PROTOCOL

PROTOCOL TITLE:	**A PHASE III, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, TREAT-THROUGH STUDY TO ASSESS THE EFFICACY AND SAFETY OF INDUCTION AND MAINTENANCE THERAPY WITH RO7790121 IN PATIENTS WITH MODERATELY TO SEVERELY ACTIVE CROHN'S DISEASE**
PROTOCOL NUMBER:	GA45331
STUDY NAME:	SIBERITE-1
VERSION NUMBER:	1
TEST PRODUCT:	RO7790121
STUDY PHASE:	Phase III
REGULATORY AGENCY IDENTIFIERS:	IND Number: 118298 EU CT Number: 2024-513053-69-00 NCT Number: To be determined
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4058 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

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I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor to the contact provided below.

|Name|
|Address|

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**A PHASE III, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, TREAT-THROUGH STUDY TO ASSESS THE EFFICACY AND SAFETY OF INDUCTION AND MAINTENANCE THERAPY WITH RO7790121 IN PATIENTS WITH MODERATELY TO SEVERELY ACTIVE CROHN'S DISEASE**
REGULATORY AGENCY IDENTIFIERS:	IND Number: 118298 EU CT Number: 2024-513053-69-00 NCT Number: To be determined

STUDY RATIONALE

The purpose of this study is to assess the efficacy and safety of RO7790121 (formerly PF-06480605 and RVT-3101) in patients with moderately to severely active Crohn's disease (CD). RO7790121 is a fully human neutralizing immunoglobulin G monoclonal antibody (mAb) against tumor necrosis factor-like ligand 1A (TL1A). TL1A plays a central role in the regulation of gut mucosal immunity and participates in immunological and fibrosis pathways involved in inflammatory bowel disease pathogenesis by binding its receptor, death receptor 3.

Therapeutic options have expanded substantially over the past decade, with biologics (e.g., anti-tumor necrosis factor, anti-IL 12/IL 23, and anti-integrin molecule mAbs) and small molecule treatments (e.g., Janus kinase inhibitor upadacitinib) now available in addition to conventional therapies. However, a high unmet medical need remains for treatments with better benefit–risk profiles that attenuate inflammation and clinical sequelae and provide sustained control to improve the long-term prognosis of patients with CD.

OBJECTIVES AND ENDPOINTS

Primary Objective	Corresponding Endpoints
• To evaluate the efficacy of RO7790121 compared with placebo in maintaining remission	• Clinical remission, defined as CDAI <150, at Week 52 • Endoscopic response, defined as decrease in SES-CD from baseline $\geq 50\%$, at Week 52

CDAI = Crohn's disease activity index; SES-CD = Simple Endoscopic Score for Crohn's disease.

Key Secondary Objectives	Corresponding Endpoints
• To evaluate the efficacy of RO7790121 compared with placebo in inducing response	• Clinical remission, as defined above, at Week 12 • Endoscopic response, as defined above, at Week 12 • Symptomatic remission, defined as SF ≤ 2.8 and APS ≤ 1 with neither score greater than baseline, at Week 12 • Endoscopic remission, defined as SES-CD = 0 to 4 with decrease from baseline ≥ 2 and no subscore >1, at Week 12 • Ulcer-free endoscopy, defined as SES-CD ulcerated surface subscore of 0, at Week 12 • SF, from baseline through Week 12 • APS, from baseline through Week 12

Key Secondary Objectives (cont.)	Corresponding Endpoints (cont.)
To evaluate the efficacy of RO7790121 compared with placebo in maintaining response	• Endoscopic remission, as defined above, at Week 52 • Symptomatic remission, as defined above, at Week 52 • Corticosteroid-free clinical remission, defined as clinical remission at Week 52 and no use of corticosteroids for CD at least 8 weeks prior to Week 52 • Maintenance of clinical remission, defined as clinical remission at both Weeks 12 and 52 • Maintenance of endoscopic response, defined as endoscopic response at both Weeks 12 and 52 • Clinical remission and endoscopic remission at Week 52 • Ulcer-free endoscopy, as defined above, at Week 52
To evaluate the efficacy of RO7790121 compared with placebo in terms of CD related symptoms and health-related quality of life	• Bowel urgency, from baseline through Week 12 and Week 52 • Fatigue, as measured by FACIT-F, from baseline to Week 12 and Week 52 • IBDQ score, from baseline to Week 12 and Week 52
To evaluate the efficacy of RO7790121 compared with placebo in TL1A biomarker-defined subgroups	Among TL1A biomarker-defined subgroups of participants: • Clinical remission at Week 12 • Clinical remission at Week 52 • Endoscopic response at Week 12 • Endoscopic response at Week 52

APS = average of daily abdominal pain scores in the past week; CD = Crohn's disease; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue Scale; IBDQ = Inflammatory Bowel Disease Questionnaire; SES-CD = Simple Endoscopic Score for Crohn's disease; SF = average of daily number of liquid or very soft stools in the past week; TL1A = tumor necrosis factor-like ligand 1A.

Other Secondary Objectives	Corresponding Endpoints
To evaluate the efficacy of RO7790121 compared with placebo in inducing and/or maintaining response	• Clinical response, defined as a decrease in CDAI from baseline ≥ 100, at Week 12 • Symptomatic response, defined as decrease in SF and APS ≥ 30% with neither greater than baseline, at Week 12
To evaluate the efficacy of RO7790121 compared with placebo in terms of the participant's global impressions and general well-being	• Overall change in CD symptoms, as measured by PGIC, from baseline to Weeks 2, 6, 12, and 52 • Overall severity in CD symptoms, as measured by PGIS, from baseline to Weeks 2, 6, 12, and 52 • General well-being, from baseline through Week 52
To evaluate the safety of RO7790121 compared with placebo	• Incidence and severity of the following: • Adverse events • Serious adverse events • Adverse events leading to study treatment discontinuation • Adverse events of special interest

Other Secondary Objectives (cont.)	Corresponding Endpoints (cont.)
To evaluate the persistence of fistulas of participants treated with RO7790121 compared to placebo	Presence of draining fistulas from baseline through Week 12 and Week 52

APS = average of daily abdominal pain scores in the past week; CD = Crohn's disease; CDAI = Crohn's disease activity index; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; SF = average of daily number of liquid or very soft stools in the past week.

As noted by the ICH E9(R1), the availability or interpretation of endpoint measurements may be affected by the occurrence of intercurrent events (ICH 2020) arising between randomization and endpoint assessment. Strategies to address anticipated intercurrent events are summarized in Table 5.

OVERALL DESIGN AND STUDY POPULATION

This Phase III, multicenter, double-blind, placebo-controlled, treat-through study will evaluate the efficacy and safety of RO7790121 compared with placebo in patients with moderately to severely active CD.

Several key aspects of the study design and study population are summarized below.

Phase:	Phase III	**Population Type:**	Adult patients and patients aged 16 to < 18 years where locally permissible
Control Method:	Placebo	**Population Diagnosis or Condition:**	Moderately to severely active Crohn's disease
Interventional Model:	Parallel groups	**Population Age:**	Age ≥ 18 to ≤ 80 years and patients aged 16 to < 18 years where locally permissible
Test Product:	RO7790121	**Site Distribution:**	Multi-site
Active Comparator:	Not applicable	**Study Treatment Assignment Method:**	Randomization
Number of Arms:	Three arms	**Number of Participants to Be Enrolled:**	Approximately 600

STUDY TREATMENT

RO7790121 (500 mg) or placebo will be administered IV at Weeks 0, 2, 6, and 10 (induction phase). RO7790121 (450 mg or 150 mg) or placebo will then be administered SC every 4 weeks (Q4W) from Week 12 through Week 52 (maintenance phase). In the open-label extension phase, RO7790121 will be administered either 450 mg SC Q4W or 450 mg SC every 2 weeks (Q2W) (see Section 4.1.3.3). Modification of the study drug dose is not permitted during the double-blind phases of the study. However, dose intensification or de-escalation (either from Q4W to Q2W or from Q2W to Q4W, respectively) may be permitted during the OLE phase (see Section 4.1.3). Any other dosing frequencies (e.g., weekly dosing) are not permitted (see Section 6.1.1).

DURATION OF PARTICIPATION

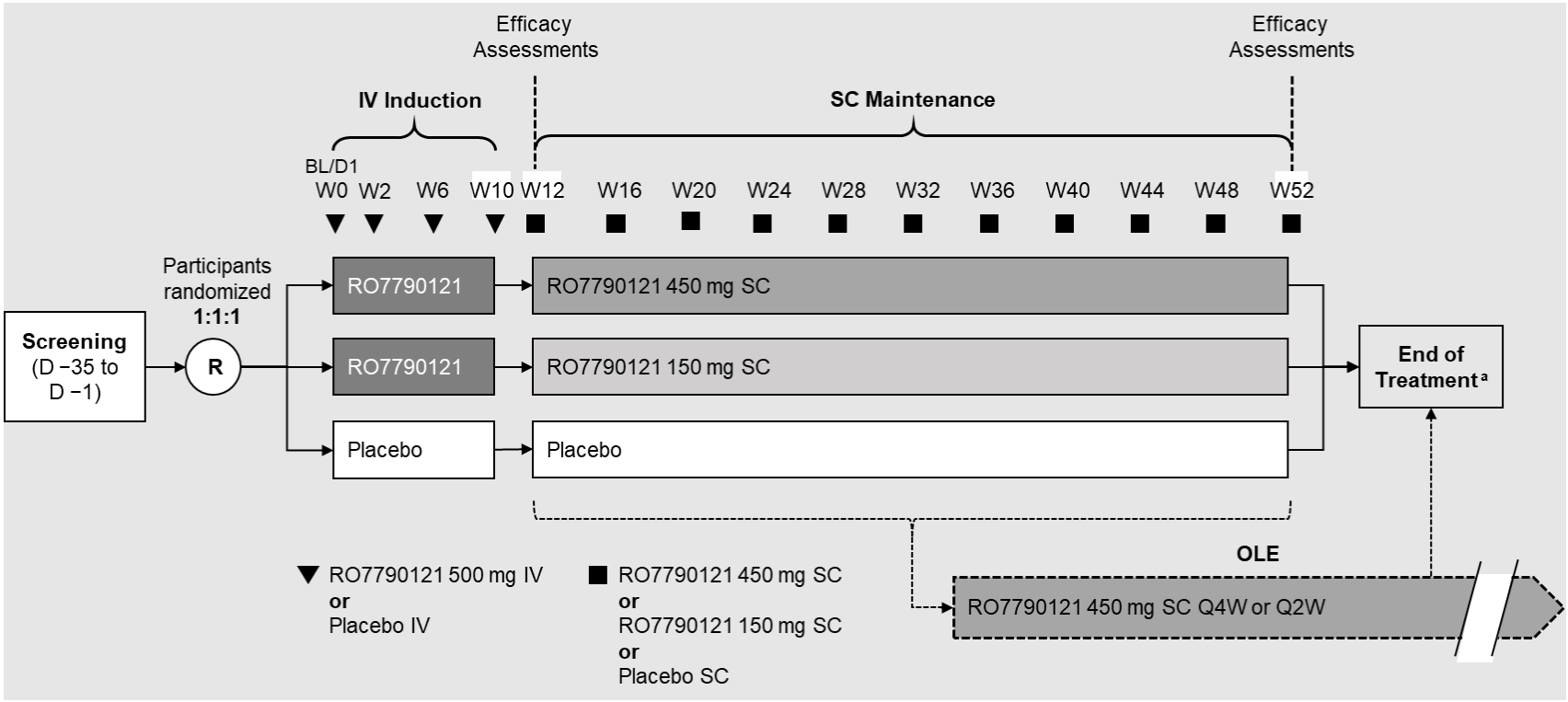
The total maximum duration of study participation for an individual is expected to be approximately 70 weeks without OLE participation. With OLE participation, treatment will continue until RO7790121 is commercially available in that region or until the Sponsor decides to terminate the study, whichever is earlier.

COMMITTEES

Independent Committees:	Independent Data Monitoring Committee
Other Committees:	Not applicable

1.2 STUDY SCHEMA

Figure 1 Study Schema



BL = baseline; D = Day; OLE = open-label extension; Q2W = every 2 weeks; Q4W = every 4 weeks; R = randomization; W = Week.

Notes: At applicable study visits, all efficacy assessments must be completed prior to study treatment dosing. For OLE eligibility and dose schedule, see Section 4.1.3.

[a] Participants who discontinue treatment prematurely will have a treatment discontinuation/early withdrawal visit. Safety follow-up visits will occur 6 and 12 weeks after the final dose of study treatment.

1.3 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION SCHEDULE

Table 1 Schedule of Activities: Induction Phase

Week(s) (Window, Days)	Protocol Reference	Screening [a]	Treatment				Efficacy Assess [b]	UV [c]	Tx Disc/ Early Withdrawal [d]	Post-Treatment [e]	
		−35 to −1 Days	0	2 (±3)	6 (±3)	10 (±3)	12 (±7)			6-Wk SFU [d] (±7)	12-Wk SFU (±7)
Informed consent [f]	8, A1–3	x									
Review eligibility criteria	5.1, 5.2	x	x [g]								
Demographics	8	x									
Medical history and baseline conditions	8	x									
Randomization	6.3		x								
Single 12-lead ECG [h]	8.2.3	x					x	(x)	x		
Vital signs	8.2.2	x	x	x	x	x	x	x	x		x
Weight	—	x	x	x	x	x	x	(x)	x		
Height	—	x									
Physical examination [i]	8.2.1	x			x		x	(x)	x		x
Fistula examination [j]	8.1.9	x	x		x		x		x		x
eDiary training	A6–1	x									
eDiary PROs (SF, AP, general well-being, BU) [k]	8.1	x	x	x	x	x	x	x	x		
eDiary review	8.1	x	x	x	x	x	x	x	x		
IBDQ, FACIT-F, WPAI:CD [l]	8.1.5, 8.1.6		x	x			x		x		
PGIS, PGIC [l]	8.1.7, 8.1.8		x (PGIS only)	x	x	x	x		x		

Table 1 Schedule of Activities: Induction Phase (cont.)

Week(s) (Window, Days)	Protocol Reference	Screening [a]	Treatment				Efficacy Assess [b]	UV [c]	Tx Disc/ Early Withdrawal [d]	Post-Treatment [e]	
		−35 to −1 Days	0	2 (±3)	6 (±3)	10 (±3)	12 (±7)			6-Wk SFU [d] (±7)	12-Wk SFU (±7)
EQ-5D-5L [l]	8.1		x				x		x		
Ileocolonoscopy with biopsies [m, n]	8.1.1, 8.7	x [o]					x	(x)	x [p]		
CMV test, if required [n, q, r]	Appendix 2	(x)						(x)			
CDAI assessment	8.1.1	x	x	x	x	x	x	(x)	x		
Pregnancy test [s]	Appendix 2	x	x	x	x	x	x	(x)	x	x	x
Hematology	Appendix 2	x	x	x	x	x	x	(x)	x		
Chemistry	Appendix 2	x	x	x	x	x	x	(x)	x		
Coagulation	Appendix 2	x									
HBV and HCV serology	Appendix 2	x						(x)			
HBV DNA test [t]	Appendix 2	x					x	(x)	x		
TB test [u]	Appendix 2	x									
HIV test	Appendix 2	x									
Urinalysis	Appendix 2	x	x	x	x	x	x	(x)	x		
Serum PK sample [v, w]	8.4, Table 4		x	x	x	x	x	(x)	x		
Serum ADA sample [v, w]	8.8, Table 4		x		x		x	(x)	x		
Serum NAb sample [v, w]	8.8, Table 4		x		x		x	x	x		
Serum PD sample (total sTL1A) [v]	8.7, Table 4		x		x		x	(x)	x		
Serum tryptase sample [w]	Appendix 2							(x)			
Serum biomarker sample [v]	8.7	x	x	x	x		x	(x)	x		

Table 1 Schedule of Activities: Induction Phase (cont.)

Week(s) (Window, Days)	Protocol Reference	Screening [a]	Treatment				Efficacy Assess [b]	UV [c]	Tx Disc/ Early Withdrawal [d]	Post-Treatment [e]	
		−35 to −1 Days	0	2 (±3)	6 (±3)	10 (±3)	12 (±7)			6-Wk SFU [d] (±7)	12-Wk SFU (±7)
PAXgene® blood RNA biomarker sample [v]	8.7		x				x	(x)	x		
Optional: Blood sample for RBR [x, y]	8.10.2		x								
Blood sample for TL1A biomarker [y]	8.7	x									
Stool sample for enteric pathogens [r, z, aa]	Appendix 2	x						(x)	x		
Stool sample for FeCal [z]	8.7	x	x	x	x		x	(x)	x		
Serum sample for CRP	8.7	x	x	x	x		x	(x)	x		
Concomitant medications	6.8	x	x	x	x	x	x	x	x	x	x
Study treatment administration	6.1.1		x	x	x	x					
Adverse events [bb]	8.3, Appendix 3, Appendix 4	x	x	x	x	x	x	x	x	x	x

Table 1 Schedule of Activities: Induction Phase (cont.)

ADA = anti-drug antibody; AP = abdominal pain; Assess = assessment; BU = bowel urgency; *C. difficile* = *Clostridioides difficile*; CD = Crohn's Disease; CDAI = Crohn's Disease Activity Index; CMV = cytomegalovirus; CRP = C-reactive protein; ECG = electrocardiogram; eDiary = electronic diary; EQ-5D-5L = EuroQol 5-Dimension 5-Level; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue Scale; FeCal = fecal calprotectin; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; IBDQ = Inflammatory Bowel Disease Questionnaire; NAb = neutralizing antibody; PD = pharmacodynamic; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetic; PRO = patient-reported outcome; QFT = QuantiFERON-TB Gold®; RBR = Research Biosample Repository; SF = stool frequency; SFU = safety follow-up; (s)TL1A = (soluble) tumor necrosis factor-like ligand 1A; TB = tuberculosis; Tx Disc = treatment discontinuation; UV = unscheduled visit; Wk = week; WPAI:CD = Work Productivity and Activity Impairment Questionnaire: Crohn's Disease Questionnaire.

Notes: On treatment days, all assessments should be performed, and all samples should be collected prior to dosing, unless otherwise specified. Assessments listed in parentheses as "(x)" are not required but may be performed, at the investigator's discretion. Refer to the cited protocol reference for activity-specific details.

[a] Results of standard-of-care assessments performed prior to obtaining informed consent and within ≤ 35 days prior to Day 1 of Week 0 (baseline) may be used; such assessments do not need to be repeated for screening. The screening period is up to 35 days; however, if required due to unforeseen circumstances, the screening period may be extended by a maximum of 7 days (for a total of 42 days).

[b] Week 12 efficacy assessments must be completed prior to the first Week 12 dose of SC study treatment in the maintenance phase (Table 2).

[c] Unscheduled visits may be performed if clinically indicated. Participants will undergo the specified assessments (at a minimum: vital signs, eDiary review, concomitant medications, and adverse events). Participants who discontinue from treatment at the Unscheduled Visit must complete the specified assessments as indicated in the Tx Disc/Early Withdrawal visit.

[d] Participants who discontinue treatment prematurely, regardless of the reason, should be instructed to return for a Tx Disc/Early Withdrawal visit before initiation of any new CD treatments to complete all of the Tx Disc/Early Withdrawal assessments. If the Tx Disc/Early Withdrawal visit is ≥ 6 weeks after the final administration of study treatment, the 6-week SFU visit is not required. If a participant discontinues due to pregnancy, they are not required to complete the endoscopy (ileocolonoscopy). If the Tx Disc/Early Withdrawal visit is within ≤ 6 weeks after the previous endoscopy (ileocolonoscopy) and biopsy, this procedure does not need to be repeated.

[e] SFU visits will occur 6 and 12 weeks after the final dose of study treatment. The 6-week visit may be done by phone. If the 6-week SFU visit is done by phone, home pregnancy tests will be provided as applicable.

[f] Informed consent must be obtained before any study-mandated screening assessment or procedure is performed and may be obtained up to 35 (+7) days prior to first administration of study treatment.

[g] Eligibility criteria should be reviewed prior to randomization.

[h] ECG recordings should be performed prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws).

[i] A complete physical examination should be performed at screening and may be performed at other timepoints at the discretion of the investigator. A symptom-directed physical examination should be performed at all specified visits except screening.

Table 1 Schedule of Activities: Induction Phase (cont.)

[j] Fistula examination only applies to patients presenting with actively draining fistulas at baseline (Week 0). Any fistulas developed while on study should be reported as an adverse event and followed up as clinically appropriate.

[k] Participants will complete eDiary PROs daily.

[l] Instruments will be administered before the participant receives any information on disease status, prior to any invasive procedures (i.e., blood draws) and prior to the administration of study treatment, unless otherwise specified.

[m] All participants will undergo ileocolonoscopy at specified timepoints within $-3/+5$ days of the scheduled visit. Video recordings should be taken of the entire procedure, starting from insertion into the bowel. Biopsies should be performed during withdrawal of the endoscope from the bowel. Technical instructions for video recording and biopsy collection will be provided in the endoscopy procedural manual/charter and/or laboratory manual.

[n] Tissue sample collected at screening will be analyzed for CMV, as determined by histologic examination or immunohistochemistry per local standards and will undergo histopathologic examination for participants without a prior histopathology report. Tissue samples collected at screening and subsequent timepoints will also be used for histologic assessments and biomarker research.

[o] The screening ileocolonoscopy will be used as efficacy baseline and for inclusion and must be completed within -16 to -4 days prior to baseline (Day 1 of Week 0). Participants without documentation of a surveillance colonoscopy within one year prior to baseline must undergo a surveillance colonoscopy at screening to rule out dysplasia in participants with colonic disease lasting for >8 years or with risk factors for bowel cancer.

[p] For participants exiting the treatment period early for any reason, an ileocolonoscopy to document disease activity may be performed based on assessment by the investigator. A repeat procedure is not required if completed ≤ 6 weeks of this visit.

[q] If there is suspicion for clinically significant CMV colitis, one biopsy sample should be obtained from the base or edge of the ulcer to evaluate for histological presence of CMV. Analysis should be performed locally. The result must be negative for CMV prior to dosing on Day 1.

[r] In the evaluation of disease worsening or potential differential diagnoses the presence of enteric pathogens should be ruled out by stool culture (ova and parasite evaluation) and should include *C. difficile* testing. If CMV infection is suspected, tissue biopsy should be performed. This testing should be conducted as per local standard of care and management.

[s] A serum pregnancy test must be performed at screening for all female participants of childbearing potential as defined in Section 5.1. Urine pregnancy tests must be performed at all other visits within 24 hours prior to initiation of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Study drug should not be administered unless the serum pregnancy test result is negative.

[t] HBV DNA test should be performed for individuals with negative HBsAg and HbsAb tests and a positive total HbcAb test at screening.

[u] TB test is not required if a participant is receiving TB prophylaxis treatment or if a negative QFT test result is available within 3 months prior to screening. Some exceptions to a positive or indeterminant QFT test result apply, including chest X-ray requirements (see Section 5.2).

Table 1 Schedule of Activities: Induction Phase (cont.)

[v] Sample should be collected prior to and at the end of administration of study treatment unless otherwise specified. For further details on PK, ADA, and PD biomarker (i.e., total sTL1A) samples, please refer to Table 4.

[w] A blood sample should be collected between 1 and 6 hours after a suspected infusion-related reaction or suspected systemic hypersensitivity reaction. A second sample should be collected at the next scheduled visit after the event. Refer to Table 4 for additional immunogenicity and PK sample requirements for infusion-related reactions, systemic hypersensitivity, and injection site reactions, as well as other potential adverse events considered immunogenicity-related.

[x] Not applicable at a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.

[y] If sample cannot be collected at the specified time point, it can be collected at any other time point.

[z] Stool samples should be obtained prior to bowel preparation.

[aa] Samples will be analyzed for culture and sensitivity, ova and parasites, and *C. difficile*, and results must be available prior to randomization (Day 1).

[bb] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 95 days after the final dose of study treatment. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Appendix 3).

Table 2 Schedule of Activities: Maintenance Phase

Weeks (Window, Days)	Protocol Reference	Treatment											UV [b]	Tx Disc/ EW [c]	Post-Treatment [d]	
		12 [a] (±7)	16 (±7)	20 (±7)	24 (±7)	28 (±7)	32 (±7)	36 (±7)	40 (±7)	44 (±7)	48 (±7)	52 (±7)			6-Wk SFU [c] (±7)	12-Wk SFU (±7)
Single 12-lead ECG [e]	8.2.3											x	(x)	x		
Vital signs	8.2.2		x	x	x	x	x	x	x	x	x	x	x	x		x
Weight	—		x	x	x	x	x	x	x	x	x	x	(x)	x		
Physical examination [f]	8.2.1			x			x			x		x	(x)	x		x
Fistula examination [g]	8.1.9	x		x		x		x		x		x		x		x
eDiary PROs (SF, AP, general well-being, BU) [h]	8.1		x	x	x	x	x	x	x	x	x	x	(x)	x		
eDiary Review	8.1		x	x	x	x	x	x	x	x	x	x	x	x		
IBDQ, FACITF, WPAI:CD [i]	8.1.5, 8.1.6						x					x		x		
PGIS, PGIC [i]	8.1.7, 8.1.8						x					x		x		
EQ-5D-5L [i]	8.1											x		x		
Ileocolonoscopy with biopsies [j, k]	8.1.1, 8.7											x	(x)	x [l]		
CMV test, if required [k, m, n]	Appendix 2												(x)			
CDAI assessment	8.1.1		x	x	x	x	x	x	x	x	x	x	(x)	x		
Pregnancy test [o]	Appendix 2		x	x	x	x	x	x	x	x	x	x	(x)	x	x	x
Hematology	Appendix 2		x	x	x	x	x	x	x	x	x	x	(x)	x		
Chemistry	Appendix 2		x	x	x	x	x	x	x	x	x	x	(x)	x		
HBV DNA test [p]	Appendix 2				x			x				x	(x)	x		
Urinalysis	Appendix 2		x	x	x	x	x	x	x	x	x	x	(x)	x		

Table 2 Schedule of Activities: Maintenance Phase (cont.)

