo dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. These records will be used to calculate treatment compliance.

The total number of capsules administered will be summarized using descriptive statistics.

The presumed total number of capsules administered will be determined by the data collected on the eCRF.

Total number of capsules administered = (Sum of No. of capsules) minus (Sum of capsules missed)

The level of treatment compliance will be expressed as a percentage using the following formula:

*Treatment compliance for EXL01 (%) = 100 * total number of capsules administered / total number of capsules that should been taken while on study.*

Descriptive statistics for compliance rate along with the frequency and percentage of participants belonging to compliance categories (e.g., < 80%, 80% to <100%, 100% to < 120%, ≥ 120%) will be provided by treatment group for the applicable Safety Population (iSAF or mSAF). No formal statistical testing is planned.

A by-participant listing of study drug administration and drug accountability will be provided separately by treatment group and participant ID number (in ascending order).

6 EFFICACY ANALYSES

6.1 DERIVATION OF EFFICACY ANALYSES

6.1.1 CROHN'S DISEASE ACTIVITY INDEX

The CDAI consists of 8 items including physical examination items, extraintestinal manifestations, the haematocrit, and patient-reported outcome measures (number of liquid or very soft stools/day, abdominal pain, and general well-being), which are recorded in a participant diary card for the 7 days prior to the clinic visit. At Screening the PRO measures may be based on participant recall for the preceding week if no diary data is available. At Visit 1, to avoid delays in reconfirming eligibility, the CDAI score will be based on the haematocrit value obtained at Screening. Each item is multiplied by a weighting factor and summed up to give a total CDAI score. The total CDAI score ranges from 0 to 600 points, with a higher score representing more severe disease activity.[1]

Endpoints based on the CDAI score are defined below:

- Clinical response: defined as CDAI decrease from baseline $\geq$ 70
- Clinical remission: defined as CDAI score < 150
- Clinical relapse: defined as > 70-point increase in CDAI from baseline of the Maintenance Period for 2 consecutive weeks
- Time to clinical relapse: defined as the time from the first dose of study treatment to first documented clinical relapse

6.1.2 SIMPLE ENDOSCOPIC SCORE FOR CROHN'S DISEASE

The SES-CD scores 4 endoscopic items (ulcer size, proportion of ulcerated surface, proportion of the surface area affected by any disease lesion, and stenosis), from 0 to 3, with higher scores representing more severe endoscopic disease activity.[2] Each item is scored for the 5 intestinal segments (ileum, right colon, transverse colon, left colon, and rectum) and summed to provide the total item score. The SES-CD score is then calculated as the total sum of the item scores (Appendix 1). Each participant will have a single SES-CD score per time point provided by a central reader based on consensus scoring rules.

Endpoints based on the SES-CD score are defined below:

- Mucosal healing: defined as a SES-CD < 4 with no deep ulcers
- Endoscopic response: defined as an SES-CD score decrease by 50%

6.1.3 GLOBAL HISTOLOGY ACTIVITY SCORE

The Global Histology Activity Score (GHAS) is comprised of the extent and/or severity of 7 histologic variables. Four variables (epithelial damage, architectural changes, infiltration of mononuclear cells in the lamina propria, and infiltration of polymorphonuclear cells in the lamina propria) are scored from 0 to 2, and 1 variable (polymorphonuclear cells in epithelium) is scored from 0 to 3 (Appendix 2).[3] The presence of erosions and/or ulcers, and the presence of granuloma are scored 1 if present, or 0 if absent. Finally, an adjustment for the number of affected biopsies is provided by scoring from 0 (none) to 3 (> 66% of biopsies).

The total GHAS is calculated by summing the scores for each histological variable (range: 0 to 16), with higher scores representing more severe disease activity. Disease activity is scored separately for colonic (Colonic Global Histologic Disease Activity Score) and ileal (Ileal Global Histologic Disease Activity Score) biopsies.