Weeks (Window, Days)	Protocol Reference	Treatment											UV [b]	Tx Disc/ EW [c]	Post-Treatment [d]	
		12 [a] (±7)	16 (±7)	20 (±7)	24 (±7)	28 (±7)	32 (±7)	36 (±7)	40 (±7)	44 (±7)	48 (±7)	52 (±7)			6-Wk SFU [c] (±7)	12-Wk SFU (±7)
Serum PK sample [q, r]	8.4, Table 4		x	x	x	x	x	x	x	x	x	x	(x)	x		
Serum ADA sample [q, r]	8.8, Table 4			x		x		x		x		x	(x)	x		
Serum NAb sample [r]	8.8, Table 4			x		x		x		x		x	(x)	x		
Serum PD sample (total sTL1A) [q]	8.7, Table 4			x		x		x		x		x	(x)	x		
Serum tryptase sample [r]	Appendix 2												(x)			
Serum biomarker sample	8.7		x			x			x			x	(x)	x		
PAXgene® blood RNA biomarker sample	8.7		x									x	(x)	x		
Stool sample for enteric pathogens [n, s, t]	Appendix 2												(x)	x		
Stool sample for FeCal [s]	8.7		x			x			x			x	(x)	x		
Serum sample for CRP	8.7		x			x			x			x	(x)	x		
Concomitant medications	6.8		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Study treatment administration	6.1.1	x	x	x	x	x	x	x	x	x	x	x [u]				
Adverse events [v]	8.3, Appendix 3, Appendix 4		x	x	x	x	x	x	x	x	x	x	x	x	x	x

Table 2 Schedule of Activities: Maintenance Phase (cont.)

ADA = anti-drug antibody; AP = abdominal pain; BU = bowel urgency; *C. difficile* = *Clostridioides difficile*; CD = Crohn's Disease; CDAI = Crohn's Disease Activity Index; CMV = cytomegalovirus; CRP = C-reactive protein; ECG = electrocardiogram; eDiary = electronic diary; EQ-5D-5L = EuroQol 5-Dimension 5-Level; EW = early withdrawal; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue Scale; FeCal = fecal calprotectin; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; IBDQ = Inflammatory Bowel Disease Questionnaire; NAb = neutralizing antibody; PD = pharmacodynamic; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetic; PRO = patient-reported outcome; SF = stool frequency; SFU = safety follow-up; (s)TL1A = (soluble) tumor necrosis factor-like ligand 1A; Tx Disc = treatment discontinuation; UV = unscheduled visit; Wk = week; WPAI:CD = Work Productivity and Activity Impairment Questionnaire: Crohn's Disease Questionnaire.

Notes: On treatment days, all assessments should be performed and all samples should be collected prior to dosing, unless otherwise specified. Assessments listed in parentheses as "(x)" are not required but may be performed at the investigator's discretion. Refer to the cited protocol reference for activity-specific details.

[a] Week 12 efficacy assessments (Table 1) must be completed prior to the first Week 12 dose of SC study treatment in the maintenance phase.

[b] Unscheduled visits may be performed if clinically indicated. Participants will undergo the specified assessments (at a minimum: vital signs, eDiary review, concomitant medications, and adverse events). Participants who discontinue from treatment at the Unscheduled Visit must complete the specified assessments as indicated in the Tx Disc/Early Withdrawal visit.

[c] Participants who discontinue treatment prematurely, regardless of the reason, should be instructed to return for a Tx Disc/Early Withdrawal visit before initiation of any new CD treatments to complete all of the Tx Disc/Early Withdrawal assessments. If the Tx Disc/EW visit is ≥ 6 weeks after the final administration of study treatment, the 6-week SFU visit is not required. If a participant discontinues due to pregnancy, they are not required to complete the endoscopy (ileocolonoscopy). If the Tx Disc/EW visit is within ≤ 6 weeks after the previous endoscopy (ileocolonoscopy) and biopsy, this procedure does not need to be repeated.

[d] SFU visits will occur 6 and 12 weeks after the final dose of study treatment. The 6-week visit may be done by phone. If the 6-week SFU visit is done by phone, home pregnancy tests will be provided as applicable.

[e] ECG recordings should be performed prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws).

[f] A symptoms-directed physical examination should be performed at all specified visits. A complete physical examination may be performed at other timepoints at the discretion of the investigator.

[g] Fistula examination only applies to patients presenting with actively draining fistulas at baseline (Week 0). Any fistulas developed while on study should be reported as an adverse event.

[h] Participants will complete eDiary PROs daily.

[i] Instruments will be administered before the participant receives any information on disease status, prior to any invasive procedures (i.e., blood draws) and prior to the administration of study treatment, unless otherwise specified.

Table 2 Schedule of Activities: Maintenance Phase (cont.)

[j] All participants will undergo ileocolonoscopy at specified timepoints within −3/+5 days of the scheduled visit. Video recordings should be taken of the entire endoscopic procedure, starting from insertion into the bowel. Biopsies should be performed upon withdrawal of the endoscope from the bowel. Technical instructions for video recording and biopsy collection will be provided in the endoscopy procedural manual/charter and/or laboratory manual.

[k] Tissue samples will be analyzed for CMV, as determined by histologic examination or immunohistochemistry per local standards and will undergo histopathologic examination. Tissue samples will also be used for histologic assessments and biomarker research.

[l] For participants exiting the treatment period early for any reason, an endoscopy to document disease activity may be performed based on assessment by the investigator. This assessment is not required if completed ≤6 weeks of this visit.

[m] If there is suspicion for clinically significant CMV colitis, one biopsy sample should be obtained from the base or edge of the ulcer to evaluate for histological presence of CMV. Analysis should be performed locally.

[n] In the evaluation of disease worsening or potential differential diagnoses the presence of enteric pathogens should be ruled out by stool culture (ova and parasite evaluation) and should include *C. difficile* testing. This testing should be conducted as per local standard of care and management.

[o] Urine pregnancy tests must be performed at all visits within 24 hours prior to administration of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Study drug should not be administered unless the serum pregnancy test result is negative.

[p] HBV DNA test should be performed for individuals with negative HBsAg and HBsAb tests and a positive total HBcAb test at screening.

[q] Sample should be collected prior to administration of study treatment otherwise specified. For further details on PK, ADA, and PD biomarker (i.e., total sTL1A) samples please refer to Table 4.

[r] A blood sample should be collected between 1 and 6 hours after a suspected infusion-related reaction or suspected systemic hypersensitivity reaction. A second sample should be collected at the next scheduled visit after the event. Refer to Table 4 for additional immunogenicity and PK sample requirements for infusion-related reactions, systemic hypersensitivity, and injection site reactions, as well as other potential adverse events considered immunogenicity-related.

[s] Stool samples should be obtained prior to bowel preparation.

[t] Samples will be analyzed for culture and sensitivity, ova and parasites, and *C. difficile.*

[u] For those participants not participating in the open-label extension phase, Week 52 will be the final dose of study treatment.

[v] All adverse events will be reported until 95 days after the final dose of study treatment. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Appendix 3).

Table 3 Schedule of Activities: Open-Label Extension Phase

Timing (Window, Days)	Protocol Reference	Treatment OLE Year 1				Treatment OLE Years 2+		UV [c]	Tx Disc/ EW/Study Comp [d]	Post-Treatment [e]	
		OLE Wk 0	Q2W (±3) or Q4W(±7) [a]	Q3M (±7)	1 Year (±3 or ±7) [b]	Q2W (±3) or Q4W(±7) [a]	Q12M (±3 or ±7) [b]			6-Wk SFU [d] (±7)	12-Wk SFU (±7)
Informed consent [f]	8, A1–3	x									
Single 12-lead ECG [g]	8.2.3	(x)	(x)		x		x	(x)	x		
Vital signs [h]	8.2.2	x	x	x	x	x	x	x	x		x
Weight [h]				(x)	x		x	(x)	x		
Physical examination [h, i]	8.2.1	(x)	(x)	x	x		x	(x)	x		x
Fistula examination [j]	8.1.9				x		x		x		x
eDiary PROs (SF, AP, general well-being, BU) [h, k]	8.1			x	x		x	(x)	x		
eDiary review [h]	8.1	x	x	x	x		x	(x)	x		
IBDQ, FACIT-F, WPAI:CD [h, l]	8.1.5, 8.1.6			x	x		x		x		
PGIC, PGIS [h, l]	8.1.7, 8.1.8			x	x		x		x		
EQ-5D-5L [h, l]	8.1			x	x		x		x		
Ileocolonoscopy with biopsies [m, n]	8.1.1, 8.7			(x)	x		x	(x)	x [o]		
CMV test, if required [n, p, q]	Appendix 2							(x)			
CDAI assessment	8.1.1			(x)	x		x	(x)	x		
Pregnancy test [h, r]	Appendix 2	x	x	x	x	x	x	(x)	x	x	x

Table 3 Schedule of Activities: Open-Label Extension Phase (cont.)

Timing (Window, Days)	Protocol Reference	Treatment OLE Year 1				Treatment OLE Years 2+		UV [c]	Tx Disc/ EW/Study Comp [d]	Post-Treatment [e]	
		OLE Wk 0	Q2W (±3) or Q4W (±7) [a]	Q3M (±7)	1 Year (±3 or ±7) [b]	Q2W (±3) or Q4W (±7) [a]	Q12M (±3 or ±7) [b]			6-Wk SFU [d] (±7)	12-Wk SFU (±7)
Hematology [h]	Appendix 2			x	x		x	(x)	x		
Chemistry [h]	Appendix 2			x	x		x	(x)	x		
HBV DNA test [h, s]	Appendix 2			x			x	(x)	x		
Urinalysis [h]	Appendix 2			x	x		x	(x)	x		
Serum PK sample [h, t]	8.4, Table 4	Refer to Table 4.						(x)	x		
Serum ADA sample [h, t]	8.8, Table 4	Refer to Table 4.						(x)	x		
Serum NAb sample [h, t]	8.8, Table 4	Refer to Table 4.						(x)	x		
Serum PD sample (total soluble TL1A) [h, t]	8.7, Table 4	Refer to Table 4.						(x)	x		
Serum tryptase [h, u]	Appendix 2							(x)			
Serum biomarker sample [h]	8.7			x	x		x	(x)	x		
PAXgene® blood RNA biomarker sample [h]	8.7			x	x		x	(x)	x		
Stool sample for enteric pathogens [h, q, v, u]	Appendix 2	(x)	(x)	(x)	x	(x)	x	(x)	x		
Stool sample for FeCal [h, v]	8.7			x	x		x	(x)	x		
Serum sample for CRP [h]	8.7			x	x		x	(x)	x		
Concomitant medications [h]	6.8	x	x	x	x	x	x	x	x	x	x

Table 3 Schedule of Activities: Open-Label Extension Phase (cont.)

Timing (Window, Days)	Protocol Reference	Treatment OLE Year 1				Treatment OLE Years 2+		UV [c]	Tx Disc/ EW/Study Comp [d]	Post-Treatment [e]	
		OLE Wk 0	Q2W (±3) or Q4W (±7) [a]	Q3M (±7)	1 Year (±3 or ±7) [b]	Q2W (±3) or Q4W (±7) [a]	Q12M (±3 or ±7) [b]			6-Wk SFU [d] (±7)	12-Wk SFU (±7)
RO7790121 administration [h, x]	6.1.1	x[a]	x	x	x	x	x				
Adverse events [h, y]	8.3, Appendix 3, Appendix 4	x	x	x	x	x	x	x	x	x	x

ADA = anti-drug antibody; AP = abdominal pain; BU = bowel urgency; *C. difficile* = *Clostridioides difficile*; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CMV = cytomegalovirus; Comp = completion; CRP = C-reactive protein; ECG = electrocardiogram; eDiary = electronic diary; EQ-5D-5L = EuroQol 5-Dimension 5-Level; EW = early withdrawal; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue Scale; FeCal = fecal calprotectin; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; IBDQ = Inflammatory Bowel Disease Questionnaire; MN = mobile nursing; NAb = neutralizing antibody; OLE = open-label extension; PD = pharmacodynamic; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetic; PRO = patient-reported outcome; Q12M = every 12 months; Q2W = every 2 weeks; Q3M = every 3 months; Q4W = every 4 weeks; SF = stool frequency; SFU = safety follow-up; TL1A = tumor necrosis factor-like ligand 1A; Tx Disc = treatment discontinuation; UV = unscheduled visit; Wk = week; WPAI:CD = Work Productivity and Activity Impairment Questionnaire: Crohn's Disease Questionnaire.

Notes: On treatment days, all assessments should be performed and all samples should be collected prior to dosing, unless otherwise specified. Assessments listed in parentheses as "(x)" are not required but may be performed, at the investigator's discretion. Refer to the cited protocol reference for activity-specific details.

[a] Participants who meet disease worsening criteria after Week 12 and before Week 52 will start on a Q2W dose schedule in the OLE phase. Participants who complete the maintenance phase can move to the OLE phase and start on a Q4W dose schedule. If participants meet disease worsening criteria during the OLE phase, they may increase the dose frequency to Q2W (Section 4.1.3.3).

[b] The visit window will be ±3 days for the Q2W dose regimen or ±7 days for the Q4W dose regimen.

[c] Unscheduled visits may be performed if clinically indicated. Participants will undergo the specified assessments (at a minimum: vital signs, eDiary review, concomitant medications, and adverse events). Participants who discontinue treatment at the UV must complete the specified assessments as indicated in the Tx Disc/EW/Study Comp visit.

Table 3 Schedule of Activities: Open-Label Extension Phase (cont.)

[d] Participants who discontinue treatment prematurely, regardless of the reason, should be instructed to return for a Tx Disc/EW visit before initiation of any new CD treatments to complete all of the Tx Disc/EW assessments. If the Tx Disc/EW visit is ≥6 weeks after the final administration of study treatment, the 6-week SFU visit is not required. If a participant discontinues due to pregnancy, they are not required to complete the endoscopy. If the Tx Disc/EW visit is within ≤6 weeks after the previous endoscopy and biopsy, this procedure does not need to be repeated.

[e] SFU visits will occur 6 and 12 weeks after the final dose of study treatment, with the exception of participants who transition out of the OLE phase to commercially available RO7790121. The 6-week visit may be done by phone. If the 6-week SFU visit is done by phone, home pregnancy tests will be provided as applicable. The 12-week visit must be at the site (not available as MN visit).

[f] OLE informed consent must be documented before any OLE phase-specific procedure and the administration of the first dose of the OLE phase treatment.

[g] ECG recordings should be performed prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws).

[h] For participants at participating sites who have provided written informed consent to participate in MN visits, this assessment, procedure, or treatment may be performed or administered by a trained nursing professional at the participant's home or another suitable location as local capabilities and regulations allow.

[i] A symptoms-directed physical examination should be performed at all specified timepoints. A complete physical examination may be performed at other timepoints at the discretion of the investigator.

[j] Fistula examination only applies to patients presenting with actively draining fistulas at baseline (Week 0). Any fistulas developed while on-study should be reported as an adverse event.

[k] Participants will complete eDiary PROs for at least 7 days prior to each Q3M study visit during the first year and at the annual study visit thereafter. If disease worsening criteria assessment is required, eDiary PROs will be collected for at least 3 weeks prior to the study visit at which the assessment is being conducted.

[l] Instruments will be administered before the participant receives any information on disease status, prior to any invasive procedures (i.e., blood draws), and prior to the administration of study treatment, unless otherwise specified.

[m] All participants will undergo, at a minimum, an annual endoscopy (ileocolonoscopy) per local requirements and guidelines for CD management at the discretion of the investigator. Video recordings should be taken of the entire endoscopic procedure, starting from insertion into the bowel. Biopsies should be performed during withdrawal of the endoscope from the bowel. Technical instructions for video recording and biopsy collection will be provided in the endoscopy procedural manual/charter and/or laboratory manual.

[n] Tissue samples will be analyzed for CMV, as determined by histologic examination or immunohistochemistry per local standards and will undergo histopathologic examination for participants without a prior histopathology report. Tissue samples will also be used for histologic assessments and biomarker research.

[o] For participants exiting the treatment period early for any reason, an endoscopy (ileocolonoscopy) to document disease activity may be performed based on assessment by the investigator. A repeat procedure is not required if completed ≤6 weeks of this visit.

Table 3 Schedule of Activities: Open-Label Extension Phase (cont.)

[p] If there is suspicion for clinically significant CMV colitis, one biopsy sample should be obtained from the base or edge of the ulcer to evaluate for histological presence of CMV. Analysis should be performed locally.

[q] In the evaluation of disease worsening or potential differential diagnoses the presence of enteric pathogens should be ruled out by stool culture (ova and parasite evaluation) and should include *C. difficile* testing. If CMV infection is suspected, tissue biopsy should be performed. This testing should be conducted as per local standard of care and management.

[r] Urine pregnancy tests must be performed at all visits within 24 hours prior to initiation of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Study drug should not be administered unless the serum pregnancy test result is negative.

[s] HBV DNA test should be performed for individuals with negative HBsAg and HBsAb tests and a positive total HBcAb test at screening.

[t] Sample should be collected prior to administration of study drug unless otherwise specified. For further details on PK, ADA, and PD biomarker (i.e., total sTL1A) samples please refer to Table 4.

[u] A blood sample should be collected between 1 and 6 hours after a suspected infusion-related reaction or suspected systemic hypersensitivity reaction. A second sample should be collected at the next scheduled visit after the event. Refer to Table 4 for additional immunogenicity and PK sample requirements for infusion-related reactions, systemic hypersensitivity, and injection site reactions, as well as other potential adverse events considered immunogenicity-related.

[v] Stool samples should be obtained prior to bowel preparation.

[w] Samples will be analyzed for culture and sensitivity, ova and parasites, and *C. difficile.*

[x] For the first 12 weeks of the OLE phase, study drug will be administered at the site and requires at least a 60-minute post-dose observation period. MN may be initiated at participating sites after the first Q3M visit.

[y] All adverse events will be reported until 95 days after the final dose of study treatment. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Appendix 3).

Table 4 Schedule of Pharmacokinetic, Immunogenicity, and Pharmacodynamic Biomarker Samples

Induction Phase and Maintenance Phase				
Treatment	Timing	Pharmacokinetics RO7790121 (serum [a, b])	Immunogenicity ADA and NAb (serum [a])	Pharmacodynamics Total soluble TL1A (serum)
Induction Phase and Maintenance Phase				
Induction phase (IV infusion) [c]	Prior to IV infusion (pre-dose samples) [d]	Weeks 0 (Day 1), 2, 6, 10	Weeks 0 (Day 1) and 6	
	At the end of the IV infusion (within 1 h after end of infusion) [d]	Weeks 0 (Day 1), 2, 6, 10	NA	NA
Maintenance phase (SC administration) [e]	Prior to SC dosing (pre-dose samples)	Weeks 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52	Weeks 12, 20, 28, 36, 44, 52	
Open-Label Extension Phase				
Open-label extension phase (SC administration) (±2 weeks) [e]	Prior to SC dosing (pre-dose samples)	Weeks 4, 8, 12, 24, 36, 48 Annually (Q12M) thereafter	Weeks 12, 24, 36, 48 Annually (Q12M) thereafter	
Treatment Discontinuation/Early Withdrawal				
Treatment discontinuation/ Early withdrawal	NA	One serum sample (Table 1, Table 2, and Table 3)		

ADA = anti-drug antibody; eCRF = electronic Case Report Form; NA = not applicable; NAb = neutralizing antibody; PK = pharmacokinetic; Q12M = every 12 months; TL1A = tumor necrosis factor-like ligand 1A.

[a] Additional immunogenicity (ADA, NAb) samples and a PK sample should be collected in participants with signs and symptoms of infusion related reactions, systemic hypersensitivity, and injection site reactions, as well as other adverse events considered potentially immunogenicity-related.

A serum tryptase sample should be collected between 1 and 6 hours after a suspected infusion-related reaction or suspected systemic hypersensitivity reaction. A second sample should be collected at the next scheduled visit after the event (see Table 1).

[b] For all samples, the date and time of sampling should be recorded on the eCRF.

[c] IV infusions should be delivered over 60 (±10) minutes. The infusion start and end time should be recorded on the eCRF.

[d] Samples collected after the end of the infusion should be collected from the arm that is contralateral to the dosing arm.

[e] The SC start time should be recorded on the eCRF.

2. INTRODUCTION

2.1 STUDY RATIONALE

The purpose of this study is to assess the efficacy and safety of RO7790121 (formerly PF-06480605 and RVT-3101) in patients with moderately to severely active Crohn's disease (CD). RO7790121 is a fully human neutralizing immunoglobulin G1 (IgG1) monoclonal antibody (mAb) against tumor necrosis factor-like ligand 1A (TL1A). TL1A plays a central role in the regulation of gut mucosal immunity and participates in immunological and fibrosis pathways involved in inflammatory bowel disease (IBD) pathogenesis by binding its receptor, death receptor 3 (DR3) (Shih et al. 2014; Xu et al. 2022).

Therapeutic options have expanded substantially over the past decade, with biologics (e.g., anti-tumor necrosis factor [TNF], anti–IL-12/IL-23, and anti-integrin molecule mAbs) and small-molecule treatments (e.g., Janus kinase [JAK] inhibitor upadacitinib) now available in addition to conventional therapies. However, a high unmet medical need remains for treatments with better benefit–risk profiles that attenuate inflammation and clinical sequelae and provide sustained control to improve the long-term prognosis of patients with CD.

2.2 BACKGROUND

2.2.1 Background on Crohn's Disease

CD is a chronic, progressive inflammatory disease of the gastrointestinal tract, characterized by periods of relapse and remission, which can ultimately lead to bowel damage and disability. Most patients present with an inflammatory phenotype, but over time, uncontrolled inflammation can lead to complications such as fibrotic strictures, fistula formation, or intestinal neoplasia (Torres et al. 2017). Half of all patients with CD develop intestinal complications within 20 years of diagnosis leading to surgical intervention (Peyrin-Biroulet et al. 2010).

The current goals of CD treatment are to induce and maintain clinical and endoscopic remission, halt the progressive course of disease, and prevent long-term complications. Current available therapies such as corticosteroids, immunosuppressants, and advanced therapies, including biological agents, are effective in many patients; however, the long-term efficacy rates remain unsatisfactory, with up to 30% of patients not exhibiting an initial response to treatment, and up to 50% of patients losing response over time (Chang 2020; Wetwittayakhlang and Lakatos 2023). Furthermore, currently available advanced therapies are associated with various risks or adverse drug reactions such as serious infections, cardiovascular events, thrombosis, and malignancies (Bhat et al. 2024).

Despite available treatments, disease progression and complications result in an estimated 50%–80% of CD patients requiring surgery in their lifetime

(Khoudari et al. 2022). While timely surgery is appropriate to avoid complications, surgery is not curative and carries risks of postoperative complications with associated risks of mortality. Furthermore, postoperative recurrence is common, depending on patient risk factors, such that approximately 50% of patients have endoscopic recurrence within one year of ileocolic resection (Geldof et al. 2024; Joustra et al. 2022). Repeated surgical procedures can result in short bowel syndrome with chronic malabsorption and potential dependence on total parenteral nutrition (Cushing and Higgins 2021). Therefore, an unmet need exists for more safe and effective treatments for CD.

2.2.2 Background on RO7790121

RO7790121 is a fully human IgG1 mAb against TL1A. TL1A is a member of the TNF superfamily of proteins (TNFSF) that is encoded by the *TNFSF15* gene. TL1A plays a central role in the regulation of gut mucosal immunity and participates in immunological and fibrosis pathways involved in IBD pathogenesis (Shih et al. 2014; Bamias et al. 2017; Xu et al. 2022). Detailed information on RO7790121 is provided in the RO7790121 Investigator's Brochure.

2.3 BENEFIT–RISK ASSESSMENT

The purpose of this study is to assess the efficacy and safety of RO7790121, a novel anti-TL1A therapy, to address a significant unmet medical need in patients with moderately to severely active CD. Data on currently available treatments underscores the need for new medications in addressing the high unmet need in CD. Published literature strongly supports targeting the TL1A/DR3 signaling pathway as a promising approach in developing therapies for CD (Section 2.2).

In nonclinical trials, RO7790121 has been well tolerated, exhibiting no adverse effects and no identified target organs affected, even at the highest doses tested over a period of up to 6 months in the repeat-dose toxicity studies. Furthermore, RO7790121 did not provoke cytokine release in mice or monkeys in in vivo studies (see RO7790121 Investigator’s Brochure).

In completed Phase I clinical trials in healthy volunteers and Phase II trials in patients with UC, RO7790121 had a generally safe and well-tolerated profile. The incidence rates of treatment-emergent adverse events (TEAEs), severe TEAEs, serious adverse events, and TEAEs leading to discontinuation were notably low. There were no observed fatalities, and no clinically significant trends were observed in vital signs, laboratory parameters, or ECG results. These favorable safety outcomes were consistent across both the induction and maintenance phases of a Phase IIb study, B7541007 in patients with UC. Overall, these completed clinical studies did not reveal any significant safety concerns.

The clinical benefits of RO7790121 for patients with UC have been shown in two completed Phase II studies. In Study B7541002, a Phase IIa induction therapy-only trial, the primary efficacy endpoint was successfully achieved with RO7790121 IV treatment,

which showed a significant increase in endoscopic improvement compared to baseline. In Study B7541007, a Phase IIb induction and maintenance therapy trial, SC administration of RO7790121 demonstrated improvement in achieving both clinical remission (based on U.S. Food and Drug Administration [FDA] guidance-defined modified Mayo Score) and endoscopic improvement compared to placebo. The efficacy signals observed in the Phase II UC trials with RO7790121 serve as proof of concept for RO7790121 in CD based on the role of TL1A in both diseases. Shared genetic and immunological pathways are implicated in the pathogenesis of both CD and UC, with some specific findings suggesting a solid plausibility of the anti-TL1A mechanism of action to treat CD pathophysiology.

Based on the existing safety data from the completed Phase I studies and Phase II studies, the safety profile has been generally consistent, and there have been no identified risks or adverse drug reactions identified for RO7790121 to date. More information on the safety date and potential risks are included in the RO7780121 (RVT-3101) investigator's Brochure and in Appendix 4.

The selection of the RO7790121 dose levels and regimens for this study was informed by nonclinical and clinical data and analyses encompassing safety, efficacy, and pharmacokinetic (PK) data (Section 4.3). In addition, an external independent data monitoring committee (iDMC) will evaluate the accumulating data from the clinical trial data at prespecified, regular intervals during the study to monitor any risk for participant safety and data integrity (Section 4.1.1). This independent assessment of the clinical trial data will contribute to the overall ongoing evaluation and management of potential risks associated with RO7790121 administration and to unbiased benefit–risk assessment.

Considering the available nonclinical data and clinical safety and efficacy data from the completed Phase I and Phase II clinical trials, in conjunction with the TL1A mechanistic plausibility and evident medical need among patients with CD, the benefits of RO7790121 outweigh its associated risks. This conclusion supports the continued development of RO7790121 for the proposed indication in adults with moderately to severely active CD.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

This study will evaluate the efficacy and safety of RO7790121 compared with placebo in patients with moderately to severely active CD.

3.1 PRIMARY OBJECTIVE AND CORRESPONDING ESTIMAND

The primary objective of the trial is to evaluate the efficacy of RO7790121 in maintaining clinical remission and endoscopic response compared with placebo. Clinical remission is defined on the basis of the Crohn's disease activity index (CDAI), and endoscopic response is defined with the Simple Endoscopic Score for Crohn's disease (SES-CD).

Statistical inference supporting this evaluation will target estimands representing the effect of assignment to the treatment conditions (Section 6) on a specified outcome (endpoint) in the population of patients with moderately to severely active CD, as identified by key trial inclusion and exclusion criteria (Section 5).

Primary Objective	Endpoints
To evaluate the efficacy of RO7790121 compared with placebo in maintaining response	• Clinical remission, defined as CDAI < 150, at Week 52 • Endoscopic response, defined as decrease in SES-CD from baseline ≥ 50%, at Week 52

CDAI = Crohn's disease activity index; SES-CD = Simple Endoscopic Score for Crohn's disease.

As noted by the ICH E9(R1), the availability or interpretation of endpoint measurements may be affected by the occurrence of intercurrent events (ICH 2020) arising between randomization and endpoint assessment. Strategies to address anticipated intercurrent events are summarized in Table 5.

Table 5 Strategies for Anticipated Intercurrent Events

Anticipated Intercurrent Event	Strategy
Discontinuation of blinded treatment	Composite: Intercurrent event is considered indicative of treatment failure, and the affected endpoint measurement will be imputed to a value that is deemed unfavorable. For the primary endpoints, this value corresponds to not achieving remission or response.
Increase from baseline or initiation of permitted or prohibited concomitant medications to treat CD (Table 7, Section 6.7), due to lack of efficacy	
CD-related surgery with the exception of seton management for perianal fistula	
Decrease in permitted concomitant medications for CD	Treatment policy: Ignore intercurrent event in statistical inference

CD = Crohn's disease.

Under these strategies, the estimands considered in the evaluation of clinical remission at Week 52 amounts to a treatment effect summarized by the difference between two proportions:

- the percentage of patients from the target population in clinical remission upon a successful 52-week course of therapy, after assignment to a particular dosing regimen of RO7790121; versus
- this same percentage, had these patients been instead assigned to placebo.

The estimands for endoscopic response at Week 52 are defined similarly.

Primary analysis of the study data will yield estimates for these induction and maintenance treatment effects. Should estimates on all co-primary endpoints favor at least one dosing regimen of RO7790121 over placebo and be deemed statistically significant, the study will be considered positive. Details on statistical hypothesis testing are described in Section 9.1.

3.2 SECONDARY OBJECTIVES AND CORRESPONDING ENDPOINTS

Efficacy is further considered in key secondary objectives, described below.

Key Secondary Objectives	Corresponding Endpoints
To evaluate the efficacy of RO7790121 compared with placebo in inducing response	• Clinical remission, as defined above, at Week 12 • Endoscopic response, as defined above, at Week 12 • Symptomatic remission, defined as SF $\leq$2.8 and APS $\leq$1 with neither score greater than baseline, at Week 12 • Endoscopic remission, defined as SES-CD = 0 to 4 with decrease from baseline $\geq$2 and no subscore $>$1, at Week 12 • Ulcer-free endoscopy, defined as SES-CD ulcerated surface subscore of 0, at Week 12 • SF, from baseline through Week 12 • APS, from baseline through Week 12
To evaluate the efficacy of RO7790121 compared with placebo in maintaining response	• Endoscopic remission, as defined above, at Week 52 • Symptomatic remission, as defined above, at Week 52 • Corticosteroid-free clinical remission, defined as clinical remission at Week 52 and no use of corticosteroids for CD at least 8 weeks prior to Week 52 • Maintenance of clinical remission, defined as clinical remission at both Weeks 12 and 52 • Maintenance of endoscopic response, defined as endoscopic response at both Weeks 12 and 52 • Clinical remission and endoscopic remission, as defined above, at Week 52 • Ulcer-free endoscopy, as defined above, at Week 52
To evaluate the efficacy of RO7790121 compared with placebo in terms of CD-related symptoms and health-related quality of life	• Bowel urgency, from baseline through Week 12 and Week 52 • Fatigue, as measured by FACIT-F, from baseline to Week 12 and Week 52 • IBDQ score, from baseline to Week 12 and Week 52
To evaluate the efficacy of RO7790121 compared with placebo in TL1A biomarker-defined subgroups	Among TL1A biomarker-defined subgroups of participants: • Clinical remission at Week 12 • Clinical remission at Week 52 • Endoscopic response at Week 12 • Endoscopic response at Week 52

APS = average of daily abdominal pain scores in the past week; CD = Crohn's disease; CDAI = Crohn's disease activity index; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue Scale; IBDQ = Inflammatory Bowel Disease Questionnaire; SES-CD = Simple Endoscopic Score for Crohn's disease; SF = average of daily number of liquid or very soft stools in the past week.

The secondary efficacy objectives likewise have corresponding estimands of interest representing an effect comparing the same treatment conditions (RO7790121 vs. placebo; Section 6) on a specified endpoint, within the same overall population of patients (Section 5), and using the same strategies for anticipated intercurrent events (Table 5). These treatment effects are defined in the same manner as those for the primary endpoints, with effects on binary efficacy endpoints summarized by a RO7790121 versus placebo difference between proportions. For other efficacy endpoints, the effect is generally a difference in a summary outcome measure, such as a mean score or mean change from baseline score. Further details on the assessment and evaluation of different efficacy endpoint types are provided in Sections 8.1 and 9.3, respectively.

Should the study be positive per the co-primary endpoints, statistical hypothesis testing will proceed to a specified subset of secondary objectives. An overview of hypothesis testing is provided in Section 9.1.

Other secondary objectives also consider both efficacy and safety. Safety endpoints refer to a summary outcome measure, rather than a participant-level outcome variable.

Other Secondary Objectives	Endpoints
To evaluate the efficacy of RO7790121 compared with placebo in inducing and/or maintaining response	• Clinical response, defined as a decrease in CDAI from baseline ≥100, at Week 12 • Symptomatic response, defined as decrease in SF and APS ≥30% with neither greater than baseline, at Week 12
To evaluate the efficacy of RO7790121 compared with placebo in terms of the participant's global impressions and general well-being	• Overall change in CD symptoms, as measured by PGIC, from baseline to Weeks 2, 6, 12, and 52 • Overall severity in CD symptoms, as measured by PGIS, from baseline to Weeks 2, 6, 12, and 52 • General well-being, from baseline through Week 52
To evaluate the safety of RO7790121 compared with placebo	• Incidence and severity of the following: • Adverse events • Serious adverse events • Adverse events leading to study treatment discontinuation • Adverse events of special interest
To evaluate the persistence of fistulas of participants treated with RO7790121 compared to placebo	Presence of draining fistulas from baseline through Week 12 and Week 52

APS = average of daily abdominal pain scores in the past week; CD = Crohn's disease; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; SF = average of daily number of liquid or very soft stools in the past week.

3.3 EXPLORATORY OBJECTIVES AND ENDPOINTS

Exploratory objectives and corresponding endpoints are described below. Estimands for exploratory efficacy objectives are defined in a similar manner to those supporting primary and secondary objectives. As with safety domains, exploratory objectives beyond efficacy may have endpoints that describe a summary outcome measure rather than a participant-level outcome variable.

Exploratory Objectives	Endpoints
To evaluate the efficacy of RO7790121 compared with placebo in inducing and/or maintaining response	• Change in CDAI from baseline through Week 52 • Change in SES-CD from baseline to Week 12 and Week 52 • Change in Geboes Grading Scale from baseline to Week 12 and Week 52
To characterize the pharmacokinetics of RO7790121	• Pre-dose and peak concentration of RO7790121 in serum at specified timepoints
To evaluate potential effects of immunogenicity of RO7790121	• ADA and NAb detection in serum at specified timepoints • Association of ADA and NAb status (or titers) with efficacy, safety, PK, or PD endpoints
To evaluate the pharmacodynamics of RO7790121	• Total soluble TL1A concentration in serum at specified timepoints • Association of these levels with PK, immunogenicity, and disease activity
To evaluate the health utility of participants treated with RO7790121 compared with placebo	• EQ-5D-5L index-based and VAS scores from baseline to Week 12 and Week 52 • WPAI:CD score from baseline to Week 12 and Week 52
To evaluate biomarkers in participants treated with RO7790121 compared with placebo	• Fecal calprotectin at specified timepoints • C-reactive protein at specified timepoints • Pathway and pathophysiology biomarker levels from baseline through Week 52, and associations of these levels amongst each other and with PK, PD, and disease activity
To evaluate automated endoscopy assessments in participants treated with RO7790121 or placebo	• AI-based assessment of endoscopic activity from baseline to Week 12 and Week 52 • AI-based spatial measurements of mucosal features, from baseline to Week 12 and Week 52 • Association of these assessments with treatment arm and with disease activity

ADA = anti-drug antibody; AI = artificial intelligence; EQ-5D-5L = EuroQol 5-Dimension 5-Level; NAb = neutralizing antibody; PD = pharmacodynamic; PK = pharmacokinetic; SES-CD = Simple Endoscopic Score for Crohn's disease; TL1A = tumor necrosis factor-like ligand 1A; VAS = visual analog scale; WPAI:CD= Work Productivity and Activity Impairment Questionnaire: Crohn's Disease.

4. STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase III, multicenter, randomized, double-blind, placebo-controlled, treat-through study to evaluate the efficacy and safety of the induction and maintenance therapy with RO7790121 in patients with moderately to severely active CD (Figure 1).

The study population will include participants with moderately to severely active CD for whom at least one of the following prior therapy types have failed:

- Conventional therapy (aminosalicylates, corticosteroids, and/or immunosuppressants)
- Advanced therapy (biologics or targeted small molecules, e.g., anti-TNF, anti–IL-12/IL-23, anti-integrin, JAK inhibitors etc.)

Complete definitions of conventional therapy failure and advanced therapy failure can be found in Section 5.1.

Approximately 600 total participants will be enrolled across global investigational sites, with balanced representation of participants who have demonstrated conventional or advanced therapy failure. Enrollment of participants who have failed three or more advanced therapies (i.e., three therapies, not three classes of therapies) will be capped to at most 30% of the total number of participants.

The study has a treat-through design that consists of a screening period of up to 35 days (+7 days) to determine eligibility; a 12-week induction treatment phase; a 40-week maintenance treatment phase; an optional open-label extension (OLE) treatment phase; and a safety follow-up period of 12 weeks (consisting of two visits, one at 6 weeks and one at 12 weeks) following the final dose of study treatment.

Entry criteria will be based on confirmation of moderately to severely active CD during screening, defined as a CDAI score $\geq$220 and $\leq$450 and SES-CD score of $\geq$6 (or $\geq$4 for isolated ileal disease) at baseline.

Eligible study participants will be randomly assigned to one of the following three treatment arms:

1) RO7790121: 500 mg IV at Weeks 0, 2, 6, and 10, followed by 450 mg SC every 4 weeks (Q4W) from Week 12 through Week 52
2) RO7790121: 500 mg IV at Weeks 0, 2, 6, and 10, followed by 150 mg SC Q4W from Week 12 through Week 52
3) Placebo: placebo IV at Weeks 0, 2, 6, and 10, followed by placebo SC Q4W from Week 12 through Week 52

This randomization will be performed according to a 1:1:1 allocation ratio and stratified by the following factors:

a) Prior advanced therapy use (yes/no)

b) Baseline corticosteroid use (yes/no)

c) Baseline endoscopic activity (moderate [SES-CD ≤15] or severe [SES-CD >15])

d) Baseline CDAI ≤330 (yes/no)

The induction phase (dosing at Weeks 0–10) will evaluate the induction of clinical remission and endoscopic response, measured at Week 12. After completion of the induction phase, participants will continue with the SC administration of RO7790121 or matching placebo during the maintenance phase (SC dosing at Weeks 12–52), in which the durability of the clinical remission and endoscopic response will be examined. From Week 12 onwards, participants who have completed Week 12 will be eligible to enter the optional OLE phase, provided that their condition meets the disease worsening criteria (Section 4.1.3.2). Participants who do not complete the 12-week induction period for any reason will be withdrawn from blinded treatment and proceed into the mandatory treatment discontinuation/early withdrawal visit followed by the post-treatment safety follow-up visits.

Disease worsening will continue to be monitored by the investigator after Week 12. Participants who complete all trial procedures, including study treatment administration at Week 52, or who meet the disease worsening criteria (Section 4.1.3.2) at any time during the maintenance phase will have the option to continue to the OLE phase and receive active treatment (Section 4.1.3.2). Participants who discontinue the maintenance phase before Week 52 and who do not enter the OLE phase will proceed to the mandatory treatment discontinuation/early withdrawal visit followed by the post-treatment safety follow-up visits.

The aim of this study is to assess the efficacy and safety of RO7790121 compared to placebo. Efficacy will be assessed by the co-primary endpoints of clinical remission (defined as CDAI <150) at Week 52 and endoscopic response (defined ≥50% reduction from baseline in SES-CD) at Week 52.

The primary, secondary, exploratory, safety, PK, pharmacodynamic (PD), and immunogenicity objectives, as well as any other objectives and the corresponding endpoints in this study, are in Section 3. Participants will undergo efficacy and safety assessments as shown in the schedules of activities (see Table 1, Table 2, Table 3, and Table 4).

Participants will be assessed for efficacy using instruments to measure clinical and endoscopic disease activity, including CDAI (and its patient-reported outcome [PRO] components) and SES-CD. The CDAI score is a composite of eight assessments: SF,

APS, general well-being, presence of complications, use of anti-diarrheals, presence of an abdominal mass, hematocrit, and percentage deviation from standard weight. SES-CD is based on centrally-read endoscopy and a composite of four assessments (size of ulcers, proportion of the surface covered by ulcers, proportion of the surface with any other lesions, and presence of narrowing) across five anatomic locations (terminal ileum, right colon, transverse colon, sigmoid and left colon, and rectum).

During the screening, induction, and maintenance phases, eDiary PROs will be collected daily. During the OLE phase, participants will complete eDiary PROs daily for at least 7 days prior to each Q3M study visit during the first year, and prior to annual study visits thereafter. If disease worsening criteria assessment is required in the OLE phase (see Section 4.1.3.2), eDiary PROs will be collected for at least 7 days prior to the study visit at which the assessment is conducted (Section 4.1.3.3).

All efficacy assessments are described in Section 8.1.

4.1.1 Independent Data Monitoring Committee

An iDMC will be utilized to monitor the safety data at specific intervals on an ongoing basis to protect the safety of participants as well as enhance the integrity and credibility of the trial (FDA 2006; EMA 2005). The iDMC will consist of at least one medical expert in the relevant therapeutic area and one independent statistician. Members of the iDMC will not be directly involved in the ongoing trial conduct and management of the trial.

A separate iDMC charter will be prepared outside the protocol and approved by the Sponsor and the iDMC members before a participant is initiated into the trial. The iDMC charter describes the composition of the iDMC, the roles and responsibilities of the iDMC members, frequency of data reviews and relevant safety data to be assessed, meeting occasions, and communication with the Sponsor as well as relevant competent authorities.

Communications from the iDMC to the trial team will not contain information that could potentially unblind the team to participant treatment assignment.

4.1.2 Overview of Study Design

A study schema is provided in Section 1.2 (see Figure 1). Schedules of activities and a sample collection schedule are provided in Section 1.3 (see Table 1, Table 2, Table 3, and Table 4).

4.1.3 Open-Label Extension Phase

All participants will have the opportunity to participate in the optional OLE phase of the study with access to RO7790121 and monitoring, provided they meet specified eligibility criteria.

4.1.3.1 Open-Label Extension Phase Eligibility Criteria

Participants will be eligible to enter the OLE phase once they have provided consent to participate and, per the investigator's assessment, participant safety is not at risk to continue participation in the optional OLE phase of the study.

Participants may be eligible to enter the OLE phase at the following time points:

- At any time after completion of the 12-week induction phase and upon completion of the Week 12 assessments and first dose of maintenance, if the participant meets disease worsening criteria (Section 4.1.3.2). Participants will not be eligible for the OLE phase before Week 12.
- After completion of the 40-week maintenance phase and upon completion of the Week 52 assessments.

4.1.3.2 Disease Worsening Criteria

Starting after the Week 12 assessments and the first dose of maintenance therapy, participants who, based on an assessment by the investigator, have not improved or have worsened compared with baseline (Day 1 of Week 0), may be eligible to enroll in the OLE, provided they meet both of the following symptomatic and endoscopic criteria.

1. For at least 2 of the past 3 weeks, the daily stool frequency and abdominal pain eDiary entries averaged over a weekly period indicate moderate-to-severe activity with no meaningful improvement; either:
    a) SF ≥ 4 with decrease from baseline < 2, or
    b) APS ≥ 2 with decrease from baseline < 0.5
2. Centrally-read endoscopy indicates moderate-to-severe endoscopic activity with no meaningful improvement; both:
    a) SES-CD ≥ 6 (or ≥ 4 for isolated ileal disease), and
    b) $<$ 3-point decrease from baseline in SES-CD

An endoscopy is required to confirm OLE eligibility for participants discontinuing the double-blind maintenance phase prior to Week 52 and should be performed upon the appearance of CD symptoms. However, the procedure need not be repeated if performed within the last 4 weeks.

The thresholds on post-baseline SF, APS and SES-CD in criteria 1a, 1b, and 2a, respectively, clinically identify moderately-to-severely active CD patients. In particular, the endoscopic (SES-CD) thresholds in 2a are identical to the study population inclusion criteria (Section 5.1). The thresholds on decrease from baseline in SF, APS, and SES-CD in criteria 1a, 1b, and 2b, respectively, correspond to values that would generally not be considered a clinically meaningful change, provided that the post-baseline score remains moderate to severe. Such decreases are similar to typical symptomatic and endoscopic change scores observed in placebo-treated trial participants (Colombel et al. 2024a, b). Therefore, the above criteria will enable the identification of participants who have not demonstrated clinically meaningful

improvement from baseline moderate-to-severe disease activity and thus will be eligible for rollover to the open-label extension phase.

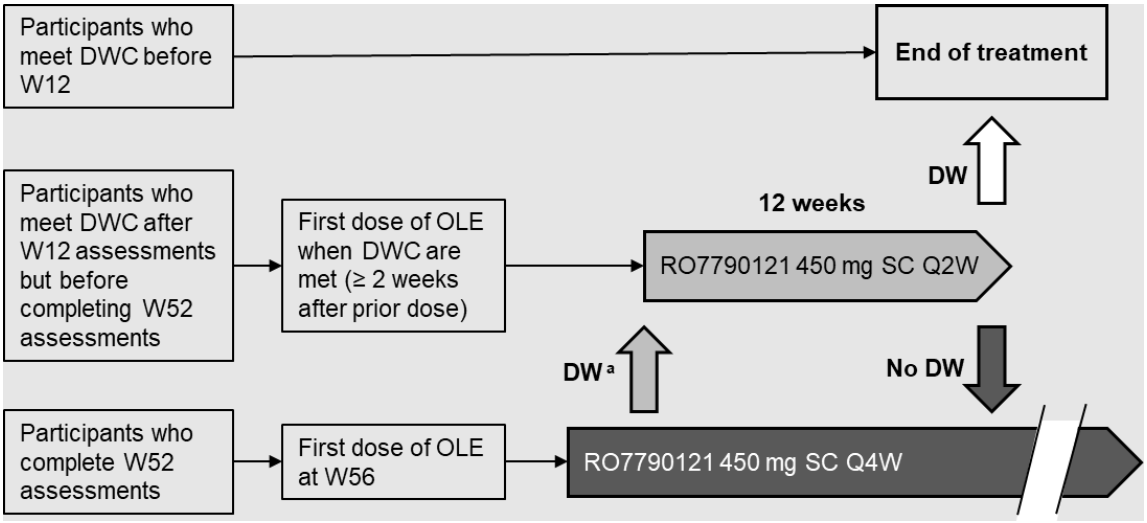
Fulfillment of the disease worsening criteria will be captured by efficacy assessments. Potential differential diagnoses, such as the presence of enteric infection, should be ruled out by stool culture (ova and parasite evaluation) including *C. difficile* testing. If cytomegalovirus (CMV) infection is suspected, tissue biopsy should be performed. This testing should be conducted as per local standard of care and management. In general, there should be no duplication of reporting on the Adverse Events Case Report Form (CRF), unless the disease worsening is unanticipated given the expected pattern of the underlying disease (e.g., deemed by the investigator to be related to study drug; Section A3–7.9).

4.1.3.3 Open-Label Extension Phase Dose Schedule

During the maintenance phase (after Week 12), if the participant's condition meets the disease worsening criteria (Section 4.1.3.2), the participant may discontinue blinded treatment and either enter the OLE phase using an every 2 weeks (Q2W) dose intensification schedule (450 mg SC Q2W) for 12 weeks or be withdrawn from the study, as assessed by the investigator. Participants who follow the Q2W dose schedule will have the opportunity to de-escalate to the 450 mg SC Q4W dose schedule after 12 weeks or be withdrawn from the study, as assessed by the investigator (Figure 2 and Appendix 11).

Participants who complete the 52-week study and roll over into the OLE phase will receive open-label treatment at 450 mg SC Q4W. The first OLE visit for such participants will be at Week 56, and the participants will continue in the OLE phase on the Q4W dose regimen until the end of the study (Section 4.4). However, if at any point during the OLE phase the participant’s condition meets the disease worsening criteria (Section 4.1.3.2), the option for dose intensification to 450 mg SC Q2W or withdrawal from the study will be assessed by the investigator. Participants who follow the 450 mg SC Q2W dose schedule may de-escalate to the 450 mg SC Q4W dose schedule after 12 weeks or be withdrawn from the study, as assessed by the investigator. Doses of RO7790121 should be administered at least 7 days apart. Every effort should be made to maintain the original dosing schedule. There will be a maximum of two dose intensifications to Q2W allowed in the OLE phase of the study.

Figure 2 Open-Label Extension Phase Dosing Schedule



DW = disease worsening; DWC = disease worsening criteria; OLE = open-label extension phase; Q2W = every 2 weeks; Q4W = every 4 weeks; W = Week.

[a] There will be a maximum of two dose intensifications (Q4W dosing to Q2W dosing) allowed in the OLE phase of the study.

4.1.4 Patient Input into Study Design

The insight and feedback from the patient representatives were obtained through patient focus meetings. The patients provided insights on the following aspects of the study:

- Study design, endpoints, inclusion and exclusion criteria activities, and PROs
- Recruitment and retention (e.g., inclusivity of underserved patient communities, potential recruitment challenges, possible retention challenges)

This feedback was taken into consideration when developing the protocol.

4.2 RATIONALE FOR STUDY DESIGN

This trial is designed to evaluate the efficacy and safety of RO7790121 as an induction and maintenance therapy in patients with moderately to severely active CD.
A treat-through design will be employed to allow continued observation beyond a fixed induction time frame, which is consistent with clinical practice and also with recent European Medicines Agency (EMA) and FDA guidelines (EMA 2018; FDA 2022).
Compared to recent re-randomized IBD treatment trials, which enriched for treatment responders, a treat-through design also avoids re-randomizing responder participants to placebo. In addition, certain participants who meet disease worsening criteria based on assessment by the investigator will be able to participate in the OLE phase and receive active treatment (see Section 4.1.3.2). The proposed disease worsening criteria balance safeguarding participants from worsening of their underlying disease with ensuring that

participants who may benefit from continued treatment are not prematurely discontinued from the study.

The co-primary endpoints of participants achieving clinical remission and endoscopic response at Week 12 and maintaining clinical remission and endoscopic response at Week 52, as assessed using the CDAI and SES-CD, are consistent with current clinical practice (FDA 2022). Standard statistical, clinical, and laboratory procedures utilized are widely used and considered reliable measures of efficacy and safety. Central reading of endoscopy will increase study rigor and ensure enrollment of patients with moderately to severely active CD. The safety follow-up visits will be 6 and 12 weeks after the final dose of study treatment, which will allow for drug washout (12-week washout period corresponding to 4.4 half-lives, based on the estimated half-life of approximately 19 days for RO7790121) and provide sufficient safety monitoring.

4.2.1 Rationale for Study Population

There is an ongoing high unmet medical need in the treatment of patients with moderately to severely active CD. Additionally, patients with moderately to severely active CD and uncontrolled or inadequately controlled disease are at risk for developing strictures or penetrating complications of inflammation, as well as symptoms that are detrimental to QoL. The current goals of CD treatment are to induce and maintain clinical and endoscopic remission, halt the progressive course of disease, and prevent long-term complications. Therapeutic options have expanded substantially over the past decade, with biologics (e.g., anti-TNF, anti–IL-12/IL-23, and anti-integrin molecule mAbs) and small molecule treatment (e.g., JAK inhibitor upadacitinib) now available in addition to conventional therapies. However, the sustained remission rates overall are relatively low, and additional treatment options are needed, as patients with CD require life-long therapy. In addition to inadequately controlling disease, current treatments have various risks and adverse drug reactions, which must be balanced with patient-specific considerations to mitigate safety issues (Bhat et al. 2024). Due to the limitations of currently available therapies, there persists a need for treatments with better benefit–risk profiles that attenuate inflammation and clinical sequelae and provide sustained control to improve the long-term prognosis of patients with CD.

RO7790121 is being developed as a novel therapeutic agent to achieve clinical remission and to control of the underlying mucosal inflammation and its complications in patients with moderately to severely active CD who have demonstrated an inadequate response to, loss of response to, or intolerance to prior conventional or advanced therapies as defined in Section 6.1. Conventional therapies include corticosteroids, immunomodulators, or oral aminosalicylates (Klag et al. 2015; Yu et al. 2018; Hart et al. 2020, Seigel et al. 2020). Including patients who fail aminosalicylate–only prior treatment is consistent with modern treatment paradigms (such as STRIDE II) and allows these patients to be eligible for new, potentially effective treatment options with a favorable benefit–risk profile.

RO7790121 is a fully human neutralizing IgG1 mAb against TL1A. TL1A plays a central role in the regulation of gut mucosal immunity and participates in immunological and fibrosis pathways involved in the IBD pathogenesis by binding its receptor DR3. TL1A is a type 2 transmembrane protein encoded by the *TNFSF15* gene (Chr 9q32) and is a member of the TNFSF. Variants in the *TNFSF15* gene have been associated with increased susceptibility to developing IBD, especially in CD and across multiple ancestries (Kakuta et al. 2006; Hirano et al. 2013; Yang et al. 2014; Endo et al. 2020). TL1A has also been reported to be associated with some clinical phenotypes in CD, including anal lesions, ileocecal location, strictures, and penetrating behavior (Kakuta et al. 2006; Hirano et al. 2013; Yang et al. 2014; Endo et al. 2020). Therefore, *TNFSF15* variants are not only associated with susceptibility but also with some disease complications in CD. Hence, the mechanism of action of RO7790121 may be especially relevant for this patient population.

The eligibility criteria for this study (Sections 5.1 and 5.2) define patients with moderately to severe active CD disease as having a confirmed SES-CD $\geq$6 and a CDAI score $\geq$220 to$\leq$450 at baseline and a balanced representation of prior treatment exposure, consistent with regulatory guidance (EMA 2018; FDA 2022), who may benefit from the anticipated effects of RO7790121.