Endpoints based on the GHAS score are defined below:

- Mean change in GHAS score

6.1.4 ROBARTS HISTOPATHOLOGY INDEX

The RHI includes 4 items: 1) the extent of chronic inflammatory cell infiltration, 2) neutrophils in the lamina propria, 3) neutrophils in the epithelium, and 4) erosions and ulceration (Appendix 3).[4] Each item is scored from 0 to 3 and multiplied by a weighting factor and summed to give the overall RHI score, with total scores ranging from 0 (no disease activity) to 33 (severe disease activity).

Endpoints based on the RHI score are defined below:

- Mean change in RHI score

6.2 EFFICACY ENDPOINTS

Unless otherwise stated, all efficacy variables will be analysed for the mSAF and PP analysis sets.

By-participant listings for all efficacy endpoints will be provided for the final analysis.

6.2.1 BINARY EFFICACY ENDPOINTS

The definition of the binary efficacy endpoints (i.e., responders or nonresponders) are listed in order of importance in Table 2. All binary endpoints will be summarized by treatment group using frequency distribution. As Part A only includes one treatment group, between-group comparisons will not be performed. Missing values in the categorical endpoint will be imputed as nonresponders.

Table 2 Definition of Binary Efficacy Endpoints

Binary Endpoint	Measure	Definition
Clinical Remission	CDAI	CDAI score < 150
Mucosal Healing	SES-CD	SES-CD < 4 with no deep ulcers
Endoscopic Response	SES-CD	SES-CD score decrease by 50%

Abbreviations: CDAI, Crohn's Disease Activity Index; SES-CD, Simple Endoscopic Score for Crohn's Disease.

6.2.2 CONTINUOUS EFFICACY ENDPOINTS

The definition of the continuous efficacy endpoints (mean change from baseline) are listed in Table 3.

Table 3 Definition of Continuous Efficacy Endpoints

Measure	Definition
GHAS	Mean change in GHAS score
RHI	Mean Change in RHI score

Abbreviations: GHAS, Global Histologic Disease Activity Score; RHI, Robarts Histopathology Index.

Continuous endpoints will be summarized by treatment group using descriptive statistics of the values at each visit and the change from baseline at maintenance to each post-baseline visit. Descriptive statistics will include mean, median, SD, minimum, and maximum. Missing values of the continuous endpoints will not be imputed, and the analysis will be performed based on observed data. As Part A only includes one treatment group, between-group comparisons will not be performed.

6.2.3 MULTIPLICITY

As this analysis is exploratory in nature, no adjustment for multiplicity or gatekeeping of endpoints is required.

7 SAFETY ANALYSES

All AEs will be coded according to the MedDRA dictionary version 25.0 or newer. AEs will be presented by SOC and PT, unless stated otherwise.

Safety analyses will be performed using the applicable Safety Population (iSAF or mSAF). Assessments will be made by evaluating all reported AEs, physical examination findings, and changes in laboratory analytes, ECGs, and vital signs. Safety will be evaluated via descriptive statistics. No statistical analysis will be performed.

For the interim analysis, safety endpoints will be evaluated for participants who have completed a minimum of 6 weeks of EXL01 treatment or follow-up in Part A. For the final analysis, safety endpoints will be evaluated for all participants in Parts A.

7.1 DEFINITIONS

7.1.1 PRETREATMENT ADVERSE EVENTS

A PTAE is defined as any untoward medical occurrence in a clinical study participant, who has provided documented informed consent to participate in a study, that occurs prior to administration of EXL01; it does not necessarily have to have a causal relationship with study participation.

Collection of PTAEs will commence from the time informed consent to participate in the study is documented and continue until the participant is first administered study medication (EXL01). For participants who discontinue prior to study medication (EXL01) administration, PTAEs will be collected until the participant discontinues study participation.

Medical occurrences that begin before the start of study treatment (EXL01) but after starting the Induction Period corticosteroid treatment will be recorded as a PTAE in the CRF.

7.1.2 TREATMENT-EMERGENT ADVERSE EVENTS

Treatment-Emergent Adverse Events (TEAE) are defined as AE onset date ≥ first study treatment (EXL01) date. The frequencies of TEAEs will be presented including frequency and percentage of participants having experienced an event and the total number of events.