Patients with moderately to severely active CD between the ages of 16 and 80 years will be studied. This age range is typical for patients enrolled in clinical trials of new investigational agents for CD and reflects the observation that in adults CD can become or persist as moderately to severely active disease at any age. Patients $\geq$16 years of age and $\geq$40 kg body weight will be eligible to participate to allow older adolescents access to clinical trials. In Phase IIa and Phase IIb ulcerative colitis (UC) studies, the median (range) body weight was 71.85 (40.7–107.6) kg and 68.2 (33.9–130) kg, respectively. Patients $>$80 years of age at screening will not be eligible for study entry, since advanced age in CD has been associated with an increased risk of adverse events, comorbidities, or other conditions that may mimic symptoms of IBD, such as colorectal cancer, ischemic colitis, and segmental colitis associated with diverticula.

Based on the composition of SES-CD, patients with isolated ileitis can be expected to have a lower baseline score compared with patients with ileocolonic disease, regardless of whether the extent of inflammation and ulceration is the same in affected segments. As such, different SES-CD entry scores are proposed for these subgroups of patients. Also, it is acknowledged that patients with fistulizing disease are not well served by current therapeutic options. The protocol includes this subgroup to assess the impact of RO7790121 on draining fistulas.

4.2.2 Rationale for Control Group

In accordance with the International Council for Harmonisation (ICH) E10 guideline, the European Medicines Agency (EMA) "Guideline on the Development of New Medicinal Products for the Treatment of Crohn's Disease" (EMA 2018), and the FDA draft "Crohn's

Disease: Developing Drugs for Treatment" Guidance for Industry (FDA 2022), a placebo-treated control group will be used to provide the optimal evaluation of differences in efficacy, safety, and tolerability in participants who receive RO7790121 and non-biologic background CD therapy compared with participants who receive placebo and non-biologic background CD therapy. The use of a control group controls for the variability in outcome measures associated with subjective assessments, such as PROs, and with disease factors, such as spontaneous remission and inherent variability in disease flares. Participants in the control group will undergo the same study assessments as the RO7790121-treated patients. Participants in the placebo arm who complete the induction period at Week 12 but meet disease worsening criteria thereafter, based on an assessment by the investigator (Section 4.1.3.2), will be provided the option to receive active treatment with RO7790121 in the optional OLE phase of the study (Section 4.1.3).

4.2.3 Rationale for Biomarker Assessments

CD is a heterogeneous disease, and participants may not be equally likely to benefit from treatment with RO7790121. Peripheral blood samples will be assessed for TL1A biomarker status (Section 8.7) in all study participants in order to evaluate efficacy in biomarker-defined subgroups. These blood samples may be used in the possible future development and validation of an in vitro diagnostic assay. Since these biomarkers may also have prognostic value, their potential association with disease activity will also be explored.

The PD biomarker (total sTL1A) will be assessed in the peripheral blood or blood-derived samples to demonstrate evidence of the PD activity of RO7790121 and for PK/PD analysis.

Additional exploratory biomarkers of the TL1A pathway and pathophysiology biomarkers will also be interrogated in blood, colonic tissue, and stool to provide a comprehensive view on how RO7790121 impacts the immune system and processes associated with disease and disease severity.

Exploratory research on safety biomarkers may be conducted to support future drug development. Research may include further characterization of a safety biomarker or identification of safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation. Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on participant management.

4.3 JUSTIFICATION FOR DOSE AND SCHEDULE

The proposed doses and schedules for RO7790121 in Study GA45331 are as follows:

- Induction phase: 500 mg IV at Weeks 0, 2, 6, and 10
- Maintenance phase: 150 mg SC Q4W or 450 mg SC Q4W, from Week 12 to Week 52
- Open label extension phase: 450 mg SC Q4W or Q2W.

The proposed doses and regimens of 500 mg IV, 150 mg SC, and 450 mg SC RO7790121 have established clinical efficacy and well tolerated safety profiles based on previously conducted Phase IIa (IV dosing) and IIb (SC dosing) trials in UC.

Historical data for biologics in IBD have shown that maximizing the induction regimen and serum concentrations when patients have higher disease activity is paramount in order to establish efficacious concentrations at inflamed tissue levels. While staying within safe exposure limits, maximizing drug concentrations during induction with mAbs has been associated with better clinical outcomes such as greater rates of clinical response and remission, lower C-reactive protein (CRP), endoscopic improvement, mucosal healing, and lower risk for colectomy (Reinisch et al. 2012; Adedokun et al. 2014; Rosario et al. 2015; Dreesen et al. 2018).

Another important consideration when treating patients with mAbs is the development of anti-drug antibodies (ADAs), since ADAs are associated with lower serum drug concentrations, loss of response, reduced duration of response to treatment, and adverse effects such as infusion-related and injection site reactions (Baert et al. 2003; Bots et al. 2021). It has been shown that higher anti-TNF dosing is associated with lower ADA detection (Hanauer 2004; Adedokun et al. 2019). ADA formation typically has a negative impact on clinical, biochemical, and endoscopic outcomes (Vande Casteele and Gils 2015; Bots et al. 2021).

Variability in response to treatment with therapeutic mAbs in IBD is largely driven by interindividual differences in PK and drug exposure. Factors affecting drug exposure for these therapies in IBD include patient- and disease-related covariates, as well as distribution of the target (soluble and membrane associated forms). Factors influencing PK include body weight, gender, serum albumin, inflammatory burden (e.g., reflected by serum CRP, fecal calprotectin concentrations, and endoscopic severity), concomitant immunosuppression, and immunogenicity (Lefevre 2019). These factors are similarly distributed among patients with UC and CD, and for most therapeutic mAbs in IBD the same dose regimen is approved in UC and CD (e.g., infliximab, adalimumab, vedolizumab, ustekinumab). Similarly, within-class TL1A Phase IIa studies have demonstrated safety and efficacy utilizing the same dose in both UC and CD. Therefore, assuming similarity in PK (and covariates influencing PK) and target expression/distribution in UC and CD, the proposed dosing regimen for this CD study is based on the same principles as for the Phase III UC studies.

4.3.1 Induction Phase Dose Selection

The proposed dose and schedule of RO7790121 during the induction phase (500 mg IV at Weeks 0, 2, 6, and 10) is designed to meet the following goals:

- To increase the likelihood of maximal blockade of membrane TL1A and maximal suppression of soluble TL1A (sTL1A) in inflamed tissues in conditions such as IBD that show higher TL1A expression in gut tissue (Bamias et al. 2003). This is based on the finding that TL1A mRNA expression is upregulated in inflamed CD and UC colonic tissue compared with noninflamed and normal tissue (Meng et al. 2023). The 500 mg IV induction regimen aims to increase the likelihood of maximal blockade of TL1A while utilizing a dose and regimen that falls within the previous clinical safety experience of the Phase IIa study, which demonstrated that 500 mg IV Q2W for 7 doses was safe and well tolerated.
- To mitigate the impact of ADAs and neutralizing antibodies (NAbs) on PK, efficacy, and safety. IV dosing in the Phase IIa study was associated with lower ADA titers and a delayed median time to first ADA (and NAb) detection as compared to SC dosing in the Phase IIb study.

In the Phase IIa study in UC, multiple IV infusions of RO7790121 were generally safe and well tolerated, and a statistically significant result in the primary efficacy endpoint was shown, with an endoscopic improvement rate at Week 14 of 38% (95% CI: 23.8% to 53.7%).

In this study, the 500 mg Q2W IV regimen was associated with significantly lower ADA titers as compared to the SC regimen in the Phase IIb study (50, 150, and 450 mg Q4W during induction). There were no statistically significant effects of ADA and NAb status on endoscopic and remission endpoints at Week 14. Also, the similarity of the PK profiles in ADA-positive and ADA-negative participants and in NAb positive and NAb-negative participants, suggested a limited impact on PK (higher ADA titers were associated with lower exposure, with considerable overlap). The median times to first detection of ADA and NAb were 140 and 114 days, respectively, with the 500 mg IV regimen, and were 30–57 days and 58–85 days, respectively, during induction with the SC regimen. In the Phase IIb study (SC regimen), ADA-positive participants with the highest ADA titers in the 150 mg and 450 mg groups had numerically lower mean serum RO7790121 concentrations than the ADA-negative participants.

Considering all of the above, the median time to first detection of ADA, and low ADA titers after IV dosing, as opposed to higher titers developing earlier after induction SC dosing, IV dosing is favored over SC dosing during the 12-week induction period, in order to mitigate any potential impact of immunogenicity on PK, efficacy, and safety.

4.3.2 Maintenance Phase Dose Selection

Following the IV induction regimen, starting at Week 12, a 40-week maintenance phase will commence with SC dosing of either 150 mg or 450 mg SC RO7790121 Q4W. The first SC maintenance dose will be given at Week 12 to maximize RO7790121 exposure during the transition from Induction to Maintenance phase.

Based on the totality of efficacy, safety, PK and immunogenicity data of RO7790121 in the Phase IIb Study in UC, it is appropriate to evaluate the 150 mg and 450 mg SC regimens in the maintenance phase. The 150 mg and 450 mg RO7790121 SC Q4W regimens have demonstrated clinically meaningful efficacy response, as well as a favorable safety profile in the Phase IIb study. These doses are expected to minimize the potential impact of ADA and NAb on PK as compared to the 50 mg regimen assessed in Phase IIb in UC. In addition, the SC route of administration is convenient for long-term treatment in patients with CD.

4.3.2.1 Justification for the 450 mg RO7790121 SC Q4W Regimen

In the Phase IIb study in UC, during the 12-week induction period, participants were randomized to receive 50 mg, 150 mg, 450 mg, or placebo SC Q4W. During the maintenance phase, all participants, including those initially on placebo, received active drug. Participants initially on 50 mg, 150 mg, or 450 mg during induction received either the same dose or a lower dose throughout maintenance.

The 450 mg maintenance dose is supported by the observation that among the participants that received the 450 mg dose during induction, numerically higher efficacy for endoscopic improvement, modified remission, sustained endoscopic improvement, and sustained modified remission was observed for participants on the 450 mg → 450 mg sequence versus lower doses.

Exposure-response analysis with individual exposures ($C_{ave,56wk}$; predicted average concentration over 56 weeks) suggested that participants with the highest tertile $C_{ave,56wk}$ had numerically higher modified remission, endoscopic improvement, sustained modified remission, and sustained endoscopic improvement response than the lower two tertiles. Almost all of the patients that received the 450 mg dose had exposures in the highest tertile, indicating that this dose was necessary to achieve systemic exposures that corresponded to maximal and sustained efficacy over the long term.

During maintenance in the Phase IIb study, in the 450 mg → 450 mg treatment sequence arm, the ADA and NAb persistent response rates were the lowest as compared to other treatment sequence rates. Also, there appeared to be minimal to no impact of ADA status on serum RO7790121 in the 450 mg → 450 mg sequence.

4.3.2.2 Justification for the 150 mg RO7790121 SC Q4W Regimen

The Phase IIb study in UC explored the efficacy and safety of RO7790121, randomizing participants to receive either 50, 150, or 450 mg SC RO7790121 or placebo during the study (12-week induction period and 40-week maintenance period).

At Week 56, when the primary outcome was measured, all treatment doses differentiated from placebo. The proportion of patients achieving modified clinical remission at Week 14 was 35.0% (90% CI: 25.1% to 45.2%) and 31.8% (90% CI: 23.7% to 40.8%) for participants receiving 150 mg and 450 mg RO7790121, respectively. The improvements in modified clinical remission were sustained throughout the maintenance period, 38.5% (90% CI: 23.3% to 56.4%) and 35.7% (90% CI: 20.9% to 52.7%) in patients receiving 150 mg and 450 mg RO7790121, respectively. Additionally, a greater proportion of patients demonstrated endoscopic improvement across all doses compared to placebo at Week 14 (150 mg: 38.3% [90% CI: 27.8% to 48.6%] and 450 mg: 40.9% [90% CI: 32.1% to 50.0%]) and at Week 56 (150 mg: 39.3% [90% CI: 23.8% to 56.5%] and 450 mg: 50.0% [90 CI: 33.3% to 66.7%]). No relationship was seen in the incidences of adverse events across the different doses.

Based on the previously demonstrated efficacy of RO7790121 in UC, and also to further assess dose (exposure)-response in CD, the lower dose of 150 mg will be evaluated in addition to the 450 mg dose during the maintenance treatment phase. It is reasonable to explore a lower dose (150 mg) in the maintenance phase, following the IV regimen during Induction, when patients have less inflammatory burden, and therefore less risk for suboptimal exposure and/or immunogenicity).

The 150 mg and 450 mg doses appeared to have similar ADA profiles. During the maintenance treatment phase, there appeared to be minimal to no impact of ADA status on serum RO7790121 concentration in the 150 mg → 150 mg and 450 mg → 450 mg sequences, in contrast to the 50 mg → 50 mg sequence, where the ADA-positive participants had a numerically lower mean serum RO7790121 concentration than the ADA-negative participants.

Based on the totality of efficacy, safety, and PK considerations, these results support the proposed 150 mg SC Q4W and 450 mg SC Q4W regimens for the maintenance treatment phase in order to characterize dose (exposure)-response in the CD population.

4.3.3 Open-Label Extension Phase Dose Selection

To allow for access to active treatment, all participants entering the OLE (regardless of double-blind dosing arm) will receive RO7790121 450 mg SC. Participants who complete Week 52 of the maintenance phase will enter the OLE following a 450 mg Q4W dosing schedule. For those participants meeting disease worsening criteria between Weeks 12 and 52, a dose intensified schedule of 450 mg SC Q2W will be followed for 12 weeks. Dose intensification is a commonly used steroid-sparing strategy

to recapture clinical response in IBD, and timely dose intensification has been associated with clinical improvements. Therefore, the Q2W dose frequency in the OLE phase allows for dose intensification in all participants who may benefit after disease worsening. In the case of participants with disease worsening rolling over from placebo, the increased Q2W dosing for 12 weeks will serve as an induction regimen. The dose of 450 mg SC Q2W for 12 weeks is within the established clinical safety profile from the Phase IIa study (500 mg IV Q2W). Participants who follow the Q2W dose schedule will have the opportunity to de-escalate to the 450 mg SC Q4W dose schedule after 12 weeks or be withdrawn from the study, as assessed by the investigator (Figure 2 and Appendix 11).

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study, including the last visit shown in the schedules of activities (Section 1.3).

The end of this study is defined as the date of the last visit of the last participant in the study or the date at which the last data point required for statistical follow-up, or statistical analysis follow-up is received from the last participant, whichever occurs later.

The end of the study is expected to occur approximately 70 weeks after the last participant is enrolled, unless at least one participant enters the OLE phase. In this case, the study end is expected to occur when RO7790121 becomes commercially available to all participants who are receiving it in the OLE phase. Site discontinuation will occur upon commercial availability of RO7790121 in order for participants to transition off of this trial and onto commercially available RO7790121. Discontinuation may also occur with cessation of RO7790121 development in CD by the Sponsor. In addition, the Sponsor may decide to terminate the study at any time.

4.5 DURATION OF PARTICIPATION

The total maximum duration of study participation for an individual is expected to be approximately 70 weeks without OLE participation. With OLE participation, treatment will continue until RO7790121 is commercially available in that region or until the Sponsor decides to terminate the study, whichever is earlier.

5. STUDY POPULATION

Approximately 600 participants with CD will be enrolled during the global enrollment phase of this study.

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

5.1 INCLUSION CRITERIA

Potential participants are eligible to be included in the study only if all of the following criteria apply:

General Inclusion Criteria

- Signed Informed Consent Form
- Signed Assent Form, when appropriate, as determined by the potential participant's age and individual site and country standards
- Age ≥ 18 to ≤ 80 years at the time of signing Informed Consent Form

  Patients aged ≥ 16 to < 18 years may be eligible to participate in the study where locally permissible (e.g., if permitted by local guidelines and regulations).
- Bodyweight ≥ 40 kg

Crohn's Disease-Specific Inclusion Criteria

- Confirmed diagnosis of CD with supportive clinical, endoscopic and histopathological evidence
- Moderately to severely active CD, meeting all of the following:
  - Centrally-read SES-CD of ≥ 6 (or ≥ 4 for isolated ileal disease)
  - CDAI ≥ 220 and ≤ 450
- Involvement of ileum and/or colon, with at least four colonic segments traversable by an endoscope or a pediatric endoscope, or three segments (colon and/or ileum) for patients who have undergone a bowel resection
- Up-to-date screening for colorectal cancer for all participants (performed according to local standards)
  - Receipt of a surveillance colonoscopy at screening or within one year prior to baseline (performed according to local standards) to rule out dysplasia in participants with colonic disease lasting for > 8 years or with risk factors for bowel cancer

  Any adenomatous polyps must be removed according to routine practice prior to their first dose of study drug.

Reproductive Inclusion Criteria

- For female participants of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use adequate contraception during the treatment period and for 95 days after the final dose of RO7790121.

  A female participant is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a female participant with a tubal ligation is considered to be of childbearing potential. The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  The following are examples of adequate contraceptive methods: bilateral tubal ligation; male sterilization; hormonal contraceptives; hormone-releasing intrauterine devices; copper intrauterine devices; male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide. A male condom and a female condom should not be used together because of risk of failure due to friction.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

  Female participants of childbearing potential must refrain from donating eggs or undergoing fertility treatment during this same period.

- For male participants: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agree to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, male participants must remain abstinent or use a condom during the treatment period and for 95 days after the final dose of RO7790121 to avoid exposing the embryo. Male participants must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

Prior Medications Inclusion Criteria

- Must have had at least one of the following treatments in the past with inadequate response, loss of response, and/or intolerance

  Inadequate response is defined as having signs and symptoms of persistently active disease despite completing at least the approved dosing regimen in the product label.

  Intolerance may include, but is not limited to, infusion-related reactions, injection site reactions, rash, serum sickness, hepatic abnormalities, demyelination, congestive heart failure, and infections. There is no minimum requirement for dose or duration if a potential participant was determined to be intolerant to prior treatment.

  Loss of response is defined as the recurrence of signs and symptoms of active disease during approved treatment following prior clinical benefit (discontinuation despite clinical benefit does not qualify as having failed or being intolerant to CD advanced therapy).

  The medication used to qualify the participant for entry into this category must be approved for the treatment of CD, including biosimilars. Participants previously exposed to investigational therapies for the treatment of CD must still meet inclusion criteria "Conventional Therapy Failure" or "Advanced Therapy Failure."

  Conventional Therapy Failure

  – Steroids (e.g., systemic prednisone, oral budesonide)

    The following definitions will be used as guidelines for the use of corticosteroids in this trial:

    - Corticosteroid refractory: Persistent active disease despite treatment with at least one 4-week induction regimen, including a starting dose of ≥30 mg of oral prednisone (or equivalent) for at least 2 weeks or IV prednisone for ≥ 5 days, or persistently active disease after at least 4 weeks of oral budesonide given 9 mg/day
    - Corticosteroid dependent: At least two failed attempts to taper corticosteroids below 10 mg oral prednisone daily (or its equivalent) or inability to taper oral budesonide to 6 mg/day or below without active disease
    - Corticosteroid intolerant: History of intolerance to corticosteroids (including but not limited to Cushing syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, infection)

- At least 12 weeks of an immunomodulator, which can include:
  - $\geq$1.5 mg/kg/day of oral azathioprine (AZA) (or per local standard of care)
  - $\geq$0.75 mg/kg/day of 6-mercaptopurine (6-MP) (or per local standard of care)
  - $\geq$15 mg/week of intramuscular or SC methotrexate (MTX)
  - Persistent signs and symptoms of active disease despite a 6-TG level of $\geq$230 pmol/8×10^8 RBCs during at least one 12-week regimen of oral AZA or 6-MP at a stable or increasing dose
  - History of intolerance to AZA, 6-MP, or MTX (including, but not limited to, nausea/vomiting, abdominal pain, pancreatitis, LFT abnormalities, lymphopenia, TPMT genetic mutation, infection)
- At least 4 weeks of an oral aminosalicylate, which can include a minimum dose of the following:
  - 2.4 g/day of mesalamine (or per local standard of care)
  - 4.0 g/day of sulfasalazine (or per local standard of care)
  - 1.0 g/day of olsalazine (or per local standard of care)
  - 6.75 g/day of balsalazide (or per local standard of care)

The conventional therapy failure population will also include patients who have received advanced therapy (biologics or small molecules) in the past but stopped therapy based on reasons other than failure (e.g., change in reimbursement coverage, well-controlled disease).

<u>Advanced Therapy Failure</u>

- Anti-TNF agents, including and not limited to the following:
  - At least one 6-week induction regimen of infliximab ($\geq$5 mg/kg IV at 0, 2, and 6 weeks or per local label) or equivalent biosimilar
  - At least one 8-week induction regimen of adalimumab (one 160 mg SC dose followed by one 80 mg SC dose [or one 80 mg SC dose in countries where this dosing regimen is allowed] followed by one 40 mg SC dose at least 2 weeks apart or per local label) or equivalent biosimilar
- Anti-integrins, including and not limited to the following:
  - At least one 6-week induction regimen of vedolizumab (300 mg IV at 0, 2, and 6 weeks or per local label)

- Anti−IL-12/IL-23, including and not limited to the following:
  - At least one 8-week induction regimen of ustekinumab (a single IV dose using weight-based dosing: 260 mg for participants with body weight ≤55 kg; 390 mg for participants with body weight >55 kg to ≤85 kg; 520 mg for participants with body weight >85 kg or per local label) (single weight-based dose) or equivalent biosimilar
  - At least one 8-week induction regimen of risankizumab (600 mg IV at 0, 4, and 8 weeks, or per local label)
- JAK inhibitors, including and not limited to the following:
  - At least one 8-week induction course of upadacitinib (45 mg orally daily or per local label)
- Any newly approved sphingosine-1-phosphate receptor modulators for CD treatment, including but not limited to the following:
  - At least one 14-week induction course of etrasimod (2 mg or 3 mg orally daily)

5.2 EXCLUSION CRITERIA

Potential participants are excluded from the study if any of the following criteria apply.

Inflammatory Bowel Disease Exclusion Criteria

- Participant with a history of ≥3 bowel resections

  >2 missing segments of the following five segments: terminal ileum, right colon, transverse colon, sigmoid and left colon, and rectum
- Diagnosis of short gut or short bowel syndrome
- Presence of ileostomy, colostomy, or ileo-anal pouch
- Patients with symptomatic bowel strictures, fulminant colitis, or toxic megacolon
- Current diagnosis of UC or indeterminate colitis, ischemic colitis, infectious colitis, radiation colitis, or microscopic colitis
- Presence of abdominal or perianal abscess
- Presence of rectovaginal fistula or perianal fistulas with >3 openings and/or the anticipated need for perianal surgery during the study (except surgery for seton placement and/or removal)
- Current diagnosis or suspicion of primary sclerosing cholangitis

Medical History Exclusion Criteria

- Lack of peripheral venous access
- Any major surgery within 6 weeks prior to screening or a major surgery planned during the study
- Any serious, chronic, and/or unstable preexisting medical, psychiatric, or other condition that could interfere with the potential participant's safety, provision of informed consent, or compliance with trial procedures
- Pregnancy or breastfeeding, or intention of becoming pregnant during the study or within 95 days after the final dose of RO7790121

    Female participants of childbearing potential must have a negative serum pregnancy test result at screening and a negative urine pregnancy test on Day 1 prior to initiation of study treatment.
- Any condition that would preclude endoscopic evaluation
- Past or current evidence of definite low-grade or high-grade colonic dysplasia or adenomas or neoplasia not completely removed
- History of malignancy within 5 years prior to screening visit, with the exception of malignancies adequately treated with resection for non-metastatic basal cell or squamous cell cancer or in situ cervical cancer
- History of alcohol, drug, or chemical abuse <1 year prior to screening

Infection or Infection Risk Exclusion Criteria

- Any clinically significant infection <4 weeks prior to randomization that required hospitalization, IV antibiotics and did not resolve, or was opportunistic in nature
- Evidence of or treatment for *Clostridioides difficile* (*C. difficile*; formerly known as *Clostridium difficile*) as assessed by *C. difficile* toxin testing within 60 days prior to randomization (Day 1) or other enteric pathogens (as assessed by stool culture and ova and parasite evaluation) within 30 days prior to randomization (Day 1)
- Any diagnosis of CMV colitis in the past 60 days (including diagnosis during screening)

    Laboratory confirmation of CMV from a colon biopsy sample is required during screening evaluation only if clinical suspicion is high and to determine the need for CMV treatment.
- Positive HIV test at screening
- Positive test results for hepatitis B infection at screening, defined as meeting either of the following criteria:
    - Positive hepatitis B surface antigen (HBsAg) test at screening
    - Quantitative HBV DNA above the lower limit of quantification in patients with a negative hepatitis B surface antibody (HBsAb) test and positive total hepatitis B core antibody (HBcAb) test
- Positive hepatitis C virus (HCV) antibody test at screening

- Positive for tuberculosis (TB) during screening or within 3 months prior to screening, defined as a positive QuantiFERON-TB Gold test® (QFT) or, if QFT is not available, a positive purified protein derivative (PPD) skin test according to local guidelines or regulations or other locally approved TB ELISA tests (e.g., TSPOT®), with the following exceptions:
  - Potential participants with a history of Bacillus Calmette-Guérin (BCG) vaccination who have a positive PPD skin test will not be excluded if they have a negative QFT at screening
  - Potential participants who have a positive or indeterminate QFT and those with no history of BCG vaccination who have a positive PPD skin test will not be excluded if they meet all of the following criteria:
    - No symptoms that are consistent with TB
    - Documented history of a completed course of adequate prophylaxis (completed treated for latent TB) per local standard of care prior to randomization (Day 1)
    - No known exposure to a case of active TB after most recent prophylaxis
    - No evidence of active TB on chest X-ray performed during screening or within 3 months prior to screening
- History of organ transplant
- Acquired or congenital immunodeficiency

Laboratory Results Exclusion Criteria

- Clinically significant abnormality on laboratory tests during screening (hematology, serum chemistry, and urinalysis) that, in the opinion of the investigator, may pose an additional risk in administering study treatment to the potential participant
- ALT, AST, or ALP $\geq 2.5 \times$ upper limit of normal (ULN), total bilirubin $\geq 2 \times$ ULN, or presence of abnormalities in synthetic liver function tests judged to be clinically significant by the investigator

  Patients with known Gilbert syndrome who have unconjugated hyperbilirubinemia will not be excluded.
- ANC $< 1.5 \times 10^9$/L (1500/μL) with one exception:
  - Participants with benign ethnic neutropenia (BEN): ANC $< 1.3 \times 10^9$/L (1300/μL)

    BEN (also known as constitutional neutropenia) is an inherited cause of mild or moderate neutropenia that is not associated with any increased risk for infections or other clinical manifestations (Atallah-Yunes et al. 2019). BEN is referred to as ethnic neutropenia because of its increased prevalence in people of African descent and other specific ethnic groups.
- Platelet count $< 100{,}000/\mu$L
- Hemoglobin < 8 g/dL
- Absolute lymphocyte count $< 500/\mu$L

- **<u>Prohibited Medications Exclusion Criteria</u>**
- Any of the following related to previous or current treatment:
  - Use of approved CD treatments including approved oral small molecule (e.g., JAK inhibitor) treatments within 2 weeks, or approved biologic agents within 8 weeks or 5 half-lives, whichever is longer

    If there is proper documentation of undetectable drug level measured by a commercially available assay for any of the approved biologics, there is no minimum washout prior to screening.
  - Use of any investigational or experimental therapy within approximately 30 days for non-biologic therapy or 8 weeks for biologic therapy, OR 5 half-lives (whichever is longer), prior to randomization (Day 1)
  - Treatment with IV corticosteroids $\leq$2 weeks prior to screening or during the study
  - Presence of conditions other than CD (e.g., uncontrolled asthma) that could require treatment with $>$20 mg/day of prednisone (or equivalent) during the course of the study
  - Treatment with corticosteroid enemas or suppositories and/or topical (rectal) 5-aminosalicyclic acid (5-ASA) preparations $\leq$2 weeks prior to screening or during the study
  - Treatment with topical rectal traditional medicine (e.g., Chinese medicine), herbal enemas, or suppositories $\leq$2 weeks prior to screening or during the study
  - Treatment with approved oral traditional medicine (e.g., Chinese medicine) $\leq$ 4 Weeks prior to screening or during the study.
  - Transplant/stem cell therapy at any time prior to or during the study
  - Treatment $\leq$16 weeks prior to or during screening with cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil
  - Apheresis $\leq$2 weeks prior to screening or intent to receive during the study
  - Currently receiving total parenteral nutrition
  - Continued tube feeding, exclusive enteral nutrition or defined formula diets, and/or parenteral alimentation/nutrition as treatment for CD $\leq$3 weeks prior to randomization or during the study
  - Receipt of fecal microbial transplantation within 4 weeks prior to randomization (Day 1)
  - Current or prior use of anti-TL1A (RO7790121/RVT-3101/PF-06480605) or any type of anti-TL1A therapy
  - Receipt of a live or attenuated vaccine $\leq$4 weeks prior to screening

    Use of non-live (inactivated) vaccines is allowed.