7.1.3 SERIOUS ADVERSE EVENTS

Serious adverse events will be identified and captured as SAEs if AEs met the definitions of SAEs that were specified in the study protocol (Section 10.6.1.5).

7.2 Classification of Adverse Events

7.2.1 SEVERITY

The severity of AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The general categories for each grade are presented in Table 4.

Table 4 Adverse Event Severity Grading

Grade	Severity	Alternate Description
1	Mild (apply event-specific NCI-CTCAE grading criteria)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate (apply event-specific NCI-CTCAE grading criteria)	Minimal; local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
3	Severe (apply event-specific NCI-CTCAE grading criteria)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
4	Very severe, life-threatening, or disabling (apply event-specific NCI-CTCAE grading criteria)	Life-threatening consequences; urgent intervention indicated
5	Death related to AE	Death related to AE

Abbreviations: AE, adverse event; ADL, activities of daily living; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Instrumental activities of daily living (ADL) refers to preparing meals, shopping for groceries, or clothes, using the telephone, managing money, etc. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

7.2.2 Assessment of Causality

The investigator will assess the relationship of the AE to study treatment (study drug) as “not related”, “unlikely”, “possible”, “probable”, or “definite”. For the purposes of safety analyses, all AEs classified with a relationship to study treatment as “possible”, “probable”, or “definite” will be considered drug-related events.

7.2.3 Incomplete Dates

If the onset date of AE is incomplete and the AE stop date is not prior to the first dosing date of study treatment, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment-emergent. An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study treatment, will be considered treatment-emergent. In addition, an AE with onset date missing and incomplete stop

date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study treatment will be considered treatment-emergent.

7.3 SUMMARIES OF ADVERSE EVENTS

AEs will be summarized based on the applicable Safety Analysis Set (iSAF or mSAF). If a participant experienced more than 2 AEs for a given PT, severity is defined as the severity of the most severe event and relationship to study drug is the relationship of the most related event.

A high-level summary table will be provided summarizing the frequency and percentage of participants experiencing any AEs, any AEs leading to study drug discontinuation, any EXL01-related AEs, any SAEs, any SAEs leading to study drug discontinuation, any EXL01-related SAEs, and any AEs leading to death.

Summary tables of AEs listed below will be provided for induction and maintenance periods:

- AEs, in total and sorted by frequency
- Drug-related AEs
- CD related AEs
- AEs by CTCAE Grade and maximum CTCAE Grade
- AEs CTCAE Grade 3-5
- AEs leading to discontinuation of study drug
- Drug-related AEs leading to discontinuation of study drug
- COVID-related AEs
- SAEs
- Drug-related SAEs leading to discontinuation of study drug
- SAEs CTCAE Grade 3-5
- Special Interest AEs including septicaemia/sepsis, anaphylactoid reaction/allergic reaction, and severe anaemia requiring blood transfusion
- AEs leading to study drug-interruption
- AEs leading to dose reduction during the Induction Period
- Fatal AEs

7.4 PHYSICAL EXAMINATION

A full physical examination will be performed at Screening and the End of Study visit. A full physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems.

Clinically significant abnormal findings at Screening will be recorded as medical history. After the first dose of study intervention (start of the Induction Period), new clinically significant

abnormal findings will be recorded as pretreatment AEs (during the Induction Period) or AEs (during the Maintenance Period, after start of EXL01).

All abnormal physical examination findings will be presented in a by-participant listing.

7.5 VITAL SIGNS

Descriptive statistics and abnormal clinical findings will be provided by treatment group for vital signs (blood pressure [mm Hg], pulse rate [bpm], respiratory rate, temperature), as follows:

- Baseline values
- Values at each post-baseline visit
- Change from baseline at each post-baseline visit

In the case of multiple values in an analysis visit, data will be selected for analysis as described in Section 4.3.

A by-participant listing of vital signs will be provided by treatment group, participant ID number, and visit in chronological order.

7.6 CLINICAL LABORATORY TESTS

Descriptive statistics will be provided for each laboratory test (haematology, clinical chemistry, and urinalysis).

Abnormal findings and their clinical significance for each clinical laboratory parameter will be summarized in a separate table. In the case of multiple values in an analysis visit, data will be selected for analysis as described in Section 4.3.

In the by participant listings, laboratory values which fall outside the reference ranges and abnormal findings will be flagged. The listing will include treatment group, participant ID, laboratory parameter, analyte name, laboratory collection date/time, and analyte finding.

7.7 ELECTROCARDIOGRAMS

Single 12-lead ECG will be obtained using an ECG machine that automatically reports heart rate and PR, QRS, and QT intervals.

ECG values outside the normal range will be summarized. The overall interpretation of the ECG results (Normal; Abnormal, not Clinically Significant; and Abnormal, Clinically Significant) will be included.

ECG data will be included in a by-participant listing.

Clinically significant abnormal findings at Screening should be recorded as medical history and clinically significant abnormal findings of any subsequent ECGs, that are not detected at Screening, should be recorded as PTAEs or AEs.

7.8 LIVER SAFETY MONITORING – HY'S LAW CASES

Following Hy's law, the frequency and percentage of participants with the following elevations in hepatic laboratory tests will be summarized for the Induction period and Maintenance period:

- ALT ≥ 3x upper limit of normal (ULN) **or** AST ≥ 3x upper limit of normal (ULN) and

- Total bilirubin level (TBL) ≥ 2xULN

They will be broken up between Normal and Abnormal (clinically significant or nonclinically significant). Participants with the above elevations will be presented in a by-participant listing.

8 OTHER ANALYSES

8.1 TIME TO EVENT ANALYSIS

Time to event analysis using the Kaplan-Meier method (SAS PROC LIFETEST) will be used to assess time to clinical relapse, defined as the time from the first dose of study treatment to first documented clinical relapse. Participants who can no longer be assessed for the event will be censored at their last evaluable visit. The time to event analysis will be performed on the mSAF population.

8.2 HEALTH-RELATED QUALITY OF LIFE ANALYSIS

Health-related quality of life (HRQoL) endpoints will be summarised descriptively for the mSAF analysis set.

8.2.1 INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE

The Inflammatory Bowel Disease Questionnaire (IBDQ) is a self-administered disease-specific HRQoL instrument for patients with inflammatory bowel disease. The IBDQ covers 4 dimensions: bowel symptoms, systemic symptoms, emotional function, and social function. Items are scored on a 7-point Likert scale, for a total global score in the range 32 to 224 (with higher scores indicating better HRQoL).[5] See Appendix 4.

Summary statistics of the absolute and change from baseline scores for IBDQ total score and each subscale score will be displayed by treatment group and visit.

IBDQ Scores will be calculated as follows:

- The question on the same day of measurement will be used for calculation of each subscore and total score.
- The value of each question after imputing missing data will be used for the calculation of each subscore.
- For each subscore, sum of the questions will be round off to the first decimal place.
- IBDQ total score: sum of all questions and round off to the first decimal places.

The instructions on how the IBDQ score is calculated in the presence of missing or incomplete information is provided below with detailed scenarios given in Table 5. Rules for handing missing data:

1. If all domains have at most 1 missing item, a missing item may be imputed by using the average score of the remaining items of each respective domain. Both the subscores of all 4 domains and the full IBDQ score will be computed. See example scenarios A, B, and C.
2. If (a) 1 domain has 2 missing items, (b) the other 3 domains have at most 1 missing item, and (c) the total number of missing items across all domains does not exceed 4, then the full IBDQ score will be computed by imputing each missing item by using the average

score of the remaining items of each respective domain. However, the subscores will be computed only for the domains with at most 1 missing item (as described in Rule 1 above). See example scenarios D, E, and F.

3. If (a) more than 1 domain has 2 missing items or (b) at least 1 domain has at least 3 missing items, then the full IBDQ score will be set as missing. However, the subscores will be computed only for the domains with at most 1 missing items (as described in Rule 1 above). See example scenarios G and H.