- Chronic (e.g., $>$7 days) nonsteroidal anti-inflammatory drug (NSAID) use

  Occasional use of NSAIDs and acetaminophen (e.g., headache, arthritis, myalgias, or menstrual cramps) and aspirin $\leq$325 mg/day is permitted.
- Treatment with immunoglobulin or blood products within 4 weeks prior to screening, or any condition that is likely to require such treatment during the course of the study
- Previous severe allergic reaction or anaphylactic reaction to biologic agents or to any excipients of the study drug

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

This study has no meal or dietary restrictions.

5.3.2 Caffeine, Alcohol, and Tobacco

This study has no caffeine, alcohol, or tobacco restrictions.

5.3.3 Activity

This study has no activity restrictions.

5.3.4 Contraception Requirements

During the study, participants must use contraception or take other precautions as described in Section 5.1.

5.4 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per individual) at the investigator's discretion, with the exception of participants who screen fail due to an ineligible SES-CD or CDAI score at baseline.

The screening endoscopy and colonic biopsies do not need to be repeated during re-screening, provided that the initial endoscopy has been performed within 35 ($+$7) days prior to the day of randomization for the second screening, and colonic biopsies as specified in the protocol have been obtained. The screening period is up to 35 days; however, if required due to unforeseen circumstances, the screening period may be extended a maximum of 7 days.

Participants who are classified as screen failures due to presence of *C. difficile* or CMV infection may be re-screened 60 days after successful treatment.

Individuals are not required to re-sign the consent form if they are re-screened within 6 weeks after previously signing the consent form. The investigator will maintain a record of reasons for screen failure (see Section 8).

6. STUDY TREATMENT, OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN, AND CONCOMITANT THERAPY

The investigational medicinal products (IMPs) for this study are RO7790121 and placebo

6.1 STUDY TREATMENT ADMINISTERED

Table 6 provides a description of assigned study treatments for this study.

Table 6 Study Treatment Description

	RO7790121	RO7790121 Placebo
Use	Experimental	Placebo comparator
Drug form	Solution for infusion/injection	Solution for infusion/injection
Unit dose strength	225 mg/1.5 mL (150 mg/mL)	Not applicable
Dosage levels	Induction: 500 mg IV at Weeks 0, 2, 6, and 10 Maintenance: 150 mg or 450 mg SC Q4W OLE: 450 mg SC Q2W or Q4W	Not applicable
Formulation(s)	Refer to pharmacy manual and/or Investigator's Brochure	Refer to pharmacy manual and/or Investigator's Brochure
Packaging	RO7790121 is supplied as liquid in a 2-mL glass vial with a 1.5-mL deliverable volume	The placebo is provided in an identical 2-mL glass vial with a 1.5-mL deliverable volume
Labeling	Per local requirements	
Route of administration	Intravenous infusion or subcutaneous injection	Intravenous infusion or subcutaneous injection
Source	Sponsor	Sponsor

OLE = open-label extension; Q2W = every 2 weeks; Q4W = every 4 weeks.

At applicable sites, SC study treatment in the OLE phase may be administered by a trained nursing professional at the participant's home or another suitable location if the participant has given written informed consent to participate in mobile nursing (MN) visits. MN administration will be available after the first Q3M visit in Year 1 of the OLE phase.

Guidelines for dose modification and treatment interruption or discontinuation for participants who experience adverse events are provided in Appendix 4.

6.1.1 RO7790121 and Placebo

Intravenous administration of RO7790121 will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 8.

The IV infusion will be delivered over 60 (±10 minutes). The post-dose observation period for IV infusions is 60 minutes.

For participants who experience an infusion-related reaction (IRR), subsequent infusions may be given in accordance with institutional/local clinical guidelines or IRR management guidance in Appendix 9. Guidelines for medical management of IRRs are provided in Appendix 9.

The post-dose observation period for SC injection is 30 minutes, with the exception of the first 12 weeks of the OLE phase, which will have a post-dose observation period of at least 60 minutes. Visits in the first 12 weeks of the OLE are not eligible for MN, i.e., the first 3 doses for participants following the Q4W dose regimen and the first 6 doses for participants following the Q2W dose regimen are not eligible for MN. Guidelines for medical management of injection site reactions (ISRs) are provided in Appendix 10.

For information on SC study drug administration, where participants experience an ISR considered to be related to study drug administration, follow institutional/local clinical guidelines for ISR treatment and report these as adverse events per A3–7. There may be a risk of serious reactions during the SC treatments; therefore, SC treatment will be performed by trained personnel with immediate ability to manage potentially serious reactions. Investigators will educate participants about signs and symptoms of anaphylaxis, and they will be instructed to seek immediate medical care should signs or symptoms occur.

Every effort should be made to adhere to the dosing schedule and associated dosing window during induction (Table 1), maintenance (Table 2) and OLE (Table 3) phases. If a dose is administered outside of the specified visit window, the next dose should be administered according to the original dosing schedule. Consecutive doses of RO7790121 should not be administered <7 days apart.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

Refer to the Pharmacy Manual for detailed instructions on drug preparation, handling, storage, and accountability.

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel e.g., pharmacist or mobile nurse), is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site,

IMP use by each participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that participants are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor using an interactive voice or web-based response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced. Temperature conditions for all IMPs will be monitored during transit, and any discrepancies will be reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only participants enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or the RO7790121 Investigator's Brochure for information on IMP preparation, storage, handling, and accountability.

6.3 TREATMENT ASSIGNMENT AND BLINDING

6.3.1 Treatment Assignment

This is a randomized, double-blind study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a participant, the study site will obtain the participant's identification number and treatment assignment from an IxRS.

Participants will be randomly assigned to one of three treatment arms: RO7790121 at 500 mg IV during the induction phase and 450 mg SC during the maintenance phase; RO7790121 500 mg IV during the induction phase and 150 mg SC during the maintenance phase; or placebo. Randomization will occur in a 1:1:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified by prior advanced therapy use (yes/no), baseline corticosteroid use (yes/no), and baseline endoscopic activity (moderate, defined as SES-CD < 15, or severe, defined as SES-CD ≥ 15).

6.3.2 Blinding

Study site personnel (with the exception of the unblinded pharmacist at sites where pharmacist blinding is not possible), and participants will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to participant treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, operational assay group personnel, IxRS service provider, and iDMC members.

While PK and immunogenicity samples must be collected from participants assigned to the comparator arm to maintain the blinding of treatment assignment, PK and ADA assay results for such participants are generally not needed for the safe conduct or proper interpretation of the study data. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to participant treatment assignments to identify appropriate samples for analysis. PK samples from participants assigned to the comparator arm will not be analyzed for study drug PK concentration except by request (e.g., to evaluate a possible error in dosing). Baseline immunogenicity samples will be analyzed for all participants. Postbaseline immunogenicity samples from participants assigned to the comparator arm will not be analyzed for ADAs except by request.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which participant management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The treatment code should not be broken except in emergency situations. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code. However, the investigator should inform the Medical Monitor that the treatment code has been broken.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. Unblinding may be permitted if an investigator is determining the suitability of subsequent medical care for a participant. However, unblinding will not be permitted if an investigator is determining a participant's eligibility for a subsequent clinical trial testing investigational medicinal products or procedures.

The Investigator should document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agrees to participant unblinding, the investigator will be able to break the treatment code by contacting the IxRS.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions that are considered by the investigator or Sponsor to be related to a drug listed in Section 8.3.4. The participant may continue to receive treatment, and the investigator, participant, and Sponsor personnel, with the exception of the Drug Safety representative

and personnel who must have access to participant treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

6.4 STUDY TREATMENT COMPLIANCE

When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision.

Details on treatment administration (e.g., dose and timing) should be noted in the source documents and on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Appendix 3.

6.5 DOSE MODIFICATION

Modification of the study drug dose is not permitted during the double-blind phases of the study. However, dose intensification or de-escalation (either from Q4W to Q2W or from Q2W to Q4W, respectively) may be permitted during the OLE phase (see Section 4.1.3). Any other dosing frequencies (e.g., weekly dosing) are not permitted (see Section 6.1.1).

6.6 CONTINUED ACCESS TO STUDY TREATMENT AFTER THE END OF THE STUDY

Currently, the Sponsor does not have any plans to provide Roche IMP (RO7790121) or any other study treatments to participants who have completed the study (Section 4.4). The Sponsor may evaluate whether to continue providing RO7790121 in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

https://assets.cwp.roche.com/f/176343/x/92d6b13ee6/policy_continued_access_to_investigational_medicines.pdf

6.7 TREATMENT OF OVERDOSE

An overdose is the administration of a drug in a quantity that is higher than the assigned dose. There is no known antidote for treating an overdose. Cases of overdose, along with any associated adverse events, should be reported as described in Section A3–8.

6.8 CONCOMITANT THERAPY

Any medication and/or vaccine and/or apheresis and/or stem cell therapy (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) used by a participant in addition to protocol–mandated treatment at any time between the start of the screening period and the final safety follow-up visit must be recorded on the Concomitant Medications and associated eCRFs along with the following information:

- Reason for use
- Dates of administration, including start and end dates

- Dosage information, including dose and frequency

The Medical Monitor may be consulted if there are any questions related to concomitant or prior therapy.

Participants requiring a prohibited therapy (Table 7) will be discontinued from study treatment and will undergo follow-up assessments as described in Table 1, Table 2, Table 3.

Permitted and prohibited concomitant therapies for CD are outlined in Table 7. Any new or increased use of these therapies due to lack of efficacy (Table 5) should be indicated as such on the Concomitant Medications eCRF. Permitted and prohibited concomitant therapies not related to CD are outlined in Table 8. Concomitant medication restrictions apply to all phases of the study, including the OLE phase.

Table 7 Permitted and Prohibited Concomitant Therapies for Crohn's Disease

Therapy	Permitted	Prohibited
Anti-inflammatories	• Oral 5-ASA if on stable dose for ≥ 2 weeks prior to screening endoscopy; stable dose throughout the study is permitted unless it is causing toxicity, in which case the dose should be discontinued. • Oral prednisone ≤30 mg/day (or dose equivalent of other oral corticosteroids) if on stable dose for ≥2 weeks prior to screening endoscopy and if dose stability continues through the induction phase; must initiate oral corticosteroid tapering in the maintenance phase (see Section 6.8.4).	• Oral 5-ASA initiation or dose change throughout the duration of the study • Topical (rectal) 5-ASA ≤2 weeks prior to screening endoscopy and throughout the duration of the study • IV corticosteroids and rectal corticosteroids (i.e., enemas or suppositories) ≤2 weeks prior to screening and for the duration of the study, with the exception of a single administration of IV steroid for potential IRR management • Initiation of oral corticosteroids from randomization and for the duration of the study
Immuno-suppressants	AZA, 6-MP, or MTX if on stable dose 12 weeks prior to randomization and continue stable dosing throughout the duration of the study; discontinuation of concomitant medication permitted if the dose is reduced or discontinued due to toxicity	• Cyclosporine, tacrolimus, sirolimus or mycophenolate mofetil ≤16 weeks prior to baseline and throughout the duration of the study

Table 7 Permitted and Prohibited Concomitant Therapies for Crohn's Disease (cont.)

Therapy	Permitted	Prohibited
Advanced Therapies	• No advanced therapies are permitted	• Small molecule (JAK inhibitor) ≤2 weeks prior to screening endoscopy and throughout the duration of the study • Any newly approved S1P receptor modulators ≤2 weeks prior to screening endoscopy and throughout the duration of the study • Biologics (anti-TNF, anti-integrin, and anti-interleukin, including biosimilars) within 8 weeks or 5 half-lives prior to screening endoscopy, whichever is longer, and throughout the duration of the study. Note: If there is proper documentation of undetectable drug level measured by a commercially available assay for any of the approved biologics, there is no minimum washout prior to screening endoscopy.
Other Therapies	• Oral probiotics if dose is stable ≥2 weeks prior to baseline and continue stable dosing throughout the duration of the study • CD-related antibiotics (e.g., ciprofloxacin or metronidazole) if dose is stable ≥2 weeks prior to screening endoscopy and through randomization	• Initiation of CD-related antibiotics throughout the duration of study, with the exception of those for the treatment of fistulas • Anti-TL1A agents at any time prior to or during the study (except RO7790121 administered as study treatment in this study) • Continued tube feeding, exclusive enteral nutrition or defined formula diets, and/or parenteral alimentation/nutrition as treatment for CD ≤3 weeks prior to randomization or during the study

5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; AZA = azathioprine; CD = Crohn's disease; IRR = infusion-related reaction; JAK = Janus kinase; MTX = methotrexate; S1P = sphingosine-1-phosphate; TL1A = tumor necrosis factor-like ligand 1A; TNF = tumor necrosis factor.

Table 8 Permitted and Prohibited Concomitant Therapies Not Related to Crohn's Disease

Permitted	Prohibited
• Occasional use of NSAIDs and acetaminophen and aspirin ≤325 mg/day • Non-live (inactivated) vaccines • CYP substrates with a narrow therapeutic window, including but not limited to aminoglycosides, ciclosporin, carbamazepine, digoxin, digitoxin, flecainide, lithium, phenytoin, phenobarbital, rifampicin, theophylline, and warfarin Monitoring the effect of drug concentration of the concomitant treatment (on initiation or discontinuation of RO7790121) is strongly recommended.	• Any investigational or experimental therapy within 30 days for non-biologic therapy or 8 weeks for biologic therapy, **or** 5 half-lives prior to randomization, whichever is longer Note: If there is proper documentation of undetectable drug level measured by a commercially available assay for any of the approved biologics, there is no minimum washout prior to screening endoscopy and throughout the study. • Topical rectal traditional medicine (e.g., Chinese medicine), herbal enemas, or suppositories ≤2 weeks prior to screening • Fecal microbial transplantation ≤4 weeks prior to baseline • Live or attenuated vaccines ≤4 weeks prior to screening • IV antibiotics ≤3 months prior to randomization • Apheresis ≤2 weeks prior to screening • Immunoglobulin or blood products ≤4 weeks prior to screening • Transplant/stem cell therapy at any time prior to or during the study • Chronic (e.g., >7 days) use of NSAIDs >325 mg/day during the study

CYP = cytochrome P450; NSAID = non-steroid anti-inflammatory drug.

6.8.1 Permitted Therapy

Permitted concomitant therapies for CD are outlined in Table 7. In general, investigators may manage a participant's care (including preexisting conditions) through use of supportive therapies, as clinically indicated and per local standard practice, with the exception of prohibited therapies defined in Table 7.

6.8.2 Medications Given with Precaution due to Effects Related to CYP Enzymes

RO7790121 is an IgG type mAb and is not anticipated to interact directly with drug-metabolizing cytochrome P450 (CYP) enzymes.

Proinflammatory cytokines have been shown to modulate expression of CYP enzymes and transporters (Lee et al. 2010). TL1A acts in synergy with IL-12, IL-15 and IL-18 on T cells and natural killer cells to produce multiple cytokines, including, IFN-g, IL-6, and granulocyte-macrophage colony-stimulating factor. Therefore, dosing with RO7790121 may affect CYP enzyme and transporter levels through normalization of inflammatory states, and consequently modulate the clearance of concomitant medications that are substrates for these enzymes or transporters. Cytokine-mediated drug interactions observed in the clinic to date have been modest for other therapeutic mAbs, generally resulting in a less than 2-fold change in the exposure of a co-administered small

molecule drug (Huang et al. 2010; Evers et al. 2013; Khalilieh et al. 2018; de Jong et al. 2022).

For RO7790121, the risk for disease-related drug-drug interactions (DDIs) is expected to be low based on literature data which indicated similar proinflammatory cytokines levels (or slight increase but below the level of impacting CYP expression) in patients with CD compared to healthy participants; and comparable exposure of CYP substrate drugs between healthy participants versus patients with CD (Sun et al. 2021).

Based on these considerations, the risk for RO7790121 to have direct or disease-related DDIs with concomitant medication in CD is low.

A dedicated clinical disease-related DDI study in the intended target population has not yet been conducted with RO7790121. The potential of RO7790121 to indirectly change the drug metabolism of concurrent medicated CYP substrates via immunomodulation has not been fully characterized in the indicated disease population (high inflammatory burden) to inform on the risk of disease-related DDIs.

As such, monitoring the effect or drug concentration (on initiation or discontinuation of RO7790121) is recommended for concurrent medicated CYP substrates with a narrow therapeutic window. The most common medications with a narrow therapeutic index include aminoglycosides, ciclosporin, carbamazepine, digoxin, digitoxin, flecainide, lithium, phenytoin, phenobarbital, rifampicin, theophylline, and warfarin (Blix et al. 2010).

The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the investigator may contact the Medical Monitor if questions arise regarding medications not listed above.

6.8.3 Prohibited Therapy

Prohibited concomitant therapies for CD are outlined in Table 7.

6.8.4 Corticosteroid Tapering

During their 12-week induction phase, participants are to maintain their stable baseline corticosteroid dose.

Following the Week 12 assessment, participants will begin corticosteroid tapering during the maintenance phase. The recommended tapering schedule for oral corticosteroids is shown in Table 9.

Table 9 Tapering Schedule for Oral Corticosteroids

Corticosteroid	Dose	Tapering Rate
Oral prednisone or equivalent	>10 mg/day	Taper daily dose by 5 mg/week until receiving 10 mg/day, and then continue tapering at 2.5 mg/week until 0 mg/day
	≤10 mg/day	Taper daily dose by 2.5 mg/week until 0 mg/day
Oral budesonide	≤9 mg/day	Taper tablets to 9 mg every other day for 2 weeks, followed by 9 mg every third day for 2 weeks, and then discontinue

For participants who cannot tolerate the corticosteroid taper without recurrence of CD clinical symptoms or steroid withdrawal, the corticosteroid dose may be increased (up to the dose at trial entry if required) per the investigator's discretion during the study, but tapering should begin again within 2 weeks.Discontinuation of Study Treatment and Participant Discontinuation or Withdrawal

Study and site closure is described in Appendix 1.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

7.1 DISCONTINUATION OF STUDY TREATMENT

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study treatment. If study treatment is definitively discontinued, the participant will not remain in the study for additional assessments. Refer to the schedule of activities (see Section 1.3) for data to be collected at the time of discontinuation of study treatment and for any further follow-up evaluations that need to be completed.

Participants must permanently discontinue study treatment if any of the following criteria are met:

- Any medical condition that the investigator determines may jeopardize the participant's safety if he or she continues to receive study treatment
- Investigator determination that treatment discontinuation is in the best interest of the participant
- Pregnancy
- Use of a prohibited therapy (see Table 7 and Table 8)
- Confirmed anaphylaxis to study treatment

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Participants will return to the clinic for a treatment discontinuation/early withdrawal visit before initiation of any new CD treatments to complete all of the assessments at that

visit. Note that if a participant discontinues due to pregnancy, they are not required to complete the endoscopy.

Refer to the schedule of activities in Section 1.3 for details on follow-up assessments to be performed for participants who permanently discontinue study treatment. If a participant requests to be withdrawn from treatment or follow-up assessments, this request must be documented in the source documents and signed by the investigator.

7.2 PARTICIPANT DISCONTINUATION OR WITHDRAWAL FROM THE STUDY

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

The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a participant requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the schedule of activities (see Section 1.3). Refer to the schedule of activities 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 treatment and from the study at that time.

If a participant withdraws consent from the study, the Sponsor may retain and continue to use any data collected before withdrawal of consent. Samples collected prior to withdrawal may be analyzed, unless the participant specifically requests that the samples be destroyed (as documented in the source documents) or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

7.3 PARTICIPANTS 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 counsel the participant on the importance of maintaining the assigned visit schedule. If the participant is unable or unwilling to comply with study visits, site personnel should assess reasons the participant is unable or unwilling to return to the clinic and determine if there are ways to support participant participation.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three 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 or she will be considered lost to follow-up and will be withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled individuals and for individuals who are not subsequently enrolled will be maintained at the study site.

Study procedures and their timing are summarized in the schedule of activities (see Section 1.3). Protocol waivers or exemptions are not allowed.

Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

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

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a detailed record of all participants screened, to document eligibility or record reasons for screening failure, as applicable.

Medical history and baseline conditions, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive

status, smoking history, and use of alcohol and drugs of abuse will be recorded at screening. Any medication or vaccine or stem cell therapy or apheresis (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) used by the participant in the two months prior to initiation of study treatment will be recorded.

A CD-specific medical history, including complications and surgeries related to CD, and a detailed history of CD medications used by the participant prior to the screening visit will be recorded. In addition, a detailed history of all prior advanced therapies used by the participant (e.g., name and duration of previous therapies and reason for discontinuation) will be recorded.

The extent and duration of the participant's disease, as recorded in the participant's medical record, will be captured in the eCRF. The extent of disease should be identified as one of the following:

- Ileal
- Colonic
- Ileo-colonic

Extraintestinal manifestations (e.g., arthritis, uveitis, erythema nodosum, etc.) should also be documented in the Medical History eCRF.

Demographic data, including age, sex, and self-reported race or ethnicity, will also be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Participants will be closely monitored for safety throughout the study. Participants should be assessed for toxicity prior to each dose; treatment will be administered only if the clinical assessment and most recent central laboratory test values are acceptable.

At applicable sites, certain study assessments and procedures may be performed by a MN professional at the participant's home or another suitable location, such as locations convenient to the participant and allowed by local regulations and guidelines, to improve access and convenience for participants participating in the study. The Sponsor will select a health-care company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, trained, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a participant and the participant gives written informed consent to participate in MN visits, the MN network will communicate with the participant and the participant's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments and procedures to be performed by the MN professional. The schedule of activities

(see Section 1.3) and MN Manual will specify the assessments and procedures that may be performed by an MN professional.

8.1 EFFICACY ASSESSMENTS

PRO and clinician-reported outcome (ClinRO) instruments will be completed to assess the treatment benefit of RO7790121. In addition, PRO instruments will enable the capture of each participant's direct experience with RO7790121. PRO data will be collected through the instruments summarized in Table 10 and described in this section as well as Section 8.9.

Table 10 Patient-Reported Outcome Instruments

PRO Instrument	Copy of Items	Collection	Recall Period	Approximate Time to Complete
Stool frequency	A6–1.1	Using eDiary	24 hours	1 minute
Abdominal pain				
General well-being				
Bowel urgency	A6–1.4			
FACIT-F	A6–1.5	At specified visits (Section 1.3)	7 days	5 minutes
IBDQ	A6–1.6		2 weeks	15 minutes
PGIC	A6–1.8		Current versus baseline	1–2 minutes
PGIS	A6–1.7		7 days	1–2 minutes
EQ-5D-5L [a]	A6–1.9		Current	3 minutes
WPAI-CD [a]	A6–1.10		7 days	2–3 minutes

EQ-5D-5L = EuroQol 5-Dimension 5-Level; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; IBDQ = Inflammatory Bowel Disease Questionnaire; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; WPAI:CD = Work Productivity and Activity Impairment Questionnaire: Crohn's Disease Questionnaire.

[a] This patient-reported instrument will be used to evaluate health economics rather than efficacy; see Section 8.9.

PRO instruments will be collected by eDiary or during visits to clinic or by MN (see schedule of activities in Section 1.3). In general, eDiary PROs should be completed daily during screening, induction and maintenance. During the OLE phase, participants will complete the eDiary PROs for at least 7 days prior to each quarterly (Q3M) visit during the first year and prior to the annual visit thereafter. If disease worsening criteria assessment (Section 4.1.3.2) is required in the OLE phase, eDiary PROs should be collected for at least 3 weeks prior to the visit at which the assessment is being conducted. For all phases of the study, eDiary entries are not required the day the participant receives medication for bowel preparation prior to endoscopy and the day the participant undergoes an endoscopy.

To ensure participant compliance with eDiary completion, eDiary review by study site personnel will take place at specified visits (Section 1.3). Details regarding the frequency of eDiary reporting and other aspects of direct patient entries, such as the particular methods of data collection, will be provided in a PRO manual.

ClinRO data will be collected, in part, through the CDAI, Section 8.1.1). Additional ClinRO data will be evaluated through central endoscopy and histology assessments by the Simple Endoscopic Score for Crohn's Disease (SES-CD, Section 8.1.2) and the Geboes Grading Scale (Section 8.1.3), respectively.

8.1.1 Crohn's Disease Activity Index

CDAI (Best et al. 1976) will be evaluated at specified timepoints (Section 1.3) to quantify signs and symptoms of CD. This index is a weighted sum of scores on eight components: number of liquid or soft stools (stool frequency), abdominal pain, general well-being, number of complications, use of anti-diarrheal medication, presence of an abdominal mass, hematocrit, and percentage deviation from standard body weight. Stool frequency, abdominal pain and general well-being components are PROs reported via eDiary. Remaining CDAI components are evaluated by physician or laboratory assessment. CDAI generally ranges from 0 to roughly 600, with higher values indicating greater activity (Section A6–1.1).