Table 5 IBDQ Missing Data Instructions

	Number of Missing Values				Comments/Actions
Scenario	**Bowel Symptoms Subscore**	**Systemic Symptoms Subscore**	**Emotional Function Subscore**	**Social Function Subscore**	
A	0	0	0	0	We can compute both the 4 subscores and the full IBDQ
B	1	0	0	0	We can compute both the full IBDQ and the 4 subscores, by replacing the missing value with the average of the available items in Bowel Symptoms Subscore
C	1	1	1	1	We can compute both the full IBDQ and the 4 subscores, by replacing the missing value with the average of the available items in each domain respectively
D	2	0	0	0	We can compute the full IBDQ by replacing the 2 missing values with the average of the available items in Bowel Sumptoms subscore. We can compute only 3 subscores (systemic symptoms, emotional function, social function)
E	2	1	0	1	We can compute the full IBDQ by replacing the missing values with the average of the available items in each of the domains respectively. We can compute only 3 subscores (systemic symptoms, emotional function, social function).
F	2	1	1	1	We cannot compute the full IBDQ (as more than 4 items are missing). We can compute only 3 subscores (systemic symptoms, emotional function, social function).
G	2	2	0	0	We cannot compute the full IBDQ because 2 items are missing in more than one domain (even though the total number of missing value does is not exceeding 4). We can compute only 2 subscores (emotional function, social function).
H	0	0	3	0	We cannot compute the full IBDQ because more than 2 items are missing in one domain. We can compute only 3 subscores (bowel symptoms, systemic symptoms, social function).

Abbreviations: IBDQ, Inflammatory Bowel Disease Questionnaire.

8.2.2 SF-36

The SF-36 consists of 36 questions in 8 different dimensions: general health, physical functioning, physical limitations, emotional limitations, bodily pain, vitality, social functioning and mental health. These 8 dimensions are summarized by 2 component scales – the physical component and mental component summary scales, with each scale ranging from 0 to 100, with higher scores representing a better health state.

8.2.3 2-ITEM PATIENT-REPORTED OUTCOME MEASURE

The 2-item patient-reported outcome measure (PRO2) consists of the 2 CDAI component items: daily stool frequency and abdominal pain. Participants record the number of liquid or very soft stools and a rating for abdominal pain (from 0-3; with higher scores indicating worse pain) (see Protocol Table 6). The average of the daily entries for the 7-day period is calculated and multiplied by a weighting factor to provide a total score for each component item. The total PRO2 score is then calculated by summing the component item scores. Summary statistics of the absolute and change from baseline scores for PRO2 will be displayed by visit.

8.3 BIOMARKER ANALYSIS

Biomarker endpoints as defined in Table 6 will be summarised descriptively for the mSAF analysis set.

Table 6 Definition of Biomarker Endpoints

Measure	Definition
Fecal calprotectin	Mean change in fecal calprotectin from baseline
CRP	Mean change in CRP from baseline

Abbreviations: C-reactive protein.

Listings and descriptive statistics will be provided by treatment group for each biomarker specified in the study protocol as follows:

- Baseline values
- Values at each post-baseline visit
- Change from baseline at each post-baseline visit
- % change from baseline at each post-baseline visit

In the case of multiple values in an analysis visit, data will be selected for analysis as described in Section 4.3.

9 INTERIM ANALYSIS

A safety interim analysis was conducted after a minimum of 6 weeks of EXL01 treatment or follow-up data for a target of 6 participants in Part A had been collected. Results of the safety interim analysis were be reviewed by the IDMC. The analyses provided for the interim analysis are outlined in SAP Version 1.0.

10 SUMMARY OF CHANGES

10.1 SUMMARY OF CHANGES BETWEEN THE PROTOCOL AND SAP

The statistical changes between the current SAP and the latest version of protocol are listed below:

- Hy's law cases will be summarized as described in Section 7.8.
- As Part A only includes one treatment group, efficacy endpoints are now being described descriptively.

10.2 SUMMARY OF CHANGES FROM PREVIOUS SAP

This version 2 of the SAP has been updated to remove references to Part B of the study and adjust for final analysis of Part A only.

11 SAP REVISION HISTORY

Version	Effective Date	Reason
01	12DEC2022	New
02	31OCT2024	Removed references to Part B; final to be performed on Part A only

12 REFERENCES

1. Best WR, Becktel JM, Singleton JW, Kern F, Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology. 1976 Mar;70(3):439-44. doi:10.1016/S0016-5085(76)80163-1
2. Daperno M, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc. 2004 Oct;60(4):505-12. doi:10.1016/s0016-5107(04)01878-4
3. D'Haens GR, Geboes K, Peeters M, Baert F, Penninckx F, Rutgeerts P. Early lesions of recurrent Crohn's disease caused by infusion of intestinal contents in excluded ileum. Gastroenterology. 1998 Feb;114(2):262-7. doi:10.1016/s0016-5085(98)70476-7
4. Mosli MH, Feagan BG, Zou G, Sandborn WJ, D'Haens G, Khanna R, et al. Development and validation of a histological index for UC. Gut. 2017 Jan;66(1):50-8. doi:10.1136/gutjnl-2015-310393
5. Guyatt G, Mitchell A, Irvine EJ, Singer J, Williams N, Goodacre R, et al. A new measure of health status for clinical trials in inflammatory bowel disease. Gastroenterology. 1989 Mar;96(3):804-10.

APPENDIX 1: Simple Endoscopic Score for Crohn's Disease

Variable	SES-CD Values			
	0	**1**	**2**	**3**
Size of ulcers	None	Aphthous ulcers (0.1 < 0.5 cm)	Large ulcers (> 0.5 – 2 cm)	Very large ulcers (> 2.0 cm)
Ulcerated surface (%)	None	< 10%	10-30%	> 30%
Affected surface (%)	Unaffected segment	< 50%	50-75%	> 75%
Presence of narrowing	None	Single, can be passed	Multiple, can be passed	Cannot be passed

	Ileum	Right colon	Transverse colon	Left colon	Rectum	Total
Presence and size of ulcers (0-3)						
Extent of ulcerated surface (0-3)						
Extent of affected surface (0-3)						
Presence and type of narrowings (0-3)						
					Total SES-CD =	

Source: Daperno M et al. Gastrointest Endosc. 2004.

APPENDIX 2: Global Histologic Disease Activity Score

Histological Variable	Description	Scores Allowed for Histologic Remission
Epithelial damage	0 normal 1 focal pathology 2 extensive pathology	0
Architectural changes	0 normal 1 moderately disturbed (<50%) 2 severely disturbed (>50%)	0-2
Infiltration of mononuclear cells in the lamina propria	0 normal 1 moderate increase* 2 severe increase**	0-2
Infiltration of polymorphonuclear cells in the lamina propria	0 normal 1 moderate increase* 2 severe increase**	0
Polymorphonuclear cells in epithelium	0 absent 1 in surface epithelium 2 cryptitis 3 crypt abscess	0
Presence of erosion and/or ulcers	0 no 1 yes	0
Presence of granuloma	0 no 1 yes	0-1
Number of biopsy specimens affected	0 none 1 < 33% (1 or 2 of 6) 2 33–66% (3 or 4 of 6) 3 > 66% (5 or 6 of 6)	0-3

Note: *Moderate increase, up to twice the number of cells that can normally be expected; ** Severe increase, more than twice the normal number of cells.
Source: D'Haens GR et al. Gastroenterology. 1998.

APPENDIX 3: Robarts Histopathology Index

Histological Variable	Grading	Multiplication Factor
Chronic inflammatory infiltrate	0=No increase 1=Mild but unequivocal increase 2=Moderate increase 3=Marked increase	X1
Lamina propria neutrophils	0=None 1=Mild but unequivocal increase 2=Moderate increase 3=Marked increase	X2
Neutrophils in epithelium	0=None 1= < 5% crypts involved 2= < 50% crypts involved 3= > 50% crypts involved	X3
Erosion or ulceration	0=No erosion, ulceration, or granulation tissue 1=Recovering epithelium + adjacent inflammation 1=Probably erosion-focally stripped 2=Unequivocal erosion 3=Ulcer or granulation tissue	X5

Source: Mosli MH et al. Gut. 2017.