8.1.1.1 Stool Frequency, Abdominal Pain and General Well-Being

Each PRO component of CDAI contributes a summary (e.g., a sum or average) of daily eDiary entries over 7 days prior to the relevant timepoint. These weekly summaries are further used to evaluate disease worsening criteria (Section 4.1.3.2) and endpoints (Section 3). To permit eDiary review at visits, calculation of weekly summaries will be performed electronically. The PRO components take approximately 1 minute to complete. Further details on the calculation will be provided in the PRO manual.

8.1.2 Endoscopy

All participants will undergo an ileocolonoscopy at specified visits (Section 1.3). At screening, requirements for the extent and timing of this endoscopy assessment are determined by CD-specific study inclusion criteria (Section 5.1). After enrollment, every effort should be made to schedule planned endoscopies within the protocol-specified study visit window. After Week 12, additional endoscopies at unscheduled visits may be necessary in order to facilitate the evaluation of disease worsening criteria (Section 4.1.3.2), which determines OLE eligibility or dose intensification in OLE (Section 4.1.3.3). Since disease worsening criteria requires demonstration of both symptomatic and endoscopic activity, these unscheduled endoscopies should be carried out under the Investigator's discretion once the symptomatic criteria have been met.

Bowel preparation prior to endoscopy should be done per local practice. Medications used for bowel preparation should be reported on the Concomitant Medications eCRF. Scheduled stool samples should be taken prior to bowel preparation.

For each participant, a video recording will be performed during the endoscopy procedure through the use of high-definition video recording. Video recordings should be taken of the entire endoscopic procedure, starting from insertion into the bowel. Technical instructions for video recording will be provided in the endoscopy manual. All video recordings will be submitted to a central reading facility for evaluation of SES-CD (Daperno et al. 2004) by an independent gastroenterologist experienced in CD. Central readers will be blinded to the participant's clinical assessments, study visit and treatment assignment. Any discrepancies between the findings by the endoscopist and the central reader will be adjudicated as per the endoscopy manual/charter.

The SES-CD is a composite of four features of endoscopic activity (presence and size of ulcers, extent of ulcerated surface, extent of affected and presence and type of narrowings or stenosis) in up to five ileocolonic segments (terminal ileum, right colon, transverse colon, sigmoid and left colon, and rectum). Each feature is scored on a scale from 0 to 3, giving segment subscores of 0 to 12 points and a total SES-CD range of 0–60, with a higher value indicating greater severity (Section A6–1.2).

Biopsies should be collected during withdrawal of the endoscope from the bowel. Technical instructions for biopsy collection will be provided in the endoscopy and laboratory manuals.

8.1.3 Geboes Grading Scale

Biopsy specimens collected during ileocolonoscopy will be used to evaluate histologic activity per centrally-read Geboes Grading Scale (Geboes et al. 2000). This scale is a seven-item classification system to evaluate histological activity originally developed for UC, with items graded from least to most severe features of activity. Each grade is assigned a subgrade ranging from 0 to 3 or 4, with higher values associated with greater severity of the corresponding feature (Section A6–1.3).

Although originally developed for UC, the Geboes scale has been previously used to evaluate histologic activity in CD and its use in CD is endorsed by expert consensus (Magro et al. 2022). Further details on biopsy collection and histologic scoring will be provided in the endoscopy and laboratory manuals and histology reading charter.

8.1.4 Bowel Urgency

Bowel urgency is a single-item self-reported assessment of sudden or immediate need to have a bowel movement in the past 24 hours. The item response is reported on a 4-point Likert scale, from "None" to "Severe" (Section A6–1.4) and should take approximately 1 minute to complete.

8.1.5 Functional Assessment of Chronic Illness Therapy-Fatigue

The Functional Assessment of Chronic Illness-Fatigue (FACIT-F; Version 4) is a 13-item self-reported assessment of fatigue. FACIT-F has been validated for use in a variety of conditions, including anemia and IBD (Yellen et al. 1997; Cella et al. 2005; Lai et al.

2011; Tinsley et al. 2011; Acaster et al. 2015). Each item response option indicates the degree to which a given statement describing the level or impact of fatigue applies in the past 7 days. Response options are graded on a 5-point Likert-type scale, from "Not at all" to "Very much" (Section A6–1.5). The FACIT-F takes approximately 5 minutes to complete.

8.1.6 Inflammatory Bowel Disease Questionnaire

The Inflammatory Bowel Disease Questionnaire (IBDQ) is a validated self-reported 32-item assessment of health-related QoL in patients with IBD (Guyatt et al. 1989; Irvine 1999). IBDQ covers four domains: bowel symptoms (10 questions); systemic symptoms including sleep disorders and fatigue (5 questions); emotional function such as depression, aggression, and irritation (12 questions); and social function, meaning the ability to participate in social activities and work (5 questions). Each question has a recall period of the past 2 weeks. Response options are graded on a 7-point Likert-type scale (Section A6–1.6). The IBDQ takes approximately 15 minutes to complete.

8.1.7 Patient Global Impression of Change

The Patient Global Impression of Change (PGIC) is a single-item self-reported assessment of the change in overall CD symptoms, from the start of the study to current status. The item response is reported on a 5-point Likert-type scale, from "Much worse" to "Much better" (Section A6–1.7). The PGIC takes approximately 1 to 2 minutes to complete.

8.1.8 Patient Global Impression of Severity

The Patient Global Impression of Severity (PGIS) is a single-item self-reported assessment of the severity of overall CD symptoms. The item response is reported on a 6-point Likert scale, from "None" to "Very severe" (Section A6–1.7). The PGIS takes approximately 1 to 2 minutes to complete.

8.1.9 Fistula Examination

Fistula examinations will be performed only on participants presenting with actively draining fistulas at baseline (Week 0). Fistulas will be assessed for draining or closed status, where closed fistulas will be assessed by the investigator as no longer draining despite gentle finger compression. Fistulas newly developed on study should be recorded as adverse events and followed-up and managed as clinically appropriate. Setons (placed previously or placed during the study per standard of care) are allowed. Seton removal will also be conducted per local standard of care.

8.2 SAFETY ASSESSMENTS

Planned timepoints for all safety assessments are provided in the schedule of activities (see Section 1.3). Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, measurement of protocol-specified safety laboratory assessments, measurement of

protocol-specified vital signs, ECGs, and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

8.2.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, dermatologic, musculoskeletal, respiratory, genitourinary, gastrointestinal, and neurologic systems.

A limited physical examination will include, at a minimum, an abdominal examination. Other investigations should be symptom-directed. Investigators should pay special attention to clinical signs related to previous serious illnesses. Changes from abnormalities identified at screening should be recorded in participant notes. New or worsened clinically significant abnormalities (i.e., beyond expected variation or normal age-related changes) should be recorded as adverse events on the Adverse Event eCRF. Physical examinations may be performed by a certified MN professional.

Any abnormality identified at screening or prior to initiation of study treatment should be recorded on the General Medical History and Baseline Conditions eCRF (unless considered related to a protocol-mandated intervention). After initiation of study treatment, any new or worsened clinically significant abnormalities (i.e., beyond expected variation or normal age-related changes) should be recorded as adverse events on the Adverse Event eCRF.

8.2.2 Vital Signs

Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.

Blood pressure and pulse measurements will be assessed while the participant is in a seated 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 (e.g., television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of one pulse and three blood pressure measurements (three consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the three blood pressure readings will be recorded on the eCRF.

Any abnormality identified at screening or prior to initiation of study treatment should be recorded on the General Medical History and Baseline Conditions eCRF (unless considered related to a protocol-mandated intervention). After initiation of study treatment, any new or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF. Vital sign measurement may be performed by an MN professional.

8.2.3 Electrocardiograms

Single 12-lead ECG recordings will be obtained at specified timepoints (see Table 1, Table 2, and Table 3) and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed on a device that is equipped with reliable, automated algorithms for measuring heart rate and ECG intervals and capable of local printing. Paper copies of ECG tracings will be kept as part of the participant's permanent study file at the site.

Lead placement should be as consistent as possible. ECG recordings should be performed after the participant has been resting in a supine or semi-supine position for at least 10 minutes, and the participant should remain in a supine or semi-supine position during recording. The same positioning should be maintained for each participant throughout the study. ECG recordings should be performed prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

Paper copies of all ECG tracings must be reviewed, annotated to indicate any clinical findings, signed, and dated by a medically qualified member of the site staff. For each timepoint, heart rate, uncorrected QT interval, and QT rate corrected using Fridericia's formula (QTcF) based on machine readings of ECG tracings should be recorded on the appropriate eCRF. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

If at a particular postdose timepoint the mean QTcF is $>$500 ms or $>$60 ms longer than the baseline value (i.e., last value prior to initiation of study treatment), another ECG must be recorded, ideally within the next 5 minutes, and ECGs should be repeated at least hourly until two successive ECGs show resolution of the findings. A PK sample should be obtained if not already scheduled for that timepoint. Guidelines for management of increases in QT interval are provided in Appendix 4.

8.2.4 Clinical Safety Laboratory Tests

See Appendix 2 for the list of clinical laboratory tests to be performed and to the schedule of activities (see Section 1.3) for the timing and frequency. Clinical laboratory tests conducted by a central laboratory must be conducted in accordance with the laboratory manual.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event CRF (see Appendix 3).

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 95 days of the final dose of study treatment should be repeated until the values return to normal or baseline or are considered to be stable and no longer considered clinically significant by the investigator. If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the Sponsor notified.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., serious adverse event or adverse event or dose modification), the results must be recorded on the eCRF.

Sample collection may be performed by an MN professional.

Samples collected for safety laboratory tests will be destroyed no later than the time of completion of the final Clinical Study Report.

8.2.5 Pregnancy Testing

The schedule for pregnancy testing for enrolled female participants is outlined in Section 1.3 and will be conducted as outlined in Appendix 2.

8.3 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

The definitions of adverse event and serious adverse event can be found in Appendix 3.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or serious adverse event and remain responsible for following up adverse events that are serious, are considered related to the study treatment or study procedures, or caused the participant to discontinue the study treatment/study (see Section 7).

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported (see Appendix 3). All other medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the General Medical History and Baseline Conditions eCRF, not the Adverse Event eCRF.

All adverse events will be reported from the start of treatment until 95 days after the final dose of study treatment at the timepoints specified in the schedule of activities (see Section 1.3).

All serious adverse events will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek adverse event or serious adverse event information after conclusion of study participation. However, if the investigator learns of any serious adverse event, including a death, at any time after a participant has been discharged from the study, and he or she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about adverse event occurrences.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All adverse events will be followed until the event has resolved to baseline grade or better, or the event is assessed as stable by the investigator, or the participant is lost to follow-up (as defined in Section 7.3), or the participant withdraws consent. Further information on follow-up procedures is provided in Appendix 3.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification (i.e., within 24 hours of awareness) by the investigator to the Sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements for expedited safety reporting to regulatory authorities (which includes the

use of applicable systems, such as EudraVigilance), Institutional Review Boards or Ethics Committees (IRBs/ECs), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

To determine reporting requirements for serious adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the document listed below:

Drug	Document
RO7790121	RO7790121 Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An investigator who receives an investigator safety report describing a serious adverse event or other specific safety information (e.g., summary or listing of serious adverse events) from the Sponsor will review and then file it along with the RO7790121 Investigator's Brochure and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5 Pregnancy

If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Appendix 5. The Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

8.3.6 Death Events

Information on reporting deaths is provided in Appendix 3.

8.3.7 Anticipated Events Not Qualifying for Expedited Reporting

Certain adverse events are anticipated to occur in the study population at some frequency independent of study treatment exposure and will be excluded from expedited reporting. These anticipated events include, but are not limited to, disease worsening (Section 4.1.3.2) that is not considered related to study treatment.

An iDMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

8.3.8 Adverse Events of Special Interest

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section A3–7.6)
- Suspected transmission of an infectious agent by a study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a participant exposed to a medicinal product. This term applies only when contamination of the study treatment is suspected.
- Suspected systemic hypersensitivity reactions (Grade 3 or greater)
- Suspected infusion related reactions (Grade 3 or greater)

Descriptions of risks and management of the above-listed adverse events are provided in Appendix 4.

8.3.9 Medical Monitors and Emergency Medical Contacts

Investigators will be provided with contact information for the Medical Monitor. An Emergency Medical Call Center will also be available 24 hours per day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

8.4 PHARMACOKINETICS

Serum samples will be used to evaluate the pharmacokinetics of RO7790121.

PK samples from participants receiving placebo may not be assessed but will be retained for subsequent analysis if appropriate. Samples will not be analyzed in real time but will be batched for analysis throughout the study.

PK samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed to allow for assay development and validation (if needed).

Information on unblinding of personnel responsible for performing PK assays is provided in Section 6.3.

8.5 PHARMACODYNAMICS

Refer to Section 8.7 for information on PD biomarkers.

Serum samples for PD biomarker assessment will be collected from all participants and be batched for analyses using a fit for purpose method.

8.6 GENETICS

Blood samples for exploratory genetic analyses will be collected from all participants and be batched for analyses using standard methods.

Refer to Section 8.7 for information on genetic biomarkers.

8.7 BIOMARKER ASSESSMENTS

The following biomarker samples will be collected, as applicable, from screened patients and participants at all pre- and post-treatment timepoints at all sites (Section 1.3):

- Blood samples for determination of TL1A biomarker status will be collected from all screened patients, and nucleic acids will be used to assess predictive biomarkers and may be used to support potential development of diagnostic and other biomarker assays.
- For PD biomarker assessments, peripheral blood will be collected and processed to assess total sTL1A levels.
- Non-invasive biomarker measurements of hsCRP and fecal calprotectin will be conducted in peripheral blood and stool samples, respectively.
- Exploratory peripheral blood, serum, and stool will be collected to measure other biomarkers of the TL1A pathway and pathophysiology biomarkers. Methods may include but will not be limited to RNA-sequencing, immunoassays, mass spectrometry, and PCR.
- Colonic biopsy tissues will be collected at designated endoscopy visits and will be used for exploratory biomarker determination, which may include but will not be limited to the assessment of local PD biomarkers, TL1A pathway biomarkers, drug exposure, and pathophysiology biomarkers related to inflammation and histology. These assessments may include RNA sequencing, immunoassays, IHC, mass spectrometry, PCR, and spatial imaging methods.

Biomarker samples collected at participating sites and biomarker samples requiring separate consent are described in Section 8.10.

Exploratory biomarker research may include, but will not be limited to, cytokines/chemokines, target and pathway proteins or genes, inflammatory genes or proteins, microbiome and products thereof in blood, serum or plasma, stool, and mucosal tissues. Genomic research may include exploration of germline variants. Genomic profiling may include whole genome sequencing (WGS) or whole exome sequencing (WES) of blood samples, but only at participating sites if the participant gives specific consent for optional exploratory research (see Section 8.10.2).

Biomarkers will be assessed at baseline and at subsequent timepoints following administration of RO7790121 or matching placebo. Biomarker levels at baseline or over time may be compared with efficacy, other biomarkers, or safety measurements to assess prognostic or predictive properties. Biomarkers may also be analyzed over time as absolute values and/or percent change relative to baseline over time, and may be compared with efficacy, PK, other biomarkers, or safety measurements to determine PD properties. Exploratory biomarker analyses may include prognostic, predictive, and PD biomarker analyses from DNA/RNA-based assays. After PK or immunogenicity analyses have been completed, any remaining plasma and/or serum may be used for exploratory biomarker research described above.

Biomarker samples will be collected according to the schedule outlined in Section 1.3 (see Table 1, Table 2, and Table 3). Sample collection may be performed by an MN professional. Biomarker samples will be sent to one or several central laboratories or to the Sponsor or a designee. Instructions for the collection and handling of biomarker samples, including sampling procedures, storage conditions, and shipment instructions, are provided in the laboratory manual.

Unless the participant gives specific consent for any remaining blood, serum, plasma, stool, mucosal tissue sections or whole biopsies, extracted DNA and mRNA to be stored for optional exploratory research (see Section 8.10.2), biomarker samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed. The exception is blood samples for testing for the TL1A biomarker, which will be stored for 15 years after the final study results have been reported. The storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

8.7.1 TL1A Biomarker Status

For the TL1A biomarker, a mandatory blood sample for DNA isolation will be collected from consenting participants at screening. Details on the processes for collection and shipment and destruction of these samples can be found in the Laboratory Manual. Biomarker status will be evaluated in all available samples to evaluate efficacy in biomarker-defined subgroups (Section 9.3.3).

8.8 IMMUNOGENICITY ASSESSMENTS

Antibodies to RO7790121 will be evaluated in serum samples collected according to the schedule of activities (Section 1.2).

Serum samples will be screened for antibodies binding to RO7790121 and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of RO7790121.

The detection and characterization of antibodies to RO7790121 will be performed through use of a validated assay by or under the supervision of the Sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study treatment. Samples may be stored for a maximum of 5 years (or according to local regulations) after the final Clinical Study Report has been completed at a facility selected by the Sponsor to enable further analysis of immunogenicity of RO7790121.

ADA samples collected from participants receiving placebo will not be assessed in the first instance but retained for subsequent analysis if appropriate.

Information on unblinding of personnel responsible for performing ADA assays is provided in Section 6.3.2.

8.9 HEALTH ECONOMICS AND MEDICAL RESOURCE UTILIZATION

For all participants throughout the study, the investigator and study site personnel will collect data about health care resource utilization associated with medical encounters. The data collected will include the reasons and duration of hospitalizations and emergency room visits and exclude procedures, tests, and encounters mandated by the protocol. The Sponsor may use the collected data to conduct economic analyses.

8.9.1 EuroQol 5-Dimension 5-Level

The EuroQol 5-Dimension 5-Level (EQ-5D-5L) is a validated self-reported health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a Visual Analog Scale (VAS) that measures health state (Section A6–1.9). The EQ-5D-5L is designed to capture a participant's current health

status. Published weighting systems allow for the creation of a single composite score of the participant's health status. The EQ-5D-5L takes approximately 3 minutes to complete. It will be used in this study for informing pharmacoeconomic evaluations.

8.9.2 Work Productivity and Activity Impairment Questionnaire: Crohn's Disease

The Work Productivity and Activity Impairment Questionnaire: Crohn's Disease Questionnaire (WPAI:CD) v2.0 is an adaptation of the WPAI: Specific Health Profile (Reilly et al. 1993; Reilly et al. 2008). WPAI:CD is a self-reported questionnaire regarding absenteeism, presenteeism, work productivity, and activity impairment in the past 7 days. Scores obtained from the questionnaire are expressed as impairment percentages, with higher values indicating greater impairment and less productivity. The WPAI:CD v2.0 takes approximately 2–3 minutes to complete (Section A6–1.10).

8.10 ADDITIONAL ASSESSMENTS AND PROCEDURES REQUIRING SEPARATE CONSENT OR PERFORMED ONLY AT PARTICIPATING SITES

8.10.1 Use of Screen-Fail Samples (Patients at Participating Sites)

At participating sites, screening blood and tissue samples collected from patients who do not enroll in the study (screen-fail samples) may be used for research related to the disease under study and the development of disease-related tests or tools and may be used in the possible future development and validation of an in vitro diagnostic assay.

If a site does not permit research on screen-fail samples, this section of the protocol (Section 8.10.1) will not be applicable at that site.

8.10.2 Samples for Research Biosample Repository (Participants Providing Separate Consent at Participating Sites)

8.10.2.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from participants who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety

- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

8.10.2.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 8.10.2.2) will not be applicable at that site.

8.10.2.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to RO7790121, TL1A pathway, diseases, or drug safety:

- Blood for DNA collected at Week 0 (or at a later time point if collection at Week 0 was not feasible)
- Any residual blood, serum, plasma, stool, mucosal tissue sections, or whole biopsies, and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), including any remaining tissue from medically indicated procedures (e.g., ileocolonoscopy) performed at the investigator's discretion during the course of the study.

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the

IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

8.10.2.4 Data Protection, Use, and Sharing

RBR samples and associated data will be labeled with a unique participant identification number.

Participant medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Data generated from RBR samples will be analyzed in aggregate rather than on an individual participant basis. Thus, there will be no identification and reporting of incidental findings to investigators or participants. In addition, given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or participants, unless required by law, with the exception of data generated from blood samples collected for WGS or WES as described below.

If permitted by local law, a participant may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a participant wishes to access these data, the investigator must inform the Sponsor, using the following email address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file but will not provide any interpretation of the data. The investigator should not include the data file in the participant's medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

8.10.2.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will

be told that they are free to choose not to provide optional RBR samples and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a participant's agreement to provide optional RBR samples. Participants who choose not to provide optional RBR samples will not provide a separate signature. The investigator should document whether or not the participant has given consent to provide optional RBR samples and (if applicable) the date of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

8.10.2.6 Withdrawal from the Research Biosample Repository

Participants who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples (i.e., all biological material) will be destroyed. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a participant wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the participant's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the Sample Informed Consent/Withdrawal eCRF. If a participant wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and participant number to the following email address:

global.rcr-withdrawal@roche.com

A participant's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a participant's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

8.10.2.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to an individual's participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

9. STATISTICAL CONSIDERATIONS

This section is a summary of the statistical aspects of the study design and the general approach to analysis of endpoints supporting the study objectives. A more technical and detailed description of the statistical analyses described in this section will be provided in the Statistical Analysis Plan, which will be finalized prior to unblinding.

Analysis of study data will be documented in primary and final Clinical Study Reports, respectively anchored upon the following milestones:

- Primary completion, given by the date at which the last participant in the maintenance treatment phase completes all Week 52 primary endpoint assessments
- Study completion, given by the date of the last-participant, last-visit across all phases of the study, including OLE phase

9.1 STATISTICAL HYPOTHESES

Under the primary objectives for this study, it is hypothesized that RO7790121 is superior to placebo in inducing and maintaining clinical remission and endoscopic response, at either of the RO7790121 dosing regimens (IV induction followed by 150 mg or 450 mg SC Q4W maintenance). In statistical testing, the relevant null and alternative hypotheses are formulated as follows:

$$H_0: p_{RO7790121} - p_{placebo} = 0 \text{ versus } H_A: p_{RO7790121} - p_{placebo} \neq 0,$$

where $p_{RO7790121} - p_{placebo}$ represents the treatment effect (estimand) of interest, the difference in the proportion of patients achieving the endpoint of interest (clinical remission or endoscopic response at Week 52) after assignment to a particular RO7790121 dosing regimen versus placebo, as described in Section 3.1.

The study will be deemed positive if all null hypotheses based on the co-primary endpoints are rejected in favor of RO7790121. Each of these two-sided tests will be carried out at the 5% significance level. Should the primary results be positive, testing will proceed to a specified subset of key secondary endpoints (Section 3.2). All tests will be prioritized into a hierarchy of families and evaluated according to a multiple testing procedure that will ensure overall type 1 error control at 5%, accounting for multiplicity due to multiple treatment arms and multiple endpoints. Prioritization of these tests and details on the multiple testing strategy will be specified in the Statistical Analysis Plan.

Tests on secondary endpoints will consider null and alternative hypotheses like those defined for the primary endpoints above. For secondary efficacy endpoints that correspond to a continuous or ordinal outcome measurement, the treatment effect will generally be summarized by a difference in mean outcome. Testing of ordinal endpoints may instead be based on the difference in outcome distribution, in which case treatment arm mean outcome estimates will be generated to aid interpretation. Where a

continuous or ordinal endpoint has a relevant baseline measurement, the treatment arm means for the change from baseline may be estimated for interpretability. The Statistical Analysis Plan will specify further details on the treatment effects and any associated tests for the secondary efficacy endpoints.

9.1.1 Sample Size Determination

A total of approximately 600 participants will be enrolled and randomly assigned to either RO7790121 with a 450 mg or 150 mg maintenance dose or placebo under a 1:1:1 randomization ratio. This will allocate approximately 200 participants to each of the three treatment arms. Marginal power to reject one of the null hypotheses in primary analysis at the significance level of 5% depends (in part) on the outcome rate under placebo treatment.

In a meta-analysis of recent Phase II and III CD trials, placebo induction of clinical remission and endoscopic response were estimated to be 18% (95% CI: 16% to 21%) and 13% (95% CI: 10% to 16%). In a meta-analysis of randomized withdrawal trials, placebo maintenance of clinical remission and endoscopic response were estimated to be 44% (95% CI: 26% to 63%; Almradi et al. 2022) and 7% (95% CI: 1% to 31%; Vuyyuru et al. 2024), respectively. Placebo rates in general vary according to a variety of factors, such as the proportion of participants with prior advanced therapy (Almradi et al. 2022; Vuyyuru et al. 2024).

Under this study's treat-through design, where participants enter maintenance without necessarily achieving clinical or symptomatic response and remain on either experimental or placebo treatment, it is anticipated that the placebo maintenance outcome rates will be no greater than the rate at induction and lower than rates observed in randomized withdrawal, provided that intercurrent events are appropriately addressed (Table 5).

Safety objectives further require a placebo arm large enough to ensure that there are placebo-treated participants through the 52-week treatment period. Observed rates of completion of blinded treatment in the placebo arm of recent randomized withdrawal studies U-ENDURE and FORTIFY were 45/165 (27%; Figure S2C in Loftus et al. 2023) and approximately 95/164 (58%; Figure 1 and Table S5 in Ferrante et al. 2022), respectively.

The rate of completion of this study's 52-week treat-through treatment period in the placebo arm may be lower. Rather than assume the completion rate directly, the anticipated number of placebo-treated completers can be estimated from the assumed maintenance outcome rate (be it clinical remission or endoscopic response), both overall and among treatment completers. In U-ENDURE and FORTIFY, the clinical remission rates at Week 52 among treatment completers in the placebo arm were 74% and approximately 71%, respectively. The corresponding rates for endoscopic response at Week 52 were 59% and 38%, respectively.

Table 11 shows marginal power to detect a clinically meaningful treatment effect of at least 10% to 15% on any one primary endpoint, under a range of values the placebo outcome rate. Considering the potential for few participants completing blinded treatment in the placebo arm, the rate of rollover from maintenance to OLE or dropout from the maintenance treatment period will be monitored via iDMC (Section 9.4).

Table 11 Operating Characteristics for the Proposed Study Design

RO7790121 vs. Placebo Treatment Effect	Marginal Power	Anticipated Number in Placebo Arm Completing Blinded Treatment at Week 52
55% vs. 40%	83%	106 to 133
39% vs. 25%	83%	66 to 125
33% vs. 20%	81%	53 to 100
27% vs. 15%	81%	40 to 75
16% vs. 6%	88%	16 to 30

Notes: Marginal power is evaluated using Fisher's exact test. Lower (upper) range value for the anticipated number of participants in the placebo arm who complete treatment at Week 52 is given by the planned placebo arm size of 200, multiplied by the placebo outcome rate assuming the given effect at Week 52, and divided by an assumed placebo rate in completers: 75% (60% or 40%, whichever is higher than the overall placebo rate).

9.2 ANALYSIS SETS

Each planned analysis will incorporate data from a particular set of participants. These participant analysis sets are broadly defined in Table 12. In general, the relevant data for a given participant in an analysis set may consider all measurements for parameters under analysis, from baseline up to the timing of the endpoint in question, such as Week 12 for induction endpoints and Week 52 for maintenance endpoints.

Table 12 Participant Analysis Sets

Analysis Set	Description
Full	All enrolled participants
Efficacy	All randomized participants who were exposed to study treatment, grouped by assigned treatment arm
Biomarker-evaluable	All randomized participants who were exposed to study treatment and have TL1A biomarker status (Section 4.2.3) measured at baseline, grouped by assigned treatment arm
Safety	All enrolled participants who were exposed to study treatment, grouped by actual treatment arm (i.e., treatment arm most representative of treatment received)
PK-evaluable	All enrolled participants who received at least one dose of RO7790121 and have at least one concentration value measured, grouped by actual treatment arm
ADA-evaluable	All enrolled participants who received at least one dose of RO7790121 and have at least one post-baseline anti-RO7790121 antibody determination, grouped by actual treatment arm
PD-evaluable	All enrolled participants who received at least one dose of RO7790121 and have at least one total soluble TL1A concentration value measured, grouped by actual treatment arm

ADA = anti-drug antibodies; PD = pharmacodynamic; PK = pharmacokinetic; TL1A = tumor necrosis factor-like ligand 1A.

Baseline for a given parameter will generally be defined as the last value measured prior to first dose of study drug. Post-baseline measurements assessed outside the planned schedule, at unscheduled or early termination visits, will be allocated to a scheduled visit according to prespecified visit windows. Further details on the visit windows and, more generally, analysis sets and their relevant datapoints, will be described in the Statistical Analysis Plan.

9.3 STATISTICAL ANALYSES

This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints. The analyses specified in the Statistical Analysis Plan supersede those specified here.

9.3.1 General Considerations

All endpoints supporting efficacy, safety, PK, PD, and immunogenicity objectives (Section 3) will be evaluated in the corresponding analysis set (Table 12). Apart from the hypothesis testing for selected efficacy endpoints described in Section 9.1, no formal statistical tests will be carried out. To aid in endpoint comparison between RO7790121 versus placebo, treatment group summaries or differences thereof with 95% confidence intervals may be generated. In the analysis of efficacy endpoints, these differences will generally correspond to estimates for treatment effects. For other endpoints, analysis will be limited to descriptive treatment group summaries.

In statistical inference on treatment effects, intercurrent events will be addressed using the strategies described in Table 5. Any missing data relevant for inference on treatment effects that remain after application of these strategies will be resolved by multiple imputation, assuming the data are missing at random. These data include both outcome measurements as well as variables needed for covariate adjustment, which will be applied to improve statistical precision. The variables used for multiple imputation and covariate adjustment will be specified in the Statistical Analysis Plan, but will generally include key prognostic factors, such as prior advanced therapy experience and baseline disease activity.

Although covariate-adjusted, treatment effect estimation will generally target marginal effects through an approach often referred to as standardization. For treatment effects summarized by a difference in proportions or means, the standardized estimator is given by the treatment arm difference in mean predicted outcome based on a working regression model that includes treatment assignment and baseline covariates. This working model need not be correctly specified for the estimator to be valid (i.e., asymptotically normal with mean zero). An overview of this approach is described by Moore and van der Laan (2009) and Rosenblum and van der Laan (2010), with further adaptation to stratified randomization and other types of effect summaries by Wang et al. (2023). Details on its implementation in this study will be described in the Statistical Analysis Plan.

9.3.2 Analysis of Primary Endpoints

Treatment effects on clinical remission and endoscopic response at Week 52 (Section 3.1) will be inferred following the general approach described in Section 9.3.1. Robustness of findings from this main analysis to the handling of missing data will be assessed by tipping point sensitivity analysis, where statistical inference is repeated under missing data resolved by systematic imputation over a plausible range of values. This alternative imputation scheme and additional sensitivity or supplementary analyses (where appropriate) will be specified in the Statistical Analysis Plan.

9.3.3 Analysis of Secondary Endpoints

All secondary efficacy endpoints (Section 3.2) will be analyzed using the general approach described in Section 9.3.1. Similar tipping point sensitivity analysis as described above for the co-primary endpoints will be carried out on secondary efficacy endpoints prioritized for multiple testing. The Statistical Analysis Plan will further specify the analysis of these efficacy endpoints.

The analysis approach supporting efficacy objectives related to PROs and the TL1A biomarker will be additionally described in the Statistical Analysis Plan, in order to adequately specify clinically meaningful change and biomarker subgroups, respectively. Specific details on the TL1A biomarker test will be described in a Biomarker Analysis Plan.

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs. Study treatment exposure (such as treatment duration, total dose received, and dosing intensity) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms, and adverse event severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 6.0. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment–emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in these summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital signs, and ECG data will be displayed by time, with grades identified where appropriate. Changes in these measurements from baseline to selected post-baseline timepoints will be summarized, where appropriate.

9.3.4 Analysis of Exploratory Endpoints

The approach to analysis of selected PK and ADA endpoints is described below. Analysis of other exploratory endpoints (Section 3.3) will be specified in the Statistical Analysis Plan.

9.3.4.1 Pharmacokinetic Analyses

Concentration of RO7790121 will be summarized in the PK-evaluable analysis set defined in Table 12. A population PK model may be developed and documented separately from this study for the following:

- To describe the pharmacokinetics of RO7790121
- To estimate the effect of potential covariates on exposure
- To determine empirical Bayes estimates for the individual PK parameters to be used for the description of RO7790121 dose-exposure-response relationship in patients with CD

9.3.4.2 Immunogenicity Analyses

Development of ADA and of NAb will be summarized in terms of incidence, both overall and across timepoints. These summaries will include participants in the ADA-evaluable analysis set (Table 12).

When determining post-baseline ADA incidence, participants will be considered ADA positive if their baseline ADA status is negative or unknown and they develop an ADA response following RO7790121 exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of at least one post-baseline sample is at least

4-fold higher than the titer of the baseline sample (treatment-enhanced ADA response). Participants will be considered ADA negative if their baseline ADA status is negative or unknown and all post-baseline samples are negative, or if they are ADA positive at baseline and no post-baseline sample has a titer that is at least 4-fold higher than the titer of the baseline sample (treatment unaffected).

9.3.5 Other Analyses

To support the overall interpretation of study findings on endpoints, other study data will be tabulated by treatment arm. These descriptive summaries are broadly specified below.

9.3.5.1 Summaries of Conduct of Study

Enrollment, study treatment administration, and discontinuation from the study will be summarized in the full analysis set (Table 12). The reasons for study treatment discontinuation will also be tabulated. Descriptive summaries will also be generated for major protocol deviations, including major deviations from the study inclusion and exclusion criteria.

9.3.5.2 Summaries of Demographics and Baseline Characteristics

Descriptive statistics for demographics (such as age, sex, race) and baseline characteristics (such as prior CD therapy experience and disease activity) will be tabulated on the efficacy analysis set (Table 12). These summaries will assess comparability of the treatment groups at baseline. In the evaluation of efficacy endpoints, any imbalances will generally be addressed by covariate adjustment (Section 9.3.1).

9.3.5.3 Summaries of Intercurrent Events

The frequency and timing of intercurrent events (Table 5) will be summarized in the efficacy analysis set (Table 12). In general, timing will be described with respect to the assessment schedule (Section 1.3), and in particular the timepoints at which efficacy endpoints are specified (e.g., Week 12 and Week 52; see Sections 3.1 and 3.2).

9.4 INTERIM ANALYSIS

Interim analyses to evaluate futility, safety, or adequacy of the safety database for longer-term RO7790121 exposure will be conducted by an external statistical group and reviewed by the iDMC. On the basis of these analyses, the iDMC may recommend increasing the overall sample size to ensure sufficient data to draw longer-term safety comparisons between RO77910121 and placebo or stopping the trial early. Interactions between the iDMC and the Sponsor will be carried out as specified in the iDMC Charter. The timing and statistical details for interim analysis will be specified in the Statistical Analysis Plan, which will be submitted to relevant health authorities prior to the conduct of any interim analysis.

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Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

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A1–1 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 international ethical guidelines
- Applicable International Council for Harmonisation (ICH) E6 guideline for Good Clinical Practice
- Applicable laws and regulations.

The protocol, Informed Consent Form, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board or Ethics Committee (IRB/EC) by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or 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/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
- Notifying the IRB/EC of serious adverse events or other significant safety findings, as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and ensuring adherence to requirements of 21 CFR (U.S. sites only), the ICH Guideline for Good Clinical Practice, the IRB/EC, Clinical Trials Directive (2001/20/EC) or Clinical Trials Regulation (536/2014) (EEA sites only), and all other applicable local regulations

A1–2 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study (see definition of end of study in Section 4.4).

A1–3 INFORMED CONSENT PROCESS

The investigator or authorized designee will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (U.S. sites only), the ICH Guideline for Good Clinical Practice, and the IRB/EC.

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 authorized person obtaining the informed consent must also sign the Informed Consent Form.

If the Informed Consent Form is revised (through an amendment or an addendum) to communicate information that might affect a participant's willingness to continue in the study, the participant or their legally authorized representative must re-consent by signing the most current version of the Informed Consent Form or the addendum, in accordance with applicable laws and IRB/EC policy.

A copy of each Informed Consent Form must be provided to the participant or their legally authorized representative.

A1–4 DATA PROTECTION

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

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; the participant's name or any information that would make the participant identifiable will not be transferred.

Participants must be informed that their 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 participants, who will be required to give consent for their data to be used as described in the Informed Consent Form.

Participants must be informed that their medical records may be examined by auditors or other authorized individuals representing the Sponsor or Sponsor collaborators and licensees, by appropriate IRB/EC members, and by inspectors from health authorities.

A1–5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 250 sites globally will participate to enroll approximately 400 participants. Enrollment will occur through an interactive voice or web-based response system.

Central facilities will be used for certain assessments throughout the study (e.g., specified laboratory tests, biomarker and pharmacokinetic analyses), as specified in Section 8 and Appendix 2. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An iDMC will be employed to monitor and evaluate participant safety throughout the study. An IRF will collect, store, and potentially review imaging data.

A1–6 DISSEMINATION OF CLINICAL STUDY DATA

Study data, which may include imaging data and data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and will be provided upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

A1–7 DATA QUALITY ASSURANCE

All participant data relating to the study will be recorded on printed or electronic Case Report Forms (CRFs) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

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

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., 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 non-compliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided prior to study initiation, in the various functional monitoring plans (including, but not limited to, Quality Tolerance Limit Management Plan and Trial Monitoring 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 (e.g., contract research organizations).

Study monitors will perform ongoing monitoring activities as specified in the Trial Monitoring Plan to confirm that data entered into the CRF by authorized 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, the ICH Guideline for Good Clinical Practice, and all applicable regulatory requirements.

Records and documents pertaining to the conduct of this study, including signed Informed Consent Forms, must be retained by the investigator for 15 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.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

A1–8 SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the electronic Case Report Form (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 and its origin can be found in the Trial Monitoring Plan.

A1–9 STUDY AND SITE CLOSURE

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. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to participants.
- Participant enrollment is unsatisfactory.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigators shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

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 site closure visit has been performed.

The investigator may initiate 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, the following:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or the ICH Guideline for Good Clinical Practice
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

A1–10 PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings. If this is foreseen, 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 results of multicenter 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.

A1–11 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on participant safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

Appendix 2
Clinical Safety Laboratory Tests

The tests detailed in Table A2-1 will be performed by the local or central laboratory. Refer to the Laboratory Manual for specific requirements for each visit.

Additional tests may be performed at any time during the study if determined to be necessary by the investigator or if required by local regulations.

Table A2-1 Protocol-Required Safety Laboratory Assessments

Central Laboratory Tests
• Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells • Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, urate, creatinine phosphokinase, and lactate dehydrogenase • Serum tryptase • HIV serology: HIV-1 antibody/HIV-1/2 antibody/HIV-2 antibody • HBV serology: HBsAg, HBsAb, and total HBcAb for all individuals; HBV DNA for individuals with negative HBsAg and HBsAb tests and a positive total HBcAb test • HCV serology: HCV antibody for all individuals • Coagulation: INR, aPTT, and PT • Serum pregnancy test All female participants of childbearing potential will have a serum pregnancy test performed at screening. Test for follicle-stimulating hormone may be performed at screening to confirm postmenopausal state, if required per local guidelines. • Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, and blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria) • Tuberculosis: QFT [a] • Enteric pathogens (stool): culture and sensitivity, ova and parasites, and *C. difficile* toxin [b]
Local Laboratory Tests
• CMV test: Tissue biopsy (if required) • Tuberculosis: PPD skin testing or locally approved TB ELISA tests (i.e., T-SPOT®) • Urine pregnancy test Urine pregnancy tests will be performed at specified subsequent visits by local laboratory tests. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test by central lab. • Enteric pathogens (stool): Culture and sensitivity, ova and parasites, and *C. difficile* toxins

C. difficile = *Clostridioides difficile*; ELISA = enzyme-linked immunosorbent assay; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; PPD = purified protein derivative; TB = tuberculosis; QFT = QuantiFERON TB-Gold® test.

[a] If a QFT test is not available, a PPD skin test or other locally-approved TB ELISA test (e.g., T-SPOT®) may be performed by a local laboratory according to local guidelines or regulations.

[b] Stool samples will be sent to the study site's local laboratory for analysis but may be sent to a central laboratory for analysis if local analysis is not available.

Investigators must document their review of each laboratory safety report.

Appendix 3
Safety Parameters: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

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A3–1 DEFINITION OF ADVERSE EVENT

Adverse Event Definition

An adverse event is any untoward medical occurrence in a patient or clinical study participant temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the Adverse Event Definition

The following events meet the definition of adverse event:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study treatment administration, even though it may have been present before the start of the study
- Signs, symptoms, or clinical sequelae of a suspected drug–drug interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study treatment or a concomitant medication

  Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal or self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. 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 adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Definition of Adverse Event

The following events do not meet the definition of adverse event:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy)

  The condition that leads to the procedure is the adverse event.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of a preexisting disease or condition present or detected at the start of the study that do not worsen

A3–2 DEFINITION OF SERIOUS ADVERSE EVENT

If an event is not an adverse event per the definition in Section A3–1, it cannot be a serious adverse event even if serious conditions are met (e.g., hospitalization for signs or symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life threatening

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization

  In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event.

- Results in persistent disability or 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, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect
- Medically significant:

  Medical or scientific judgment should be exercised in deciding whether serious adverse event 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 medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE]; see Section A3–3.2); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the electronic Case Report Form (eCRF).

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event) (see Section A3–5 for reporting instructions).

A3–3 RECORDING AND FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.1 ADVERSE EVENT AND SERIOUS ADVERSE EVENT RECORDING

When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant adverse event or serious adverse event information on the electronic Case Report Form (eCRF).

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs or symptoms) will be documented as the adverse event or serious adverse event.

A3–3.2 ASSESSMENT OF SEVERITY

The investigator will assess the severity of each adverse event reported during the study through use of the NCI CTCAE (v5.0) grading scale. The investigator will use the grading scale in Table A3-1 for assessing the severity of adverse events that are not specifically listed in the NCI CTCAE.

Table A3-1 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

[a] Examples of instrumental activities of daily living include preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by participants who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

A3–3.3 ASSESSMENT OF CAUSALITY

The investigator is obligated to assess the relationship between study treatment and each occurrence of each adverse event or serious adverse event.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying diseases, 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 prescribing information (for marketed products) in his or her assessment.

For each adverse event or serious adverse event, the investigator **must** document in the medical notes that he or she has reviewed the adverse event or serious adverse event and has provided an assessment of causality.

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

The investigator may change his or her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.

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

A3–3.4 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.4.1 Investigator Follow-Up

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor with a copy of any available post-mortem findings, including histopathology.

New or updated information should be recorded on the originally completed Adverse Event eCRF. For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately

(i.e., no more than 24 hours after the investigator becomes aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

During the adverse event reporting period (defined in Section 8.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification.

A3–3.4.2 Sponsor Follow-Up

For serious adverse events and adverse events of special interest, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

A3–4 REPORTING OF SERIOUS ADVERSE EVENTS

A3–4.1 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA AN ELECTRONIC COLLECTION TOOL

The primary mechanism for reporting a serious adverse event to the Sponsor will be the electronic data collection tool, as described in Section A3–5.

If the electronic system is unavailable, the site will use the paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5, to report the event within 24 hours.

The site will enter the serious adverse event data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

If a site receives a report of a new serious adverse event from a study participant or receives updated data on a previously reported serious adverse event after the electronic data collection tool has been taken off line, the site can report this information

on a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5

A3–4.2 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA PAPER CRF

Under certain circumstances, serious adverse events may be reported to the Sponsor through use of a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5.

A3–5 REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS OF SPECIAL INTEREST

A3–5.1 EVENTS THAT OCCUR PRIOR TO STUDY TREATMENT INITIATION

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., biopsy, discontinuation of medications) should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators.

A3–5.2 EVENTS THAT OCCUR AFTER STUDY TREATMENT INITIATION

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 95 days after the final dose of study treatment. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after the investigator becomes aware of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event /Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur more than 95 days after the final dose of study treatment are provided in Section A3–6.

A3–6 REPORTING ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 95 days after the final dose of study treatment), if the event is believed to be related to prior exposure to study treatment. These events should be reported through the use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event /Special Situations Form, using the fax number or email address provided to investigators.

A3–7 PROCEDURES FOR RECORDING ADVERSE EVENTS

When an adverse event occurs, it is the responsibility of the investigator to review all documentation related to the event (e.g., hospital progress notes, laboratory reports, and diagnostics reports). The investigator will then record all relevant adverse event information on the Adverse Event eCRF. It is not acceptable for the investigator to send photocopies of the participant's medical records to the Medical Monitor in lieu of completion of the eCRF. Investigators should use correct medical terminology and concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations. Only one adverse event term should be recorded in the event field of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

A3–7.1 DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

A3–7.1.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration and are considered to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion related reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a participant experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded as a separate event on the Adverse Event eCRF, with associated signs and symptoms also recorded separately on the dedicated Infusion-related Reaction eCRF. Infusion-related reactions of Grade 3 or higher should be considered an adverse event of special interest. Grading for infusion-related

reactions events should be based on the term "infusion related reaction" in the NCI CTCAE v5.0 grading scale.

A3–7.1.2 Injection Site Reactions

Adverse events that occur during or within 24 hours after study drug administration and are considered to be related to study drug SC injection should be captured as a diagnosis (e.g., "injection reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "local reaction" or "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Injection Reaction eCRF. If a patient experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Injection Reaction eCRF.

A3–7.1.3 Systemic Hypersensitivity

Systemic hypersensitivity reactions that occur during or after study drug administration and are considered to be related to study drug IV infusion or subcutaneous injection should be captured as a diagnosis (e.g., "systemic hypersensitivity" or "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms of the systemic hypersensitivity reaction should be recorded on the corresponding Infusion-Related Reaction or Injection Reaction eCRF.

A systemic reaction that occurs with IV infusion during or within 24 hours of IV infusion should be reported as either an infusion-related reaction (Section A3–7.1.1) or as systemic hypersensitivity as per medical judgment.

Investigators may use the Sampson criteria as a guideline to identify and report anaphylaxis cases (see Appendix 8). Systemic hypersensitivity events of Grade 3 or higher should be considered an adverse event of special interest. Grading for systemic hypersensitivity events should be based on the term "allergic reaction" in the NCI CTCAE v5.0 grading scale.

A3–7.1.4 Other Adverse Events

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only "liver failure" or "hepatitis" rather than "jaundice, asterixis, and elevated transaminases"). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event

report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

A3–7.2 ADVERSE EVENTS THAT ARE SECONDARY TO OTHER EVENTS

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

A3–7.3 PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware that the event became serious; see Section A3–5 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between participant evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

A3–7.4 ABNORMAL LABORATORY VALUES

Not every abnormal laboratory value qualifies as an adverse event. A laboratory value abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A laboratory value abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–7.3 for details on recording persistent adverse events).

A3–7.5 ABNORMAL VITAL SIGN VALUES

Not every abnormal vital sign value qualifies as an adverse event. A vital sign abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A vital sign abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms

- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (e.g., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–7.3 for details on recording persistent adverse events).

A3–7.6 ABNORMAL LIVER FUNCTION TESTS

The finding of an elevated ALT or AST ($>3\times$ ULN) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ ULN in combination with total bilirubin $>2\times$ ULN
- Treatment-emergent ALT or AST $>3\times$ ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section A3–7.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either as a serious adverse event or an adverse event of special interest (see Section A3–5).

A3–7.7 DEATHS

All deaths that occur during the protocol-specified adverse event reporting period (see Section 8.3.1), regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section A3–5). This includes death attributed to progression of CD.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed solely to progression of CD, "Crohn's disease progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section A3–6.

A3–7.8 PREEXISTING MEDICAL CONDITIONS

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

A3–7.9 LACK OF EFFICACY AND WORSENING OF CROHN'S DISEASE

Deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature (i.e., deterioration beyond the expected pattern of progression of the underlying disease) should be recorded as an adverse event. When recording an unanticipated worsening of CD on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of Crohn’s disease "). Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on efficacy assessments associated with the CDAI and PROs (Section 8.1). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through the use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

A3–7.10 HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section A3–2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The participant was hospitalized for an elective procedure that was planned prior to the study, was scheduled during the study despite the fact that the condition had not worsened, or was scheduled during the study when treatment became necessary because of the expected normal progression of the condition
  - The participant has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of participant requirement for outpatient care outside of normal outpatient clinic operating hours

A3–7.11 PARTICIPANT-REPORTED OUTCOME DATA

Adverse event reports will not be derived from eDiary PRO data by the Sponsor. Sites are not expected to review the eDiary PRO data for adverse events.

A3–7.12 SAFETY BIOMARKER DATA

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on participant management.

A3–8 SPECIAL SITUATIONS (ACCIDENTAL OVERDOSE AND/OR MEDICATION ERROR)

Accidental overdose and medication error (hereafter collectively referred to as "special situations") are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug (e.g., wrong drug, expired drug, accidental overdose, underdose, wrong dosing schedule, incorrect route of administration)

After initiation of study drug, special situations associated with RO7790121 and matching placebo and any associated adverse events will be reported 95 days after the final dose of study drug.

Special situations, regardless of whether they result in an adverse event, should be reported on the Special Situations eCRF. If there are any associated adverse events, each event should be recorded separately on the Adverse Event eCRF.

Special situations and any associated adverse events should be reported within 30 days after the investigator becomes aware of the situation. However, if an associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, both the event and the special situation should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), as described in Section A3–5.

Appendix 4
Safety Plan: Management of Identified and Potential Risks

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A4–1 RISKS ASSOCIATED WITH RO7790121

RO7790121 is not approved by health authorities, and clinical development is ongoing. The safety plan for participants in this study is based on clinical experience with RO7790121 in completed and ongoing studies. The anticipated important safety risks for RO7790121 are outlined below. Please refer to the current RO7790121 Investigator's Brochure for a complete summary of safety information.

A4–1.1 SYSTEMIC HYPERSENSITIVITY

Monoclonal antibodies carry a potential risk of systemic hypersensitivity reactions and anaphylaxis (allergic reactions), or hypersensitivity-like reactions (pseudoallergic reactions). In completed Phase II trials in patients with ulcerative colitis, one participant in the B7541007 450 mg→50 mg group who had a history of psoriasis developed potential hypersensitivity with two events of non-serious, mild rash (rash on both inner forearms and rash on both upper thighs), on Day 1 and again on Day 28. Both of these rashes resolved 2 days later. Study medication dosing continued for this participant. No treatment was given for these events, which were considered related to study medication by the investigator. In the same study, one participant in the 150 mg→150 mg group who had a history of psoriasis developed potential delayed hypersensitivity, reporting non-serious, mild generalized pruritus during the maintenance phase after 4 months on study treatment. This increased to moderate generalized pruritus 6 months later and then decreased to mild again 3 months after that during safety follow up. This event was considered to be recovering/resolving at the end of study. Study medication dosing continued for this participant. No treatment was given for the events, which were considered related to study medication by the investigator.

In an ongoing Phase II study in patients with Crohn's disease, a participant experienced fainting, shortness of breath, and hypotension during the first SC dosing of RO7790121, and the event was reported as an anaphylactic reaction. The participant was medically managed at the site with epinephrine and IV steroids, and the event resolved. The event was considered related to the study medication by the investigator.

Differentiating allergic reactions from pseudoallergic reactions is important because it may impact the understanding of the risk profile of the drug. In instances where the reaction occurs with the first study drug administration without any suspicion of prior sensitization, it is less likely to be an allergic reaction. When a new reaction is seen with the second or subsequent injections, or if there is an atypical presentation (e.g., rapid onset or increase in severity when compared with previous reactions), there is a higher likelihood that the reaction is allergic. Patients with a history of severe allergic reaction or anaphylactic reaction to a biologic agent are excluded from this study.

Systemic hypersensitivity reactions will be closely monitored during the study as described in Section 6.1.1.

Investigators and healthcare professionals (Appendix 8) administering study treatment should recognize and manage the signs and symptoms of such reactions and should be familiar with Sampson's criteria for defining anaphylaxis events (Appendix 8). All potential cases of anaphylaxis should be captured on the Adverse Event eCRF as instructed in A3–7.1.3. Investigators should accurately report these events immediately to the Sponsor as serious adverse events if appropriate. Healthcare professionals should also instruct patients on how to recognize the symptoms of any such events and to contact a healthcare provider or seek emergency care in case of any such symptoms.

A4–1.2 INFUSION-RELATED REACTIONS

Infusion-related reactions can present as a variety of symptoms during or within 24 hours of a study drug infusion. These symptoms may involve multiple body systems and may include fever, chills, dizziness, rash, headache, nausea or vomiting.

In completed Phase II trials in patients with UC, no patients have reported infusion-related reactions; however, these are a hypothetical risk with IV infusions and are therefore a potential risk for RO7790121, since the study medication is given intravenously during the induction phase.

Guidelines for the management of participants who develop infusion-related reactions are provided in Appendix 9.

A4–1.3 INJECTION SITE REACTIONS

An injection site reaction is any local reaction occurring at the site of injection following study drug administration. Symptoms may include redness, pain, itching or swelling around the site of injection. In completed Phase II trials in patients with UC, injection sites reactions were reported in less than 3% of participants, all being reported as mild except for one moderate injection site reaction. No injection site reactions have prevented study participants from continuing with treatment.

In a clinical setting, patients should be monitored for signs of injection site reactions in the period immediately following injections. Guidelines for management of participants who develop injection site reactions are provided in Appendix 10.

A4–2 MANAGEMENT OF PARTICIPANTS WHO EXPERIENCE ADVERSE EVENTS

A4–2.1 DOSE MODIFICATIONS

The dose of RO7790121 can be increased from 450 mg Q4W to 450 mg Q2W up to two times for management of disease worsening criteria in the OLE phase (Section 4.1.3).

A4–2.2 TREATMENT INTERRUPTION

Study treatment may be interrupted (withheld) in participants who experience a treatment-emergent adverse event considered to be related to study treatment. Study treatment may be withheld for reasons other than a treatment-emergent adverse event) at the investigator's discretion.

A4–2.3 MANAGEMENT GUIDELINES

Guidelines for management of specific adverse events (infusion-related reactions and injection site reactions) are outlined in Appendix 9 and Appendix 10. Additional guidelines are provided in the subsections below.

A4–2.4 MANAGEMENT OF INCREASES IN QT INTERVAL

RO7790121 should be discontinued in participants who develop any of the following, unless there is a clear alternative cause for the changes:

- Sustained (at least two ECG measurements $>$30 minutes apart) QT interval corrected through use of Fridericia's formula (QTcF) that is $>$500 ms and $>$60 ms longer than the baseline value
- Sustained absolute QTcF that is $>$515 ms
- An episode of torsades de pointes or a new ECG finding of clinical concern

Management of participants with sustained QTcF prolongation should include close monitoring, with ECGs repeated at least hourly until two successive ECGs show resolution of the findings, correction of any electrolyte abnormalities, and possible discontinuation of other concomitant medications that are known to prolong the QT interval. Consultation with a cardiologist or electrophysiologist is recommended, to help in the management of such participants.

Appendix 5
Collection of Pregnancy Information

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A5–1 PREGNANCIES IN FEMALE PARTICIPANTS

Female participants will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 95 days after the final dose of RO7790121. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the pregnancy), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event electronic Case Report Form (eCRF). The investigator should discontinue study treatment and counsel the participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly or birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Sharing of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A5–2 PREGNANCIES IN FEMALE PARTNERS OF MALE PARTICIPANTS

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if a female partner becomes pregnant during the study or within 95 days after the final dose of RO7790121. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Sharing of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with

additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Sharing of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A5–3 ABORTIONS

A spontaneous abortion in a female participant exposed to study treatment or the female partner of a male participant exposed to study treatment should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A5–4 ABNORMAL PREGNANCY OUTCOMES

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomaly, birth defect, ectopic pregnancy) in a female participant exposed to study treatment or the female partner of a male participant exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5).

Appendix 6
Clinical Outcome Assessment Instruments

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A6–1 CLINICAL OUTCOME ASSESSMENT INSTRUMENTS

PRO instruments will be self-administered during clinic visits and visits conducted by an MN professional at specified timepoints during the study (see schedule of activities in Section 1.3) and/or at home by eDiary, unless otherwise specified. At clinic visits and visits conducted by an MN professional, instruments will be administered before the participant receives any information on disease status and prior to the administration of study treatment, unless otherwise specified.

PRO instruments, translated into the local language as appropriate, will be completed through use of either the participant's own device or an electronic device provided by the Sponsor. The device will be pre-programmed to enable the appropriate instruments to be administered in the correct order at each specified timepoint. The electronic device and instructions for completing the instruments electronically will be provided by the site staff. The data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel.

Participants should be given the following instructions for completing PRO instruments at home:

- Participants should complete the instruments in a quiet area with minimal distractions and disruptions.
- Participants should answer questions to the best of their ability; there are no right or wrong answers.
- Participants should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

During clinic visits and visits conducted by an MN professional, PRO instruments should be administered as outlined below:

- Participants' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for participants to complete the instruments, estimated to be 25 minutes at each specified visit (see Section 8.1).
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Participants should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions but may read questions verbatim upon request.

- Participants should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

ClinRO instruments (i.e., CDAI, SES-CD, Geboes Grading Scale) will be completed at the clinic at specified timepoints during the study (see the Schedules of Activities in Section 1.3). The instruments will be completed on the designated eCRF. Clinicians must complete the official version of each ClinRO instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.

If collected electronically, the data will be transmitted to a centralized database maintained by the electronic device vendor and/or Sponsor.

A6–1.1 CROHN'S DISEASE ACTIVITY INDEX

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Component	Description	Weight
Stool frequency	Sum of 7 daily frequencies: Number of liquid or very soft stools	2
Abdominal pain	Sum of 7 daily ratings: 0 = none, 1 = mild, 2 = moderate, 3 = severe	5
General well-being	Sum of 7 daily ratings: 0 = generally well, 1 = slightly under par, 2 = poor, 3 = very poor, 4 = terrible	7
Complications (extra-intestinal manifestations)	Number of six listed complications the patient now has: 1. arthritis or arthralgia 2. iritis or uveitis 3. erythema nodosum or pyoderma gangrenosum or aphthous stomatitis 4. anal fissure or fistula or abscess 5. other fistula 6. fever over 37.8°C/100°F	20
Anti-diarrheal medications	Taking diphenoxylate or loperamide for diarrhea: 0 = no, 1 = yes	30
Abdominal mass	0 = none, 2 = questionable, 5 = definite	10
Hematocrit	max(0, (47 if male or 42 if female) – hematocrit lab value)	6

Body weight	max(–10, (1 – body weight/standard weight) × 100))	1

Note: During screening patients will be instructed on how to calculate the number of liquid and very soft stools.

A6–1.2 SIMPLE ENDOSCOPIC SCORE FOR CROHN'S DISEASE

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Variable / Score	0	1	2	3
Size of ulcers	None	Aphthous ulcers (diameter 0.1–0.5 cm)	Large ulcers (diameter 0.5–2 cm)	Very large ulcers (diameter > 2cm)
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

A6–1.3 GEBOES GRADING SCALE

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Grade 0 Structural (architectural change)	0.0 No abnormality
	0.1 Mild abnormality
	0.2 Mild or moderate diffuse or multifocal abnormalities
	0.3 Severe diffuse or multifocal abnormalities
Grade 1 Chronic inflammatory infiltrate	1.0 No increase
	1.1 Mild but unequivocal increase
	1.2 Moderate increase
	1.3 Marked increase
Grade 2A Eosinophils in lamina propria	2A. 0 No increase
	2A.1 Mild but unequivocal increase
	2A.2 Moderate increase
	2A.3 Marked increase
	2B. 0 None

Grade 2B Neutrophils in lamina propria	2B.1 Mild but unequivocal increase
	2B.2 Moderate increase
	2B.3 Marked increase
Grade 3 Neutrophils in epithelium	3.0 None
	3.1 < 5% crypts involved
	3.2 < 50% crypts involved
	3.3 > 50% crypts involved
Grade 4 Crypt destruction	4.0 None
	4.1 Probable—local excess of neutrophils in part of crypt
	4.2 Probable—marked attenuation
	4.3 Unequivocal crypt destruction
Grade 5 Erosion or ulceration	5.0 No erosion, ulceration, or granulation tissue
	5.1 Recovering epithelium + adjacent inflammation
	5.2 Probable erosion—focally stripped
	5.3 Unequivocal erosion
	5.4 Ulcer or granulation tissue

A6–1.4 SINGLE-ITEM BOWEL URGENCY QUESTION

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Bowel Urgency Item

Please choose the response that best describes your **bowel urgency during the past 24 hours**.

(Bowel urgency means that when you feel the need for a bowel movement, you have to rush to the toilet to avoid an accident.)

- None
- Mild – Aware but tolerable
- Moderate – Interferes with usual activity
- Severe – Intolerable

A6–1.5 FUNCTIONAL ASSESSMENT OF CHRONIC ILLNESS THERAPY–FATIGUE

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F)

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

A6–1.6 INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

The Inflammatory Bowel Disease Questionnaire (IBDQ)

Patient Name: ..... File No: ..... Date: .....

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. Please tick **one** answer for each of the questions. If you are unsure about how to answer any question, just give the best answer you can. Do not spend too much time answering, as your first thoughts are likely to be the most accurate.

1 How frequent have your bowel movements been during the last 2 weeks?
Please choose an option from:

Bowel movements as or more frequent than they have ever been	1
Extremely frequent	2
Very frequent	3
Moderate increase in frequency of bowel movements	4
Some increase in frequency of bowel movements	5
Slight increase in frequency of bowel movements	6
Normal, no increase in frequency of bowel movements	7

2 How often has the feeling of fatigue or of being tired and worn out been a problem for you during the past 2 weeks?
Please choose an option from:

All of the time	1
Most of the time	2
A good bit of the time	3
Some of the time	4
A little of the time	5
Hardly any of the time	6
None of the time	7

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

All of the time	1
Most of the time	2
A good bit of the time	3
Some of the time	4
A little of the time	5
Hardly any of the time	6
None of the time	7

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:

All of the time	1
Most of the time	2
A good bit of the time	3
Some of the time	4
A little of the time	5
Hardly any of the time	6
None of the time	7

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

All of the time	1
Most of the time	2
A good bit of the time	3
Some of the time	4
A little of the time	5
Hardly any of the time	6
None of the time	7

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

No energy at all	1
Very little energy	2
A little energy	3
Some energy	4
A moderate amount of energy	5
A lot of energy	6
Full of energy	7

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:

All of the time	1
Most of the time	2
A good bit of the time	3
Some of the time	4
A little of the time	5
Hardly any of the time	6
None of the time	7

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:

All of the time	1
Most of the time	2
A good bit of the time	3
Some of the time	4
A little of the time	5
Hardly any of the time	6
None of the time	7

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

All of the time	1
Most of the time	2
A good bit of the time	3
Some of the time	4
A little of the time	5
Hardly any of the time	6
None of the time	7

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

All of the time	1
Most of the time	2
A good bit of the time	3
Some of the time	4
A little of the time	5
Hardly any of the time	6
None of the time	7

11 How often during the last 2 weeks have you been troubled because of fear of not finding a washroom (bathroom, toilet)?
Please choose an option from:

All of the time	1
Most of the time	2
A good bit of the time	3
Some of the time	4
A little of the time	5
Hardly any of the time	6
None of the time	7

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:

A great deal of difficulty; activities made impossible	1
A lot of difficulty	2
A fair bit of difficulty	3
Some difficulty	4
A little difficulty	5
Hardly any difficulty	6
No difficulty; the bowel problems did not limit sports or leisure	7

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

All of the time	1
Most of the time	2
A good bit of the time	3
Some of the time	4
A little of the time	5
Hardly any of the time	6
None of the time	7

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:

All of the time	1
Most of the time	2
A good bit of the time	3
Some of the time	4
A little of the time	5
Hardly any of the time	6
None of the time	7

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

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- Hardly any of the time
- None of the time

16 How often during the last 2 weeks have you had to avoid attending events where there was no washroom (bathroom, toilet) close to hand?
Please choose an option from:

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- Hardly any of the time
- 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:

- A major problem
- A big problem
- A significant problem
- Some trouble
- A little trouble
- Hardly any trouble
- No trouble

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

- A major problem
- A big problem
- A significant problem
- Some trouble
- A little trouble
- Hardly any trouble
- No trouble

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

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- Hardly any of the time
- None of the time

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:

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- Hardly any of the time
- 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:

- None of the time
- A little of the time
- Some of the time
- A good bit of the time
- Most of the time
- Almost all of the time
- 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:

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- Hardly any of the time
- 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:

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- Hardly any of the time
- None of the time

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:

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- Hardly any of the time
- 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:

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- Hardly any of the time
- 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:

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- Hardly any of the time
- 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:

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- Hardly any of the time
- None of the time

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

- No sex as a result of bowel disease
- Major limitation as a result of bowel disease
- Moderate limitation as a result of bowel disease
- Some limitation as a result of bowel disease
- A little limitation as a result of bowel disease
- Hardly any limitation as a result of bowel disease
- 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:

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- Hardly any of the time
- None of the time

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

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- Hardly any of the time
- 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:

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- Hardly any of the time
- None of the time

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:

- Very dissatisfied, unhappy most of the time
- Generally dissatisfied, unhappy
- Somewhat dissatisfied, unhappy
- Generally satisfied, pleased
- Satisfied most of the time, happy
- Very satisfied most of the time, happy
- Extremely satisfied, could not have been more happy or pleased

A6–1.7 PATIENT GLOBAL IMPRESSION OF SEVERITY

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Patient Global Impression of Severity (PGIS)

Please choose the response that best describes the severity of your **overall Crohn's disease symptoms during the past 7 days.**

- ☐ None
- ☐ Very mild
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

A6–1.8 PATIENT GLOBAL IMPRESSION OF CHANGE

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Patient Global Impression of Change (PGIC)

Please choose the response that best describes the change in your **overall Crohn's disease symptoms since the start of the study.**

- ☐ Much better
- ☐ A little better
- ☐ No change
- ☐ A little worse
- ☐ Much worse

A6–1.9 EUROQOL 5-DIMENSION 5-LEVEL

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EuroQol 5-Dimension 5-Level (EQ-5D-5L)

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES (e.g., work, study, housework, family or leisure activities)

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

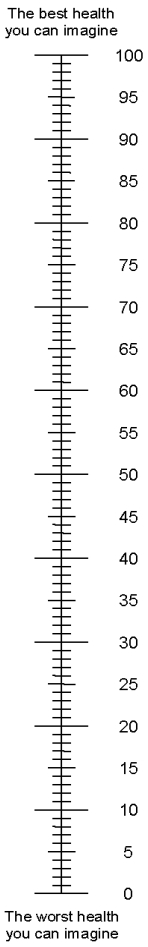
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



A6–1.10 WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE: CROHN'S DISEASE

Work Productivity and Activity Impairment Questionnaire: CROHN'S DISEASE (WPAI-CD) Version 2.0

The following questions ask about the effect of your Crohn's disease on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____NO _____YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your Crohn's disease? *Include hours you missed on sick days, times you went in late, left early, etc., because of your Crohn's disease. Do not include time you missed to participate in this study.*

   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your Crohn's disease affect your productivity while you were working?

   Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If Crohn's disease affected your work only a little, choose a low number. Choose a high number if Crohn's disease affected your work a great deal.

Crohn's disease had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Crohn's disease completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your Crohn's disease affect your ability to do your regular daily activities, other than work at a job?

   By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If Crohn's disease affected your activities only a little, choose a low number. Choose a high number if Crohn's disease affected your activities a great deal.

Crohn's disease had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Crohn's disease completely prevented me from doing my daily activities

CIRCLE A NUMBER

WPAI-CD (US English)

Appendix 7
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment administration in a clinical setting:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intramuscular (preferred route), subcutaneous, intravenous, or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment administration, the following procedures should be performed:

- Stop the study treatment administration, if possible.
- Call for additional medical assistance.
- Maintain an adequate airway.
- Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
- Administer antihistamines, epinephrine, or other medications and IV fluids as required by participant status and as directed by the physician in charge.
- Continue to observe the participant and document observations.
- Collect serum samples for immunogenicity testing.
- Ask the participant to return for immunogenicity sample collection at the time of washout, if appropriate.

Note: Additional immunogenicity (ADA, NAb) samples and a PK sample should be collected in participants with signs and symptoms of systemic hypersensitivity. A serum tryptase sample should be collected between 1 and 6 hours after a suspected systemic hypersensitivity reaction. A second sample should be collected at the next scheduled visit after the event.

Appendix 8
Sampson Criteria for Diagnosing Potential Cases of Anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING:

   a) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)

   b) Reduced blood pressure (BP) or associated symptoms of end organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

   a) Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)

   b) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

   c) Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)

   d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):

   a) Systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline

REFERENCE

Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report: Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol 2006;117:3917.

Appendix 9
Management Guidelines for Infusion-Related Reactions

Event	Management
IRR, Grade 1	• If event occurs during RO7790121 administration, immediately slow infusion to ≤ 50% of initial infusion rate. • Monitor participant until event has completely resolved. • Infusion rate may be increased to the initial rate 30 minutes after event has completely resolved. However, if symptoms reoccur, immediately slow infusion to ≤ 50% of initial infusion rate and maintain that rate for remainder of infusion. • If event does not resolve at reduced infusion rate, follow guidelines for Grade 2 events.
IRR, Grade 2	• If event occurs during RO7790121 administration, immediately interrupt infusion. • Provide supportive care. [a] • Monitor participant until event has completely resolved. • Infusion may be restarted 30 minutes after event has completely resolved, at ≤ 50% of initial infusion rate. • If symptoms reoccur, immediately stop infusion. Do not restart infusion. <u>Next dose:</u> • Administer premedication in accordance with institutional/local clinical guidelines/investigator discretion which may include acetaminophen (or paracetamol), an antihistamine (e.g., diphenhydramine) and/or a single dose of IV corticosteroids. • If event occurred during or within 24 hours after infusion, administer next dose at ≤ 50% of initial infusion rate. <u>Subsequent doses:</u> • If clinically indicated, administer subsequent doses at ≤ 50% of initial infusion rate. However, if a dose is administered at a reduced infusion rate without signs or symptoms of IRR, subsequent doses can be administered at an increased infusion rate at the investigator's discretion. • For Grade ≥ 2 wheezing, bronchospasm, or urticaria, administer premedication prior to subsequent doses.

Appendix 9: Management Guidelines for Infusion-Related Reactions

Event	• Management
• IRR, Grade 3	• If event occurs during RO7790121 administration, immediately stop infusion. Do not restart infusion. • Provide supportive care. [a] • Monitor participant until event has completely resolved; monitoring in ICU is recommended. • Monitor cardiopulmonary and other organ function closely. • For participants with hypotension, provide vasopressor support as clinically indicated. • For participants with hypoxia, provide oxygen as clinically indicated. • Contact the Medical Monitor. **Participants with Grade ≥ 3 wheezing, bronchospasm, or urticaria and/or with prior Grade 2 or 3 event:** • Permanently discontinue RO7790121. **Participants without Grade ≥ 3 wheezing, bronchospasm, or urticaria and without prior Grade 2 or 3 event:** • Next and subsequent doses can be administered as outlined below. • <u>Next dose</u>: – If event resolves completely within 4 hours after event onset, administer next dose according to guidelines below. If not, permanently discontinue RO7790121. – Ensure IRR signs and symptoms have been completely resolved for at least 72 hours prior to dosing. – Hospitalize participant until at least 24 hours after completion of infusion. – Notify Medical Monitor. – Administer premedication in accordance with institutional/local clinical guidelines/investigator discretion which may include acetaminophen (or paracetamol), an antihistamine (e.g., diphenhydramine) and/or a single dose of IV corticosteroids. – If event occurred during or within 24 hours after infusion, administer next dose at ≤ 50% of initial infusion rate. <u>Subsequent doses:</u> – If clinically indicated, administer subsequent doses at ≤ 50% of initial infusion rate. However, if a dose is administered at a reduced infusion rate without signs or symptoms of IRR, subsequent doses can be administered at an increased infusion rate at the investigator's discretion. – For Grade 2 wheezing, bronchospasm, or urticaria, administer premedication prior to subsequent doses.

Appendix 9: Management Guidelines for Infusion-Related Reactions

Event	Management
• IRR, Grade 4	• If event occurs during RO7790121 administration, immediately stop infusion. Do not restart infusion. • Provide supportive care. [a] • Admit participant to ICU. Participant should remain hospitalized until event has completely resolved. • Monitor cardiopulmonary and other organ function closely. • For participants with hypotension, provide vasopressor support as clinically indicated. • For participants with hypoxia, provide oxygen and/or initiate mechanical ventilation as clinically indicated. • Contact the Medical Monitor. • Permanently discontinue RO7790121.

ADA = anti-drug antibody; ICU = intensive care unit; IRR = infusion-related reaction; NAb = neutralizing antibody; PK = pharmacokinetic.

Note: Additional immunogenicity (ADA, NAb) samples and a PK sample should be collected in participants with signs and symptoms of IRRs. A serum tryptase sample should be collected between 1 and 6 hours after a suspected IRR. A second sample should be collected at the next scheduled visit after the event (see Section 1.3).

[a] Administer acetaminophen (or paracetamol) and an antihistamine (e.g., diphenhydramine) if these have not been administered within the previous 4 hours. IV fluids may be administered as clinically indicated. For wheezing, bronchospasm, or urticaria, administer corticosteroids and/or bronchodilators as per institutional practice. For hypotension, provide vasopressor support if clinically indicated.

Appendix 10
Management Guidelines for Injection Site Reactions

Event	Action to Be Taken
ISR, Grade 1	• Observe. • Capture signs and symptoms per appropriate eCRF. • Administer non-systemic symptomatic treatment (topical corticosteroids, antihistamines).
ISR, Grades 2 and 3	• Capture signs and symptoms per appropriate eCRF. • Administer symptomatic treatment (e.g., topical steroids, antihistamines). • For subsequent doses, consider administration of oral premedication with antihistamines and/or analgesics and monitor closely for ISRs.
ISR, Grade 4	• Capture signs and symptoms per appropriate eCRF. • Administer aggressive symptomatic treatment. • Discontinue study treatment and contact the Medical Monitor.

ADA = anti-drug antibody, eCRF = electronic Case Report Form; ISR = injection-site reaction, NAb = neutralizing antibody; PK = pharmacokinetic.

Note: Additional immunogenicity (ADA, NAb) samples and a PK sample should be collected in participants with signs and symptoms of injection site reactions.

Appendix 11
Open-Label Extension Phase Dosing Schedule

Scenario	OLE Rollover?	OLE Dosage	First Dose in the OLE Phase
Study completion at W52	Yes	Q4W	W56
DWC met before W12	No OLE rollover End of treatment Study discontinuation (Tx Disc/Early With/ SFU at W6, W12)	NA	NA
DWC met > W12 to < W52	Yes	Q2W (dose intensification) for 12 weeks then de-escalate to Q4W [a]	When DWC is met (≥ 2 weeks after prior dose)
DWC met during OLE	NA	Q2W (dose intensification) for 12 weeks then de-escalate to Q4W [a]	NA

DWC = disease worsening criteria; Early With = early withdrawal; FU = follow-up; NA = not applicable; OLE = open-label extension phase; Q2W = every 2 weeks; Q4W = every 4 weeks; SFU = safety follow-up; Tx Disc = treatment discontinuation; W = Week.

Note: There will be a maximum of two dose intensifications (Q4W dosing→Q2W dosing) allowed in the OLE phase of the study.

[a] Decision to de-escalate to Q4W or discontinue the participant from the study is by investigator assessment.

Appendix 12
Investigational and Non-Investigational Medicinal Product Designations
(for Use in European Economic Area and United Kingdom)

Table A12-1 Investigational, Authorized Auxiliary, and Unauthorized Auxiliary Medicinal Product Designations for European Economic Area

Product Name	IMP/AxMP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
RO7790121	IMP (test product)	Unauthorized	Not applicable
RO7790121 placebo	IMP (placebo)	Unauthorized	Not applicable
Epinephrine [a]	AxMP (other) [b]	Authorized	Yes
Corticosteroids [a]	AxMP (other) [b, c, d]	Authorized	Yes
Antihistamines [a]	AxMP (other) [b, c, d]	Authorized	Yes
Acetaminophen [a]	AxMP (other) [c]	Authorized	Yes
Bronchodilators [a]	AxMP (other) [c]	Authorized	Yes
Vasopressor [a]	AxMP (other) [c]	Authorized	Yes
Oral analgesics [a]	AxMP (other) [d]	Authorized	Yes

AxMP = auxiliary medicinal product; EEA = European Economic Area; IBD = inflammatory bowel disease; IMP = investigational medicinal product.

[a] Recommended non-IBD related medication pertaining to adverse event management resulting from SC or IV drug administration.

[b] Used according to Appendix 7; will differ from participant to participant.

[c] Used according to Appendix 9; will differ from participant to participant.

[d] Used according to Appendix 10; will differ from participant to participant.

Table A12-2 Investigational and Non-Investigational Medicinal Product Designations for the United Kingdom

Product Name	IMP/NIMP Designation	Marketing Authorization Status in U.K.	Used within Marketing Authorization
RO7790121	IMP (test product)	Unauthorized	Not applicable
RO7790121 placebo	IMP (placebo)	Unauthorized	Not applicable
Epinephrine [a]	NIMP (other) [b]	Authorized	Yes
Corticosteroids [a]	NIMP (other) [b, c, d]	Authorized	Yes
Antihistamines [a]	NIMP (other) [b, c, d]	Authorized	Yes
Acetaminophen [a]	NIMP (other) [c]	Authorized	Yes
Bronchodilators [a]	NIMP (other) [c]	Authorized	Yes
Vasopressor [a]	NIMP (other) [c]	Authorized	Yes
Oral analgesics [a]	NIMP (other) [d]	Authorized	Yes

AxMP = auxiliary medicinal product; EEA = European Economic Area; IBD = irritable bowel disease; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; U.K. = United Kingdom.

[a] Recommended non-IBD related medication pertaining to adverse event management resulting from SC or IV drug administration.

[b] Used according to Appendix 7; will differ from participant to participant.

[c] Used according to Appendix 9; will differ from participant to participant.

[d] Used according to Appendix 10; will differ from participant to participant.

Appendix 13
Abbreviations

Abbreviation or Term	Definition
5-ASA	5-aminosalicyclic acid
6-MP	6-mercaptopurine
ADA	anti-drug antibody
AZA	azathioprine
BCG	Bacillus Calmette-Guérin
BEN	benign ethnic neutropenia
CDAI	Crohn's disease activity index
CD	Crohn's Disease
ClinRO	clinician-reported outcome
CMV	cytomegalovirus
CRP	C reactive protein
DDI	drug-drug interactions
DR3	death receptor 3
EC	Ethics Committee
eCRF	electronic Case Report Form
EQ-5D-5L	EuroQol 5-Dimension 5-Level
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	(U.S.) Food and Drug Administration
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Council for Harmonisation
iDMC	independent data monitoring committee
IgG1	immunoglobulin G1
IMP	investigational medicinal product
IRB	Institutional Review Board
IRR	infusion-related reaction

Appendix 13: Abbreviations

Abbreviation or Term	Definition
ISR	injection site reactions
IxRS	interactive voice or web-based response system
JAK	Janus kinase
mAb	monoclonal antibody
MN	mobile nursing
MTX	methotrexate
NAb	neutralizing antibody
NSAID	nonsteroidal anti-inflammatory drug
OLE	open-label extension
PD	pharmacodynamic
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression Of Severity
PK	pharmacokinetic
PPD	purified protein derivative
PRO	patient-reported outcome
Q2W	every 2 weeks
Q3M	every 3 months
Q4W	every 4 weeks
QFT	QuantiFERON TB-Gold® test
QTcF	QT rate corrected using Fridericia's formula
sTL1A	soluble TL1A
TB	tuberculosis
TEAE	treatment-emergent adverse events
TL1A	tumor necrosis factor-like ligand 1A
TNF	tumor necrosis factor
TNFSF	TNF superfamily
UC	ulcerative colitis
ULN	upper limit of normal

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