APPENDIX 4: Inflammatory Bowel Disease Questionnaire

INSTRUCTIONS FOR SELF-ADMINISTERED IBDQ

This questionnaire is designed to measure the effects of your inflammatory bowel disease on your daily function and quality of life. You will be asked about symptoms you have been having as a result of your bowel disease, the way you have been feeling in general, and how your mood has been.

There are two versions of this questionnaire, the IBDQ and IBDQ-Stoma. If you have a colostomy or ileostomy, you should complete the IBDQ-Stoma. Questions 1, 5, 17, 22, 24 and 26 are slightly different in each version. Be sure you have the correct questionnaire.

On this questionnaire there are 32 questions. Each question has a graded response numbered from I through 7. Please read each question carefully and circle/mark the number which best describes how you have been feeling in the past 2 weeks.

EXAMPLE

How often have you felt unwell as a result of your bowel problem in the past 2 weeks?

(1) ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

If you are having trouble understanding a question, **STOP** for a moment! Think about what the question means to you. How is it affected by your bowel problem? Then answer the question as best you can. You will have the chance to ask the research assistant questions after completing the questionnaire. This takes only a few minutes to complete.

QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last two weeks by picking one of the options from

1 BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN
2 EXTREMELY FREQUENT
3 VERY FREQUENT
4 MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
5 SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
6 SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
7 NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

3. How often during the last 2 weeks have you felt frustrated, impatient, or restless? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

5. How much of the time during the last 2 weeks have your bowel movements been loose? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

6. How much energy have you had during the last 2 weeks? Please choose an option from

1 NO ENERGY AT ALL
2 VERY LITTLE ENERGY
3 A LITTLE ENERGY
4 SOME ENERGY
5 A MODERATE AMOUNT OF ENERGY
6 A LOT OF ENERGY
7 FULL OF ENERGY

7. How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

8. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

9. How often during the last 2 weeks have you been troubled by cramps in your abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

10. How often during the last 2 weeks have you felt generally unwell? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

11. How often during the last 2 weeks have you been troubled because of fear of not finding a washroom? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from

1 A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
2 A LOT OF DIFFICULTY
3 A FAIR BIT OF DIFFICULTY
4 SOME DIFFICULTY
5 A LITTLE DIFFICULTY
6 HARDLY ANY DIFFICULTY
7 NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES

13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

14. How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

15. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

16. How often during the last 2 weeks have you had to avoid attending events where there was no washroom close at hand? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

17. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

18. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to, the weight you would like to be at? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

21. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option from

1 NONE OF THE TIME
2 A LITTLE OF THE TIME
3 SOME OF THE TIME
4 A GOOD BIT OF THE TIME
5 MOST OF THE TIME
6 ALMOST ALL OF THE TIME
7 ALL OF THE TIME

22. How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

23. How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

25. How much of the time during the last 2 weeks have you felt tearful or upset? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

28. To what extent has your bowel problem limited sexual activity during the last 2 weeks? Please choose an option from

1 NO SEX AS A RESULT OF BOWEL DISEASE
2 MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE
3 MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE
4 SOME LIMITATION AS A RESULT OF BOWEL DISEASE
5 A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE
6 HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE
7 NO LIMITATION AS A RESULT OF BOWEL DISEASE

29. How much of the time during the last 2 weeks have you been troubled by nausea or feeling sick to your stomach? Please choose an option. from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

30. How much of the time during the last 2 weeks have you felt irritable? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

31. How often during the past 2 weeks have you felt a lack of understanding from others? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

32. How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks? Please choose one of the following options from

1 VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
2 GENERALLY DISSATISFIED, UNHAPPY
3 SOMEWHAT DISSATISFIED, UNHAPPY
4 GENERALLY SATISFIED, PLEASED
5 SATISFIED MOST OF THE TIME, HAPPY
6 VERY SATISFIED MOST OF THE TIME, HAPPY
7 EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASED