Clinical Study Protocol

A 14-Week Phase 2b, RandomizEd, Double-BLind, Dose-Ranging Study to Determine the PharmacokInetics, Efficacy, Safety, and Tolerability of TEV-48574 in Adult PatiEnts with Moderate to Severe Ulcerative Colitis or Crohn's Disease (RELIEVE UCCD)

Study Number TV48574-IMM-20036

NCT05499130

Protocol with Amendment 04 Approval Date: 08 July 2024

Clinical Study Protocol Amendment 04 (JP05) (ES 01) (FR 01)

Study Number TV48574-IMM-20036

A 14-Week Phase 2b, RandomizEd, Double-BLind, Dose-Ranging Study to Determine the PharmacokInetics, Efficacy, Safety, and Tolerability of TEV-48574 in Adult PatiEnts with Moderate to Severe Ulcerative Colitis or Crohn's Disease (RELIEVE UCCD)

Short title: **A Randomized, Double-Blind Study on Pharmacokinetics, Efficacy, Safety, and Tolerability of TEV-48574 in Adults with IBD**

Lay title: **A Study to Test the Effect of TEV-48574 in Moderate to Severe Ulcerative Colitis or Crohn's Disease**

Dose-Ranging Study (Phase 2b)

IND number: 157634; NDA number: Not applicable; BLA number: Not applicable; EU CT number: 2024-511089-36-00

EMA Decision number of Pediatric Investigation Plan: Not applicable

Article 45 or 46 of 1901/2006 does not apply

Protocol Approval Date: 03 February 2022

Protocol with Amendment 01 Approval Date: 13 June 2022

Protocol with Amendment 01 (JP 01) Approval Date: 15 August 2022

Protocol with Amendment 01 (JP 02) Approval Date: 03 October 2022

Protocol with Amendment 02 (JP 02) Approval Date: 13 January 2023

Protocol with Amendment 02 (JP 02) (ES 01) Approval Date: 27 March 2023

Protocol with Amendment 03 (JP 03) (ES 01) Approval Date: 28 June 2023

Protocol Amendment 03 with Revision 01 (JP 03) (ES 01) Approval Date: 15 August 2023

Protocol Amendment 03 with Revision 01 (JP 04) (ES 01) Approval Date: 21 September 2023

Protocol Amendment 04 (JP 05) (ES 01) (FR 01) Version Date: 08 July 2024

Sponsor
Teva Branded Pharmaceutical
Products R&D, Inc.
145 Brandywine Parkway
West Chester, Pennsylvania 19380
United States of America

This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Council for Harmonisation (ICH); United States (US) Code of Federal Regulations (CFR), and European Union (EU) Directives and Regulations (as applicable in the

region of the study); national country legislation; and the sponsor's Standard Operating Procedures (SOPs).

Confidentiality Statement

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DOCUMENT HISTORY

Amendment 04 (JP 05) (ES 01) (FR 01)	08 July 2024 563* patients screened and 229* patients randomized to date
Administrative Letter 02	21 June 2024 563* patients screened and 229* patients randomized to date
Administrative Letter 01	25 September 2023 90 patients screened and 30 patients randomized to date
Amendment 03 with Revision 01 (JP 04) (ES 01)	21 September 2023 83 patients screened and 26 patients randomized to date
Amendment 03 with Revision 01 (JP 03) (ES 01)	15 August 2023 58 patients screened and 18 patients randomized to date
Amendment 03 (JP 03) (ES 01)	28 June 2023 35 patients screened and 09 patients randomized to date
Amendment 02 (JP 02) (ES 01)	27 March 2023 20 patients screened and 04 patients randomized to date
Amendment 02 (JP 02)	13 January 2023 05 patients screened and 02 patients randomized to date
Amendment 01 (JP 02)	03 October 2022 02 patients screened and 00 patients randomized to date
Amendment 01 (JP 01)	15 August 2022 00 patients enrolled to date
Amendment 01	13 June 2022 00 patients randomized/enrolled to date
Original Protocol	03 February 2022

* Patient numbers as of 21 June 2024

The Summary of Changes to the Protocol includes the corresponding reason/justification for each change and the respective global administrative letters are provided in Section 17.

The country specific amendments along with local administrative letters for France and Japan are provided in Appendix M.

INVESTIGATOR AGREEMENT

Original Protocol Dated 03 February 2022

Protocol with Amendment 01 Dated 13 June 2022

Protocol with Amendment 01 (JP 01) Approval Date: 15 August 2022

Protocol with Amendment 01 (JP 02) Approval Date: 03 October 2022

Protocol with Amendment 02 (JP 02) Approval Date: 13 January 2023

Protocol with Amendment 02 (JP 02) (ES 01) Approval Date: 27 March 2023

Protocol with Amendment 03 (JP 03) (ES 01) Approval Date: 28 June 2023

Protocol Amendment 03 with Revision 01 (JP 03) (ES 01) Approval Date: 15 August 2023

Protocol Amendment 03 with Revision 01 (JP 04) (ES 01) Approval Date: 21 September 2023

Protocol Amendment 04 (JP 05) (ES 01) (FR 01) Version Date: 08 July 2024

IND number: 157634; NDA number: Not applicable; BLA number: Not applicable; EU CT number: 2024-511089-36-00

EMA Decision number of Pediatric Investigation Plan: Not applicable

Article 45 or 46 of 1901/2006 does not apply

A 14-Week Phase 2b, RandomizEd, Double-BLind, Dose-Ranging Study to Determine the PharmacokInetics, Efficacy, Safety, and Tolerability of TEV-48574 in Adult PatiEnts with Moderate to Severe Ulcerative Colitis or Crohn's Disease (RELIEVE UCCD)

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel: _____

I have read the protocol Amendment 04 (JP 05) (ES 01) (FR 01) and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes agreement with this protocol and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to national or local legal and regulatory requirements and applicable regulations and guidelines.

I will make available the protocol and all information on the investigational medicinal product (IMP) that were furnished to me by the sponsor to all physicians and other study personnel

reporting to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the IMP and the conduct of the study. I agree to keep records on all patient information, IMP shipment and return forms, and all other information collected during the study, in accordance with national and local Good Clinical Practice (GCP) regulations as well as all other national and international laws and regulations.

Principal Investigator	**Signature**	**Date**

Executed signature pages are maintained within the Trial Master File

SPONSOR PROTOCOL APPROVAL

Sponsor's Authorized Representative	Signature	Date

Executed signature pages are maintained within the Trial Master File

COORDINATING INVESTIGATOR AGREEMENT

Original Protocol Dated 03 February 2022

Protocol with Amendment 01 Dated 13 June 2022

Protocol with Amendment 01 (JP 01) Approval Date: 15 August 2022

Protocol with Amendment 01 (JP 02) Approval Date: 03 October 2022

Protocol with Amendment 02 (JP 02) Approval Date: 13 January 2023

Protocol with Amendment 02 (JP 02) (ES 01) Approval Date: 27 March 2023

Protocol with Amendment 03 (JP 03) (ES 01) Approval Date: 28 June 2023

Protocol Amendment 03 with Revision 01 (JP 03) (ES 01) Approval Date: 15 August 2023

Protocol Amendment 03 with Revision 01 (JP 04) (ES 01) Approval Date: 21 September 2023

Protocol Amendment 04 (JP 05) (ES 01) (FR 01) Version Date: 08 July 2024

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EMA Decision number of Pediatric Investigation Plan: Not applicable

Article 45 or 46 of 1901/2006 does not apply

A 14-Week Phase 2b, RandomizEd, Double-BLind, Dose-Ranging Study to Determine the PharmacokInetics, Efficacy, Safety, and Tolerability of TEV-48574 in Adult PatiEnts with Moderate to Severe Ulcerative Colitis or Crohn's Disease (RELIEVE UCCD)

I have read the protocol Amendment 04 (JP 05) (ES 01) (FR 01) and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes agreement with this protocol and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to national and local legal and regulatory requirements and applicable regulations and guidelines.

I will make available the protocol and all information on the investigational medicinal product (IMP) that were furnished to me by the sponsor to all physicians and other study personnel reporting to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the IMP and the conduct of the study. I agree to keep records on patient information, IMPs shipment and return forms, and other information collected during the study, in accordance with my responsibilities under the function of the coordinating investigator and in accordance with national and local Good Clinical Practice (GCP) regulations as well as all other national and international laws and regulations. In addition, I will assume the responsibility of the coordinating investigator according to a separate contract.

Coordinating Investigator _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel: _____

Coordinating Investigator	**Signature**	**Date**

Executed signature pages are maintained within the Trial Master File

1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol Title: A 14-Week Phase 2b, RandomizEd, Double-BLind, Dose-Ranging Study to Determine the PharmacokInetics, Efficacy, Safety, and Tolerability of TEV-48574 in Adult PatiEnts with Moderate to Severe Ulcerative Colitis or Crohn's Disease (RELIEVE UCCD)
Regulatory Agency Identifier Number: IND number: 157634; NDA number: Not applicable; BLA number: Not applicable; EU CT number: 2024-511089-36-00
Rationale: Many patients with inflammatory bowel disease (IBD) do not respond, lose response, or are intolerant to currently available treatments for ulcerative colitis (UC) and Crohn's disease (CD). Furthermore, some of the available therapeutic agents for IBD have been associated with significant safety issues. The anti- tumor necrosis factor (ligand) 1A (TL1A) activity of TEV-48574 may have an anti-inflammatory and anti-fibrotic effect in patients with IBD, leading to improvement of their disease conditions, while demonstrating an acceptable safety profile. This study will determine the pharmacokinetics, efficacy, safety, and tolerability of 2 different doses of TEV-48574 subcutaneously (sc) administered every 2 weeks (Q2W) in adult patients with moderate to severe UC or CD.
Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
The primary objective of the study is to characterize the efficacy of TEV-48574 subcutaneously (sc) administered every 2 weeks (Q2W) in adult patients with inflammatory bowel disease (IBD) (moderate to severe ulcerative colitis [UC] or Crohn's disease [CD]), as assessed by induction of clinical remission (UC) and endoscopic response (CD) at week 14.	The primary efficacy endpoint is response (yes or no) at week 14, where response in UC patients is defined as clinical remission and response in CD patients is defined as endoscopic response. Clinical remission and endoscopic response are determined as follows: • Clinical remission at week 14 in patients with moderate to severe UC. Clinical remission is a modified (9-point rectal bleeding, stool frequency, and endoscopy) Mayo score of ≤2 points, which is defined by: - stool frequency subscore of 0 or 1, - rectal bleeding subscore of 0, and - endoscopic subscore of 0 or 1, where a score of 1 does not include "friability" • Endoscopic response at week 14 in patients with moderate to severe CD, defined as a reduction in Simple Endoscopic Score for Crohn's Disease (SES-CD) of at least 50% from baseline
A secondary objective of the study is to evaluate the efficacy of 2 different doses of TEV 48574 sc administered Q2W in adult patients with IBD (moderate to severe UC or CD) as assessed by multiple standard measures at week 14.	**UC:** • Clinical response at week 14, defined as a decrease from baseline in the modified (9-point rectal bleeding, stool frequency, and endoscopy) Mayo score of at least 2 points AND at least a 30% reduction from baseline with either a decrease in rectal bleeding subscore of at least 1 or an absolute rectal bleeding subscore of less than or equal to 1 • Endoscopic improvement defined as a Mayo endoscopic subscore of 0 or 1 at week 14 • Endoscopic remission defined as a Mayo endoscopic subscore of 0 at week 14 • Clinical response defined as decrease from baseline of at least 50% in 2-item patient-reported outcome (PRO2; rectal bleeding and stool frequency) at week 14 • Clinical remission defined as score of rectal bleeding = 0 and stool frequency = 0 on the PRO2 scale at week 14

	CD: • Clinical response defined as a ≥100-point decrease in Crohn's Disease Activity Index (CDAI) score from baseline at weeks 4, 8, 12 and 14 • Clinical remission defined as a CDAI score <150 at week 14 • Clinical response defined as a decrease from baseline of at least 50% in PRO2 (PRO2 is defined as having 2 components, abdominal pain and stool frequency) at week 14 • Clinical remission defined as abdominal pain ≤1 and stool frequency ≤3 on the PRO2 scale at week 14 • Endoscopic response defined as a decrease in modified multiplier (MM)-SES-CD of >50% from baseline at week 14
A secondary objective of the study is to evaluate the safety and tolerability of 2 different doses of TEV-48574 sc administered Q2W in adult patients with IBD (moderate to severe UC or CD).	• Adverse events • Change from baseline in clinical laboratory test results (serum chemistry, hematology, and urinalysis) • Change from baseline in vital signs measurements (blood pressure, pulse rate, body temperature, and respiratory rate) • Change from baseline in 12-lead electrocardiogram (ECG) findings • Patients who stopped the investigational medicinal product (IMP) due to adverse events • Local tolerability at the injection site
A secondary objective of the study is to evaluate the immunogenicity of 2 different doses of TEV-48574 sc administered Q2W in adult patients with IBD (moderate to severe UC or CD).	• Change from baseline in treatment-emergent anti-drug antibody (ADA) at weeks 2, 4, 8, 14, and follow-up visit • Presence of neutralizing ADA in ADA positive patients at weeks 2, 4, 8, 14, and follow-up visit

Overall Design: This is a Phase 2b, randomized, double-blind, dose-ranging study to determine the pharmacokinetics, efficacy, safety, and tolerability of TEV-48574 in adult patients with moderate to severe UC or CD. The study will consist of a screening period of up to 6 weeks (42 days), a 14-week treatment period, and a 4 week follow-up period. After the end of the 14 week treatment period, all patients may be offered the option to enter a long-term extension study, which is described in a separate protocol (TV48574-IMM-20038). If they choose to enter (sign the extension study informed consent form [ICF]) and will subsequently be randomized into the long-term extension study, they will not need to complete the follow-up visit in this study. All other patients will return to the site for a follow-up visit.

Trial Population: Adult of male and female (without restrictions on gender), with a diagnosis of IBD: moderate to severe UC or CD.

Number of Participants: Approximately 480 patients will be screened to achieve approximately 240 randomized patients (approximately 120 patients with UC and 120 patients with CD). The sample size does not include patients that were randomized to the 1800 mg treatment group prior to Amendment 03 with Revision 01.

Trial Arms and Duration: Patients who meet all the inclusion criteria and none of the exclusion criteria will be randomly assigned to receive TEV-48574 (single loading dose/6 induction doses): 2250/900 mg, 2250/450 mg, or placebo to match TEV-48574, stratified by diagnosis (UC or CD) and previous exposure to advanced therapy for IBD (yes/no) (biologics, Janus kinase [JAK] inhibitors, and sphingosine-1-phosphate [S1P] receptor modulators). Prior to Amendment 03 with Revision 01, patients were randomly assigned to receive 1 of 4 treatment regimens (2250/1800 mg, 2250/900 mg, 2250/450 mg, or placebo to match TEV-48574); these patients will continue to receive the same dose, volume, and rate of administration of the IMP to

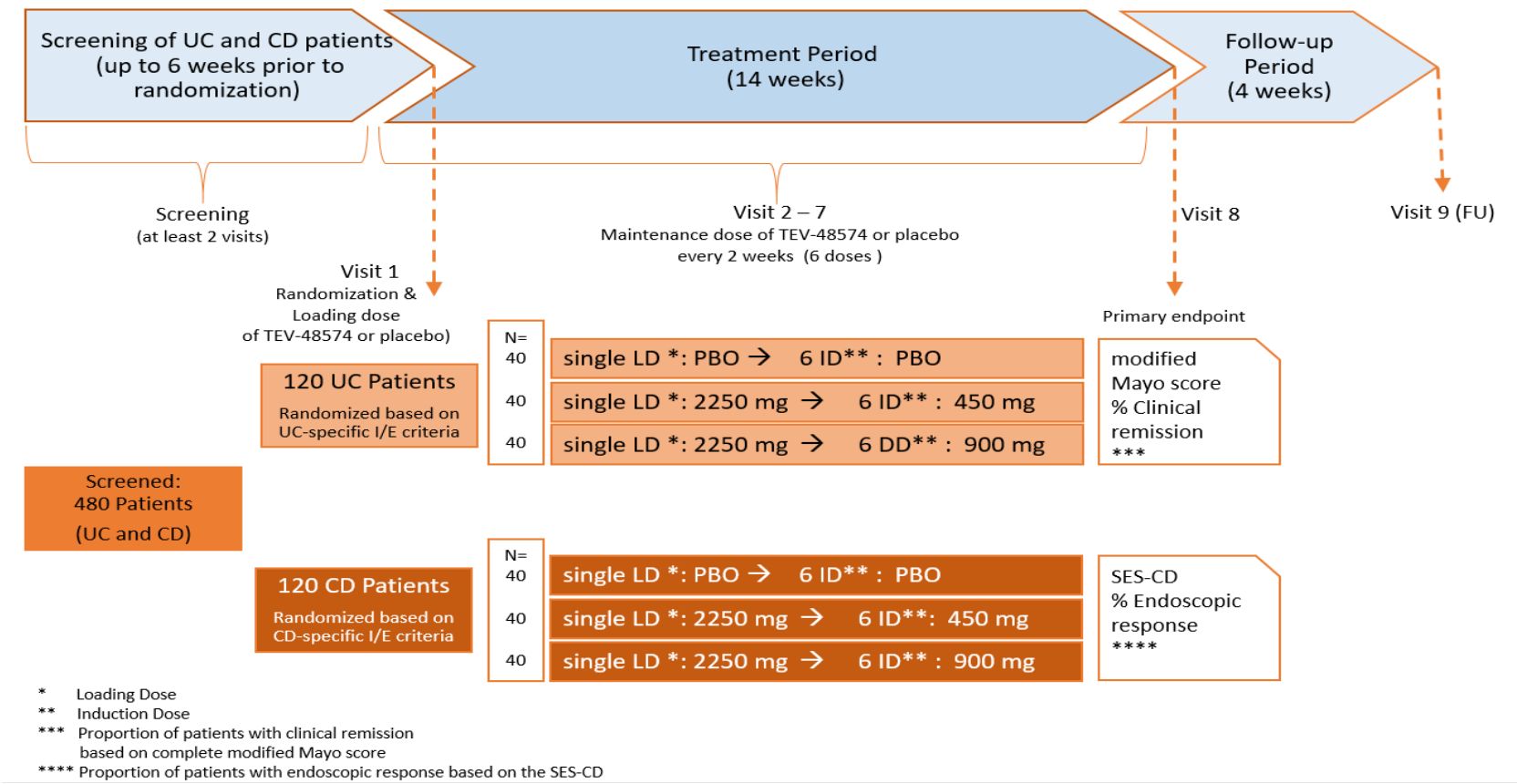
which they were initially randomized and will remain blinded. The total duration of participation for each patient is planned to be up to 24 weeks. The study duration will be approximately 27 months, from Quarter 3 (Q3) 2022 until approximately Quarter 4 (Q4) 2024.
Data Monitoring/Other Committee: Independent Data Monitoring Committee (IDMC) has been established to monitor the study while it is ongoing, including periodic reviews of safety data, and prespecified analyses of efficacy -data.
Ethical Considerations: The study was developed in a manner to protect patient safety. Overall, the risks for patients in this study are mitigated comprehensively and are considered adequate to justify the study.

1.2. Trial Schema

This figure applies only to patients randomized as of Amendment 04.

Patients randomized prior to Amendment 03 with Revision 01 will continue to receive the same dose, volume, and rate of administration of the IMP to which they were initially randomized and will remain blinded.

Figure 1: Overall Program Schematic



CD=Crohn's disease; FU=follow-up; I/E=inclusion/exclusion; ID=induction dose; LD=loading dose; PBO=placebo; SES-CD=Simple Endoscopic Score for Crohn's Disease; UC=ulcerative colitis.

Note: After the end of the 14-week treatment period, all patients may be offered the option to enter a long-term extension study (to be described in a separate protocol [TV48574-IMM-20038]). If they choose to enter (sign the extension study ICF) and will subsequently be randomized into the long-term extension study, they will not need to complete the follow-up visit in this study. All other patients will return to the site for a follow-up visit (day 127 [±3 days]).

1.3. Schedule of Activities

Study procedures and assessments with their time points are presented in Table 1. Detailed descriptions of each method of procedures and assessments are provided in Section 7 (efficacy assessments), Section 8 (safety assessments), and Section 9 (pharmacokinetic and other assessments). Study procedures and assessments by visit are listed in Appendix A.

Exclusionary laboratory values can be retested once during the screening period. If the retested laboratory value(s) remain(s) exclusionary, the subject will be considered a screen failure. Redrawing samples if previous samples were unable to be analyzed would not count as a retest since previous result was never obtained.

Table 1: Study Procedures and Assessments

Study period	**Screening (-42 to -1)**	**Induction period**								**Follow-up[a,b]**	**Early termination[b]**
		Treatment period[a]									
Study visit	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Study week	**Week -6 to -1**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 14**	**Week 18**	
Study day	**Day -42 to -1**	**Day 1**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 99**	**Day 127**	
Visit window	**N/A**	**N/A**	**±3 days based on previous visit**							**±3 days based on previous visit**	
Enrollment procedures											
Informed consent[c]	X										
Inclusion/exclusion criteria	X	X									
Demographics and medical history	X										
Vital signs											
Vital signs measurements[d]	X	X	X	X	X	X	X	X	X	X	X
Weight (lb or kg)	X	X		X		X		X	X	X	X
Height (in or cm)	X										
Medical procedures											
Full physical exam	X								X	X	X
Brief physical exam				X		X		X			
ECG (12-lead)[e]	X			X		X			X		X
Endoscopy											
Endoscopy[f]	X[g]								X		X
Disease activity analysis											
Modified Mayo score (UC only)	X								X		X

Study period	**Screening (-42 to -1)**	**Induction period**								**Follow-up[a,b]**	**Early termination[b]**
		Treatment period[a]									
Study visit	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Study week	**Week -6 to -1**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 14**	**Week 18**	
Study day	**Day -42 to -1**	**Day 1**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 99**	**Day 127**	
Visit window	**N/A**	**N/A**	**±3 days based on previous visit**							**±3 days based on previous visit**	
Stool frequency and Rectal bleeding Mayo sub-scores (PRO2 UC) [h]	X		X	X	X	X	X	X	X		X
Robarts Histopathology Index (UC only)	X								X		X
CDAI score (CD only)	X			X		X		X	X		X
Stool frequency and Abdominal pain (PRO2 CD) [h]	X		X	X	X	X	X	X	X		X
SES-CD (CD only)	X								X		X
MM-SES-CD (CD only)	X								X		X
Laboratory assessments											
Stool sample tests for enteric pathogens (including stool culture and *C difficile* toxin assay)[i]	X										
Infectious serologies[j]	X										
TB screening (QuantiFERON® TB Gold Test)[k]	X										
FSH testing (to confirm postmenopausal status)	X										

Study period	**Screening (-42 to -1)**	**Induction period**								**Follow-up[a,b]**	**Early termination[b]**
		Treatment period[a]									
Study visit	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Study week	**Week -6 to -1**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 14**	**Week 18**	
Study day	**Day -42 to -1**	**Day 1**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 99**	**Day 127**	
Visit window	**N/A**	**N/A**	**±3 days based on previous visit**							**±3 days based on previous visit**	
Pregnancy test (serum) in women of childbearing potential	X										
Pregnancy test (urine) in women of childbearing potential		X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests[l]	X	X		X		X		X	X	X	X
Urinalysis[m]	X	X		X		X			X	X	X
Pharmacodynamics/biomarkers											
Retained pharmacogenetic sample		X[n]									
Biomarker hsCRP		X	X	X		X			X	X	X
Serum free and total TL1A[o]		X	X	X		X			X	X	X
Stool sample for fecal calprotectin (FeCal) or other stool-derived markers		X	X	X		X			X	X	X
Biopsy towards tissue transcriptomics	X								X		X
Serum measure of PD[p]		X	X	X		X			X	X	X
Serum measures of tissue condition		X	X	X		X			X	X	X

Study period	**Screening (-42 to -1)**	**Induction period**								**Follow-up[a,b]**	**Early termination[b]**
		Treatment period[a]									
Study visit	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Study week	**Week -6 to -1**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 14**	**Week 18**	
Study day	**Day -42 to -1**	**Day 1**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 71**	**Day 85**	**Day 99**	**Day 127**	
Visit window	**N/A**	**N/A**	**±3 days based on previous visit**							**±3 days based on previous visit**	
Biomarker [redacted]		X	X			X			X		X
Pharmacokinetics and immunogenicity											
Serum TEV-48574 concentration[o,q]		X	X	X		X			X	X	X
ADA and neutralizing ADA[o]		X	X	X		X			X	X	X
Trial treatment procedures											
Randomization (after all screening procedures complete and eligibility confirmed)		X									
IMP administration[r]		X	X	X	X	X	X	X			
Adverse event monitoring[s]	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant medication and treatments[t]	X	X	X	X	X	X	X	X	X	X	X
Local tolerability assessment[u]		X	X	X	X	X	X	X			

[a] After the end of the 14-week treatment period, all patients may be offered the option to enter a long-term extension study (to be described in a separate protocol [TV48574-IMM-20038]). If they choose to enter (sign the extension study ICF) and will subsequently be randomized into the long-term extension study, they will not need to complete the follow-up visit in this study. All other patients will return to the site for a follow-up visit (day 127 [±3 days]).

[b] EOS is defined as the last visit of the last patient.

[c] A separate informed consent form will be provided for pharmacogenetics samples.

[d] Vital signs measurements include blood pressure, pulse rate, body temperature, and respiratory rate. Patients are to remain in a supine position for at least 5 minutes prior to measuring blood pressure and pulse rate. If possible, blood pressure measurements should be completed on the same arm at each visit. Vital signs should be measured before scheduled blood draws and after the ECG assessment when applicable.

[e] ECG assessments should precede vital sign assessments. ECGs should be performed in a supine position after 5 minutes rest. At screening, ECGs will be performed in triplicate, with each ECG taken within 1 to 5 minutes of the previous one.

[f] For UC patients, endoscopy will include a flexible sigmoidoscopy only (colonoscopy may be performed instead for baseline endoscopy if not done in the prior 12 months). For CD patients, endoscopy will include ileo-colonoscopy.

[g] The endoscopy should be performed after key eligibility criteria have been met and within approximately 10 calendar days of randomization (day 1) to allow for central endoscopy scoring. The endoscopic subscore by the central reader must be available at baseline visit. The assessment by the central reader will be used to derive the modified Mayo and SES-CD scores for study eligibility. An endoscopy is also performed at visit 8 (week 14) or at the early termination visit when applicable. Biopsies will be collected at screening and week 14 or the early termination visit.

[h] For PRO2, rectal bleeding and stool frequency (UC) and stool frequency and abdominal pain (CD) will be collected (entered) daily by the patient via a handheld e-diary. The baseline values are obtained at the last screening visit prior to randomization.

[i] Additional testing (eg, ova and parasites) may be performed at the investigator's clinical discretion.

[j] Serology includes hepatitis B core antibody and surface antigen, hepatitis C virus, and human immunodeficiency virus types 1 or 2. Patients with HBcAb positive and HBsAg negative serology and undetectable Hepatitis B viral DNA at screening may have follow-up Hepatitis B viral DNA testing throughout their participation in the study.

[k] If the QuantiFERON® TB Gold Test is deemed by the principal investigator to be a false positive, additional sample will be tested to confirm the diagnosis.

[l] Clinical laboratory tests including serum chemistry and complete blood count (hematology). Patients should be fasting for at least 8 hours prior to safety laboratory assessments only at the screening, week 14, and early termination visits (ie, visits at which low density lipoprotein, high density lipoprotein, and triglycerides will be measured). Coagulation tests (PT/PTT/INR) will be performed at screening only or in case of suspected liver injury (see Appendix K). The hematocrit value measured at screening will be used to calculate the baseline CDAI score. Screening laboratory test abnormalities, if considered by the Investigator to be transient and inconsistent with the patient's clinical condition, may be repeated once during the screening period for confirmation.

[m] When sampling urine, menstruation status should be recorded for women of childbearing potential.

[n] If sample has not been collected at this visit, it could also be collected at one of the following visits.

[o] In cases of a suspected severe systemic hypersensitivity reaction (eg, anaphylaxis), serious adverse event, or immunogenicity-related adverse event, efforts should be made to collect additional sample(s) for immunogenicity, serum total and free TL1A, and serum concentration of TEV-48574. In cases of suspected or confirmed anaphylaxis, efforts should be made to collect samples for ADA determination as close to the onset of the event as possible, at resolution, and 30 days after onset of the event. Confirmed ADA positive samples may be further evaluated for TEV-48574 neutralizing antibodies.

[p] Proteomics and potentially autoantibodies (pANCA, ASCA).

[q] At visits where IMP is administered, samples should be taken prior to IMP administration (ie, trough levels).

[r] If during administration or during post-IMP administration observation the patient develops clinical symptoms or signs, vital signs should be collected and a physical exam (brief or full, at the discretion of the investigator) performed. The patient should be assessed for anaphylaxis/hypersensitivity reactions. All device-related adverse events, malfunctions, etc will be recorded and evaluated for their impact relative to the safety and efficacy of the IMP.

[s] For each patient, adverse events will be captured from signature of the ICF to the end of study (ie, patient's last visit). For those patients who enter the long-term extension study, adverse events will be recorded in the dose-ranging study CRF up until the date of extension study randomization (defined as the study completion date for the dose-ranging study). For those patients who screen fail the long-term extension study, adverse events will be recorded in the dose-ranging study up until the follow-up visit (day 127 [±3 days]) CRF.

[t] For each patient, concomitant medication data will be captured from signature of the ICF to the end of study (ie, patient's last visit). For those patients who enter the long-term extension study, concomitant medication data will be recorded in the dose-ranging study CRF up until the date of extension study randomization (defined as the study completion date for the dose-ranging study). For those patients who screen fail the long-term extension study, concomitant medication data will be recorded in the dose-ranging study up until the follow-up visit (day 127 [±3 days]) CRF.

[u] Pain will be assessed beginning, during (approximately midway through the infusion), and after the completion of IMP administration and 1 hour later. Administration site findings will be assessed after the completion of IMP administration and 1 hour later. Additionally, after the loading dose and first induction dose, assessments will also be performed 2 hours after the completion of IMP administration. Allowed time windows for the local tolerability assessments after the completion of the infusion are ±15 minutes.

ADA=anti-drug antibody; ASCA=anti-*Saccharomyces cerevisiae* antibodies; *C difficile*=*Clostridium difficile*; CD=Crohn's disease; CDAI=Crohn's Disease Activity Index; CRF=case report form; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EOS=end of study; FSH=follicle-stimulating hormone; HBcAb=Hepatitis B core antibody; HBsAg=Hepatitis B surface antigen; hsCRP=high sensitivity C-reactive protein; ICF=informed consent form; IMP=investigational medicinal product; INR=international normalized ratio; MM-SES-CD=modified multiplier-Simple Endoscopic Score for Crohn's Disease; N/A=not applicable; pANCA=perinuclear antineutrophil cytoplasmic antibodies; [redacted]; PD=pharmacodynamics; PRO2=2-item patient-reported outcome; PT=prothrombin time; PTT=partial thromboplastin time; Q2W=every 2 weeks; SES-CD=Simple Endoscopic Score for Crohn's Disease; TB=tuberculosis; TL1A=tumor necrosis factor (ligand) 1A; UC=ulcerative colitis.

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LIST OF ABBREVIATIONS

Abbreviation	Term
21CFR	Title 21 Code of Federal Regulations
5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ADA	anti-drug antibody
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ASCA	anti-*Saccharomyces cerevisiae* antibodies
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-t}	area under the serum drug concentration-time curve from time 0 to the time of the last measurable drug concentration
AUC_{τ}	area under the concentration-time curve over 1 dosing interval
AZA	azathioprine
BLA	Biological License Application
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Endoscopic Index of Severity
CDMS	clinical data management system
CFR	Code of Federal Regulations (USA)
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL/F	apparent total body clearance after extravascular administration
C_{max}	maximum observed drug concentration
CMV	cytomegalovirus
COVID-19	coronavirus disease 2019
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DR3	death receptor 3
DRF	dose range finding
DNA	deoxyribonucleic acid

Abbreviation	Term
ECG	electrocardiogram
EMA	European Medicines Agency
EOS	end-of-study
EU	European Union
EudraCT	European Clinical Trials
FDA	Food and Drug Administration
FIH	first in human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
GPSP	Global Patient Safety and Pharmacovigilance
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HCG	human chorionic gonadotropin
hsCRP	high sensitivity C-reactive protein
HV	healthy volunteers
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IL	interleukin
IMP	investigational medicinal product
IN	Indigo naturalis
IND	Investigational New Drug
IRB	Institutional Review Board
INR	International Normalized Ratio
ITT	intent-to-treat
iv	intravenous
JAK	Janus kinase
LoAC	Loss of Asthma Control
LSO	local safety officer

Abbreviation	Term
mAb	monoclonal antibody
MAD	multiple ascending dose
MHLW	Ministry of Health, Labour and Welfare
mITT	modified intent-to-treat
MM	modified multiplier
NCI	National Cancer Institute
NCT	National Clinical Trial
NDA	New Drug Application
NOAEL	no observable adverse effect level
NRS-11	11-point numeric rating scale
pANCA	perinuclear antineutrophil cytoplasmic antibodies
PAH	pulmonary arterial hypertension
[redacted]	[redacted]
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PDAESI	protocol-defined adverse event of special interest
PoC	proof-of-concept
PRO2	2-item patient-reported outcome
Q2W	every 2 weeks
Q3	Quarter 3
Q4	Quarter 4
RHI	Robarts Histopathology Index
RNA(s)	ribonucleic acid(s)
RTSM	Randomization and Trial Supply Management
S1P	sphingosine-1-phosphate
SAD	single ascending dose
sc	subcutaneous(ly)
SES-CD	Simple Endoscopic Score for Crohn's Disease
SOP	Standard Operating Procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	elimination half-life
T2	type 2
TB	tuberculosis
TCR	tissue cross-reactivity

Abbreviation	Term
Th	T helper cell
TL1A	tumor necrosis factor (ligand) 1A
t_{max}	time to maximum observed serum drug concentration
TNF	tumor necrosis factor
TNF-α	tumor necrosis factor-alpha
TNFSF15	tumor necrosis factor (ligand) superfamily member 15
UC	ulcerative colitis
ULN	upper limit of normal
US(A)	United States (of America)
VC	videoconference
V_z/F	apparent volume of distribution after extravascular administration
WOCBP	women of childbearing potential
XML	Extensible Markup Language

2. INTRODUCTION AND BACKGROUND INFORMATION

2.1. Introduction

2.1.1. Inflammatory Bowel Disease and Current Treatment Options

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal (GI) tract that affects 5 million people worldwide. IBD presents as 1 of the 2 major forms, ulcerative colitis (UC) or Crohn's disease (CD). In UC, the inflammation is confined to the mucosa of the colon, while in CD, the transmural inflammatory process can affect the entire GI tract from the mouth to the anus, even though it is preferentially located in the terminal ileum and/or right colon (in nearly 70% of forms).

The incidence rates of UC have been reported as high as 24.3 and 19.2 per 100000 person-years in Europe and North America, respectively. The respective incidence rates for CD have been reported as high as 12.7 and 20.2 per 100000 person-years in Europe and North America, respectively. In terms of prevalence, Europe and North America have the highest reported prevalence values for IBD (Europe: UC, 505 per 100000 persons; CD, 322 per 100000 persons and North America: UC, 249 per 100000 persons; CD, 319 per 100000 persons) (Molodecky et al 2012). IBD (UC and CD) occurs more frequently in Caucasians and affects females more often than males. It is a lifelong condition with a serious effect on patients' quality of life and has an increased prevalence with each decade of life (Betteridge et al 2013).

The cause of IBD (UC and CD) is not yet known, but evidence has been accumulated to suggest that this is a multifactorial disease in which multiple environmental and genetic factors interact to trigger an excessive and deregulated mucosal immune response that is directed against normal components of the luminal flora and leads to the tissue damage (Fiocchi 2001).

UC is a chronic GI inflammatory disorder that involves the surface mucosa, the crypt epithelium, and the submucosa of the colon. Patients with UC suffer from diarrhea, rectal bleeding, weight loss, abdominal pain, and fever (Friedman and Blumberg 2015). UC is characterized by a lifelong chronic course of remissions and exacerbations. In severe UC, the bowel wall may become thin, the mucosa may denude, and the inflammation may extend to the serosa leading to dilation, toxic megacolon, and perforation (Friedman and Blumberg 2015). Toxic megacolon commonly requires an urgent colectomy to avoid perforation, peritonitis, and sepsis. In 1 study, within 10 years of diagnosis, 19.9% of patients with UC had undergone colectomy (van Limbergen et al 2008). In addition, patients with UC have an increased risk of carcinoma when compared with the general population. The estimated risk of colorectal carcinoma increases as the duration and extent of disease increases from 2% of patients with UC for 10 years, to 8% of patients with UC for 20 years, and to 18% of patients with UC for 30 years (Eaden et al 2001).

CD is characterized by a significant variety of clinical phenotypes that are related to the chronic inflammation and fibrosis in the GI tract. The phenotypic manifestations of CD are clinically relevant due to differences in disease behavior and treatment options between these phenotypes. The clinical features of CD vary according to the disease phenotype (stricturing, penetrating, inflammatory [non-stricturing and non-penetrating], and perianal disease), but commonly include

chronic diarrhea, abdominal pain, and weight loss. The course of CD is epitomized by periods of relapse and remission with recurrent cycles of inflammation leading to development of complications such as strictures and intestinal fistulas (Adegbola et al 2018).

The overall goal of treatment for patients with active UC is to induce and maintain remission and mucosal healing. Treatment of UC consists of anti-inflammatory and immunosuppressant therapies that are chosen to maximize efficacy while avoiding toxicity. The chosen therapy is therefore dependent on the patient's disease severity and their response to therapy (Kornbluth and Sachar 2010, Ng and Kamm 2009). While agents used to treat mild to moderate UC are generally well tolerated, as the severity of UC disease increases, so do the potential toxicities of the medications required to manage the disease. Mild to moderate UC treatment typically starts with topical agents (5-aminosalicylic acid [5-ASA] or corticosteroids administered via suppository or enema). In patients unresponsive to local therapy or in patients with more severe or more extensive disease, systemic treatment with an oral 5-ASA, such as mesalamine, olsalazine, sulfasalazine, and balsalazide with or without antibiotics is commonly required (Rosenberg and Peppercorn 2010, Ng and Kamm 2009).

Fifty percent (50%) to 75% of patients with mild to moderate UC improve when treated with 5-ASA, and treatment with 5-ASA is generally safe and well tolerated (Friedman and Blumberg 2015). For those patients who do not respond to treatment with 5-ASA or those with more severe, extensive disease at presentation, corticosteroids are generally the first-line treatment for inducing disease remission. Although effective in inducing disease remission, long-term treatment with corticosteroids is associated with multiple adverse effects including moon face, cataracts, acne, hypertension, diabetes, and psychosis in rare cases. Furthermore, 1 study demonstrated that although effective in induction of response, after 1 year, approximately 45% of patients who initially responded to corticosteroids have become steroid-dependent, and 5% required surgery the first year (Hyams et al 2006). For those patients who are unresponsive to or intolerant of corticosteroids, immunosuppressant drugs including azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate, and cyclosporine, or biologics (such as anti-tumor necrosis factor [TNF] agents infliximab and adalimumab) are used to induce and/or maintain remission (Rosenberg and Peppercorn 2010, Kornbluth and Sachar 2010). These medications have multiple limitations including toxicities and a delay in onset of action; AZA and 6-MP take as long as 3 months to work. The use of AZA and 6-MP can result in neutropenia, pancytopenia, pancreatitis, nephrotoxicity, hepatotoxicity, and lymphoma in rare cases (Carter et al 2004, Bousvaros 2010, Chaparro et al 2009).

Medical therapy for patients with CD is largely influenced by the type, site, and extent of lesions, as well as the presence of local and extraintestinal manifestations and activity of the disease. In general, patients with mild disease can be treated with high doses of mesalazine (5-ASA), while moderate to severe forms require the use of steroids. Immunosuppressant drugs, such as AZA, mercaptopurine, and methotrexate, are used to maintain remission either alone or in combination with biologics. This later group of compounds include the anti-TNF agents infliximab, adalimumab, and certolizumab (Friedman and Blumberg 2015).

Anti-TNF agents are used to induce and maintain remission in IBD patients resistant to other therapies. Nearly 50% of patients respond to treatment, but remission can be induced in less than 30% of patients (Fine et al 2019, Adegbola et al 2018). Moreover, response can wane with time, and treatment can associate with the development of severe side effects such as increased risk of

infections (particularly reactivation of latent tuberculosis [TB] and opportunistic fungal infections including disseminated histoplasmosis and coccidioidomycosis), acute liver injury due to reactivation of hepatitis B virus and to autoimmune effects and cholestasis, and the occurrence or exacerbations of immune-mediated pathologies (such as lupus and psoriasis) (Friedman and Blumberg 2015). Patients who do not respond to medical therapy are candidates for surgery, which, in many cases, is followed by recurrence of the disease.

Despite the recent approvals of the new therapeutic option for IBD as the anti-integrin antibodies (vedolizumab) and anti-interleukin (IL)-12/23 (ustekinumab), and small molecule Janus kinase (JAK) inhibitor (tofacitinib), efficacy of all those drugs is limited to approximately 15% to 40% over placebo, depending on the stringency of the endpoint and rates of placebo response in the respective study (Misselwitz et al 2020). In addition, some of the therapeutic agents, for example tofacitinib, have been associated with significant safety issues: serious venous thromboembolism events including pulmonary embolism, some of which were fatal, and deep vein thrombosis; serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens; and lymphoma and other malignancies (XELJANZ SmPC 2021, XELJANZ PI 2021).

In spite of the tremendous advances made in recent years in IBD therapeutics, many patients still do not respond, lose response, or are intolerant to currently available treatments for UC and CD. This, and the safety profiles of the current IBD therapies, support the notion that the development and implementation of highly effective drugs with favorable side effect profiles for patients is an important, unmet need.

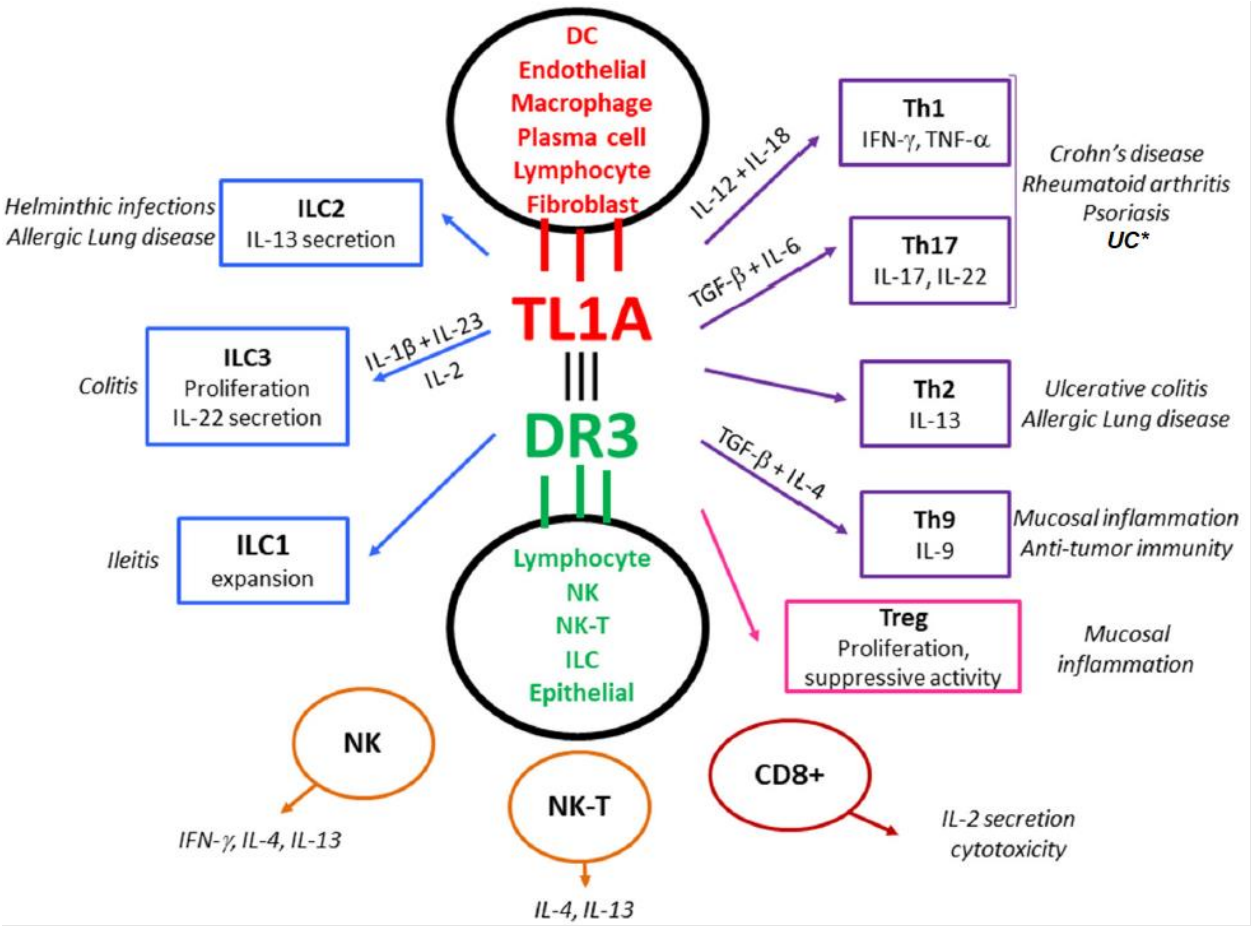
2.1.2. Relevance of Inhibition of TL1A Binding to Death Receptor 3 for Inflammatory Bowel Disease

Tumor necrosis factor (ligand) 1A (TL1A) is a co-stimulatory molecule that enhances the activation of certain types of T cells. TL1A, which is produced primarily by dendritic cells and monocyte/macrophages, acts on different T cell types (Figure 2). TL1A additionally acts directly on death receptor 3 (DR3)+ fibroblasts to trigger profibrotic pathways.

TL1A/DR3 signaling enhances proliferation and optimizes cytokine production by responding to lymphocytes, acting as a co-stimulatory signal that amplifies the primary responses. This function is of particular importance under conditions of sub-optimal lymphocyte stimulation but can also contribute to inflammatory pathology, especially in diseases with mucosal involvement, such as UC and CD. The response of all types of effector T cells (T helper cell [Th] 1, Th2, Th9, and Th17) can be enhanced by TL1A (Figure 2).

Inhibiting TL1A binding to DR3 prevents activation of the DR3 signaling pathway. A therapeutic anti-TL1A antibody (PF-06480605) was found to be efficacious in patients with UC (Hassan-Zahraee et al 2020). The results of this proof-of-concept (PoC) clinical study provide support for the clinical and histological benefits of inhibition of TL1A/DR3 signaling in patients with UC (Danese et al 2021). The results of the study demonstrated an acceptable safety profile and statistically significant endoscopic improvement in participants with moderately to severely active UC. Similar findings were reported in a Phase 2 study in patients with moderate to severe UC. In this study, treatment with PRA-023 resulted in a statistically significant greater proportion of patients with clinical remission or endoscopic improvement compared with placebo with a well-tolerated and acceptable safety profile (Sands et al 2023).

Figure 2: TL1A/DR3 Signaling Interactions



Source: Valatas et al 2019 (*modified).
CD=cluster of differentiation; DC=dendritic cell; DR3=death receptor 3; IFN=interferon; IL=interleukin; ILC=innate lymphoid cell; NK=natural killer; NK-T=natural killer T; TGF=transforming growth factor; Th=T helper cell; TL1A=tumor necrosis factor (ligand) 1A; TNF=tumor necrosis factor; Treg=regulatory lymphocytes; UC=ulcerative colitis.
Note: Although NK-T cells are designated as IL-4 and IL-13 producers in this figure, NK-T cells also produce significant amounts of IFN-γ, IL-9, IL-17, and IL-22.

2.1.3. TEV-48574 and Inflammatory Bowel Disease

TEV-48574 is a highly potent, fully human immunoglobulin G (IgG) subclass 1 (lambda) monoclonal antibody (mAb) with a molecular weight of 146 kDA that targets TL1A, encoded by the TNF superfamily member 15 (*TNFSF15*) gene.

It is a neutralizing antibody that binds TL1A and inhibits its binding to its cognate signaling receptor, DR3, preventing activation of the DR3-signaling pathway. TEV-48574 also inhibits the binding of TL1A to decoy receptor 3 (DcR3), which is a natural antagonist of the TL1A-DR3 interaction. TEV-48574 preferentially inhibits the TL1A-DR3 interaction over the TL1A-DcR3 interaction.

In colitis animal models, TEV-48574 has shown anti-inflammatory and anti-fibrotic effects during nonclinical studies.

Based on the TL1A/DR3 signaling interactions and the potential effects of TL1A inhibition on inflammation, the intended indications for UC and CD with TEV-48574 are for the treatment of adult patients with moderately to severely active UC who have had an inadequate response, loss of response, or intolerance to either conventional therapy or a biologic agent and/or JAK inhibitor; and for the treatment of adult patients with moderately to severely active CD who have had an inadequate response, loss of response, or intolerance to either conventional therapy or a biologic agent.

2.1.4. Purpose of Current Study

Many patients with IBD do not respond, lose response, or are intolerant to currently available treatments for UC and CD. Furthermore, some of the available therapeutic agents for IBD have been associated with significant safety issues. The anti-TL1A activity of TEV-48574 may have an anti-inflammatory and anti-fibrotic effect in patients with IBD, leading to improvement of their disease conditions, while demonstrating an acceptable safety profile.

The purpose of the study is to determine the pharmacokinetics, efficacy, safety, and tolerability of 2 different doses of TEV-48574 subcutaneously (sc) administered every 2 weeks (Q2W) in adult patients with moderate to severe UC or CD.

2.2. Findings from Nonclinical and Clinical Studies

Brief summaries of nonclinical pharmacology, pharmacokinetics, and toxicology studies and clinical studies are provided in the following sections. More detailed information is provided in the Investigator's Brochure (IB).

2.2.1. Nonclinical Studies

A comprehensive set of in vitro and in vivo nonclinical studies was conducted to support TEV-48574 long-term therapeutic use in humans.

TEV-48574 bioavailability following a single sc administration was on average 93.0% in monkeys and 133.8% in rats (the higher than expected bioavailability observed in rats was possibly due to inter-animal variability and/or variability with the analytical method). A typical mAb pharmacokinetic profile was observed in monkeys; low volume of distribution indicating distribution is mainly limited to vasculature, no sex differences could be observed in exposure, and systemic exposure generally increased in a dose proportional manner. TEV-48574 displayed sc absorption with time to maximum observed serum drug concentration (t_{max}) of 48 hours followed by a gradual monophasic decline in serum levels and a terminal elimination half-life ($t_{½}$) ranging between 155 and 177 hours. In rats, 90% of the animals developed anti-drug antibodies (ADAs) along with reduced exposure, while ADA prevalence was less than 20% in the repeat-dose non-Good Laboratory Practice (GLP) study in cynomolgus monkeys, with no major drop in exposure when ADAs were present. As such, the cynomolgus monkey was considered the only relevant species for long-term safety studies.

The nonclinical safety program conducted with TEV-48574 consisted of a 6-week and a 6-month repeat-dose toxicity GLP study in the cynomolgus monkey. In addition to standard assessments, the 6-week study included cardiovascular and respiratory assessments and the 6-month study conducted in sexually mature animals included fertility assessments. These studies were preceded by single-dose pharmacokinetic and tolerability studies and 2-week dose range finding

(DRF) studies in rats and monkeys. In addition, in vitro tissue cross-reactivity (TCR) studies and cytokine release assays were conducted.

The nonclinical safety program revealed no safety concerns. In the repeat-dose sc toxicology studies, there were no TEV-48574-related clinical observations, changes in body weights, food consumption, ophthalmology, and clinical pathology (hematology, coagulation, clinical chemistry, and urinalysis) following repeated administrations of TEV-48574. There were no TEV-48574-related changes in the numbers of circulating T lymphocytes, B lymphocytes, natural killer cells, and monocytes. There were no organ weight, or macroscopic or microscopic changes that could be attributed to TEV-48574. No TEV-48574-related effects were noted on blood pressure, electrocardiography, and respiratory rate nor on fertility parameters (menstrual cycle, testicular volume, echogenicity, and semen analysis). As no safety signal was observed in the studies, the no observable adverse effect level (NOAEL) was concluded to be the highest doses tested in the repeat-dose studies; 50 mg/kg for the rat (2-week study) and 100 mg/kg for the monkey (6-month study).

Results obtained from in vitro TCR studies suggested that interactions of TEV-48574 with human tissues are unlikely. TEV-48574 is considered unlikely to induce a cytokine storm/cytokine syndrome as indicated by the low level of cytokine induction from human peripheral blood mononuclear cells in cytokine release assays.

2.2.2. Clinical Studies

2.2.2.1. Phase 1 Study (TV48574-SAD-10126)

Study TV48574-SAD-10126 was a first-in-human (FIH), Phase 1, randomized, double-blind, placebo-controlled, parallel-group study to determine the safety, tolerability, pharmacokinetics, and immunogenicity of TEV-48574 in the following groups:

- healthy volunteers (HV; single ascending dose [SAD] portion of the study: single sc administration of 1, 4, 12, 36, 90, 200, 400, and 1000 mg or placebo)
- patients with asthma (multiple ascending dose [MAD] portion of the study: repeat sc administrations (3 sc administrations: 200 mg Q2W, 800 mg [loading dose]/600 mg [maintenance dose] Q2W, and 2300 mg [loading dose]/1600 mg [maintenance dose] Q2W, or placebo)

Within each of the 8 dose cohorts in the SAD portion of the study, 8 healthy subjects were randomized to receive a single sc dose of TEV-48574 (6 subjects) or placebo (2 subjects). A total of 48 subjects received TEV-48574 and 16 subjects received placebo. In the MAD portion of the study, 36 patients with mild allergic asthma were assigned to 1 of 3 cohorts (12 patients per cohort). Within each cohort, the patients were randomly assigned to receive TEV-48574 (9 patients) or placebo (3 patients). A total of 27 patients received TEV-48574 and 9 patients received placebo. The study was completed (last patient completed) on 26 February 2019.

2.2.2.1.1. Pharmacokinetics

In the SAD portion of the study, single sc doses of TEV-48574 at 1, 4, 12, 36, 90, 200, 400, and 1000 mg were administered in HV. After 1- and 4-mg doses, all TEV-48574 serum concentrations were below the limit of quantitation.

The $t_{½}$ of TEV-48574 in the SAD portion was similar across the studied dose range; generally exceeding 6.5 days in all SAD cohorts (range: approximately 6.5 to 9.6 days). TEV-48574 peak serum concentrations were typically reached between 72 and 96 hours postdose. Thereafter, TEV-48574 was eliminated gradually in a monophasic manner. For apparent total body clearance after extravascular administration (CL/F), mean estimates were similar across the dose range. The apparent volume of distribution after extravascular administration (V_z/F) was also similar across the dose range (8.24 to 15.13 L), indicating that TEV-48574 was mostly confined to the circulatory system.

From 36 to 1000 mg, the increase in TEV-48574 exposure was greater than dose proportional. However, TEV-48574 half-life, CL/F, and V_z/F appeared similar across all SAD doses, which is suggestive of linear pharmacokinetics. Over the 200- to 1000-mg dose range, dose proportionality was observed. Therefore, the overall slightly greater than dose proportional results may be less relevant as only doses of 200 mg or greater were brought forward into the MAD portion.

The pharmacokinetics of TEV-48574 was further characterized in patients with mild allergic asthma in the MAD portion of the study. Consistent with the results of the SAD portion in HV, the pharmacokinetics of TEV-48574 in patients was characterized by slow absorption. The $t_{½}$ of TEV-48574 at steady state ranged from 8.3 to 8.7 days and was not impacted by dose level. Half-life estimates appear similar to those for the SAD portion of the study, generally exceeded approximately 6.5 days in all cohorts. For CL/F, mean estimates were similar across the dose range tested in the MAD portion and were similar to the CL/F observed in the SAD portion. The V_z/F was similar across the studied dose range in the MAD portion (11.79 to 21.06 L), indicating that TEV-48574 was mostly confined to the circulatory system, consistent with what was observed in SAD portion of the study.

Across the dose range tested in the MAD portion for single and multiple-dose administration, TEV-48574 peak (maximum observed drug concentration [C_{max}]) and total (area under the concentration-time curve over 1 dosing interval [AUC_{τ}]) systemic exposure increased with increasing dose. From 200 to 2300 mg on day 1 and from 200 to 1600 mg at steady state, the increase in TEV-48574 exposure was dose proportional, indicated by the 90% confidence interval (CI) for the estimated slope for C_{max} and AUC_{τ} including unity (1.0).

Without a loading dose, there was weak accumulation following the first dose in cohort 1 in the MAD portion of the study (approximately 47%). After the loading dose administered to cohort 2, there was also weak accumulation (approximately 32%), suggesting that the loading dose may have been too low to achieve steady state as rapidly as intended, whereas the loading dose used for cohort 3 achieved steady-state conditions after the loading dose administration. Steady state was reached after the second dose for all dose regimens.

2.2.2.1.2. Safety

No deaths, serious adverse events, protocol-defined adverse events of special interest (PDAESIs; severe hypersensitivity reactions or anaphylaxis), or withdrawals due to adverse events were reported during the study.

No adverse events consistent with immunosuppression (including opportunistic or unusual infections), cytopenias, or systemic reactions were reported, and no safety signal with

treatment-emergent ADA responses was observed. The nature and incidence of the adverse events were similar between doses and comparable with those for placebo. There were no dose-related trends and no clinically meaningful differences observed between the treatment groups for laboratory tests, vital signs, electrocardiograms (ECGs), and physical examination findings.

The safety data of Study TV48574-SAD-10126 do not suggest any adverse drug reactions associated with TEV-48574 treatment except for transient nonserious injection site findings.

2.2.2.1.3. Immunogenicity

A subject/patient was classified as having a treatment-emergent ADA response if either: 1) a subject had a positive sample at any of the postdose time points, but not at the predose time point, or 2) a subject had positive samples at predose time point and 1 or more postdose time points, with at least a 4-fold increase in titers postdose relative to the predose sample ADA titers. (Note: Treatment-emergent ADA status was based on titer, but all ADA results in this document are presented as $\log_{10}$ titer.)

Of the 48 subjects who received TEV-48574 in the SAD portion of the study, 23 subjects (47.9%) were identified as having a treatment-emergent ADA response. Treatment-emergent ADA responses were not associated with a safety signal. Treatment-emergent ADA responses were also observed in the cohorts that did not have measurable serum concentrations of TEV-48574 (cohorts 1 and 2, 1 and 4 mg TEV-48574, respectively). All ADAs occurred at 200 mg or lower except for 1 patient who received 1000 mg developed 1 transient ADA (low titer) 43 days after the dose was administered, suggesting that there may be a trend toward immunological tolerance at higher doses.

Three of 27 patients who received TEV-48574 (11% of patients tested) in the MAD portion were identified as having a positive treatment-emergent ADA response. All 3 patients were in cohort 1 (200 mg). In these patients, the observed ADA $\log_{10}$ titer ranged from 0.6 to 2.5. One patient had treatment-emergent ADA responses at multiple time points starting by day 15, while the other 2 patients were ADA positive only at the end-of-study (EOS) visit (day 92), approximately 7 weeks after the last dose.

For pharmacokinetics, the single evaluable treatment-emergent ADA positive patient had C_{max} and area under the serum drug concentration-time curve from time 0 to the time of the last measurable drug concentration (AUC_{0-t}) at steady state that were 86% and 93% lower, respectively, at day 15, and 82% and 97% lower, respectively, at day 29, when compared with geometric mean values of ADA negative patients. No treatment-emergent adverse events were reported for treatment-emergent ADA positive patients in the MAD portion of the study.

2.2.2.2.Phase 1 Study (TV48574-PK-10180)

Study TV48574-PK-10180 was a Phase 1 open-label, randomized, single-dose study to evaluate the pharmacokinetics, safety, immunogenicity, and tolerability of TEV-48574 in healthy Japanese and Caucasian subjects. There were 3 single dose cohorts. Healthy Japanese subjects were randomized to 1 of 2 dose levels of TEV-48574 ([redacted] or [redacted] in cohort 1 or assigned to a dose of [redacted] TEV-48574 in cohort 2. Healthy Caucasian subjects were assigned to a dose of [redacted] in cohort 3.

The pharmacokinetic profile of TEV-48574 in Japanese subjects (n=24) was similar to pharmacokinetic profile in Caucasian subjects (n=8) across the absorption, distribution, and elimination phases; pharmacokinetic parameters in Japanese subjects were comparable to Caucasian subjects in the [redacted] dose cohorts and consistent with pharmacokinetic parameters in Caucasian subjects obtained from the TV48574-SAD-10126 study. The safety profile was consistent with that seen in the previous TEV-48574 studies with no evidence of any dose-related trends in adverse events in Japanese cohorts or differences between the Japanese and Caucasian subjects in any safety measures.

2.2.2.3.Phase 2a Study (TV48574-AS-20031)

Study TV48574-AS-20031 was a Phase 2a, PoC, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of TEV-48574 in adults with type 2 (T2)-low/non-T2 severe uncontrolled asthma. This population of asthmatics is characterized by having an endotype and phenotype characterized by low peripheral eosinophil counts; sputum that contains neutrophils or is paucigranulocytic; a history of relatively late-onset asthma symptoms; an increased association with obesity; and a relative resistance to topical, oral, and/or parenterally administered corticosteroids.

The study was initiated in Quarter 3 (Q3) of 2020. Approximately 124 to 174 patients (18 years of age and above) were planned to be enrolled, with the primary objective of the study to evaluate the effect of TEV-48574 compared with placebo on Loss of Asthma Control (LoAC). Patients were randomly assigned to receive a [redacted] of [redacted] and a maintenance dose of [redacted] TEV-48574 Q2W (1 [redacted] and 7 maintenance doses), or placebo to match TEV-48574, in a 1:1 ratio, given sc via the KORU FreedomEdge® syringe infusion system Q2W over a 16-week treatment period for a total of 8 doses.

A pre-specified interim futility analysis was conducted on 64 patients. Teva determined that the primary endpoint result, reduction in LoAC, met the decision rule for futility, meaning that the likelihood of a positive outcome of the completion of the study was small. Based on the results of the primary endpoint futility analysis, Teva decided to stop the study on 22 December 2021.

A total of 65 patients were randomized into the study; 1 patient did not receive investigational medicinal product (IMP). No deaths occurred. Two treatment-emergent serious adverse events were reported; neither were assessed as related to the IMP by the investigator and sponsor. There were 28 patients who withdrew from the study due to LoAC. There were no early terminations due to adverse events.

2.3. Known and Potential Benefits and Risks to Patients

2.3.1. Known and Potential Benefits and Risks of the Test Investigational Medicinal Product(s)

Given the targeted action of TEV-48574 on TL1A, and considering that the product is a mAb, immunosuppression (eg, higher risk for infections and malignancies or incomplete response to vaccines), systemic hypersensitivity, and immunogenicity may be considered potential risks of TEV-48574. None of these risks were observed in either portion of Study TV48574-SAD-10126, except for immunogenicity, predominantly in the low-dose level cohorts up to and including 200 mg in single and repeat-dose settings. However, the observed immunogenicity was not

associated with safety signals; a single patient with decreased serum concentration of TEV-48574 associated temporally with a treatment-emergent ADA response in the MAD portion of the study in the 200 mg cohort.

Transient, mostly mild injection site findings were evident in subjects/patients treated with TEV-48574. No risk was identified that would impact the safety of patients enrolled in clinical studies.

The anti-TL1A activity of TEV-48574 may have an anti-inflammatory and anti-fibrotic effect in patients with IBD, leading to improvement of their disease conditions (see Section 2.1).

In summary, the benefit and risk assessment for TEV-48574 is favorable following review of the outlined data.

Additional information regarding benefits and risks to patients may be found in the IB.

2.3.2. Overall Benefit and Risk Assessment for This Study

This study will investigate the pharmacokinetics, efficacy, safety, and tolerability of TEV-48574 in adult patients with IBD (UC or CD). As described in Section 2.1, such patients may benefit from the development of further therapy options.

Based on the mechanism of action of TEV-48574 and that the exposure in patients with IBD is expected to be similar to the exposure demonstrated in HV and patients with asthma, the safety profile in the IBD population is expected to be comparable with that established in HV and patients with asthma.

Management of the patients' safety during the study that is expected to mitigate risk is detailed in Section 4 (investigational plan) and Section 8 (safety measurements and assessments); also refer to Section 10.13 for a description of the futility analysis, which will determine if recruitment should be stopped due to futility.

In addition to the monitoring of individual patients, an Independent Data Monitoring Committee (IDMC), as described in Section 6.9.3, will review accumulating unblinded safety data.

Overall, the risks for patients in this study are mitigated comprehensively and are considered adequate to justify the study.

3. STUDY OBJECTIVES, ENDPOINTS, AND ESTIMANDS

3.1. Primary and Secondary Study Objectives and Endpoints

The primary and secondary study objectives and endpoints are:

Objectives	Endpoints
The **primary objective** of the study is to characterize the efficacy of TEV-48574 sc administered Q2W in adult patients with IBD (moderate to severe UC or CD), as assessed by induction of clinical remission (UC) and endoscopic response (CD) at week 14.	The primary efficacy endpoint is response (yes or no) at week 14, where response in UC patients is defined as clinical remission and response in CD patients is defined as endoscopic response. Clinical remission and endoscopic response are determined as follows: • Clinical remission at week 14 in patients with moderate to severe UC. Clinical remission is a modified (9-point rectal bleeding, stool frequency, and endoscopy) Mayo score of ≤2 points, which is defined by: o stool frequency subscore of 0 or 1, o rectal bleeding subscore of 0, and o endoscopic subscore of 0 or 1, where a score of 1 does not include "friability" • Endoscopic response at week 14 in patients with moderate to severe CD, defined as a reduction in Simple Endoscopic Score for Crohn's Disease (SES-CD) of at least 50% from baseline
A **secondary objective** of the study is to evaluate the efficacy of 2 different doses of TEV-48574 sc administered Q2W in adult patients with IBD (moderate to severe UC or CD) as assessed by multiple standard measures at week 14.	The secondary efficacy endpoints to be measured in patients with moderate to severe UC are as follows: • Clinical response at week 14, defined as a decrease from baseline in the modified (9-point rectal bleeding, stool frequency, and endoscopy) Mayo score of at least 2 points AND at least a 30% reduction from baseline with either a decrease in rectal bleeding subscore of at least 1 or an absolute rectal bleeding subscore of less than or equal to 1 • Endoscopic improvement defined as a Mayo endoscopic subscore of 0 or 1 at week 14 • Endoscopic remission defined as a Mayo endoscopic subscore of 0 at week 14 • Clinical response defined as decrease from baseline of at least 50% in 2-item patient-reported outcome (PRO2; rectal bleeding and stool frequency) at week 14 • Clinical remission defined as score of rectal bleeding = 0 and stool frequency = 0 on the PRO2 scale at week 14 The secondary efficacy endpoints to be measured in patients with moderate to severe CD are as follows: • Clinical response defined as a ≥100-point decrease in Crohn's Disease Activity Index (CDAI) score from baseline at weeks 4, 8, 12 and 14 • Clinical remission defined as a CDAI score <150 at week 14 • Clinical response defined as a decrease from baseline of at least 50% in PRO2 (PRO2 is defined as having 2 components, abdominal pain and stool frequency) at week 14

Objectives	Endpoints
	• Clinical remission defined as abdominal pain ≤1 and stool frequency ≤3 on the PRO2 scale at week 14 • Endoscopic response defined as a decrease in modified multiplier (MM)-SES-CD of >50% from baseline at week 14
A **secondary objective** of the study is to evaluate the safety and tolerability of 2 different doses of TEV-48574 sc administered Q2W in adult patients with IBD (moderate to severe UC or CD).	The safety and tolerability measures/parameters are as follows: • Adverse events • Change from baseline in clinical laboratory test results (serum chemistry, hematology, and urinalysis) • Change from baseline in vital signs measurements (blood pressure, pulse rate, body temperature, and respiratory rate) • Change from baseline in 12-lead electrocardiogram findings • Patients who stopped the investigational medicinal product due to adverse events • Local tolerability at the injection site
A **secondary objective** of the study is to evaluate the immunogenicity of 2 different doses of TEV-48574 sc administered Q2W in adult patients with IBD (moderate to severe UC or CD).	The immunogenicity endpoints for this study are as follows: • Change from baseline in treatment-emergent anti-drug antibody (ADA) at weeks 2, 4, 8, 14, and follow-up visit • Presence of neutralizing ADA in ADA positive patients at weeks 2, 4, 8, 14, and follow-up visit

3.1.1. Justification of Primary Endpoints

The selected primary endpoint for patients with moderate to severe UC is clinical remission based on the modified Mayo score. The modified Mayo score evaluates UC stage based on the following 3 parameters: stool frequency, rectal bleeding, and endoscopic evaluation. Each parameter of the score ranges from 0 (normal or inactive disease) to 3 (severe activity) and the total score from 0 to 9, respectively. Determination of disease severity by the modified Mayo score is recommended by both the Food and Drug Administration (FDA) and the European Medicines Agency (Reinisch et al 2019). In addition, the selection of primary endpoints based on endoscopy increases the objectivity of the proposed approach. Endoscopy has been the gold standard for objective assessment of UC disease activity in clinical trials since 1956 (Truelove 1956). The endoscopic component of the composite Mayo Clinic Score is used most commonly in clinical trials. There is evidence that the Mayo endoscopic subscore is a reliable measure (Samaan et al 2014).

The selected primary endpoint for patients with moderate to severe CD is endoscopic response, defined as a reduction in Simple Endoscopic Score for Crohn's Disease (SES-CD) of at least 50% from baseline. The assessment of CD activity is complicated by the heterogeneous nature of the disease. Signs and symptoms may also vary based on disease location, and endoscopic outcomes are currently favored in CD clinical trials. The most commonly used indices for endoscopic assessment of CD are the Crohn's Disease Endoscopic Index of Severity (CDEIS) and SES-CD. The CDEIS and the SES-CD are similarly reliable and responsive instruments (Abreu et al 2020). The CDEIS and the SES-CD are closely correlated; however, CDEIS is time-consuming, complicated, and not well suited for routine clinical practice (Sipponen et al 2010).

3.2. Primary Estimand

The primary estimand in this study is defined by the following attributes:

- **Treatment:** In both UC and CD indications, patients will be randomly assigned to receive any one of the study treatment regimens shown below, in a 1:1:1 ratio:
  - TEV-48574 2250 mg (single loading dose)/900 mg (6 induction doses)
  - TEV-48574 2250 mg (single loading dose)/450 mg (6 induction doses)
  - Matching placebo
- **Target population:** The target population comprises patients with a diagnosis of moderate to severe UC or moderate to severe CD.
- **Variable:** Response for the primary efficacy analysis is defined as clinical remission status at week 14 for UC patients or endoscopic response status at week 14 for CD patients.
- **Handling of intercurrent events:** Intercurrent events addressed here are (a) use of rescue medication; (b) important protocol deviations; (c) UC or CD related surgery; and (d) treatment discontinuation. These intercurrent events will be addressed as follows: (a) Patients who used rescue medications prior to their week 14 evaluation of response (clinical remission in the UC indication or endoscopic response in the CD indication) will be reported as non-responders, ie, the composite variable strategy; (b) Patients experiencing any important protocol deviations, namely, use or changes in other medications, will be analyzed as if the deviation had not occurred, ie, treatment policy strategy; (c) Patients undergoing UC or CD related surgery will be treated as non-responders, ie, the composite strategy; and (d) Patients discontinuing treatment, regardless of the reason, will be treated as non-responders, ie, the composite strategy.
- **Population-level summary:** The population-level summary of interest is the quantity *Posterior Probability* $(p_{d,i} - p_{0,i} > 0)$ estimated from a Bayesian Beta-Binomial model for the response rate (clinical remission rate for UC, or endoscopic response rate for CD), $p_{d,i}$, where i=*UC, CD* and d =0,1,2 represent placebo, TEV-48574 low dose (450 mg Q2W), and TEV-48574 high dose (900 mg Q2W), respectively.

3.2.1. Supplementary Estimand

The supplementary estimand is defined by the following attributes:

- **Treatment**: same as for the Primary Estimand.
- **Target population**: same as for the Primary Estimand.
- **Variable**: same as for the Primary Estimand.
- **Handling of intercurrent events**: same as for the Primary Estimand.
- **Population-level summary:** The population-level summary is difference in response rates of each TEV-48574 dose compared to placebo obtained from a logistic regression model fit separately to each indication, with dose as categorical variable.

3.3. Exploratory Objectives and Endpoints

The exploratory objectives and endpoints are:

Objectives	Endpoints
An **exploratory objective** of the study is to evaluate the efficacy of 2 different doses of TEV-48574 sc administered Q2W in adult patients with IBD (moderate to severe UC or CD) as assessed by multiple standard measures.	The exploratory efficacy endpoints to be measured in patients with moderate to severe UC are as follows: • Clinical response defined as decrease from baseline of at least 50% in 2-item patient-reported outcome (PRO2; rectal bleeding and stool frequency) at weeks 2, 4, 6, 8, 10, and 12 • Clinical remission defined as score of rectal bleeding = 0 and stool frequency = 0 on the PRO2 scale at weeks 2, 4, 6, 8, 10, and 12 • Histological remission defined as a Robarts Histopathology Index of ≤5 at week 14 • Histological remission defined as Geboes index score ≤3.1 at week 14 The exploratory efficacy endpoints to be measured in patients with moderate to severe CD are as follows: • Clinical response defined as a decrease from baseline of at least 50% in PRO2 (PRO2 is defined as having 2 components, abdominal pain and stool frequency) at weeks 2, 4, 6, 8, 10, and 12 • Clinical remission defined as abdominal pain ≤1 and stool frequency ≤3 on the PRO2 scale at weeks 2, 4, 6, 8, 10, and 12 • Endoscopic remission defined as SES CD score of 0-2, or SES CD score of 0-4, with no individual sub score >1 at week 14 • Histologic response defined as a ≥50% decrease in Global Histologic Activity Score from baseline at week 14
An **exploratory objective** of the study is to evaluate the safety and tolerability of 2 different doses of TEV-48574 sc administered Q2W in adult patients with IBD (moderate to severe UC or CD).	• Use of concomitant medication • Device-related adverse events and malfunctions (for the commercial sc infusion system)

Objectives	Endpoints
An **exploratory objective** of this study is to evaluate association among exploratory biomarkers and clinical efficacy of TEV-48574 in adult patients with IBD (moderate to severe UC or CD).	• Change from baseline at weeks 2, 4, 8, and 14 in protocol-specified serum-resident pharmacodynamic (PD) markers • Change from baseline in serum and/or gastrointestinal (GI) tissue markers of GI tissue condition (at weeks 2, 4, 8, and 14 for serum; at week 14 for tissue) • Change from baseline at week 14 in GI tissue transcriptome • Change from baseline in fecal calprotectin or other stool-derived markers at weeks 2, 4, 8, and 14 • Change from baseline in high sensitivity C-reactive protein at weeks 2, 4, 8, and 14 • Change from baseline in serum free and total tumor necrosis factor (ligand) 1A at weeks 2, 4, 8, and 14 • Change from baseline at week 14 in GI tissue TL1A expression • Change from baseline in UC-100 at week 14 in patients with moderate to severe UC • Change from baseline in [redacted] at weeks 2, 8, and 14
An **exploratory objective** of the study is to obtain trough serum TEV-48574 concentrations, to compare major pharmacokinetic characteristics between UC and CD patients with healthy volunteers and asthma patients, and, if data allows, to evaluate the pharmacokinetics/PD and/or exposure-response relationship of different doses of TEV-48574 sc.	• Trough serum TEV-48574 concentrations throughout the study (sparse sampling) • Population pharmacokinetic parameters (eg, clearance, volume of the central compartment, area under the concentration-time curve [AUC], maximum observed drug concentration, and trough drug concentration) • Population pharmacokinetic-PD parameters • Exposure-response parameters
An **exploratory objective** of this study is to evaluate the effect of genetic polymorphisms on clinical efficacy in adult patients with IBD (moderate to severe UC or CD).	• Primary and other efficacy endpoints

4. STUDY DESIGN

4.1. General Study Design and Study Schematic Diagram

This is a Phase 2b, randomized, double-blind, dose-ranging study to determine the pharmacokinetics, efficacy, safety, and tolerability of TEV-48574 in adult patients with moderate to severe UC or CD. The study will enroll adult patients (18 to 75 years of age, inclusive) of male and female sex (without restrictions on gender) with moderate to severe active UC or CD and who have demonstrated an inadequate response to, loss of response to, or intolerance to at least 1 of the following therapies: corticosteroids, immunosuppressants, or an advanced therapy for IBD including biologics (anti-TNF, anti-integrins, anti-IL-12/23 or anti-IL-23), JAK inhibitors, or sphingosine-1-phosphate (S1P) receptor modulators; and no more than 3 locally approved classes of biologics.

The study will consist of a screening period of up to 6 weeks (42 days), a 14-week treatment period, and a 4-week follow-up period.

Screening: After providing written informed consent, patients will be screened within 6 weeks (42 days) prior to randomization to confirm that they have met all the selection criteria for the study. At least 2 visits to the investigational site will be necessary to complete all screening procedures, including an endoscopy. The endoscopy should be performed after key eligibility criteria have been met and within approximately 10 calendar days of randomization (day 1) to allow for central endoscopy scoring.

Randomization: Patients satisfying the eligibility criteria at the end of the screening period will be randomized in a 1:1:1 ratio (stratified by diagnosis [UC or CD] and previous exposure to advanced therapy for IBD (yes/no) (biologics, JAK inhibitors, and S1P receptor modulators) to 1 of 3 treatment groups for the double-blind treatment period (Table 2).

All study treatments will be administered in a double-blind fashion as 1 sc infusion Q2W.

Table 2: Randomization Scheme

Randomization ratio	Planned approximate number randomized	Treatment (Q2W)
1	40 UC + 40 CD	TEV-48574 2250 mg (single loading dose)/900 mg (6 induction doses)
1	40 UC + 40 CD	TEV-48574 2250 mg (single loading dose)/450 mg (6 induction doses)
1	40 UC + 40 CD	Placebo

CD=Crohn's disease; Q2W=every 2 weeks; UC=ulcerative colitis.

Patients randomized prior to Amendment 03 with Revision 01 will continue to receive the same dose, volume, and rate of administration of the IMP to which they were initially randomized and will remain blinded.

Treatment and Follow-Up Period: During the 14-week treatment period, patients will visit the site Q2W on days 1, 15, 29, 43, 57, 71, and 85 (±3 days) for IMP administration (7 visits), as well as an end-of-treatment visit on day 99 (±3 days; week 14) (Table 1). After the end of the

14-week treatment period, all patients may be offered the option to enter a long-term extension study, which is described in a separate protocol (TV48574-IMM-20038). If they choose to enter (sign the extension study informed consent form [ICF]) and will subsequently be randomized into the long-term extension study, they will not need to complete the follow-up visit in this study. All other patients will return to the site for a follow-up visit (day 127 [±3 days]). For those patients who enter the long-term extension study, adverse events and concomitant medication data will be recorded in the dose-ranging study case report form (CRF) up until the date of extension study randomization (defined as the study completion date for the dose-ranging study). For those patients who screen fail the long-term extension study, adverse events and concomitant medication data will be recorded in the dose-ranging study up until the follow-up visit (day 127 [±3 days]) CRF. Patients who complete the last scheduled visit will be considered to have completed the study.

Patients who withdraw from the study before completing the 14-week treatment period will complete the assessments for the early termination visit and will be encouraged to complete the follow-up period in the study.

The end of study is defined as the last visit of the last patient.

The total duration of patient participation in the study is planned to be up to 24 weeks for each individual patient.

The study duration will be approximately 27 months, from Q3 2022 until approximately Q4 2024.

Study procedures and assessments with respective time points are shown in Table 1.

The overall study schematic diagram is shown in Figure 1.

4.2. Planned Number of Patients and Countries

Approximately 480 patients will be screened to achieve approximately 240 randomized patients (approximately 120 patients with UC and 120 patients with CD). The sample size does not include patients that were randomized to the 1800 mg treatment group prior to Amendment 03 with Revision 01.

The study is planned to be conducted in North America, Europe, Africa, and Asia in approximately 200 investigational centers. The study is expected to start in Q3 2022 and last until approximately Q4 2024.

4.3. Justification for Study Design and Selection of Population

This study includes both patients with moderate to severe UC and patients with moderate to severe CD.

The mucosal immune system components, including epithelial cells, innate and adaptive immune cells, cytokines, and chemokines, contribute to the pathogenesis of CD and UC (Wallace et al 2014). The fibrogenic factor TNF-like ligand 1A (TL1A, or TNF superfamily member 15) is one of such contributors (Shih et al 2014).

Considering that increased cytokine production leads to chronic inflammation, inhibition of TL1A may be a therapeutic target for both UC and CD (Takedatsu et al 2008; Section 2.1.2). Preclinical studies in rodent colitis models and human cells have shown that the TEV-48574 can reduce tissue fibrosis, the number of fibroblasts, and clinical disease score (Clarke et al 2018).

In addition to the pathophysiologic similarities between UC and CD, there is a commonality of the medications used to treat UC and CD. There are multiple classes approved for the treatment of patients with moderately to severely active UC and CD: 5-ASA, corticosteroids or immunosuppressant drugs, tumor necrosis factor-alpha (TNF-α) inhibitors, integrin inhibitors, and IL-12/23 inhibitors. The following approved mAbs have similar dose regimens for both UC and CD:

- REMICADE® (infliximab; REMICADE SmPC 2021, REMICADE PI 2020).
- HUMIRA® (adalimumab; HUMIRA SmPC 2020, HUMIRA PI 2021).
- ENTYVIO® (vedolizumab; ENTYVIO SmPC 2021, ENTYVIO PI 2021).
- STELARA® (ustekinumab; STELARA SmPC 2021, STELARA PI 2020).

The individual product's efficacy profiles share similarities across the 2 disease states. For example, in the induction phase of the Phase 3 clinical development program of ENTYVIO for the UC patient population, clinical remission described by a complete Mayo score of <2 with no individual score >1 at week 6 was 16.9% in the ENTYVIO cohort versus 5.4% in the placebo one (Feagan et al 2013). In comparison for the CD patient population, the clinical remission defined as Crohn's Disease Activity Index (CDAI) <150 at week 6 was 14.5% in the ENTYVIO cohort and 6.8% in the placebo one (Sandborn et al 2013). Another example is related to the STELARA Phase 3 clinical development program for both UC and CD. Utilizing the above-described measures of clinical remission (Mayo score for UC and CDAI for CD), the efficacy in the UC study was 15.6% versus 5.3% for placebo at week 8 (Sands et al 2019) and

20.9% versus 7.3% at week 8 in the CD study (Feagan et al 2016). This information gives a reason to hypothesize that the TEV-48574 may exhibit the same pattern and provide similar efficacy in both UC and CD at the same dose levels with the same dosing regimen.

There are many existing challenges associated with clinical study design and drug development in UC and CD. Current rates of patient recruitment for participation in Phase 2b UC and CD clinical studies are low. This situation is based on the significant number of clinical studies competing for recruitment of patients, as well as a reluctance to expose patients to placebo treatment considering the availability of multiple approved therapies. The timelines and invasive procedures contribute to an increased burden for patients, investigators, and industry sponsors (Abreu et al 2020).

The basket design is designed to make full use of the hypothesized commonality of the anti-TL1A mechanism of action in patients with UC and CD.

The basket DRF design offers the following efficiencies:

- Provide data in both UC and CD populations in a single study to adequately support initiation of confirmatory studies
- Operate under a single protocol, with opportunity for shared sites and Institutional Review Board (IRB)
- Allow analyses and dose selections for UC and CD under consistent conditions
- Investigate whether the same dosing regimen of TEV-48574 is efficacious for both UC and CD, as is the case with other approved mAbs for IBD

Basket studies are prospectively designed studies typically conducted in Phase 2 to allow effective evaluation of therapeutic benefit of a single investigational treatment in multiple diseases or disease subtypes. In some instances, these designs have served as a basis for regulatory approval (Hyman et al 2015, Subbiah et al 2018).

In summary, the commonality of the anti-TL1A mechanism of action in patients with UC and CD, the approved mAbs that have similar dose regimens for both UC and CD, and the opportunities for operational efficiencies make a basket design well suited for the planned study.

Refer to Section 3.1.1 for the justification for the primary endpoint selection.

Refer to Section 6.3 for justification for dose of test IMP, use of placebo IMP, and the device used for IMP administration.

4.4. Stopping Rules for the Study

4.4.1. Individual Stopping Criteria

4.4.1.1. Permanent Individual Withdrawn from IMP

IMP will be discontinued in the event of any of the following:

- The patient develops a serious or severe infection that is:
    - Life threatening

  - Requires intensive care unit admission
  - Systemic opportunistic infection including tuberculosis (including pulmonary), cytomegalovirus (CMV; including CMV colitis), and listeriosis
- The patient experiences a serious or severe hypersensitivity reaction following investigational medicinal product (IMP) administration, meeting the Common Terminology Criteria for Adverse Events (CTCAE) criteria 3 to 4:
  - Anaphylaxis
  - Allergic reaction
  - Serum sickness
- The patient experiences a serious or severe Cytokine Release Syndrome following IMP administration, defined as CTCAE grade 3 to 4.
- The patient is diagnosed with malignant neoplasm other than appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix.
- The patient experiences a serious adverse event where in the investigator, after consultation with the study sponsor's medical expert, assesses there is a reasonable possibility that the serious adverse event may be caused by the IMP.
- The patient becomes pregnant (see Section 8.3).
- The patient requires prohibited medications or an increase from baseline of the medications for the treatment of UC and CD, including surgery for UC and CD (see Section 6.6.3 and Section 6.6.4).
- Neutrophil count of:
  - Absolute neutrophil count $<0.5 \times 10^9$/L confirmed on repeat testing within 3 to 5 days
  - Absolute neutrophil count $<1.0 \times 10^9$/L that lasts for 2 weeks (retested every 3 to 5 days) or accompanied by fever ≥38.5°C
- Lymphocyte count:
  - Lymphocyte count $<0.2 \times 10^9$/L confirmed on repeat testing within 3 to 5 days
  - Lymphocyte count 0.2 to 0.5 $\times 10^9$/L that lasts for 2 weeks (retested every 3 to 5 days)
- Hemoglobin <8 g/dL or an absolute decrease of ≥3 g/dL from baseline (confirmed in repeated test)
- Platelets $<50 \times 10^9$/L (confirmed in repeated test)
- Liver Chemistry Stopping and Increased monitoring criteria
  - (Refer to Liver Safety Required Actions and Follow up Assessments section in Appendix K)

- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥5x upper limit of normal (ULN)
- ALT or AST ≥3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- AST and/or ALT ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample or in combination with clinical jaundice or in combination of International Normalized Ratio (INR) >1.5 (not applicable for patients on anticoagulants)
- ALT ≥3x ULN for 4 weeks
- ALT ≥3x ULN and cannot be monitored weekly for 4 weeks

- QTc >500 msec or change from baseline of QTc >60 msec

4.4.1.2.Temporary Withholding of IMP

IMP will be temporarily discontinued in the event of any of the following:

- Mild or moderate infusion reactions (grade 1 to 2 according to CTCAE of "allergic reaction") during the infusion. The infusion may be re-initiated, at the discretion of the investigator, at lower speed with or without appropriate premedication, if symptoms are resolved within 1 hour after the stop of infusion/injection. If symptoms return, IMP should be discontinued immediately and permanently.
- A clinically significant infection that the investigator believes may be related to, or exacerbated by, ongoing treatment with the IMP, and none of the permanent stopping rules have been met.
- Absolute neutrophil count $<1.0x10^9/L$
    - Re-testing should be undertaken within 3 to 5 days, and should be re-tested every 3 to 5 days until values have returned to $>1.5x10^9/L$, at which point dosing can be resumed. If the scheduled dose window is missed, re-initiation of study treatment intervention should be restarted as soon as possible but should not result in two consecutive doses being given less than 7 days apart.
- ALT >3x ULN and <5x ULN and bilirubin <2x ULN, without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 4 weeks may continue IMP after discussion with sponsor's medical expert. If, after 4 weeks of monitoring, ALT <3x ULN and bilirubin <2x ULN, patient will be monitored twice monthly until liver chemistries normalize or return to within baseline. (Refer to Liver Safety Required Actions and Follow up Assessments section in Appendix K).

The investigator must immediately inform Teva of these events, and repeat evaluations and testing must be conducted at an appropriate frequency until the event has resolved or stabilized, or until the patient is referred to the care of a healthcare professional.

4.4.2. Study Stopping Criteria

The study may be prematurely terminated by the sponsor in case of an unacceptable risk, any relevant toxicity, or a negative change in the risk/benefit assessment. This might include the occurrence of AEs with a character, severity or frequency that is new in comparison to the existing risk profile. In addition, any data deriving from other clinical trials or toxicological studies which negatively influence the risk/benefit assessment might cause discontinuation or termination of the study.

An IDMC will be established. The IDMC will make recommendations regarding study stopping based on criteria as described in Section 10.3 and Appendix L. The final decisions regarding modification to study conduct, including stopping, will be made by the study Sponsor, incorporating IDMC recommendations.

Written notification documenting the reason for study termination by the Sponsor or principal investigator will be provided to investigators or the Sponsor, respectively, study participants, the IEC/IRB, and regulatory authorities. Study patients will be contacted, as applicable, and be informed of any changes to the study visit schedule.

If the whole study will be stopped, the patients that are terminated early will be followed according to Withdrawal Criteria and Assessments/Procedures for the Patient (Section 5.3).

5. SELECTION AND WITHDRAWAL OF PATIENTS

Prospective waivers (exceptions) from study inclusion and exclusion criteria to allow patients to be randomized/enrolled are not granted by Teva (Appendix B).

5.1. Patient Inclusion Criteria

Patients may be randomized/enrolled in this study only if they meet all of the following criteria:

a. Adults of male and female sex (without restrictions on gender) between 18 and 75 years of age, inclusive, at the time of informed consent.

b. Diagnosis of UC or CD for ≥3 months.

c. UC patients only: Patient with moderate to severe active UC as defined by the 3-component modified Mayo score of 5 to 9, inclusive, with an endoscopic subscore of ≥2 (from central reading).

d. CD patients only: Patient with moderate to severe active CD as determined by a CDAI score of ≥220 and ≤450.

e. CD patients only: SES-CD score of ≥6 (≥4 for isolated ileal disease).

f. UC patients only: Active disease beyond the rectum (>15 cm of active disease at the screening endoscopy [sigmoidoscopy]).

g. Patient must have inadequate response to, loss of response to, or intolerance to:

- At least 1 of the following therapies: corticosteroids, immunosuppressants, or an approved advanced therapy for IBD including biologics (anti-TNF, anti-integrins, anti-IL-12/23, or anti-IL-23), JAK inhibitors, or S1P receptor modulators. No more than 3 locally approved classes of biologics.
  - Inadequate response to, loss of response to, or intolerance to corticosteroid treatment is defined as 1 or more of the following:
    - Steroid refractory: persistent symptoms of active disease despite treatment with at least one 4-week induction regimen that included a dose of ≥30 mg prednisone (oral) daily for at least 2 weeks or intravenous (iv) for at least 1 week within the previous 5 years;
    - Steroid dependent: 2 failed attempts to taper steroids below a dose equivalent to 10 mg prednisone (oral) daily within the previous year;
    - Steroid intolerant: history of intolerance to corticosteroids (including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, and infection) within the previous 5 years.
  - Inadequate response to, loss of response to, or intolerance to prior immunosuppressant treatment is defined by 1 or more of the following:

  - Persistent signs and symptoms of active disease despite a history of at least 1 regimen of oral AZA or 6-MP and/or methotrexate consistent with the regional standard of care;
  - History of intolerance to AZA, 6-MP, or methotrexate (including, but not limited to, nausea/vomiting, abdominal pain, pancreatitis, liver function testing abnormalities, lymphopenia, thiopurine methyltransferase genetic mutation, and infection).

- Inadequate response to, loss of response to, or intolerance to prior advanced therapy for IBD (biologics, JAK inhibitors, and S1P receptor modulators) defined as 1 or more of the following:
  - Loss of response: Persistent signs and symptoms of active disease despite at least one induction and one maintenance regimen of the locally approved regimen of anti-TNF, anti-integrins, anti-IL-12/23 or anti-IL-23 mAbs, JAK inhibitors, or S1P receptor modulators.
  - Inadequate response (primary non-response): Persistent signs and symptoms of active disease despite at least one induction regimen of the locally approved highest dosing regimen of anti-TNF, anti-integrins, anti-IL-12/23 or anti-IL-23 mAbs, JAK inhibitors, or S1P receptor modulators.
  - Intolerance: Discontinuation of anti-TNF, anti-integrins, anti-IL-12/23 or anti-IL-23 mAbs, JAK inhibitors, or S1P receptor modulators due to an adverse drug reaction as determined by treating physician. Such adverse drug reactions include, but are not limited to, nausea/vomiting, abdominal pain, pancreatitis, liver function testing abnormalities, lymphopenia, and infections.

h. If patient is taking the following agents, patient must have been on a stable dose for the following specified period of time: oral 5-ASA or sulfasalazine stable dose for at least 4 weeks prior to endoscopy, oral corticosteroids stable dose for at least 2 weeks prior to endoscopy, and 6-MP, AZA, or methotrexate stable dose for 4 weeks prior to endoscopy.

i. The patient is able to communicate satisfactorily with the investigator and to participate in, and comply with, the requirements of the study.

j. The patient is able to understand the nature of the study and any potential hazards associated with participating in the study.

k. The patient must be willing and able to comply with study restrictions and to remain at the investigational center for the required duration during the study period, and willing to return to the investigational center for further visits, as applicable, and the follow-up procedures and assessments as specified in this protocol.

l. Women of non-childbearing potential who are either surgically (documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally sterile as assessed by a physician, or 1-year postmenopausal (no menses for at least 12 months without an alternative medical cause plus a concentration of follicle-stimulating hormone [FSH] within the postmenopausal range [an increased concentration of FSH of more than 35 IU/L] in women not using hormonal contraception or hormonal replacement therapy).

Women of childbearing potential (WOCBP) must have a negative β-human chorionic gonadotropin (HCG) test result and practice a highly effective method of birth control (methods that can achieve a failure rate of less than 1% per year when used consistently and correctly; Appendix D) prior to IMP administration and throughout the study or 50 days after the last IMP dose, whichever is longer.

m. Male patients (including vasectomized) with WOCBP partners (whether pregnant or not) must use condoms after the first IMP administration and throughout the study or until 50 days after the last IMP dose, whichever is longer.

5.2. Patient Exclusion Criteria

Patients will not be randomized/enrolled in this study if they meet any of the following criteria:

a. The patient has any concomitant conditions or treatments that could interfere with study conduct, influence the interpretation of study observations/results, or put the patient at increased risk during the study as judged by the investigator and/or the clinical study physician.

b. Diagnosis of indeterminate colitis, ischemic colitis, radiation colitis, diverticular disease associated with colitis, or microscopic colitis.

c. Patient has colonic dysplasia or neoplasia (with exception of dysplasia on a completely excised adenomatous polyp [not a sessile one]), toxic megacolon, primary sclerosing cholangitis, known non-passable colonic stricture, presence of colonic or small bowel stoma, presence of non-passable colonic or small bowel obstruction or resection preventing the endoscopy procedure, or fulminant colitis.

d. Presence of active enteric infections (positive stool culture) or a history of serious infection (requiring parenteral antibiotic and/or hospitalization) within 4 weeks prior to the first screening visit.

e. Patient anticipates requiring major surgery during this study.

f. Hepatitis B core antibody (HBcAb) or surface antigen (HBsAg) positive. If HBcAb is positive and HBsAg negative, Hepatitis B viral deoxyribonucleic acid (DNA) will be done as reflective test, and, if undetectable, then not exclusionary. Hepatitis C antibody positive with detectable ribonucleic acids (RNAs). Positive human immunodeficiency virus types 1 or 2 at screening.

g. Tested positive for TB at screening by the QuantiFERON® TB Gold Test (unless documentation of prior TB treatment is available) or had a history of untreated latent or active TB.

h. A history of an opportunistic infection (eg, cytomegalovirus retinitis, Pneumocystis carinii, or aspergillosis).

i. A history of more than 2 herpes zoster episodes in the last 5 years or multimetameric herpes zoster.

j. A history of or ongoing chronic or recurrent serious infectious disease (eg, infected indwelling prosthesis or osteomyelitis).

k. Current or history of chronic liver or biliary disease (with the exception of Gilbert's syndrome, asymptomatic gallstones or uncomplicated fatty liver disease) at screening or baseline ALT or AST >2x ULN or bilirubin >1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at screening.

l. Absolute neutrophil count $<1.5x10^9$/L or Hemoglobin <9 g/dL or lymphocyte count $<0.8x10^9$/L or platelet count <100,000/mL

m. The patient has QTc>480 ms

n. Any acute infection which in the opinion of the investigator compromises the safety of the patient.

o. The patient is currently pregnant or lactating or is planning to become pregnant or to lactate during the study or for at least 50 days after administration of the last dose of IMP in case of early termination. Any woman becoming pregnant during the study will be withdrawn from the study.

p. The patient has a known hypersensitivity to the IMP and/or excipients.

q. Presence of a transplanted organ.

r. A history of malignancy within the last 5 years (exception: basal cell carcinoma or in situ carcinoma of the cervix if successful curative therapy occurred at least 12 months prior to screening or curatively resected papillary thyroid cancer).

s. Patient is receiving any of the following therapies within the designated time period:

- The patient is currently using any systemic immunosuppressant or immunomodulatory biologic or nonbiologic (other than those listed in inclusion criterion "h" and those that are used for IBD) within 30 days or 5 half-lives (whichever is longer) prior to the endoscopy.
- >9 mg/day of oral budesonide or >20 mg/day prednisone or equivalent within 2 weeks prior to the endoscopy.
- Topical (rectal) treatment of 5-ASA or intravenous, intramuscular (parenteral), or enema/suppository administration of corticosteroids within 2 weeks prior to the endoscopy.
- Biologics including anti-TNF, anti-integrins, anti-IL-12/23, or anti-IL-23 within 3 half-lives prior to randomization.
- Small molecules including JAK inhibitors, or S1P receptor modulators, within 5 half-lives or shorter washout duration if undetectable drug levels can be demonstrated prior to randomization.
- Other investigational procedures or products, within 30 days or 5 half-lives of investigational product prior to the endoscopy, whichever is longer.
- Live vaccine within 14 days prior to the first screening visit. Inactivated vaccines (including approved inactivated COVID-19 vaccines) should preferably be completed 14 days before first IMP dosing. If administered during the study, it is recommended

to be at least 3 days before and after IMP administration, or as required by local country regulations.

t. Current or history (within 2 years) of serious psychiatric disease or alcohol or drug abuse.

u. Patients with incurable diseases, persons in nursing homes, and patients incapable of giving written informed consent.

5.3. Withdrawal Criteria and Assessments/Procedures for the Patient

In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), patients may completely withdraw from the study (ie, with no further study participation or contact) at any time for any reason. Patients may also discontinue IMP and remain in the study for assessments after consultation with the investigator and/or sponsor. The investigator and/or sponsor may also discontinue a patient from IMP and/or withdraw a patient from the study in any of the following events:

- in the event of intercurrent illness, adverse events, pregnancy, or any other reason concerning the health or well-being of the patient that indicates to the investigator that continued participation is not in the best interest of the patient (see also Individual Stopping Rules can be found in Section 4.4.1);
- if the patient is noncompliant with the study procedures and assessments or protocol-defined study restrictions or prohibited concomitant medication

Patients who terminate the study should complete the safety and efficacy evaluations specified for early termination in the Study Procedures and Assessments schedule (Table 1) at the time they terminate study participation, and they will be encouraged to complete the follow-up period in the study.

Investigators are to discuss patients who may be considering discontinuing IMP or withdrawing completely from the study with the sponsor as soon as the site becomes aware of the situation.

Investigators should attempt to obtain information on patients in the case of withdrawal from the study or discontinuation from IMP. Results of any evaluations and observations, together with a narrative describing the reason(s) for withdrawal from the study or discontinuation from IMP, should be recorded in the source documents. The CRF should document the primary reason for withdrawal from the study or discontinuation from IMP.

See Appendix E for information regarding how the study will define and address lost to follow-up patients to help limit the amount and impact of missing data.

If an adverse event is the primary reason for discontinuation of IMP or withdrawal from the study, this should be documented in the source and in the CRF, including test results if applicable. Under these circumstances, monitoring should be continued until the event has resolved or stabilized, or until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made.

The investigator should inform the sponsor as soon as possible of each patient who is being considered for withdrawal due to adverse events. Additional reports should be provided when requested.

A patient who withdraws from the study will have the following options regarding pharmacogenetic research:

- Withdraw from the clinical study but accept that the DNA extracted from the patient's blood will be retained and used in accordance with the patient's original pharmacogenetic informed consent.
- Withdraw from the clinical study and withdraw consent for pharmacogenetic research as well, in which case the DNA sample will be destroyed, and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor site contact to request sample destruction. The sponsor site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the sample has been destroyed.
- Withdraw consent for pharmacogenetic research while remaining in the clinical study. In such a case, any DNA extracted from the patient's blood will be destroyed. The sample destruction process will proceed as described above.

5.4. Replacement of Patients

A patient who is randomized but does not complete the treatment period will not be replaced.

5.5. Rescreening

If a patient needs to be rescreened, this should be discussed with the sponsor and/or designee. If a patient is a screen failure but at some point in the future is expected to meet the patient eligibility criteria, the patient may be rescreened only after consultation with the sponsor.

Patients who are rescreened will be assigned a new patient number, will undergo the informed consent process, and will then start a new screening phase.

5.6. Screening Failure

Screen failure occurs when a patient who consents to participate in the clinical study is not subsequently randomized into the study because that patient did not meet the inclusion criteria or did meet the exclusion criteria.

Selected information about patients who screen-fail will be collected to comply with reporting and publishing requirements. This information may include, but is not limited to, demography, detailed reasons for screening failure, eligibility criteria, and any serious adverse events.

6. TREATMENTS

6.1. Investigational Medicinal Products Used in the Study

An IMP is defined as the test IMP (TEV-48574) and matching placebo IMP to the test IMP.

For patients randomized prior to Amendment 03 with Revision 01:

The volume of the solution of each IMP (TEV-48574 and placebo) will be constant (15 mL loading dose volume and 12 mL induction dose volume) and will be administered as single sc administrations.

Active IMP will be diluted with placebo to achieve the final delivered concentrations. Patients will receive the following regimens as a single sc administration Q2W using the [redacted]

- TEV-48574 2250 mg (single loading dose)/1800 mg (6 induction doses)
- TEV-48574 2250 mg (single loading dose)/900 mg (6 induction doses)
- TEV-48574 2250 mg (single loading dose)/450 mg (6 induction doses)
- Placebo to match TEV-48574 (single loading dose)/(Induction doses)

For patients randomized as of Amendment 03 with Revision 01:

The volume of the solution of each IMP (TEV-48574 and placebo) will be constant (15 mL loading dose volume and 6 mL induction dose volume) and will be administered as single sc administrations.

Active IMP will be diluted with placebo to achieve the final delivered concentrations. Patients will receive the following regimens as a single sc administration Q2W using the [redacted]

- TEV-48574 2250 mg (single loading dose)/900 mg (6 induction doses)
- TEV-48574 2250 mg (single loading dose)/450 mg (6 induction doses)
- Placebo to match TEV-48574 (single loading dose)/(Induction doses)

6.1.1. Test Investigational Medicinal Product

TEV-48574 for sc infusion is provided as a liquid solution with a concentration of 150 mg/mL. Refer to Table 3 for specific details regarding TEV-48574. Additional details may be found in the Pharmacy Manual and in the IB for TEV-48574.

6.1.2. Placebo Investigational Medicinal Product

Placebo IMP for sc infusion is provided as a liquid solution in the same formulation as TEV-48574, except for the absence of active protein. Refer to Table 3 for specific details regarding placebo IMP.

6.1.3. Test and Placebo Investigational Medicinal Product Administration

TEV-48574 or placebo IMP will be administered using a commercial sc infusion system. For this study, the [redacted] will be utilized. This syringe infusion system is cleared for use in the US under a 510(k) K092313 and CE marked for use in the EU. This infusion system is indicated for the iv or sc infusion of medications and fluids in the hospital and clinics where the use of the pump can be supervised by a clinician.

This system safely enables single-site sc administration of large volumes to avoid the need for multiple injections from individual syringes and is capable of administration of up to 60 mL syringe using a sc safety needle set. The system controls the rate of drug entry into the tissues surrounding the sc infusion site as well as the duration of infusion. The syringe infusion system is a mechanical or electromechanical syringe pump that pushes the syringe plunger at a constant rate throughout the infusion to infuse drug.

A sterile disposable 20 mL syringe is utilized with the infusion systems and is connected to a subcutaneous needle set, via a luer lock connector, which has a 6mm needle length and delivers the IMP to the subcutaneous tissue. The subcutaneous needle set, which is used in conjunction with the pump and 20 mL syringe, is the KORU (RMS 12606) 26G 6mm single needle infusion set that is cleared under 510k (K102512) and is also CE marked.

The infusion rate is fixed at 30 mL/hr for all sc infusions.

For patients randomized prior to Amendment 03 with Revision 01:

The expected infusion durations will therefore be 30 minutes for the 15 mL loading dose and 24 minutes for the 12 mL induction doses.

For patients randomized as of Amendment 03 with Revision 01:

The expected infusion durations will therefore be 30 minutes for the 15 mL loading dose and 12 minutes for the 6 mL induction doses.

The sponsor has evaluated the suitability of these types of syringe infusion systems to deliver TEV-48574 and the compatibility of TEV-48574 with the appropriate syringe and tubing sets (drug fluid path) that will be used for sc delivery of TEV-48574. The evaluation included general device performance testing and drug compatibility/stability testing of the fluid path. The testing indicated that the drug product quality and characteristics were not affected by the use of a syringe infusion system, and the associated fluid path components and materials, and all drug critical quality attribute met specifications. The sponsor only intends to use this device for clinical purposes and will develop a yet to be defined device for commercial use.

The device, syringe, and tubing and needle set to be used are documented in the study Pharmacy Manual.

Table 3: Investigational Medicinal Products Used in the Study

IMP name	Test IMP	Placebo IMP
Trade name and INN, if applicable, or company-assigned number	TEV-48574	Placebo

IMP name	Test IMP	Placebo IMP
Formulation	10 mM histidine, 5% (w/v) sucrose, 100 mM arginine-hydrochloride, 0.02% (w/v) polysorbate-80, pH 6.0. Liquid. Protein concentration: 150 mg/mL	10 mM histidine, 5% (w/v) sucrose, 100 mM arginine-hydrochloride, 0.02% (w/v) polysorbate-80, pH 6.0. Liquid absent of protein
Unit dose strengths/dosage levels	450 mg/vial	--
Route of administration	sc administration using a commercial sc infusion system	sc administration using a commercial sc infusion system
Dosing instructions/dosing schedule/titration periods/treatment periods	Refer to details in the Pharmacy Manual.	Refer to details in the Pharmacy Manual.
Packaging	IMP will be provided in a type 1 clear glass vial with 20 mm butyl elastomer stopper and an aluminum crimp seal with a plastic flip off cap.	Placebo IMP will be provided in a type 1 clear glass vial with 20 mm butyl elastomer stopper and an aluminum crimp seal with a plastic flip off cap.
Manufacturer	Teva Branded Pharmaceutical Products R&D, Inc. [redacted]	Teva Branded Pharmaceutical Products R&D, Inc. [redacted]

IMP=investigational medicinal product; INN=international nonproprietary name; sc=subcutaneous; w/v=weight/volume; USA=United States of America.

6.2. Preparation, Handling, Labeling, Storage, and Accountability for Investigational Medicinal Products and Devices

6.2.1. Preparation, Storage and Security

Prepared doses of TEV-48574 and placebo IMP will be kept for no more than 4 hours at 25ºC from time of opening the first vial, to completion of dose administration. Additional preparation details may be found in the Pharmacy Manual.

The investigator or designee must confirm appropriate temperature conditions have been maintained for all IMPs received and any discrepancies are reported and resolved before use of the IMPs.

The IMPs (TEV-48574 and placebo IMP) must be stored at a controlled temperature (2°C to 8°C) in a secure area. The site should have a process for monitoring IMP storage temperature.

6.2.2. Labeling

Supplies of IMPs will be labeled according to the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice and will include any locally required statements. If necessary, labels will be translated into the local language.

6.2.3. Accountability

Each IMP shipment will include a packing slip listing the contents of the shipment, return instructions, and any applicable forms.

The investigator is responsible for ensuring that deliveries of IMPs and other study materials from the sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with the Code of Federal Regulations (CFR) or national and local regulations, and used in accordance with this protocol.

Only patients enrolled (ie, randomized) in the study may receive IMPs, and only authorized staff at the investigational center may supply or administer IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions or appropriate instructions with access limited to the investigator and authorized staff at the investigational center.

The investigator is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

A record of IMP accountability (ie, IMP and other study materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies.

Further guidance and information are provided in the Pharmacy Manual.

6.3. Justification for Investigational Medicinal Products

6.3.1. Justification for Dose of Test Investigational Medicinal Product

The justification listed herein refers to the study doses introduced in Amendment 03 with Revision 01 of the study protocol. In this study as of Amendment 03 with Revision 01, TEV-48574 will be administered as a single loading dose of 2250 mg followed by induction doses of 450 or 900 mg sc Q2W, for a total of 7 doses. Patients randomized prior to Amendment 03 with Revision 01 will continue to receive the dose (including volume, rate, and duration) of IMP to which they were initially randomized to not disrupt potential response to treatment and maintain the integrity of the study (eg, blinding concerns and data analysis).

The 2250 mg loading dose as part of the induction dose regimen has been selected to address the significant over-production of TL1A in the colon (Wenxiu et al 2021) within the first weeks of induction, and is supported by precedents from other mAbs with multiple autoimmune disease indications. In these products (HUMIRA SmPC 2020, HUMIRA PI 2021, REMICADE PI 2020, REMICADE SmPC 2021, STELARA SmPC 2021, STELARA PI 2020), it is often observed that a loading dose is included in the IBD therapeutic regimen but not in the other indications, and that the IBD dose levels are generally higher in comparison to the other indications. This may be partially explained by the antigen-dependent clearance pathway, often described as an “antigen sink.” It is known that receptor density influences the pharmacokinetics of mAbs. One potential explanation for the lack of response to TNF inhibitors is incomplete suppression of TNF-α activity because of insufficient serum drug concentrations to block the excess of TNF. A high inflammatory burden at baseline is associated with higher concentrations of TNF-α in both tissue and serum. Patients with a higher degree of systemic inflammation may therefore require greater amounts of drug to neutralize this excess of TNF-α (Ordas et al 2012). Specifically for this

target, it has been established that the TL1A/DR3 system is significantly up regulated in patients with IBD and chronic intestinal inflammation. Intestinal tissue samples from patients with CD and UC exhibit increased TL1A transcripts and protein expression, which correlated with the severity of inflammation (Valatas et al 2019). This may require greater amounts of TL1A inhibition to neutralize the increased TL1A expression in the IBD patient population.

In line with this concept, a single loading dose of 2250 mg is used in this study. This dose level is within the range of doses safely administered to patients with asthma in the MAD portion of Study TV48574-SAD-10126 and in Study TV48574-AS-20031.

The 2 induction dose strengths in this study as of Amendment 03 with Revision 01, were selected based on a combination of safety, preclinical evidence, and pharmacokinetic considerations and will enable selection for the next stage of clinical development by discerning clinically meaningful differences in the absence of pharmacologic or biomarker data to guide dose selection for the pivotal program.

- Selection of the induction regimen of 450 mg or 900 mg Q2W TEV-48574 was done through the use of population pharmacokinetic modeling methodologies. These calculations were aimed to confirm that TEV-48574 induction doses resulted in similar exposures range as RVT-3101 (previously known as PF-06480605), another anti-TL1A antibody, which was tested at 50, 150, or 450 mg sc monthly in a Phase 2b study in UC (TUSCANY-2, National Clinical Trial [NCT] Number: NCT04090411).
- Single/loading doses of up to 1000 mg and 2300 mg and repeated doses of up to 1600 mg Q2W were safely administered in Study TV48574-SAD-10126 and Study TV48574-AS-20031, respectively. The highest exposure to drug is expected in patients enrolled in this study is 900 mg Q2W. This dose is significantly lower than that tested in previous clinical trials for TEV-48574 where no safety signal was observed. Moreover, this dose is expected to result in exposures below those seen in GLP toxicology studies. Predictions obtained from a population pharmacokinetic model suggest a steady-state median value of 67.1 µg/mL (with 37.7 µg/mL and 125.8 µg/mL being the 5th and 95th percentile, respectively) for C_{max}, and median value of 690.8 days*µg/mL (with 309.8 days*µg/mL and 1449.6 days*µg/mL being the 5th and 95th percentile, respectively) for AUCτ for the simulated [redacted] Q2W mg dose. The safety margins for the [redacted] Q2W dose based on population pharmacokinetic simulation exposure are ~20 and ~10 for C_{max} and AUC, respectively.
- As demonstrated in Study TV48574-SAD-10126, the potential for immunogenicity of TEV-48574 is increased in doses ≤200 mg in comparison to higher doses, deemed clinically relevant. No ADAs were detected at dose levels of 400 mg and above in single- and multiple-dose cohorts (except for a single patient in the 1000 mg cohort with an extremely low ADA titer detected at a single time point). Based on this consideration, the lowest dose of 450 mg Q2W is expected to have a low immunogenicity potential.
- As per ICH E4 guidance, for a proper exposure-response characterization, the sponsor should choose doses that ensure adequate spread of attained concentrations in dose-response studies. The induction doses (TEV-48574 450 mg or TEV-48574 900 mg Q2W) will provide pharmacokinetic, PD, and response information which, together with other exposure-response data collected in the program, will enable selection of doses for

subsequent development. Doses tested in this study prior to Amendment 03 with Revision 01 introduction could provide additional supportive information.

In summary, based on a combination of safety, pharmacokinetics, preclinical and clinical evidence, and disease-related considerations, the doses selected for this study are considered adequate to enable exploration of an efficacious dose and safe induction dosing regimen of TEV-48574 for patients with UC or CD. These doses are expected to establish a dose-response relationship, and to support an informed dose selection in future studies with TEV-48574 for each indication of UC and CD.

6.3.2. Justification for Use of Placebo Investigational Medicinal Product

A placebo-controlled design is scientifically appropriate as the use of a placebo-controlled design in this study will allow robust evaluation of any treatment effect of TEV-48574 and characterization of any potential adverse drug reactions.

Patients will have close medical observation throughout the study. In addition, only patients for whom it is considered safe to participate in the study, in the opinion of the investigator, will be permitted to participate.

6.3.3. Justification for Device Used for Administration

The commercial sc infusion system selected for administration of TEV-48574 and placebo IMP is capable of delivering the desired volumes over a wide range of fluid administration rates to meet the needs of the clinical study. This system safely enables single-site sc administration of large volumes to avoid the need for multiple injections from individual syringes.

6.4. Treatment After the End of the Study

After the end of the 14-week treatment period, all patients may be offered the option to enter a long-term extension study (to be described in a separate protocol [TV48574-IMM-20038]).

Otherwise, after the follow-up period, patients will be advised to return to their treating physician for appropriate treatment following completion of the study.

6.5. Restrictions

Patients will be required to comply with the following restrictions:

6.5.1. Activity

Patients must remain seated or in a supine position for safety reasons during each IMP administration and for 1 hour after each IMP administration. Patients will be allowed to use the restroom (escorted by investigational center personnel) during this time, as needed.

Patients should avoid strenuous exercise for at least 4 hours prior to any clinic visit and for at least 4 hours after IMP administration.

6.5.2. Fasting

Patients should be fasting for at least 8 hours prior to safety laboratory assessments only at the screening, week 14, and early termination visits (ie, visits at which low density lipoprotein, high density lipoprotein, and triglycerides will be measured).

6.5.3. Specific Food and Beverages

Patients are encouraged to keep their diet habits constant throughout the study.

6.5.4. Tobacco

Smoking can have an influence on the severity of UC and CD symptoms. For that reason, patients should keep their smoking habits constant throughout the study. Use of a nicotine patch should be recorded as a concomitant medication.

6.5.5. Blood Donation

Patients may not donate blood during this study.

6.6. Prior and Concomitant Medication or Therapy

6.6.1. Prior Medications

All prior medications for IBD will be recorded in the source documentation and in the CRF. Any other prior therapy, medication (including nonprescription drugs, vitamins, and dietary or herbal supplements), or procedure a patient has had 4 weeks before screening through the end of the study will be recorded in the source documentation and in the CRF. Generic or trade name, indication, and dosage will be recorded. The sponsor will encode all therapy and medication according to the World Health Organization drug dictionary (WHO Drug). Assessment of concomitant and prior medications, including a complete history of all therapies for UC and CD received since diagnosis (including treatment response), and detailed UC and CD medications (including dose, frequency, and route) prior to the screening visit will be conducted.

6.6.2. Concomitant Medication(s) and Treatment(s)

All concomitant medication(s) and treatment(s) administered/taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All patients will be questioned about concomitant medication at each site visit. Medication(s) administered/taken following the first dose of IMP will be documented as concomitant medication(s).

6.6.3. Permitted Inflammatory Bowel Disease Medications and Rescue Medications

Permitted concomitant treatment for UC and CD must remain at a stable dose (no increase or decrease) during the study treatment period (except for decreases due to adverse events); if doses are increased, patients must be withdrawn from the study. The dose of any background medication for UC and CD should not be changed during the screening and double-blind treatment period. If a patient requires initiation of a new therapy for UC or CD, the patient should be withdrawn from the study, and appropriate treatment should be administered at the discretion of the investigator.

Patients will be allowed to use the following medications as detailed below:

- Concomitant use of oral 5-ASA or sulfasalazine. Dose must be stable for at least 4 weeks prior to endoscopy and through week 14. If oral 5-ASA treatment has been recently discontinued, it must have been stopped for at least 2 weeks prior to endoscopy.
- A stable dose of oral corticosteroids (prednisone equivalent of up to 20 mg/day; budesonide of up to 9 mg/day) for at least 2 weeks prior to endoscopy and through week 14. If oral corticosteroids have been recently discontinued, they must have been stopped at least 2 weeks prior to endoscopy. Decreases in steroid use due to adverse events are allowed.
- A stable dose of immunosuppressant drugs (methotrexate, 6-MP, or AZA consistent with regional standard of care) for 4 weeks prior to endoscopy and through week 14. Decreases due to adverse events are permitted.

Following the week 14 visit if not continuing on to the long-term extension study, patients will no longer need to abstain from the medications that were prohibited or required no change in dose during the screening and induction period. Biologic treatment(s) should not be initiated during the follow-up period without discussion with the sponsor.

6.6.4. Prohibited Medications and Therapies

The following medications will be prohibited during this study:

- Any live (attenuated) vaccines from 14 days prior to the first screening visit and throughout the study.
- Topical (rectal) treatment of 5-ASA or intravenous, intramuscular (parenteral), or enema/suppository administration of corticosteroids within 2 weeks prior to endoscopy through week 14.
- Prednisone dose of >20 mg/day or equivalent oral systemic corticosteroid from 2 weeks prior to endoscopy through week 14.
- The patient is currently using any systemic immunosuppressant or immunomodulatory biologic or nonbiologic (other than those listed in inclusion criterion “h” and those that are used for IBD) within 30 days or 5 half-lives (whichever is longer) prior to the endoscopy.
- Biologics including anti-TNF, anti-integrins, anti-IL-12/23, or anti-IL-23 within 3 half-lives prior to randomization.
- Small molecules including JAK inhibitors, or S1P receptor modulators, within 5 half-lives or shorter washout duration if undetectable drug levels can be demonstrated prior to randomization.
- Oral budesonide of >9 mg/day or equivalent from 2 weeks prior to endoscopy through week 14.
- Patients requiring a surgical intervention for UC or CD will be discontinued from the study

6.7. Procedures for Monitoring Patient Compliance

The investigator will be responsible for monitoring patient compliance with this protocol from the start of the screening period through the EOS visit.

If the investigator or the sponsor determines that the patient is not in compliance with the study protocol, the investigator and the sponsor should determine whether the patient should be withdrawn from the study (Section 5.3). The Independent Ethics Committee (IEC)/IRB/competent authorities should be notified if required by local regulation.

6.8. Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study. Patients who meet all the inclusion criteria and none of the exclusion criteria will be randomly assigned to receive TEV-48574 (single loading dose/6 induction doses): 2250/900 mg, 2250/450 mg, or placebo to match TEV-48574, in a 1:1:1 ratio, stratified by diagnosis (UC or CD) and previous exposure to advanced therapy for IBD (yes/no) (biologics, JAK inhibitors, and S1P receptor modulators).

Prior to Amendment 03 with Revision 01, patients were randomly assigned to receive 1 of 4 treatment regimens (2250/1800 mg, 2250/900 mg, 2250/450 mg, or placebo to match TEV-48574); these patients will continue to receive the same dose, volume, and rate of administration of the IMP to which they were initially randomized and will remain blinded.

Approximately 120 UC patients and 120 CD patients will be randomly assigned to the treatment groups by means of a computer-generated randomization list using interactive-response technology. The specifications for randomization will be under the responsibility and oversight of Teva Global Statistics.

The randomization list will be assigned to the relevant treatment groups through a qualified service provider, eg, via the Randomization and Trial Supply Management (RTSM) system. The generation of the randomization list and management of the RTSM system will be done by a qualified service provider under the oversight of the responsible function at Teva.

6.9. Maintenance of Randomization and Blinding

6.9.1. Maintenance of Randomization

Patient randomization codes will be securely maintained by the service provider contracted to generate the codes. At the time of analysis (interim analysis and after the end of study), after receiving unblinding request from Teva statistician, the service provider will provide the unblinded IMP assignment according to the processes defined in the relevant Standard Operating Procedure (SOP).

6.9.2. Blinding and Unblinding

Personnel who may be aware of IMP assignments will not be involved in the conduct of any study procedures or assessment of any adverse events.

The patients and the site will be blinded until all patients complete the study, and the database is locked for final analysis for both indications. The sponsor study team will be blinded to treatment assignment until the database is locked for analysis of each indication.

Details regarding unblinding of an independent Teva team while maintaining the blind of the study, in case the final analysis is conducted for one indication while the other indication is ongoing, will be provided in a separate unblinding charter.

Pharmacokinetic, PD and immunogenicity samples will be collected for bioanalysis during the study. Individuals responsible for sample bioanalysis and other responsible personnel may know who received test IMP and who received placebo IMP during the study. Personnel responsible for bioanalysis will be provided with the randomization code to facilitate the analysis. However, the personnel responsible for bioanalysis will not have access to clinical safety and efficacy data and will provide concentration data to other personnel in a manner that will not identify individual patients (ie, a dummy patient identifier will be linked to the concentration data of an individual patient).

In case of a serious adverse event, pregnancy, or in cases when knowledge of the IMP assignment is needed to make treatment decisions, the investigator may unblind the patient's IMP assignment as deemed necessary, mainly in emergency situations. Individual randomization codes, indicating the IMP assignment for each randomized patient, will be available to the investigator(s) or pharmacist(s) at the investigational center via the RTSM, both via telephone and internet. Breaking of the treatment code can always be performed by the investigator without prior approval by the sponsor; however, the sponsor should be notified following the breaking of the treatment code. The patient's IMP assignment should not be revealed to the sponsor.

When a blind is broken, the patient will be withdrawn from the study, and the event will be recorded on the CRF. The circumstances leading to the breaking of the code should be fully documented in the investigator's study files and in the patient's source documentation. Assignment of IMP should not be recorded in any study documents or source document.

For an adverse event defined as a suspected unexpected serious adverse reaction (SUSAR) (ie, reasonable possibility; see Section 8.1.6), Global Patient Safety and Pharmacovigilance (GPSP) may independently request that the blind code be broken (on a case-by-case basis) to comply with regulatory requirements. The report will be provided in an unblinded manner for regulatory submission. If this occurs, blinding will be maintained for the investigator and for other personnel involved in the conduct of the study, and analysis and reporting of the data.

Interim analyses as described in Section 10.13 will be performed throughout the study by unblinded analysis groups external to Teva and will be reviewed by an IDMC.

6.9.3. Independent Data Monitoring Committee

A single review committee (IDMC) will be established to monitor the study while it is ongoing, including periodic reviews of safety data, and pre-specified analyses of efficacy data, as described below.

- The IDMC will include 2 Clinicians (external to Teva) with expertise in IBD and 1 external Statistician. The names of the external IDMC members will be included in the IDMC charter.
- The role of the IDMC will be to periodically monitor unblinded safety data to ensure the safety of study patients as well as efficacy data for pre-specified interim analysis, and make recommendations on study conduct.

- There will be an independent (external to the sponsor and the study team) statistical reporting team that will perform the planned unblinded analyses of interim efficacy and safety data for the IDMC to review.

The IDMC charter will provide details regarding procedures to protect the scientific integrity of the trial, conduct of the interim analysis, dissemination of results, and decision criteria in addition to pre-specified study stopping rules for safety.

Additional details on the procedures and conduct of the IDMC sessions will be described in the IDMC charter.

6.10. Total Blood Volume

The estimated maximum blood volume to be collected in this study is approximately 280 mL for each patient during the entire study. Details on blood volumes to be collected during the study are provided in the ICF and the Laboratory Manual.

7. ASSESSMENT OF EFFICACY

7.1. Assessments of Efficacy

The following efficacy assessments will be performed at the time points specified in Table 1. Endoscopy and histology assessments will be scored centrally.

7.1.1. Modified Mayo Score (Ulcerative Colitis)

The modified Mayo score evaluates UC stage based on the following 3 parameters:

- stool frequency
- rectal bleeding
- endoscopic evaluation

Each parameter of the score ranges from 0 (normal or inactive disease) to 3 (severe activity) and the total score from 0 to 9, respectively (Ulcerative Colitis: Clinical Trial Endpoints Guidance for Industry 2016, Naegeli et al 2018).

7.1.2. Endoscopy

Endoscopy will be performed at screening and week 14 or the early termination visit. Assessments and procedures performed during the endoscopy, including biopsy collection, SES-CD, and modified multiplier (MM)-SES-CD, are described below.

7.1.2.1. Biopsy Collection

For patients with CD, an ileo-colonoscopy will be performed at screening and week 14. During each endoscopy, a total of 11 to 18 mucosal biopsies will be obtained from the area with the greatest inflammation in each segment at screening and at the same location at week 14 or early termination. If ulceration is present, biopsies should be taken from the edge of the largest ulcer. If no ulceration is present, then biopsies should be taken from the most affected area of the segment. If the mucosa appears normal (eg, at follow-up), then random biopsies of the segment should be obtained.

For patients with UC, a flexible sigmoidoscopy will be performed at screening and week 14 (colonoscopy may be performed instead for baseline endoscopy if not done in the prior 12 months). During each endoscopy, a total of 7 to 12 biopsies will be obtained from the area with the worst disease 15 to 25 cm from the anal verge. If ulceration is present, biopsies should be taken from the edge of the largest ulcer. If no ulceration is present, then biopsy should be taken from the most affected area. If mucosa appears normal (eg, at follow-up), then random biopsies should be taken from the area 15 to 25 cm from the anal verge.

Endoscopic biopsies and will be evaluated by microscopic and histologic analyses, as well as for exploratory measures involving established and novel biomarkers of intestinal inflammation and fibrosis. There are several different approaches for obtaining these endoscopic biopsy samples, and the preferred procedures are described in the Laboratory Manual and Quick Reference Card.

Histology samples will be scored by qualified independent, blinded central readers and digitized to enable the use of digital pathology for histology endpoints adjudication and computational quantification of inflammation and fibrosis severity. Details of adjudication strategies will provided in the associated charter.

7.1.2.2.Simple Endoscopic Score for Crohn's Disease

The SES-CD takes into account 4 parameters (presence of ulcers, percentage of ulcerated surfaces, affected surface, and presence of strictures) that need to be scored in 5 bowel segments (the rectum, sigmoid and left colon, transverse colon, right colon, and ileum) (Daperno et al 2004).

7.1.2.3.Modified Multiplier-Simple Endoscopic Score for Crohn's Disease

The MM-SES-CD is an endoscopic scoring tool, which takes into consideration each individual parameter's prognostic value for achieving endoscopic remission while on active therapy (Narula et al 2021).

7.1.2.4.Robarts Histopathology Index (Ulcerative Colitis)

The Robarts Histopathology Index (RHI) final score is obtained by combining the subscores of 4 main items:

- chronic inflammatory infiltrate level (4 levels)
- lamina propria neutrophils (4 levels)
- neutrophils in the epithelium (4 levels)
- erosion or ulceration (4 levels)

The 4 components are classified from 0 to 3, yielding a final score that ranges between 0 and 33 (Mosli et al 2017).

7.1.2.5.Geboes Score (Ulcerative Colitis)

Geboes score is a scoring system for microscopic disease activity that incorporates a number of histological items classified in 5 grades (Mosli et al 2014).

7.1.2.6.Global Histologic Activity Score (Crohn's Disease)

The Global Histologic Activity Score consists of 8 items assessing acute and chronic inflammatory changes, epithelial damage, and the extent of inflammation (ie, the proportion of biopsy specimens affected). Each of the 8 items is scored, with the totals subsequently added together (D'Haens et al 1998).

7.1.3. Crohn's Disease Activity Index

The CDAI (Yoshida 1999) consists of 8 factors added up after adjustment with a weighting factor:

- Number of liquid or soft stools each day for 7 days × 2
- Abdominal pain (graded from 0 to 3 on severity) each day for 7 days × 5

- General well-being, subjectively assessed from 0 (well) to 4 (terrible) each day for 7 days × 7
- Presence of complications × 20
- Taking Lomotil, Imodium, or opiates for diarrhea × 30
- Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite) × 10
- Hematocrit of <0.47 in men and <0.42 in women × 6
- Percentage deviation from standard weight × 1

7.1.4. Two-item Patient-Reported Outcome (Ulcerative Colitis and Crohn's Disease)

UC: The 2-item patient-reported outcome (PRO2) includes daily evaluation of the 2 subjected items of the Mayo score: stool frequency and rectal bleeding. Each parameter of the score ranges from 0 (normal or inactive disease) to 3 (severe activity) and the total score from 0 to 6, respectively (Dragasevic et al 2020, Jairath et al 2015).

CD: PRO2 is the sum of the daily stool frequency (0 to 3) and abdominal pain (0 to 3) from the CDAI (Khanna et al 2015).

8. ASSESSMENT OF SAFETY

In this study, safety will be assessed by qualified study personnel by evaluating reported adverse events, clinical laboratory test results, vital signs measurements, ECG findings, use of concomitant medication, local tolerability, and device-related adverse events and malfunctions.

Device deficiencies that are not associated with an adverse event, as well as those that have the potential to cause a serious adverse event, are covered in Appendix G.

There will be an IDMC to monitor safety in this study (Section 6.9.3).

8.1. Adverse Events and Adverse Device Effects

8.1.1. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or significant worsening of the disease under study, or of any concurrent disease, whether or not considered related to TEV-48574.

Accordingly, an adverse event can include any of the following:

- a new condition or the worsening of a pre-existing condition
- intercurrent illnesses
- physical injuries and the mechanism that caused the injury
- events possibly related to concomitant medication
- drug or drug/device or device/device interactions
- events occurring during diagnostic procedures or during any washout phase of this study
- laboratory or diagnostic test abnormalities

(Note: Abnormal laboratory or diagnostic test results at the screening visit that preclude a patient from entering the study or receiving study treatment are not considered adverse events.)

IBD manifestations are efficacy variables for this study and should be captured on the relevant specific CRF; accordingly, these events should not be recorded as adverse events unless assessed as more severe than the patient's usual disease course. Extraintestinal manifestations of the patient's disease (eg, arthralgias, arthritis, or uveitis) that develop or worsen during the study should be reported as adverse events. IBD manifestations that are more severe than the patient's usual course of disease and meet the criteria for a serious adverse event (eg, required hospitalization) should be reported as a serious adverse event.

8.1.2. Definition of an Adverse Device Effect

An adverse device effect is an adverse event related to the use of an investigational medical device or a combination product. This includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, or any malfunction of the investigational medical device, including any event resulting from user error or from intentional misuse of the investigational medical device. This definition includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices.

8.1.3. Recording and Reporting of Adverse Events

For recording of adverse event, the study period is defined for each patient as the time period from signature of the ICF to the end of study (ie, patient's last visit). Treatment-emergent adverse events are defined as adverse events that occurred after the first dose of IMP and/or device was administered through the end of the study.

All adverse events that occur during the defined study period must be recorded both on the source documentation and the CRF, regardless of the severity of the event or judged relationship to the IMP and/or device. For serious adverse events and PDAESI for expedited reporting to GPSP, the serious adverse event and PDAESI form must be completed and the serious adverse event and the PDAESI must be reported immediately (Section 8.1.8.1). The investigator does not need to actively monitor patients for new adverse events after the end of the study.

At each contact with the patient, the investigator or designee must question the patient about adverse events by asking an open-ended question such as "Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe." All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single diagnosis on the CRF and, if it is a serious adverse event or PDAESI for expedited reporting to GPSP, on the serious adverse event and PDAESI form.

The clinical course of each adverse event will be monitored at suitable intervals until resolved, stabilized, or returned to baseline; or until the patient is referred for continued care to a health care professional; or until a determination of a cause unrelated to the IMP and/or device or study procedure is made.

The onset and end dates, duration (in case of adverse event duration of less than 24 hours), action taken regarding IMP and/or device, treatment administered, and outcome for each adverse event must be recorded both on the source documentation and the CRF.

The relationship of each adverse event to IMP (including to the device, if applicable), and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described below in Section 8.1.5.

Further details are given in the Safety Monitoring Plan.

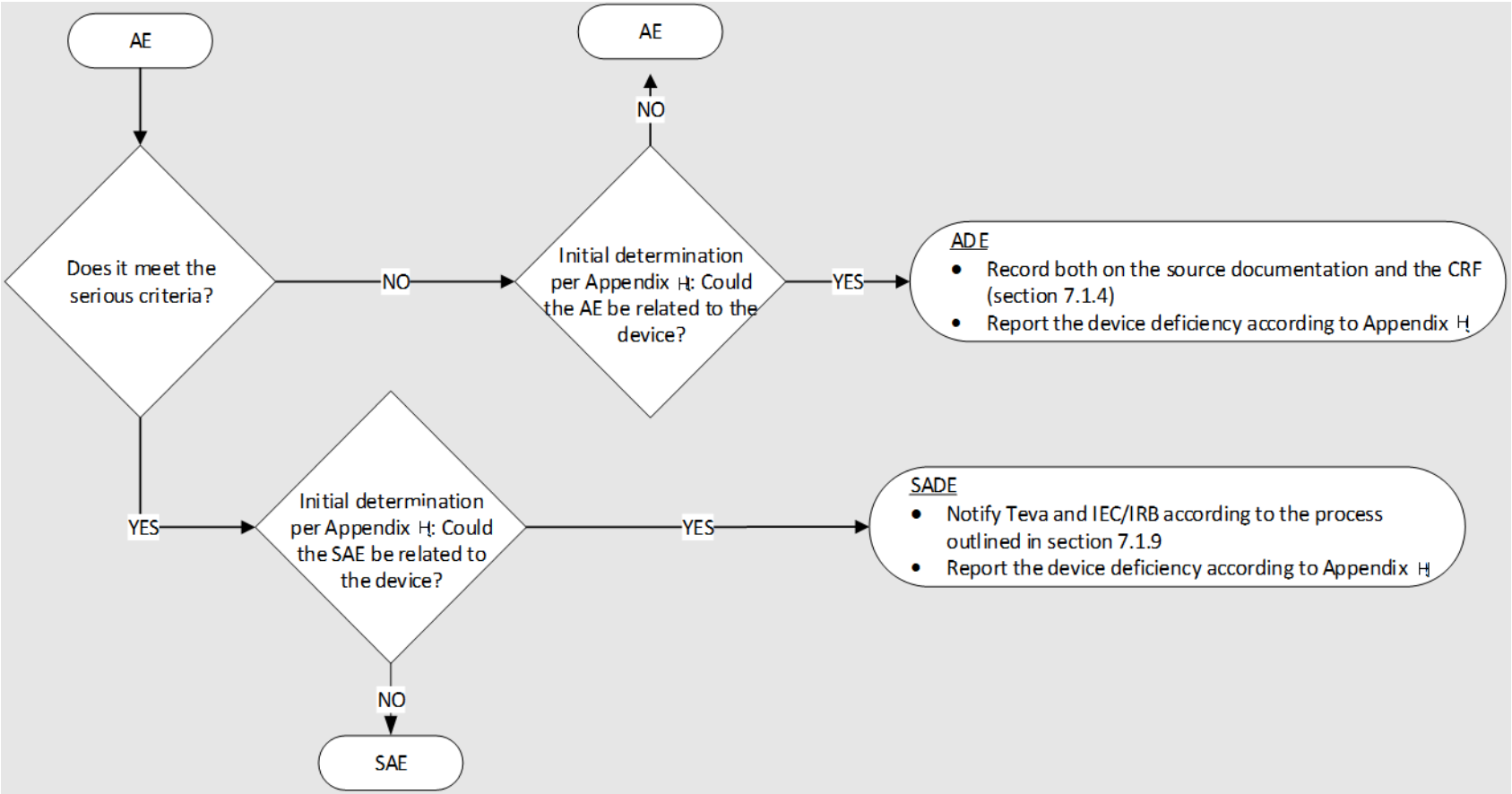
8.1.4. Recording and Reporting of Adverse Device Effect

Adverse device effects (Figure 3) must be recorded on both the source documentation and the CRF.

The investigator and sponsor will record all relevant information regarding every adverse device effect/serious adverse device effect and device deficiency.

The investigator should make an initial determination whether the adverse event may be related to a device deficiency.

Figure 3: Decision Tree for Adverse Events and Adverse Device Effects Classification



ADE=adverse device effect; AE=adverse event; CRF=case report form; IEC=Independent Ethics Committee; IRB=Institutional Review Board; SADE=serious adverse device effect; SAE=serious adverse event.

8.1.5. Severity of an Adverse Event

The severity of each adverse event must be recorded. The adverse event severity grading scale for the current version of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; version 5) will be used for assessing adverse event severity. Table 4 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 4: 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; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; 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; limiting self-care activities of daily living. [a,b]
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to adverse event (AE).

[a] Instrumental activities of daily living refer to 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 patients who are not bedridden.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

8.1.6. Relationship of an Adverse Event to the Investigational Medicinal Product and/or Device

The relationship of an adverse event to the IMP and/or device is characterized as follows:

Table 5: The Relationship of an Adverse Event to the Investigational Medicinal Product and/or Device

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events that, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to adverse events that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the IMP and/or device.	The relationship of an adverse event may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least 2 of the following apply: • It does not follow a reasonable temporal sequence from the administration of the IMP and/or device. • It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It does not follow a known pattern of response to the IMP and/or device. • It does not reappear or worsen when the IMP and/or device is re-administered.
Reasonable possibility (related)	This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the administration of IMP and/or device cannot be ruled out with certainty.	The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply: • It follows a reasonable temporal sequence from administration of the IMP and/or device. • It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear after discontinuation of the IMP and/or device, yet an IMP and/or device relationship clearly exists. • It follows a known pattern of response to the IMP and/or device.

IMP=investigational medicinal product.

8.1.7. Serious Adverse Events and Serious Adverse Device Effects

For recording of a serious adverse event or serious adverse device effect, the study period is defined for each patient as that time period from signature of the ICF to the end of study (ie, patient's last visit). Serious adverse events or serious adverse device effects occurring in a patient after the end of study for that patient (ie, patient's last visit) should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 8.1.8.1.

8.1.7.1. Definition of a Serious Adverse Event

A serious adverse event is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- results in death

- is a life-threatening adverse event (ie, the patient was at risk of death at the time of the event); it does not refer to an event which hypothetically might have caused death if it were more severe
- requires inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission or prolongation of hospital stay was required for treatment of an adverse event, or that they occurred as a consequence of the event.

  Hospitalizations scheduled before the patient signed the ICF will not be considered serious adverse events unless there was worsening of the pre-existing condition during the patient's participation in this study.
- results in persistent or significant disability/incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- is a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent 1 of the outcomes listed in this definition.

  Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or liver injury that meets the criteria for Hy's law; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious adverse event.

8.1.7.2.Definition of a Serious Adverse Device Effect

A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event (Section 8.1.7.1).

8.1.7.3.Expectedness

In this study, the reference safety information for determination of expectedness of suspected serious adverse reaction is included in the IB. A serious adverse event that is not included in the relevant reference safety information by its specificity, severity, outcome, or frequency is considered an unexpected adverse event.

The sponsor's Pharmacovigilance Department will determine the expectedness for all serious adverse events.

For the purpose of SUSAR reporting, the version of the IB at the time of occurrence of the SUSAR applies.

8.1.8. Reporting a Serious Adverse Event

8.1.8.1. Investigator Responsibility

To satisfy regulatory requirements, all serious adverse events that occur during the study, regardless of judged relationship to administration of the IMP, must be reported to the sponsor by the investigator. The event must be reported within 24 hours of when the investigator learns about it. Completing the serious adverse event form and reporting the event must not be delayed, even if not all the information is available. The investigator does not need to actively monitor patients for new adverse events once this study has ended.

Serious adverse events occurring after the patient has ended the study should be reported to the sponsor if the investigator becomes aware of them.

The serious adverse event form should be sent to the local safety officer (LSO) or designee (as applicable, for example, a contract research organization [CRO] in a country without a sponsor LSO); the LSO will forward the report to the sponsor's GPSP.

The following information should be provided to record the event accurately and completely:

- study number
- investigator and investigational center identification
- patient number
- onset date and detailed description of adverse event
- investigator's assessment of the relationship of the adverse event to the IMP (no reasonable possibility, reasonable possibility)

Additional information includes:

- age and sex of patient
- date of first dose of IMP
- date and amount of last administered dose of IMP
- action taken
- outcome, if known
- severity
- explanation of assessment of relatedness
- concomitant medication (including doses, routes of administration, and regimens) and treatment of the event
- pertinent laboratory or other diagnostic test data
- medical history
- results of dechallenge/rechallenge, if known
- for an adverse event resulting in death

- cause of death (whether or not the death was related to IMP)
- autopsy findings (if available)

Each report of a serious adverse event will be reviewed and evaluated by the investigator and the sponsor to assess the nature of the event and the relationship of the event to the IMP, study procedures, and to underlying disease.

Additional information (follow-up) about any serious adverse event unavailable at the initial reporting should be forwarded by the investigator within 24 hours of when it becomes known to the same address as the initial report.

For all countries, the sponsor's GPSP will distribute the Council for International Organizations of Medical Sciences (CIOMS) form and/or Extensible Markup Language (XML) file to the LSO/CRO for local submission to the competent authorities, IEC/IRBs, and investigators, according to regulations. For studies in the European Economic Area, submission of SUSARs is done electronically to the EudraVigilance database (via EVWEB or by electronically using the E2B(R3) electronic ICSR form) by the GPSP. The investigator must ensure that the IEC/IRB is also informed of the event, in accordance with national and local regulations.

Blinding will be maintained for all study personnel. Therefore, in case of a SUSAR, only the LSO/CRO unblinded personnel will receive the unblinded report for regulatory submission; the others will receive a blinded report.

8.1.8.2.Sponsor Responsibility

If a serious unexpected adverse event is believed to be related to the IMP (ie, Suspected Unexpected Serious Adverse Drug Reaction, SUSAR), the sponsor will take appropriate steps to notify all investigators participating in sponsored clinical studies of TEV-48574 and the appropriate competent authorities (and IEC/IRB, as appropriate).

In addition to notifying the investigators and competent authorities (and IEC/IRB, as appropriate), other action may be required, including the following:

- modifying the protocol and/or ICF
- discontinuing or suspending the study
- modifying listings of expected toxicities to include adverse events newly identified as related to TEV-48574

8.1.9. Reporting a Serious Adverse Device Effect

The process and contact details for serious adverse device effect reporting are the same as for serious adverse event reporting provided in Section 8.1.8.

Events shall be reported to the IEC/IRB by the investigator and to the regulatory authorities by the sponsor using the appropriate form according to national and local regulations.

The investigator should use Appendix G to make an initial determination whether the serious adverse event may be related to a device deficiency.

8.1.10. Protocol-Defined Adverse Events of Special Interest

Adverse events of special interest (AESIs)—which are not necessarily adverse drug reactions (ADRs) but are of special interest based on standard drug registration topics, safety findings from previous studies, potential risks associated with biologic immunomodulators, are listed below.

8.1.10.1. Protocol-Defined Adverse Events of Special Interest that Require Reporting to Sponsor's Global Patient Safety and Pharmacovigilance

For purposes of this protocol, the following are considered protocol-defined adverse events of special interest to be sent to the sponsor's GPSP for evaluation:

- systemic severe reactions (including anaphylaxis)
- opportunistic or severe and/or serious infections
- malignancies (including non-melanoma skin cancer)
- liver injury
- severe hematology abnormalities

The process for reporting a protocol-defined adverse event of special interest is the same as that for reporting a serious adverse event (Section 8.1.8). Protocol-defined adverse events of special interest to be reported to GPSP can be either serious or nonserious, according to the criteria outlined in Section 8.1.7.1. Protocol-defined adverse events of special interest that occur before study drug administration and are not serious do not require reporting to GPSP.

Systemic severe reactions (including anaphylaxis)

In the event of suspected anaphylaxis while the patient is at the site, vital signs, including blood pressure, oxygen saturation, and respiration rate, should be measured. Blood samples to test TEV-48574 serum concentration, ADA, and free and total serum TL1A levels should be collected if possible. Collection of blood samples to test tryptase and/or histamine levels are encouraged if available locally at the time of the suspected hypersensitivity event. Other assessments may be performed at the discretion of the investigator. As a precaution, each site should have a resuscitation medication/equipment nearby. If a patient has symptoms of anaphylaxis or severe hypersensitivity, the administration of study drug must be discontinued permanently. In addition, information about all suspected anaphylaxis and hypersensitivity events will be recorded on the Suspected Anaphylaxis CRF, which is based on the 2006 Joint National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network Second Symposium on Anaphylaxis (Sampson et al 2006). These events should be reported to the Sponsor immediately (ie, no more than 24 hours after learning of the event).

Opportunistic or severe and/or serious infections

In the event of opportunistic or severe infections (CTCAE grade 3 to 4), the patient should not receive further study drug until the event has completely resolved. Study drug will be permanently stopped in case of infections following stopping criteria (see Section 4.4.1). Study drug may be restarted following consultation with the Medical Monitor. Treatment of infections should be initiated promptly according to standard of care and all efforts should be made to identify the infectious agent. Events should be reported to the Sponsor immediately (ie, no more

than 24 hours after learning of the event). Examples for opportunistic infections are included in Appendix J.

Malignancies

Any signs or symptoms that could be suggestive of malignancy should be promptly and aggressively evaluated. Patients who develop a malignancy (with the exception of an appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix) should be withdrawn from study drug and must not receive additional doses of study drug. Malignancies should be reported to the Sponsor immediately (ie, no more than 24 hours after learning of the event).

Liver injury

If any of the following criteria occur, study drug should be withheld and additional monitoring and follow-up assessment will be required (as detailed in the Liver Safety Required Actions and Follow-up Assessments section in Appendix K):

- ALT or AST ≥5x ULN
- ALT or AST ≥3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- AST and/or ALT ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample or in combination with clinical jaundice or INR>1.5 (not applicable for patients on anticoagulants)

The additional information will be recorded on the Liver Event CRF.

The most appropriate diagnosis or the abnormal laboratory values (if a diagnosis cannot be established) should be recorded on the Adverse Event eCRF (see Section 8.1.3) and reported to the Sponsor immediately (ie, no more than 24 hours after learning of the event).

Severe hematology abnormalities

Predefined confirmed hematology stopping criteria (see Section 4.4.1) should be re-tested every 3 to 5 days until values have returned to above the hematological exclusion criteria threshold, at which point dosing can be resumed (however, two consecutive doses of IMP, should never be given less than 7 days apart).

8.1.10.2. Protocol-Defined Adverse Events of Special Interest that Do Not Require Reporting to Sponsor's Global Patient Safety and Pharmacovigilance

The following are considered protocol-defined adverse events of special interest that do not need to be sent to the sponsor's GPSP department (unless assessed as serious) and will be recorded only in the clinical database:

- administration site reactions (as described in Section 8.2)

8.1.11. Protocol Deviations Because of an Adverse Event

If a patient experiences an adverse event or medical emergency, deviations from the protocol may be allowed on a case-by-case basis. To ensure patient safety, after the event has stabilized or treatment has been administered (or both), the investigator or other physician in attendance must

contact the physician identified in the Clinical Study Personnel Contact Information section of this protocol as soon as possible to discuss the situation. The investigator, in consultation with the sponsor, will decide whether the patient should continue to participate in the study.

8.2. Assessment of Local Tolerability and Pain

Local tolerability assessments should be performed at each administration of IMP (Table 1) and include administration site findings and pain. Administration site findings (erythema, ecchymosis, induration, tenderness, warmth, and swelling) will be assessed using the scales provided in Table 6. Pain at the administration site will be reported using a standardized 11-point numeric rating scale (NRS-11) for pain intensity, where 0 is "No pain" and 10 is "Worst possible pain." Patients will be asked to respond to the following question: "How much pain do you feel at the drug injection site?"

Pain will be assessed beginning, during (approximately midway through the infusion), and after the completion of IMP administration and 1 hour later. Administration site findings will be assessed after the completion of IMP administration and 1 hour later. Additionally, after the loading dose and first induction dose, assessments will also be performed 2 hours after the completion of IMP administration. Allowed time windows for the local tolerability assessments after the completion of the infusion are ±15 minutes.

Severity of local tolerability symptoms should be assessed as described in Table 6. The surface diameter in millimeters should be recorded, and erythema, induration, and ecchymosis at the administration site will be graded according to the diameter measurements: absent, 5 mm to ≤50 mm (mild), >50 to ≤100 mm (moderate), and >100 mm (severe). Erythema, ecchymosis, and induration under 5 mm in diameter should be assessed as absent. Care should be taken to avoid pressuring or squeezing the administration site while assessing induration via careful superficial palpation.

In the case that findings do not resolve while the patient remains at the study center, additional evaluation should take place thereafter at each visit until resolution occurs. Administration sites may be photographed, including between visits to the study center, to provide visual representation in addition to comments in the source documents. Any features that could be used to identify the patient will not be captured on the photograph. Appropriate treatment for administration site finding or pain may be provided if necessary, in which case such treatments must be recorded as concomitant medication(s).

Table 6: Administration Site Finding Severity Assessment

Test	Response
Erythema	- Absent - Erythema surface diameter 5 to ≤50 mm (mild) - Erythema surface diameter >50 to ≤100 mm (moderate) - Erythema surface diameter >100 mm (severe)
Ecchymosis	- Absent - Ecchymosis surface diameter 5 to ≤50 mm (mild) - Ecchymosis surface diameter >50 to ≤100 mm (moderate) - Ecchymosis surface diameter >100 mm (severe)
Induration	- Absent - Induration surface diameter 5 to ≤50 mm (mild) - Induration surface diameter >50 to ≤100 mm (moderate) - Induration surface diameter >100 mm (severe)
Tenderness Warmth Swelling	- None - Mild - Moderate - Severe

Administration site findings described in Table 6 and administration site pain will be recorded on specified CRF and will not require additional recording in the adverse events form. Administration site findings with characteristics that are not described in Table 6 (eg, lipoatrophy, necrosis, abscess) or fulfill seriousness criteria must be recorded and reported as adverse events or serious adverse events as specified in Section 8.1.3 and Section 8.1.8.

8.3. Pregnancy

Any female patient becoming pregnant during the screening period will be considered a screen failure and will not be allowed to rescreen.

Any female patient becoming pregnant during the study will discontinue IMP.

All pregnancies of women participating in the study and female partners of men participating in the study, if applicable, that occur during the study, or within 5 half-lives (50 days) of the last IMP administration, are to be reported immediately to the individual identified in the Clinical Study Personnel Contact Information section of this protocol, and the investigator must provide the sponsor (LSO/CRO) with the completed pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event but using the pregnancy form (Section 8.1.8).

All female patients and female partners of men participating in the study (female partners of men participating in the study who become pregnant will be asked to sign an ICF) who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous, elective, or voluntary abortion). If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the sponsor. Any

complication of pregnancy during the study and any complication of pregnancy that the investigator becomes aware of after withdrawal from the study will be reported as an adverse event or serious adverse event, as appropriate.

If the pregnancy in the woman participating in the study and/or the female partners of men participating in the study does not continue to term, 1 of the following actions will be taken:

- For a spontaneous abortion, report as a serious adverse event (in addition to the pregnancy form).
- For an elective abortion due to developmental anomalies, report as a serious adverse event (in addition to the pregnancy form).
- For an elective abortion **not** due to developmental anomalies, report on the pregnancy form; do not report as an adverse event.

8.4. Medication Error and Special Situations Related to the Investigational Medicinal Products

Any administration of IMP that is not in accordance with the study protocol should be reported in the patients' source documents, regardless of whether or not an adverse event occurs as a result. When meeting important protocol deviation criteria (Appendix B), all instances of incorrect IMP administration should be categorized as "Noncompliance to Investigational Medicinal Product (IMP)."

The following are types of medication errors and special situations:

1. Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer.
2. Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorized product information/study protocol. Clinical judgment should always be applied. Any dose of IMP (whether the test IMP or placebo IMP), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor.
3. Misuse: Situations where the IMP is intentionally and inappropriately used not in accordance with the authorized product information/study protocol.
4. Abuse: Persistent or sporadic, intentional excessive use of IMP, which is accompanied by harmful physical or psychological effects.
5. Off-label use: Situations where an IMP is intentionally used for a medical purpose not in accordance with the authorized product information/study protocol.
6. Occupational exposure: Exposure to an IMP, as a result of one's professional or non-professional occupation.
7. Breastfeeding: Suspected adverse reactions, which occur in infants following exposure to a medicinal product from breast milk.

8.5. Clinical Laboratory Tests

All clinical laboratory test results outside of the reference range will be judged by the investigator as belonging to 1 of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

A laboratory test result that is judged by the investigator as clinically significant will be recorded both on the source documentation and the CRF as an adverse event and monitored as described in Section 8.1.3. A laboratory or diagnostic test abnormality (once confirmed by repeated testing) that results in the withdrawal of the patient from the study; the temporary or permanent withdrawal of IMP or medical treatment, or further diagnostic work-up may be considered adverse events. If further diagnostic work-up of abnormal laboratory result leads to the investigator concluding that the initial abnormality was not clinically significant, it is at the investigator's discretion whether or not the laboratory result triggering the work-up is an adverse event. (Note: Abnormal laboratory or diagnostic test results at the screening visit(s) that preclude a patient from entering the study or receiving IMP are not considered adverse events.)

Table 7: Clinical Laboratory Tests

Serum Chemistry	**Hematology and Coagulation**[a]	**Urinalysis**
Calcium Phosphate Sodium Potassium Chloride Creatinine Glucose Blood urea nitrogen (BUN) Low density lipoprotein (LDL)[b] High density lipoprotein (HDL)[b] Triglycerides[b] Urate Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Lactate dehydrogenase (LDH) Gamma-glutamyl transpeptidase (GGT) Alkaline phosphatase Bicarbonate Protein Albumin Total bilirubin[c]	Hemoglobin Hematocrit Erythrocytes Platelets Leucocytes • Neutrophils • Lymphocytes • Eosinophils • Monocytes • Basophils Prothrombin International Normalized Ratio (INR) Prothrombin time (PT) Partial thromboplastin time (PTT)	Protein Glucose Ketones Hemoglobin pH Specific gravity Microscopic tests • Bacteria • Erythrocytes • Leucocytes • Crystals • Casts

[a] Coagulation tests will be performed at screening only. INR will be tested in case of a suspected liver injury (see Appendix K)

[b] Only measured at the screening, week 14, and early termination visits (ie, visits at which patients are in a fasting state).

[c] Direct and indirect bilirubin will be measured if total bilirubin is elevated.

8.5.1. Serum Chemistry, Hematology, and Urinalysis

Clinical laboratory tests (serum chemistry, hematology and coagulation, urinalysis) will be performed at the time points detailed in Table 1. Patients should be fasting for at least 8 hours prior to safety laboratory assessments only at the screening, week 14, and early termination visits. Clinical laboratory tests will be performed using the central laboratory. Local laboratory testing can be used under extenuating circumstances and only following agreement with the sponsor.

Screening laboratory test abnormalities, if considered by the Investigator to be transient and inconsistent with the patient's clinical condition, may be repeated once during the screening period for confirmation. Redrawing samples if previous samples were unable to be analyzed would not count as a retest since previous result was never obtained.

8.5.2. Other Clinical Laboratory Tests

At screening, patients will be tested for HBcAb and HBsAg, antibodies to hepatitis C virus (reflex viral RNA testing if hepatitis C antibodies present), human immunodeficiency virus types 1 or 2, and enteric pathogens (including stool culture and *Clostridium difficile* toxin assay; additional testing [eg, ova and parasites] may be performed at the investigator's clinical discretion).

If HBcAb is positive and HBsAg negative, hepatitis B viral DNA will be done as reflective test, and, if undetectable, then not exclusionary.

Patients will also be tested for TB at screening (QuantiFERON® TB Gold Test). Patients with confirmed positive results will not be eligible to participate in the study (unless documentation of prior TB treatment is available).

If the QuantiFERON® TB Gold Test is negative at screening, then the patient may proceed in the screening period. However, if the QuantiFERON® TB Gold Test is deemed by the principal investigator to be a false positive at screening, then a second sample should be drawn and the following steps taken:

- If the second QuantiFERON® TB Gold Test is positive (ie, results match the first test), then the patient will be a screen failure.
- If the second QuantiFERON® TB Gold Test is negative (ie, results do not match the first test), then a third sample should be drawn.
  - If the third QuantiFERON® TB Gold Test is positive (ie, results match the first test), then the patient will be a screen failure.
  - If the third QuantiFERON® TB Gold Test is negative (ie, results match the second test), then the patient may proceed in the screening period.

In case of a suspected liver injury, additional laboratory tests will be required (see Appendix K).

8.5.2.1.Human Chorionic Gonadotropin Tests

HCG tests in serum and in urine will be performed for women of childbearing potential at the time points detailed in Table 1.

8.5.2.2.Follicle-Stimulating Hormone

At screening, women who have been amenorrheic for at least 1 year without an alternative medical cause will have a serum FSH assessment to confirm postmenopausal status (an increased concentration of FSH of more than 35 IU/L in women not using hormonal contraception or hormonal replacement therapy).

8.6. Physical Examinations

Physical examinations will be performed at the time points detailed in Table 1. Any physical examination finding that is judged by the investigator as clinically significant (except at the initial screening visit, which will be captured as medical history) may be considered an adverse event, recorded on the CRF, and monitored as described in Section 8.1.3. Physical exam findings that are attributable to another adverse event would not be reported as separate adverse events.

A full physical examination will include at a minimum the following organ systems:

- General appearance
- Head, eyes, ears, nose, mouth, and throat
- Chest and lungs
- Heart
- Abdomen
- Musculoskeletal
- Skin
- Extremities
- Lymph nodes
- Neurological

Height and weight will be obtained at the at the time points detailed in Table 1.

A brief physical examination will include at a minimum general appearance; head, eyes, ears, nose, mouth, and throat; chest and lung; heart and extremities (including pulses).

8.7. Vital Signs

Vital signs (blood pressure [systolic/diastolic], respiratory rate, body temperature, and pulse rate) will be measured at the time points detailed in Table 1. Patients are to remain in a supine position for at least 5 minutes prior to measuring blood pressure and pulse rate. If possible, blood pressure measurements should be completed on the same arm at each visit. All vital signs results outside of the reference ranges will be judged by the investigator as belonging to 1 of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

For any abnormal vital sign value, the measurement should be repeated as soon as possible. Any vital sign value that is judged by the investigator as clinically significant will be recorded both on the source documentation and the CRF as an adverse event and monitored as described in Section 8.1.3.

8.8. Electrocardiography

A 12-lead ECG will be recorded at the time points detailed in Table 1. ECGs should be performed in a supine position after 5 minutes rest.

ECG review and assessment will be done both by the investigators and by a centralized ECG reading vendor.

All ECG results outside of the reference ranges will be judged by the investigator as belonging to 1 of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

Any ECG finding that is judged by the investigator as clinically significant (except at the screening visit[s]) will be considered an adverse event, recorded on the source documentation and in the CRF, and monitored as described in Section 8.1.3.

Where triplicate measurements are required (at screening), each ECG will be taken within 1 to 5 minutes of the previous one.

9. ASSESSMENT OF PHARMACOKINETICS/ PHARMACODYNAMICS/BIOMARKERS/ PHARMACOGENETICS/IMMUNOGENICITY

9.1. Pharmacokinetic Assessment

Blood samples will be collected via venipuncture at the time points detailed in Table 1 for measurements of serum concentration of TEV-48574. At visits where IMP is administered, samples should be taken prior to IMP administration (ie, trough levels).

Additionally, efforts should be made to determine serum concentration of TEV-48574 in cases of suspected severe, systemic hypersensitivity reaction, or anaphylaxis; serious adverse event; or immunogenicity-related adverse events.

The dates and times of IMP administration and the date and time point (24-hour clock time) of each pharmacokinetic sample will be recorded both on the source documentation and the CRF.

Samples will be analyzed for concentration of TEV-48574 using an appropriate validated method. Incurred sample reanalysis may be performed. Blood samples from patients who received placebo will not be analyzed.

Blood volumes are provided in the ICF and Laboratory Manual. Details on sample handling, storage, shipment, and analysis are provided in the Laboratory Manual.

9.2. Pharmacodynamics Assessment

All PD potential parameters tested in this study are exploratory markers and are described in Section 9.4.

9.3. Immunogenicity Testing

Blood samples for ADA testing will be collected via venipuncture at the time points detailed in Table 1. Details on sample handling, storage, shipment, and analysis are provided in the Laboratory Manual.

Additionally, efforts should be made to collect ADA samples in cases of suspected severe, systemic hypersensitivity reaction, or anaphylaxis; serious adverse event; or immunogenicity-related adverse events. In cases of suspected or confirmed anaphylaxis, efforts should be made to collect samples as close to the onset of the event as possible, at resolution, and 30 days after onset of the event. Antibodies to TEV-48574 will be evaluated in serum samples. All samples collected for detection of antibodies to TEV-48574 may also be evaluated for TEV-48574 serum concentration to facilitate interpretation of the antibody data. Confirmed ADA positive samples may be further evaluated for TEV-48574 neutralizing antibodies.

The dates and times of IMP administration and the date and time point of each immunogenicity sample will be recorded both on the source documentation and the CRF.

The detection and characterization of antibodies to TEV-48574 will be performed using validated assay methods. Blood samples from patients who received placebo will not be analyzed by the ADA assay.

A patient will be classified as having a treatment-emergent ADA response if either: 1) the patient had a positive sample at any of the time points after first dose of IMP but not at the time point before first dose of IMP, or 2) the patient had positive samples before first dose of IMP and 1 or more time points after first dose of IMP, with at least a 4-fold increase in titers after first dose relative to the sample ADA titers before first dose. Where possible, the impact of the presence of ADAs on pharmacokinetics and clinical safety will be evaluated.

Samples may be stored if permitted by the ICF and local regulations after the last patient's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to TEV-48574.

9.4. Assessment of Exploratory Biomarkers

Potential exploratory biomarker objectives include characterization of TEV-48574 responders, identification of tissue-, fecal-, and blood-based-resident proteomic or transcriptomic biomarkers indicative of TEV-48574 mechanism of action and PD, development of scalable tools to identify likely responders in future studies, and elucidation of TL1A-mediated pathway(s) that drive IBD in responders within the target patient population.

The following exploratory biomarker assessments will be pursued from samples collected at indicated time points (Table 1):

- Serum free and total TL1A levels will be measured using qualified/validated assay methods. Tissue TL1A protein expression will also be assessed.
- Serum proteomic markers assertive of PD and mechanism of action effects will be pursued by singleplex or multiplex assays. [redacted] will be collected and may be analyzed for evaluation of target engagement, PD, and mechanism of action.
- Serum level of autoantibodies involved in IBD, such as perinuclear antineutrophil cytoplasmic antibodies (pANCA) or anti-*Saccharomyces cerevisiae* antibodies (ASCA), could also be measured to test the correlation with the response to TEV-48574
- Serum and tissue markers of GI tissue condition (eg, fibrosis/remodeling) will be assessed by transcriptomic and/or specific proteomic assays.
- GI transcriptome will be assessed from biopsies by RNASeq to characterize TEV-48574-mediated responses or TEV-48574-responsive patients.
- Fecal calprotectin or other stool-derived markers as a tissue proximal marker of GI inflammation
- High sensitivity C-reactive protein (hsCRP) as a peripheral marker of inflammation
- UC-100 score (1+16 × Mayo stool frequency subscore [0 to 3]+6 × Mayo endoscopic subscore [0 to 3]+1 × RHI score [0 to 33]); ranges from 1 (no disease activity) to 100 (severe disease activity) (Jairath et al 2019)

Details of the specimen collection, processing, and handling requirements are provided in the Laboratory Manual.

Residual biopsy, fecal, and blood samples, after appropriate analysis to support this study, may be stored at a Teva-secured facility for up to 15 years towards future analysis related to TEV-48574 or IBD if permitted by the ICF and local regulations.

Exploratory biomarker analyses may be presented in a separate analytical plan and report at the end of the study.

9.5. Pharmacogenetics

Pharmacogenetic analyses will be performed on samples of patients who signed the dedicated informed consent. The candidate genes that will be analyzed may be related or hypothesized to be related to pharmacokinetics, safety features, drug mechanism of action, or related to study diseases. The final list of genes to be evaluated will be determined at the time of analysis to be able to account for the most current research. The planned pharmacogenetic analysis and results of other potential genetic factors will be detailed in a separate document that will encompass the latest scientific advances related to this evaluation.

For information regarding pharmacogenetic assessments, see Appendix F.

10. STATISTICS

This section describes the statistical analysis methods for this study. Further details on analysis methods will be described in the Statistical Analysis Plan. Any changes or additions from the planned analysis methods described in the protocol will be disclosed in the Statistical Analysis Plan and in the clinical study report (CSR).

10.1. Sample Size and Power Considerations

A total study sample size of 240 patients is planned, with 120 patients (40 patients per dose arm) each for the 2 indications of UC and CD.

The sample size does not include patients that were randomized to the 1800 mg treatment group prior to Amendment 03 with Revision 01.

Assumptions:

The clinical remission and endoscopic response rates assumed in the sample size and related operating characteristics computations are as follows:

- Clinical remission rates in UC indication: 8% for placebo; 30% for TEV-48574 low- and high-dose groups, respectively
- Endoscopic response rates in CD indication: 12% for placebo; 34% for TEV-48574 low- and high-dose groups, respectively

Simulation-based operating characteristics for the analysis of the primary efficacy variable using a Bayesian Beta Binomial model are presented in Table 8. This model uses a posterior probability cutoff of <0.30 for the assessment of futility at the interim analysis and a posterior probability cutoff of ≥0.90 to declare success at the final analysis.

For UC, the family-wise false-positive rate (ie, probability of making at least 1 false-positive conclusion under the null assumption for both doses) is 13%, and the probability of declaring success for at least 1 dose group is 98%, under the assumptions above.

For CD, the family-wise false-positive rate is 16%, and the probability of declaring success for at least 1 dose is 95%, under the assumptions above.

Table 8: Operating Characteristics of Interim and Final Analysis

	UC						CD					
	% Futile at interim analysis			% Successful at end of trial			% Futile at interim analysis			% Successful at end of trial		
	TEV-48574 doses											
	450 mg Q2W	900 mg Q2W	Both Doses	450 mg Q2W	900 mg Q2W	At least 1 dose	450 mg Q2W	900 mg Q2W	Both Doses	450 mg Q2W	900 mg Q2W	At least 1 dose
Null	25%	24%	11%	8%	8%	13%	24%	24%	12%	9%	10%	16%

	UC						CD					
	% Futile at interim analysis			% Successful at end of trial			% Futile at interim analysis			% Successful at end of trial		
	TEV-48574 doses											
	450 mg Q2W	900 mg Q2W	Both Doses	450 mg Q2W	900 mg Q2W	At least 1 dose	450 mg Q2W	900 mg Q2W	Both Doses	450 mg Q2W	900 mg Q2W	At least 1 dose
Intermediate efficacy both doses	4%	4%	1%	61%	61%	77%	4%	4%	1%	59%	59%	76%
Efficacy both doses	1%	1%	<1%	91%	91%	98%	1%	1%	<1%	87%	87%	95%

CD=Crohn's disease; Q2W=every 2 weeks; UC=ulcerative colitis.
Note: Beta-Binomial model with non-informative prior; posterior probability futility cutoff: <0.30; final analysis posterior probability cutoff of ≥0.90.
Note: Operating characteristics based on 500,000 simulations.

Under a less optimistic scenario where the placebo response rates remain the same while the clinical remission rate in the UC indication is reduced to 20% for both doses, and the endoscopic response rate in the CD indication is reduced to 25% for both doses, the probability of declaring success in at least 1 dose is 77% for UC and 76% for CD.

Details regarding the statistical decision criteria and Bayesian model, as well as operating characteristics in case only 1 active dose is effective are provided in Appendix L.

For comparison, a frequentist logistic regression analysis with 40 patients per dose per indication would provide at least 90% power using a Mantel-Haenszel test with a 1-sided Type 1 error rate of 10% and the assumptions about response rate specified above. This power does not take into account the planned futility analysis.

10.2. Analysis Sets

10.2.1. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set for each indication (UC or CD) will include all randomized patients.

In the ITT analysis set, patients will be categorized by treatment to which patients were randomized, regardless of which treatment they actually received.

Data collected from patients after treatment discontinuation will be included in the ITT analysis set.

10.2.2. Modified Intent-to-Treat Analysis Set

The modified intent-to-treat (mITT) analysis set for each indication (UC or CD) is a subset of the ITT analysis set including only patients who receive at least 1 dose of placebo, TEV-48574 450 mg (low dose), or TEV-48574 900 mg (high dose).

In the mITT analysis set, patients will be categorized by treatment to which patients were randomized, regardless of which treatment they actually receive.

10.2.3. Safety Analysis Set

The safety analysis set for each indication (UC or CD) will include all randomized patients who receive at least 1 dose of IMP.

In the safety analysis set, patients will be categorized by treatment actually received, regardless of the treatment to which they were randomized, unless otherwise specified.

10.2.4. Pharmacokinetic Analysis Set

All patients in the safety analysis set who have at least 1 measurable concentration of TEV-48574 will be included in the pharmacokinetic analysis set.

10.2.5. Pharmacogenetic and Biomarker Analysis Set

All patients in the safety analysis set who provided consent for pharmacogenetic or biomarker sampling will be included in the analysis of pharmacogenetic or biomarker data.

10.2.6. Immunogenicity Analysis Set

The immunogenicity analysis set will include all patients in the safety set who receive TEV-48574 and who have at least 1 reportable immunogenicity result.

10.3. Data Handling Conventions

For all variables, only the observed data from the patients will be used in the statistical analyses; ie, there is no plan to estimate missing data, unless otherwise specified. Detailed data imputation rules will be described in the Statistical Analysis Plan.

10.3.1. Handling Withdrawals and Missing Data

The mITT analysis set will be used for efficacy analyses. UC patients who did not complete evaluation for clinical remission at week 14 will be reported as non-remitters. CD patients who did not complete evaluation for endoscopic response at week 14 will be reported as non-responders.

10.4. Study Population

The ITT analysis set (Section 10.2.1) will be used for all study population summaries. Summaries will be presented by treatment group, pooled TEV-48574, and all patients, separately by indication (UC or CD) and pooled (UC and CD).

10.4.1. Patient Disposition

Data from patients screened; patients screened but not randomized and reason for not randomized; patients who are randomized/enrolled; patients randomized/enrolled but not treated and reason; patients in the ITT, safety, and other analysis sets; patients who complete the study; patients who withdraw from the study; and patients who discontinue IMP will be summarized using descriptive statistics. Data from patients who withdraw from the study or discontinue IMP will also be summarized by reason for withdrawal using descriptive statistics.

10.4.2. Demographic and Baseline Characteristics

Patient demographic and baseline characteristics, including detailed IBD history, general medical history, prior medications and therapies, and ECG findings, will be examined to assess the comparability of the treatment groups by treatment, underlying disease, and all patients using descriptive statistics. For continuous variables, descriptive statistics (number [n], mean, standard deviation, median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented if necessary.

10.5. Efficacy Analysis

10.5.1. Primary Estimand

Refer to Section 3.2 for the primary estimand for UC patients and CD patients.

10.5.2. Primary Endpoints and Secondary Endpoints

Refer to Section 3.1 for primary and secondary endpoints.

10.5.3. Exploratory Endpoints

Refer to Section 3.3 for exploratory endpoints.

10.5.4. Planned Method of Analysis

The mITT analysis set (Section 10.2.2) will be used as the primary analysis set for all efficacy analyses. Summaries will be presented by treatment group, underlying disease, and for all patients.

Note that patients that were randomized to the 1800 mg treatment group are excluded from the mITT analysis set. Efficacy endpoints for these patients will be analyzed using descriptive statistics, in separate summary tables.

10.5.4.1. Primary Efficacy Analysis

A Beta-binomial model with a non-informative Beta(1,1) prior will be used to analyze the primary response endpoint, clinical remission (for UC) or endoscopic response (for CD), hereafter denoted as “response”. The model will be fit separately for each dose within each indication.

Inference will be based on posterior distribution of the response rates. A TEV-48574 dose will be declared successful at the final analysis if the posterior probability that the response rate in the TEV-48574 dose is higher than the response rate in the placebo arm is ≥0.90. Put another way, the success criterion for each dose within indication can be written as:

Posterior Probability (TEV-48574 response rate – placebo response rate >0) ≥0.90

The following quantities will be presented:

- Posterior means of the response rates for TEV-48574 high dose (900 mg Q2W), TEV-48574 low dose (450 mg Q2W) and placebo

- 95% credible intervals for difference in response rates (TEV-48574 doses – placebo)
- For each TEV-48574 dose, Posterior Probability (TEV-48574 dose – placebo response rate >0)

For further details, see Appendix L.

10.5.4.2. Sensitivity Analysis

Tipping point analysis will be performed to test the robustness of the primary analysis to the imputation of patients that discontinue the study or have missing week 14 modified Mayo score (UC patients) or SES-CD (CD patients) data as non-responders.

10.5.4.3. Supplementary Analysis

A supplementary analysis for the primary efficacy variable (defined in the supplementary estimand) will be performed using a logistic regression model fit separately to each indication with the following fixed effects: dose (as categorical variable), previous exposure to advanced IBD therapy (yes/no), and baseline modified Mayo score (UC patients) or SES-CD (CD patients). Each comparison of TEV-48574 dose versus placebo will be tested (one-sided) at a nominal significance level of α=0.1.

In addition, a Cochran-Mantel-Haenszel (CMH) test for pairwise comparisons between the active dose groups and placebo will be performed separately for UC and CD. Nominal p-values will be presented for each of the comparisons.

10.5.4.4. Secondary Efficacy Analysis

All secondary efficacy endpoints will be analyzed separately for the UC and CD indications. For each binary endpoint, a logistic regression model similar to the supplementary model described in Section 10.5.4.3 with the respective baseline measurement will be used. For each comparison of TEV-48574 dose versus placebo, the differences in proportions, odds ratios, associated 95% CIs, and nominal p-value will be reported.

10.5.4.5. Other Efficacy Analysis

Consistency of treatment effect across baseline, demographic covariates, and subgroups may be explored. The variables, corresponding models, and relevant details will be pre-specified in the Statistical Analysis Plan.

10.6. Multiple Comparisons and Multiplicity

No adjustments to control the false-positive rate will be made for the preplanned multiple comparisons/endpoints analyses for the protocol-specified endpoints.

10.7. Safety Analysis

Safety analyses will be performed on the safety analysis set (Section 10.2.3).

Safety assessments and time points are provided in Table 1.

All adverse events will be coded using the Medical Dictionary for Regulatory Activities. Each patient will be counted only once in each preferred term or system organ class category for the

analyses of safety. Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be related to test IMP and/or device (ie, reasonable possibility) (defined as related or with missing relationship) (overall and by severity), serious adverse events, serious adverse device effects, and adverse events and adverse device effects causing withdrawal from the study. Summaries will be presented by treatment group, underlying disease, and for all patients. Patient listings of serious adverse events, serious adverse device effects, and adverse events and adverse device effects leading to withdrawal will be presented.

The frequency of each score measuring local tolerability, including an NRS-11 for pain intensity, at the injection site(s) will be listed and summarized for each time point.

Changes in laboratory, ECG, and vital signs measurements data will be summarized descriptively. Values will be compared with predefined criteria to identify potentially clinically significant values or changes, and such values will be listed.

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics.

For continuous variables, descriptive statistics (number [n], mean, standard deviation, median, minimum, and maximum) will be provided for actual values and change from baseline to each time point. For categorical variables, patient counts and percentages will be provided.

If any patient dies during the study, a listing of deaths will be provided, and all relevant information will be discussed in the patient narrative included in the CSR.

10.8. Tolerability Analysis

Tolerability will be assessed by the number (%) of patients who fail to complete the study due to adverse events.

10.9. Population Pharmacokinetic, Pharmacodynamic, and Pharmacokinetic/Pharmacodynamic Analysis

All patients in the safety analysis set who have at least 1 measurable concentration of TEV-48574 will be included in the analysis of pharmacokinetic data. Serum concentrations will be expressed in mass per volume units. All concentrations below the limit of quantification or missing data will be labeled as such in the concentration data listings. TEV-48574 concentration data will be summarized by visit and treatment group.

A population pharmacokinetic analysis will be performed, and, if feasible, a pharmacokinetic/PD analysis of relevant PD variables and/or exposure-response analysis of relevant efficacy or safety endpoints may be performed and reported in a separate pharmacometrics report.

10.10. Pharmacogenetic Analysis

Exploratory analyses may be undertaken to describe the relationship between genetic polymorphisms (single-nucleotide polymorphisms) and treatment effects of TEV-48574.

10.11. Biomarker Analysis

Exploratory analyses may be undertaken to study the treatment effects of TEV-48574 on hsCRP, fecal calprotectin, autoantibodies, and other potential TL1A-mediated blood-based biomarkers.

Free and Total TL1A serum levels: Concentration data and change from baseline may be individually listed and summarized using descriptive statistics, and, when possible may be presented by treatment group, dose level, and nominal time point.

TL1A tissue expression: When feasible, level of expression at baseline may be listed and summarized.

Analysis of baseline TL1A free and/or total levels and baseline tissue TL1A level may be performed as a subpopulation analysis of treatment effects. Moreover, the level of specific autoantibodies, such as pANCA or ASCA, could also be considered.

Other potential emerging fecal, blood-based-resident proteomic, and tissue transcriptomic biomarkers reflective of PD, mechanism of action, and GI tissue condition may also be assessed. [redacted] will be collected and may also be analyzed.

An attempt may be made to correlate pharmacokinetic parameters with biomarkers.

These analyses may be reported in a separate report and may have a separate pre-specified analysis plan. These analyses may not be reported in the CSR.

10.12. Immunogenicity Analysis

Immunogenicity analyses will be performed. Listing(s) of patients with positive ADA sample(s) will be provided. Summaries may be provided if appropriate.

Treatment-emergent ADA responses and the impact of the presence of ADAs on pharmacokinetics and clinical safety may be assessed. Confirmed ADA positive samples may be further characterized (eg, testing for presence of neutralizing ADA) as needed.

Refer to Section 9.3 for the definition of treatment-emergent ADA response in this study.

10.13. Planned Interim Analysis

Interim analyses for safety and efficacy are planned for this study. An interim efficacy/futility analysis is planned in each indication (UC and CD) when approximately 50% of patients in the indication have completed the 14-week primary efficacy readout time point or had the opportunity to do so. This is expected to yield approximately 20 evaluable patients per treatment group for each indication in the interim analysis.

Due to study recruitment acceleration or other operational considerations, the interim analysis for efficacy/futility will not be conducted as it will be impractical and have limited utility.

In the interim analysis, the same Bayesian Beta-Binomial model described in the primary analysis model will be used to analyze the primary efficacy response variable for each dose within each indication. The futility criterion for each dose is:

- Posterior probability (TEV-48574 response rate – placebo response rate >0) <0.30

Refer to Table 10 and Appendix L for operating characteristics of the interim and final analysis.

In addition to futility, efficacy criteria, which is nonbinding, will be incorporated for the purpose of internal decision making for further development planning. Details of the efficacy criteria will be provided in the Statistical Analysis Plan.

Additionally periodic analysis of safety data will be done during the study. Analyses will focus on the following events:

- Incidence of serious adverse events
- Incidence of CTCAE grade 3 or grade 4 events
- Incidence of opportunistic infections and severe and/or serious infections
- Incidence of anaphylaxis

A Bayesian continuous monitoring approach will be employed for the above events, looking at the posterior probability for the incidence being greater on active treatment relative to placebo. A posterior probability exceeding 0.85 to 0.9 will trigger consideration for stopping the study or individual dose arms within the study.

All interim analyses will be performed by an external, independent, unblinded reporting team. The results of all interim analyses will be reviewed by an IDMC comprised of external medical and statistical experts. The IDMC will make recommendations regarding study conduct after evaluation of the totality of the data. Recommendations include, but are not limited to, dropping of a dose arm, termination of an indication, or termination of the study. The details regarding the statistical analysis methods will be provided in the Statistical Analysis Plan. The IDMC charter will provide details regarding procedures to protect the scientific integrity of the study, conduct of the interim analysis, dissemination of results, and decision criteria.

Individuals who may not be blinded include the bioanalytical scientists, pharmacometrician, and external biostatisticians (who are part of the unblinded analysis groups that are not directly involved in study conduct), as well as the IDMC members.

Additional Analyses:

As part of the interim analysis for efficacy/futility, additional analyses may be provided to the IDMC upon request or as deemed necessary by the sponsor.

Pharmacokinetic and PD analysis may be provided to the IDMC upon request. Population pharmacokinetic and PD analysis will be performed by an external analysis group independent of the study team. The process to ensure the study integrity, the maintenance of the double blind, and the responsibilities of the external members and relevant study personnel will be described in the IDMC charter. The details regarding the population pharmacokinetic or PD analysis will be described in the pharmacometric analysis plan.

10.14. Reporting Deviations from the Statistical Plan

Deviations from the statistical plan, along with the reasons for the deviations, will be described in protocol amendments, the Statistical Analysis Plan, the CSR, or any combination of these, as appropriate, and in accordance with applicable national, local, and regional requirements and regulations.

11. QUALITY CONTROL AND QUALITY ASSURANCE

Refer to Appendix B for information regarding quality control and quality assurance. This includes information about protocol amendments, deviations, responsibilities of the investigator to study personnel, study monitoring, and audit and inspection.

Details are given in the Study Manual.

12. COMPLIANCE STATEMENT

This study will be conducted in full accordance with the ICH Harmonised Tripartite Guideline, Guideline for Good Clinical Practice E6 and International Organization for Standardization 14155: Clinical investigation of medical devices for human subjects – Good clinical practice, as applicable, and any applicable national and local laws and regulations (eg, Title 21 Code of Federal Regulations [21CFR] Parts 11, 50, 54, 56, 312, and 314, European Union [EU] Clinical Trial Directive 2001/20/EC, EU Medical Device Regulation 2017/745, EU Clinical Trial Regulation No 536/2014, as applicable). Any episode of noncompliance will be documented.

The investigator is responsible for performing the clinical study in accordance with this protocol and the applicable GCP guidelines referenced above for collecting, recording, and reporting the data accurately and properly. Agreement of the investigator to conduct and administer this clinical study in accordance with the protocol will be documented in separate clinical study agreements with the sponsor and other forms as required by national competent authorities in the country where each investigational center is located.

The investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the clinical study; and must ensure that trained personnel are immediately available in the event of a medical emergency. The investigator and the involved clinical study personnel must be familiar with the background and requirements of the study; and with the properties of the IMPs as described in the IB or prescribing information.

The principal investigator at each investigational center has the overall responsibility for the conduct and administration of the clinical study at that investigational center and for contacts with study management, with the IEC/IRB, and with competent authorities.

See Appendix C for the ethics expectations of informed consent, competent authorities and IEC and IRB, confidentiality regarding study patients, and requirements for registration of the clinical study.

13. DATA MANAGEMENT AND RECORD KEEPING

See Appendix H for information regarding data management and record keeping. This includes direct access to source data and documents, data collection, data quality control, and archiving of CRFs and source documents.

14. FINANCING AND INSURANCE

A separate clinical study agreement, including a study budget, will be signed between each principal investigator and the sponsor (or the CRO designated by the sponsor) before the IMP is delivered.

The patients in this clinical study are insured in accordance with applicable legal provisions. The policy coverage is subject to the full policy terms, conditions, extensions, and exclusions. Excluded from the insurance coverage are eg, damages to health, and worsening of previous existing disease that would have occurred or continued if the patient had not taken part in the clinical study.

The policy of Clinical Trials Insurance will be provided to the investigational centers by the sponsor.

For covered clinical studies (see 21CFR54), the investigator will provide the sponsor with financial information required to complete FDA 3454 form. Each investigator will notify the sponsor of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

15. PUBLICATION POLICY

See Appendix I for information regarding the publication policy.

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17. SUMMARY OF CHANGES TO PROTOCOL

17.1. Amendment 04 Dated 08 July 2024

The protocol was amended for the following reasons:

- To update the protocol in line with CTR following the study transition to CTR:
  - Replacing the Eudra CT number with EU CT number
  - Shortening the information in the study synopsis to approximately 2 pages
  - To add a statement to clarify clinical study is conducted in compliance with EU Number 536/2014 [CTR Annex I 17 (a);
  - To add statement to clarify sponsors obligation in compliance with EU CTR Articles 52 through 54
- To add criterion for not performing the planned IA for futility/efficacy taking into consideration the practicality of such analyses in relation to study recruitment acceleration or other operational considerations.
- To extend the study period to approximately 27 months, from Q3 2022 until approximately Q3 Q4 2024.
- To incorporate within the protocol changes from the following administrative letters:
  - TV48574-IMM-20036 Administrative Letter 01 (dated 25 September 2023)
  - TV48574-IMM-20036 Administrative Letter 02 (dated 21 June 2024)
  - TV48574-IMM-20036 Administrative Letter 01 for Japan (JP) (dated 12 March 2024)
  - TTV48574-IMM-20036 Administrative Letter 01 for France (FR) (dated 11 March 2024)

All changes to the protocol body are listed below in the table, and are reflected in the synopsis, as applicable. Minor editorial changes (typos, punctuation, etc.) have been made to the protocol (and protocol synopsis, as appropriate).

Original text with changes shown	New wording	Reason/Justification for change
Title Page		
~~EudraCT number: 2021-006881-19;~~ EU CT number: 2024-511089-36-00	EU CT number: 2024-511089-36-00	Number changed following the transition of the study from the EU CTD to EU CTR
This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Council for Harmonisation (ICH); ~~ISO 14155: Clinical investigation of medical devices for human subjects – Good clinical practice, as applicable;~~ United States (US) Code of Federal Regulations (CFR), and European Union (EU) Directives and Regulations (as applicable in the region of the study); national country legislation; the protocol; and the sponsor's Standard Operating Procedures (SOPs).	This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Council for Harmonisation (ICH); United States (US) Code of Federal Regulations (CFR), and European Union (EU) Directives and Regulations (as applicable in the region of the study); national country legislation; the protocol; and the sponsor's Standard Operating Procedures (SOPs).	Removed text that is not relevant for this protocol.
~~CLINICAL STUDY PROTOCOL SYNOPSIS~~ 1. PROTOCOL SUMMARY		
See new wording column.	Original Clinical Study Protocol Synopsis was renamed to Protocol Summary, condensed to 2 pages, and relocated to Section 1. Protocol Summary section created with the following sections: Protocol Synopsis (information from previous synopsis condensed to just a few pages), Trial Schema (study schematic figure moved from the study design section of the protocol), and Schedule of Activities (moved from the study design section of the protocol).	Document must be compliant with CTR in Europe. All subsequent sections have been renumbered.

Original text with changes shown	New wording	Reason/Justification for change
See new wording column.	1.1 Protocol Synopsis … Trial Arms and Duration: …The study duration will be approximately 27 months, from Q3 2022 until approximately Q4 2024.	Subsection 1.1 created in compliance with CTR in Europe. Study duration extended due to increase in the initially estimated recruitment rate duration. *(change incorporated from TV48574-IMM-20036 Administrative Letter 02 (dated 21 June 2024)).* All subsequent tables have been renumbered as applicable.
Section 1.2. Trial Schema		
See new wording column.	Figure 1 (Overall Program Schematic) relocated from Section 4.1 (General Study Design and Study Schematic Diagram)	Subsection 1.2 created in compliance with ICH M11. All subsequent tables have been renumbered as applicable.
Section 1.3. Schedule of Activities		
See new wording column.	Table 4 (Study Procedures and Assessments) was relocated from Section 4.5 (Schedule of Study Procedures and Assessments) and renumbered as Table 1.	Subsection 1.3 created in compliance with ICH M11. Subsequent tables have been renumbered as applicable.
4.1. General Study Design and Study Schematic Diagram		
See new wording column.	Figure 2 Overall Study Schematic Diagram moved from the study design section of the protocol to newly created subsection 1.2 Trial Schema, Figure 2 Overall Study Schematic Diagram has been changed to Figure 1 Overall Program Schematic.	Figure 2 Overall Study Schematic Diagram moved to newly created subsection 1.2 Trial Schema in compliance with ICH M11 template. All subsequent figures have been renumbered.

Original text with changes shown	New wording	Reason/Justification for change
… The study duration will be approximately ~~**24**~~ 27 months, from Q3 2022 until approximately ~~Q3~~ ***Q4*** 2024.	… The study duration will be approximately 27 months, from Q3 2022 until approximately Q4 2024.	Increase in the initially estimated recruitment duration. *(change incorporated from TV48574-IMM-20036 Administrative Letter 02 dated 21 June 2024)*
Section 4.2 Planned Number of Patients and Countries		
The study is expected to start in Q3 2022 and last until approximately ~~Q3~~ ***Q4*** 2024.	The study is expected to start in Q3 2022 and last until Q4 2024.	Study duration extended due to increase in the initially estimated recruitment duration. *(change incorporated from TV48574-IMM-20036 Administrative Letter 02 dated 21 June 2024)*
~~3.5~~.4.5 Schedule of Study Procedures and Assessments		
See new wording column.	Schedule of Activities Table 2 moved from the study design section of the protocol to newly created subsection 1.3 Schedule of Activities. Schedule of Activities have been changed to Table 1. All subsequent tables from 1 to 3 have been renumbered.	Schedule of Activities Table 2 moved to newly created subsection 1.3 Schedule of Activities in compliance with ICH M11. All subsequent tables have been renumbered as applicable.
Pain will be assessed beginning, during ~~(~15 minutes after the start of (~~***approximately midway through*** the infusion), and after the completion of IMP administration and 1 hour later. ~~Table 4~~,**Table 1** Footnote "u" and ~~7.2~~ **8.2** Assessment of Local Tolerability and Pain	Pain will be assessed beginning, during (approximately midway through the infusion), and after the completion of IMP administration and 1 hour later. Table 1 Footnote "u" and 8.2 Assessment of Local Tolerability and Pain and	For patients randomized as of Amendment 03 with Revision 01, reduction in IMP volume administered at Visits 2 to 7 described in Section 5.1.3 results in a decreased infusion time. The volume of IMP was decreased from a 12 mL induction dose volume to a 6 mL induction dose volume, and the duration of the infusion therefore decreased from 24 minutes to 12 minutes. Since the infusion rate only lasts 12 minutes, it is not possible to perform this assessment at ~15 minutes, and therefore updated to assess pain during approximately midpoint of the infusion. *(change incorporated from TV48574-IMM-20036 Administrative letter 02 (dated 21 June 2024))*

Original text with changes shown	New wording	Reason/Justification for change
Section 7.1.2.1 Biopsy Collection		
For patients with CD, an ileo-colonoscopy will be performed at screening and week 14. During each endoscopy, a total of ~~16~~ ***11*** to 18 mucosal biopsies will be obtained from the area with the greatest inflammation in each segment at screening and at the same location at week 14 or early termination. For patients with UC, a flexible sigmoidoscopy will be performed at screening and week 14 (colonoscopy may be performed instead for baseline endoscopy if not done in the prior 12 months). During each endoscopy, a total of ~~8~~ *7* to 12 biopsies will be obtained from the area with the worst disease 15 to 25 cm from the anal verge.	For patients with CD, an ileo-colonoscopy will be performed at screening and week 14. During each endoscopy, a total of 11 to 18 mucosal biopsies will be obtained from the area with the greatest inflammation in each segment at screening and at the same location at week 14 or early termination. For patients with UC, a flexible sigmoidoscopy will be performed at screening and week 14 (colonoscopy may be performed instead for baseline endoscopy if not done in the prior 12 months). During each endoscopy, a total of 7 to 12 biopsies will be obtained from the area with the worst disease 15 to 25 cm from the anal verge.	The number of total biopsies was reduced to reduce the patient's burden. *(changes incorporated from TV48574-IMM-20036 Administrative letter 01 (dated 25 September 2023)*
Section 8.1.8.1. Investigator Responsibility		
For all countries, the sponsor's GPSP will distribute the Council for International Organizations of Medical Sciences (CIOMS) form~~/MedWatch/~~ ***and/or*** Extensible Markup Language (XML) file to the LSO/CRO for ***local*** submission to the competent authorities, IEC/IRBs, and investigators, according to regulations. ***For studies in the European Economic Area, submission of SUSARs is done electronically to the EudraVigilance database (via EVWEB or by electronically using the E2B(R3) electronic ICSR form) by the GPSP.*** The investigator must ensure that the IEC/IRB is also informed of the event, in accordance with national and local regulations.	For all countries, the sponsor's GPSP will distribute the Council for International Organizations of Medical Sciences (CIOMS) form and/or Extensible Markup Language (XML) file to the LSO/CRO for local submission to the competent authorities, IEC/IRBs, and investigators, according to regulations. For studies in the European Economic Area, submission of SUSARs is done electronically to the EudraVigilance database (via EVWEB or by electronically using the E2B(R3) electronic ICSR form) by the GPSP. The investigator must ensure that the IEC/IRB is also informed of the event, in accordance with national and local regulations.	Updated to be compliant with European Union safety reporting requirements and the EU CTR.

Original text with changes shown	New wording	Reason/Justification for change
10.13 Planned Interim Analysis		
Interim analyses for safety and efficacy are planned for this study. An interim efficacy/futility analysis is planned in each indication (UC and CD) when approximately 50% of patients in the indication have completed the 14-week primary efficacy readout time point or had the opportunity to do so. This is expected to yield approximately 20 evaluable patients per treatment group for each indication in the interim analysis. ***Due to study recruitment acceleration or other operational considerations, the interim analysis for efficacy/futility will not be conducted as it will be impractical and have limited utility.***	Interim analyses for safety and efficacy are planned for this study. An interim efficacy/futility analysis is planned in each indication (UC and CD) when approximately 50% of patients in the indication have completed the 14-week primary efficacy readout time point or had the opportunity to do so. This is expected to yield approximately 20 evaluable patients per treatment group for each indication in the interim analysis. Due to study recruitment acceleration or other operational considerations, the interim analysis for efficacy/futility will not be conducted as it will be impractical and have limited utility.	Due to the accelerated recruitment, performing IA for futility/high efficacy is not pragmatic as all participants will have almost completed the treatment period at the time of the IA. There is no impact on the safety and rights of the patients in the study as there are no changes to the planned safety monitoring as specified in the protocol, including the monthly IAs for safety and the planned safety IDMC meetings. Additionally, the study integrity and blinding are preserved and the statistical operating characteristics (e.g., type II error rate under the assumption of efficacy) are not impacted. (*change incorporated from TV48574-IMM-20036 Administrative letter 02 (dated 21 June 2024))*
Appendix A Departments and Institutions		
See new wording column.	Appendix A was deleted. All subsequent appendices renumbered.	To remove protected personal data that should not be displayed.
APPENDIX M: COUNTRY-SPECIFIC REQUIREMENTS		
See new wording column.	Added Administrative Letter 01 Dated 12 March 2024 for Japan.	To clarify concomitant use of permitted Chinese herbal supplements is associated with global inclusion criterion “h”. *(change incorporated from Administrative Letter 01 for Japan (JP) (dated 12 March 2024))*
See new wording column.	Added Administrative Letter 01 Dated 11 March 2024 for France.	To clarify patient enrolled in France will not be offered the option to enter the long-term extension study (TV48574-IMM-20038). *(change incorporated from Administrative Letter 01 for France (FR) (dated 11 March 2024)*)

17.2. Administrative Letter 02 Dated 21 June 2024

ADMINISTRATIVE LETTER 02

Study number: TV48574-IMM-20036

Clinical Study Protocol Amendment 03 with Revision 01 (JP 04) (ES 01)

A 14-Week Phase 2b, RandomizEd, Double-BLind, Dose-Ranging Study to Determine the PharmacokInetics, Efficacy, Safety, and Tolerability of TEV-48574 in Adult PatiEnts with Moderate to Severe Ulcerative Colitis or Crohn's Disease (RELIEVE UCCD)

21 September 2023

IND number: **157634**; NDA number: **Not applicable**; EudraCT number: **2021-006881-19**; EU CT number: **2024-511089-36-00**

21 JUNE 2024

Dear Investigator:

The purpose of this letter is to inform you of minor changes to the protocol:

1. extension in duration of the planned study period by 1 calendar quarter,
2. clarification of the timing of the assessment of pain during investigational medicinal product (IMP) infusion, and
3. addition of an operational criterion for not performing the planned interim analysis.

Modifications to the protocol are provided in the table below, deletions of the original text are signified by strikethrough and revisions/additions are shown in bold and italicized font.

Section	Original text with changes shown	New wording	Reason/Justification for change
3.1 (General Study Design and Study Schematic Diagram) and Synopsis (Study Duration)	… The study duration will be approximately ~~24~~ ***27*** months, from Q3 2022 until approximately ~~Q3~~ ***Q4*** 2024.	… The study duration will be approximately 27 months, from Q3 2022 until approximately Q4 2024.	Increase in the initially estimated recruitment duration.
3.2 (Planned Number of Patients and Countries) and Synopsis (Planned Study Period)	The study is expected to start in Q3 2022 and last until approximately ~~Q3~~ ***Q4*** 2024.	The study is expected to start in Q3 2022 and last until approximately Q4 2024.	

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3.5 Schedule of Study Procedures and Assessments Table 4, Footnote "u" and 7.2 Assessment of Local Tolerability and Pain	Pain will be assessed beginning, during ~~(~15 minutes after the start of~~ ***(approximately midway through*** the infusion), and after the completion of IMP administration and 1 hour later.	Pain will be assessed beginning, during (approximately midway through the infusion), and after the completion of IMP administration and 1 hour later.	For patients randomized as of Amendment 03 with Revision 01, reduction in IMP volume administered at Visits 2 to 7 described in Section 5.1.3 results in a decreased infusion time. The volume of IMP was decreased from a 12 mL induction dose volume to a 6 mL induction dose volume, and the duration of the infusion therefore decreased from 24 minutes to 12 minutes. Since the infusion rate only lasts 12 minutes, it is not possible to perform this assessment at ~15 minutes, and therefore updated to assess pain during approximately midpoint of the infusion.
9.13. Planned Interim Analysis and Synopsis (Planned Interim Analysis)	Interim analyses for safety and efficacy are planned for this study. An interim efficacy/futility analysis is planned in each indication (UC and CD) when approximately 50% of patients in the indication have completed the 14-week primary efficacy readout time point or had the opportunity to do so. This is expected to yield approximately 20 evaluable patients per treatment group for each indication in the interim analysis. ***Due to study recruitment acceleration or other operational***	Interim analyses for safety and efficacy are planned for this study. An interim efficacy/futility analysis is planned in each indication (UC and CD) when approximately 50% of patients in the indication have completed the 14-week primary efficacy readout time point or had the opportunity to do so. This is expected to yield approximately 20 evaluable patients per treatment group for each indication in the interim analysis. Due to study	Due to the accelerated recruitment, performing the planned interim analysis for futility/efficacy is not pragmatic, as all participants will have almost completed the treatment period at the time of the interim analysis. There is no impact on the safety and rights of the patients in the study as there are no changes to the planned safety monitoring as specified in the protocol, including the monthly interim analyses for safety and the planned safety independent data monitoring committee

	considerations, the interim analysis for efficacy/futility will not be conducted as it will be impractical and have limited utility.	recruitment acceleration or other operational considerations, the interim analysis for efficacy/futility will not be conducted as it will be impractical and have limited utility.	(IDMC) meetings. Additionally, the study integrity and blinding are preserved and the statistical operating characteristics (eg, type II error rate under the assumption of efficacy) are not impacted.

These modifications will be incorporated into the protocol during the next amendment, as applicable.

Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

Please feel free to contact [redacted] if you have any questions or concerns regarding this letter.

Sincerely,

[redacted]

21-Jun-2024 | 18:55 BST

[redacted]

17.3. Administrative Letter 01 Dated 15 August 2023

ADMINISTRATIVE LETTER 01

Study number: TV48574-IMM-20036

Clinical Study Protocol TV48574-IMM-20036 03 with Revision 01 (JP 03) (ES 01)

A 14-Week Phase 2b, RandomizEd, Double-BLind, Dose-Ranging Study to Determine the PharmacokInetics, Efficacy, Safety, and Tolerability of TEV-48574 in Adult PatiEnts with Moderate to Severe Ulcerative Colitis or Crohn's Disease (RELIEVE UCCD) 1

15 August 2023

IND number: **157634**; NDA number: **Not applicable**; EudraCT number: **2021-006881-19**.

25 SEP 2023

Dear Investigator:

The purpose of this letter is to provide you with additional information related to the number of total biopsies for each endoscopy procedure as noted and explained below:

Concerned section	Change or correction	Revised text
Section 6.1.2.1 Biopsy Collection	To decrease the patients' burden the number of total biopsies for each endoscopy procedure is reduced as follows: • For CD: Reduce from 16 to 18 mucosal biopsies to a total of 11 to 18 mucosal biopsies. • For UC: Reduce from 8 to 12 biopsies to a total of 7 to 12 biopsies.	For patients with CD, an ileo-colonoscopy will be performed at screening and week 14. During each endoscopy, a total of 11 to 18 mucosal biopsies will be obtained from the area with the greatest inflammation in each segment at screening and at the same location at week 14 or early termination. If ulceration is present, biopsies should be taken from the edge of the largest ulcer. If no ulceration is present, then biopsies should be taken from the most affected area of the segment. If the mucosa appears normal (eg, at follow-up), then random biopsies of the segment should be obtained.

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Concerned section	Change or correction	Revised text
		For patients with UC, a flexible sigmoidoscopy will be performed at screening and week 14 (colonoscopy may be performed instead for baseline endoscopy if not done in the prior 12 months). During each endoscopy, a total of 7 to 12 biopsies will be obtained from the area with the worst disease 15 to 25 cm from the anal verge.

These changes will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

Please feel free to contact [redacted] if you have any questions or concerns regarding this letter.

Sincerely,

[redacted]

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17.4. Amendment 03 with Revision 01 Dated 15 August 2023

Amendment 03 of the protocol was revised for the following reasons:

- To clarify that all patients randomized prior to Amendment 03 Revision 01 will continue to receive the same dose, volume, and rate of administration of the IMP to which they were initially randomized and will remain blinded.
- To clarify induction dose volume:
  - All patients randomized prior to Amendment 03 with Revision 01 will receive 12 mL induction dose volume.
  - All patients randomized as of Amendment 03 with Revision 01 will receive 6 mL induction dose volume.
- To clarify all randomized patients in this study may enroll in the long-term extension study.
- To adjust the secondary and exploratory study objectives:
  - Moved the following UC secondary endpoints to exploratory endpoints
    - Clinical response defined as decrease from baseline of at least 50% in 2-item PRO2 (rectal bleeding and stool frequency) at weeks 2, 4, 6, 8, 10, and 12
    - Clinical remission defined as score of rectal bleeding = 0 and stool frequency = 0 on the PRO2 scale at weeks 2, 4, 6, 8, 10, and 12
    - Histological remission defined as a Robarts Histopathology Index of ≤5 at week 14
    - Histological remission defined as Geboes index score ≤3.1 at week 14
    - Use of concomitant medication
    - Device-related adverse events and malfunctions (for the commercial sc infusion system)
  - Moved the following CD secondary endpoints to exploratory endpoints
    - Clinical response defined as a decrease from baseline of at least 50% in PRO2 (PRO2 is defined as having 2 components, abdominal pain and stool frequency) at weeks 2, 4, 6, 8, 10, and 12
    - Clinical remission defined as abdominal pain ≤1 and stool frequency ≤3 on the PRO2 scale at weeks 2, 4, 6, 8, 10, and 12
    - Endoscopic remission defined as SES CD score of 0-2, or SES CD score of 0-4, with no individual sub score >1 at week 14
    - Histologic response defined as a ≥50% decrease in Global Histologic Activity Score from baseline at week 14
    - Use of concomitant medication

    - Device-related adverse events and malfunctions (for the commercial sc infusion system)
  - Added/amended the following exploratory objectives:
    - Added the change from baseline in [redacted] at weeks 2, 8, and 14
    - Included the potential of other fecal/stool-derived biomarkers to be tested and analyzed, ie, change from baseline in fecal calprotectin or other stool-derived markers at weeks 2, 4, 8, and 14)

- To update the planned number of countries and investigational centers participating in the study
- To modify the justification of dose of test IMP
- To modify the hemoglobin value threshold in exclusion criterion l from <8 to <9 g/dL
- To replace exclusion criterion n, which is specific for COVID-19 infection, with any acute infection that may compromise the safety of the patient
- To remove the procedures and assessments of COVID-19 symptoms from all visits, including Appendix K (Management of Study Activities during COVID-Outbreaks)
- To add urine pregnancy testing at weeks 2, 6, and 10
- To add biomarker sample collection and potential exploratory analysis of [redacted] at weeks 0, 2, 8, 14, and early termination
- To potentially investigate additional fecal/stool derived-biomarkers
- To revise the total blood volume collected per patient from 240 mL to 280 mL to account for the [redacted] sample collections
- To revise the duration of the follow-up window from ±14 days to ±3 days
- To clarify all prior medications for IBD will be captured in the source documentation and CRF
- To clarify biopsies for patients with CD will be obtained at week 14 or early termination from the same area as the screening biopsy
- To clarify the total study sample size of 240 patients does not include patients that were randomized to the 1800 mg treatment group prior to Amendment 03 with Revision 01
- To update the statistical futility cutoff from <0.55 to <0.30
- To clarify the interim analysis will be conducted when approximately 50% of patients in the indication have completed the 14-week primary efficacy readout or had the opportunity to do so

All major changes to the protocol body are listed below in the table, and are reflected in the synopsis, as applicable. Minor editorial changes (typos, punctuation, etc.) have been made to the protocol (and protocol synopsis, as appropriate). Table 1 (Study Procedures and

Assessments) and Figure 1 (Overall Study Schematic Diagram) have been revised to reflect changes described below.

Original text with changes shown	New wording	Reason/Justification for change
Section 1.1.2 Relevance of Inhibition of TL1A Binding to Death Receptor 3 for Inflammatory Bowel Disease		
Inhibiting TL1A binding to DR3 prevents activation of the DR3 signaling pathway. A therapeutic anti-TL1A antibody (PF-06480605) was found to be efficacious in patients with UC (Hassan-Zahraee et al 2020). The results of this proof-of-concept (PoC) clinical study provide support for the clinical and histological benefits of inhibition of TL1A/DR3 signaling in patients with UC (Danese et al 2021). The results of the study demonstrated an acceptable safety profile and statistically significant endoscopic improvement in participants with moderately to severely active UC. ***Similar findings were reported in a Phase 2 study in patients with moderate to severe UC. In this study, treatment with PRA-023 resulted in a statistically significant greater proportion of patients with clinical remission or endoscopic improvement compared with placebo with a well-tolerated and acceptable safety profile (Sands et al 2023).*** …	Inhibiting TL1A binding to DR3 prevents activation of the DR3 signaling pathway. A therapeutic anti-TL1A antibody (PF-06480605) was found to be efficacious in patients with UC (Hassan-Zahraee et al 2020). The results of this proof-of-concept (PoC) clinical study provide support for the clinical and histological benefits of inhibition of TL1A/DR3 signaling in patients with UC (Danese et al 2021). The results of the study demonstrated an acceptable safety profile and statistically significant endoscopic improvement in participants with moderately to severely active UC. Similar findings were reported in a Phase 2 study in patients with moderate to severe UC. In this study, treatment with PRA-023 resulted in a statistically significant greater proportion of patients with clinical remission or endoscopic improvement compared with placebo with a well-tolerated and acceptable safety profile (Sands et al 2023). …	To provide additional support on the role of TL1A in IBD and the rationale for the study.
Section 1.2.2.1.3 Immunogenicity		
… Of the 48 subjects who received TEV-48574 in the SAD portion of the study, 23 subjects (47.9%) were identified as having a treatment-emergent ADA response. Treatment-emergent ADA responses were not associated with a safety signal. Treatment-emergent ADA responses were also observed in the cohorts that did not have measurable serum concentrations of TEV-48574 (cohorts 1 and 2, 1 and 4 mg TEV-48574, respectively). ~~The higher dose cohorts 7 (400 mg) and 8 (1000 mg) had the lowest numbers of subjects with treatment-emergent ADA responses~~ ***All ADAs occurred at 200 mg or lower except for 1 patient who received 1000 mg developed 1 transient ADA (low titer) 43 days after the dose was administered***, suggesting that there may be a trend toward immunological tolerance at higher doses. Three of 27 patients who received TEV-48574 (11% of patients tested) in the MAD portion were identified as having a positive	… Of the 48 subjects who received TEV-48574 in the SAD portion of the study, 23 subjects (47.9%) were identified as having a treatment-emergent ADA response. Treatment-emergent ADA responses were not associated with a safety signal. Treatment-emergent ADA responses were also observed in the cohorts that did not have measurable serum concentrations of TEV-48574 (cohorts 1 and 2, 1 and 4 mg TEV-48574, respectively). All ADAs occurred at 200 mg or lower except for 1 patient who received 1000 mg developed 1 transient ADA (low titer) 43 days after the dose was administered, suggesting that there may be a trend toward immunological tolerance at higher doses. Three of 27 patients who received TEV-48574 (11% of patients tested) in the MAD portion were identified as having a positive treatment-emergent ADA response. All 3 patients were in	Clarification.

Original text with changes shown	New wording	Reason/Justification for change
treatment-emergent ADA response. All 3 patients were in cohort 1 (200 mg). In these patients, the observed ADA log_{10} titer ranged from 0.6 to 2.5. One patient had treatment-emergent ADA responses at multiple time points starting by day 15, while the other 2 patients were ADA positive only at the end-of-study (EOS) visit (day 92)***, approximately 7 weeks after the last dose***. …	cohort 1 (200 mg). In these patients, the observed ADA log_{10} titer ranged from 0.6 to 2.5. One patient had treatment-emergent ADA responses at multiple time points starting by day 15, while the other 2 patients were ADA positive only at the end-of-study (EOS) visit (day 92), approximately 7 weeks after the last dose. …	
Section 1.2.2.2 Phase 1 Study (TV48574-PK-10180)		
New section added; see new wording column.	Study TV48574-PK-10180 was a Phase 1 open-label, randomized, single-dose study to evaluate the pharmacokinetics, safety, immunogenicity, and tolerability of TEV-48574 in healthy Japanese and Caucasian subjects. There were 3 single dose cohorts. Healthy Japanese subjects were randomized to 1 of 2 dose levels of TEV-48574 ([redacted] or [redacted]) in cohort 1 or assigned to a dose of [redacted] TEV-48574 in cohort 2. Healthy Caucasian subjects were assigned to a dose of [redacted] in cohort 3. The pharmacokinetic profile of TEV-48574 in Japanese subjects (n=24) was similar to pharmacokinetic profile in Caucasian subjects (n=8) across the absorption, distribution, and elimination phases; pharmacokinetic parameters in Japanese subjects were comparable to Caucasian subjects in the [redacted] dose cohorts and consistent with pharmacokinetic parameters in Caucasian subjects obtained from the TV48574-SAD-10126 study. The safety profile was consistent with that seen in the previous TEV-48574 studies with no evidence of any dose-related trends in adverse events in Japanese cohorts or differences between the Japanese and Caucasian subjects in any safety measures.	The CSR for Study TV48574-PK-10180 has been completed; therefore, a brief summary of the study results has been added.
Section 1.2.2.3 Phase 2a Study (TV48574-AS-20031)		
… A pre-specified interim futility analysis was conducted ***on 64 patients*** ~~for the first 40 patients who have completed the treatment period, experienced LoAC, or withdrawn from the study completely~~. Teva determined that the primary endpoint	… A pre-specified interim futility analysis was conducted on 64 patients. Teva determined that the primary endpoint result, reduction in LoAC, met the decision rule for futility, meaning that the likelihood of a positive outcome of the completion of	Correction.

Original text with changes shown	New wording	Reason/Justification for change
result, reduction in LoAC, met the decision rule for futility, meaning that the likelihood of a positive outcome of the completion of the study was small. Based on the results of the primary endpoint futility analysis, Teva decided to stop the study on 22 December 2021. A total of 65 patients ~~have been~~ ***were*** randomized into the study***; 1 patient did not receive investigational medicinal product (IMP)***. No deaths occurred.	the study was small. Based on the results of the primary endpoint futility analysis, Teva decided to stop the study on 22 December 2021. A total of 65 patients were randomized into the study; 1 patient did not receive investigational medicinal product (IMP). No deaths occurred.	
Section 1.3.2 Overall Benefit and Risk Assessment for This Study		
… Management of the patients' safety during the study that is expected to mitigate risk is detailed in Section 3 (investigational plan) and Section 7 (safety measurements and assessments); also refer to Section 9.13 for a description of the futility analysis, which will determine if recruitment should be stopped due to futility. ~~Management of study activities during coronavirus disease 2019 (COVID-19) outbreaks is detailed in Appendix K.~~ …	… Management of the patients' safety during the study that is expected to mitigate risk is detailed in Section 3 (investigational plan) and Section 7 (safety measurements and assessments); also refer to Section 9.13 for a description of the futility analysis, which will determine if recruitment should be stopped due to futility. …	Experience of the current stage of the pandemic does not support the contingent restrictions of COVID-19.
Section 2.1 Primary and Secondary Study Objectives and Endpoints		
The secondary efficacy endpoints to be measured in patients with moderate to severe UC are as follows: … • Clinical response defined as decrease from baseline of at least 50% in 2-item patient-reported outcome (PRO2; rectal bleeding and stool frequency) at week~~s 2, 4, 6, 8, 10, 12 and~~ 14 • Clinical remission defined as score of rectal bleeding = 0 and stool frequency = 0 on the PRO2 scale at week~~s 2, 4, 6, 8, 10, 12 and~~ 14 • ~~Histological remission defined as a Robarts Histopathology Index of ≤5 at week 14~~ • ~~Histological remission defined as Geboes index score~~	The secondary efficacy endpoints to be measured in patients with moderate to severe UC are as follows: … • Clinical response defined as decrease from baseline of at least 50% in 2-item patient-reported outcome (PRO2; rectal bleeding and stool frequency) at week 14 • Clinical remission defined as score of rectal bleeding = 0 and stool frequency = 0 on the PRO2 scale at week 14 The secondary efficacy endpoints to be measured in patients with moderate to severe CD are as follows: …	• Correction Only week 14 is the primary endpoint for clinical response and clinical remission; therefore, moved other time points to exploratory analysis. • Sample size is likely underpowered to

Original text with changes shown	New wording	Reason/Justification for change
~~≤3.1 at week 14.~~ The secondary efficacy endpoints to be measured in patients with moderate to severe CD are as follows: … • ~~Endoscopic remission defined as SES-CD score of 0-2, or SES-CD score of 0-4, with no individual sub-score >1 at week 14~~ • Clinical response defined as a decrease from baseline of at least 50% in PRO2 (PRO2 is defined as having 2 components, abdominal pain and stool frequency) at week~~s 2, 4, 6, 8, 10, 12 and~~ 14 • Clinical remission defined as abdominal pain ≤1 and stool frequency ≤3 on the PRO2 scale at week~~s 2, 4, 6, 8, 10, 12 and~~ 14 … • ~~Histologic response defined as a ≥50% decrease in Global Histologic Activity Score from baseline at week 14~~	• Clinical response defined as a decrease from baseline of at least 50% in PRO2 (PRO2 is defined as having 2 components, abdominal pain and stool frequency) at week 14 • Clinical remission defined as abdominal pain ≤1 and stool frequency ≤3 on the PRO2 scale at week 14 …	show a clinically meaningful difference for endoscopic remission; therefore, endpoints moved to exploratory analysis.
Section 2.3 Exploratory Objectives and Endpoints		
Endpoints See new wording column.	Moved the following efficacy endpoints from secondary to exploratory objectives to evaluate 2 different doses of TEV-48574 sc administered Q2W in adult patients with IBD: UC: • Clinical response defined as decrease from baseline of at least 50% in 2-item patient-reported outcome (PRO2; rectal bleeding and stool frequency) at weeks 2, 4, 6, 8, 10, and 12 • Clinical remission defined as score of rectal bleeding = 0 and stool frequency = 0 on the PRO2 scale at weeks 2, 4, 6, 8, 10, and 12 • Histological remission defined as a Robarts Histopathology Index of ≤5 at week 14 • Histological remission defined as Geboes index score	• Correction Only week 14 is the primary endpoint for clinical response and clinical remission; therefore, moved other time points to exploratory analysis. • Sample size is likely underpowered to show a clinically

Original text with changes shown	New wording	Reason/Justification for change
	≤3.1 at week 14 CD: • Clinical response defined as a decrease from baseline of at least 50% in PRO2 (PRO2 is defined as having 2 components, abdominal pain and stool frequency) at weeks 2, 4, 6, 8, 10, and 12 • Clinical remission defined as abdominal pain ≤1 and stool frequency ≤3 on the PRO2 scale at weeks 2, 4, 6, 8, 10, and 12 • Endoscopic remission defined as SES CD score of 0-2, or SES CD score of 0-4, with no individual sub score >1 at week 14 • Histologic response defined as a ≥50% decrease in Global Histologic Activity Score from baseline at week 14 Moved the following safety and tolerability endpoints from secondary to exploratory objectives for both UC and CD to evaluate 2 different doses of TEV-48574 sc administered Q2W in adult patients with IBD: • Use of concomitant medication • Device-related adverse events and malfunctions (for the commercial sc infusion system)	meaningful difference for endoscopic remission; therefore, endpoints moved to exploratory analysis. • Concomitant medication and device-related adverse event endpoints are not part of the main safety analysis.
Endpoints See new wording column.	• Added the following endpoint for the exploratory objective of evaluating association among exploratory biomarkers and clinical efficacy of TEV-48574: – Change from baseline in [redacted] at weeks 2, 8, and 14 • Amended the fecal calprotectin endpoint as follows to include potential testing/analysis for other stool-derived markers – change from baseline in fecal calprotectin or other	• [redacted] • Other fecal biomarkers may be investigated to study the treatment effect of TEV-48574.

Original text with changes shown	New wording	Reason/Justification for change
	stool-derived markers at weeks 2, 4, 8, and 14)	
An **exploratory objective** of the study is to obtain trough serum TEV-48574 concentrations, to compare major pharmacokinetic characteristics between UC and CD patients with healthy volunteers and asthma patients, and, if data allows, to evaluate the pharmacokinetics/~~pharmacodynamics~~ ***PD*** and/or exposure-response relationship of ~~2~~ different doses of TEV-48574 sc.	An **exploratory objective** of the study is to obtain trough serum TEV-48574 concentrations, to compare major pharmacokinetic characteristics between UC and CD patients with healthy volunteers and asthma patients, and, if data allows, to evaluate the pharmacokinetics/PD and/or exposure-response relationship of different doses of TEV-48574 sc.	The 1800 mg dose may be considered for exploratory analyses, if data allows.
Section 3.1 General Study Design and Study Schematic Diagram		
… Randomization: Patients satisfying the eligibility criteria at the end of the screening period will be randomized in a 1:1:1 ratio (stratified by diagnosis [UC or CD] and previous exposure to advanced therapy for IBD (yes/no) (biologics, JAK inhibitors, and S1P receptor modulators) to 1 of 3 treatment groups for the double-blind treatment period (Table 3). … ***Patients randomized prior to Amendment 03 with Revision 01 will continue to receive the same dose, volume, and rate of administration of the IMP to which they were initially randomized and will remain blinded.*** … Treatment and Follow-Up Period: During the 14-week treatment period, patients will visit the site Q2W on days 1, 15, 29, 43, 57, 71, and 85 (±3 days) for IMP administration (7 visits), as well as an end-of-treatment visit on day 99 (±3 days; week 14) (Table14). After the end of the 14-week treatment period, ***all*** patients may be offered the option to enter a long-term extension study, ~~(to be~~ ***which is*** described in a separate protocol ***(TV48574-IMM-20038***). If they choose to enter (sign the extension study informed consent form [ICF]) and will subsequently be randomized into the long-term extension study, they will not need to complete the follow-up visit in this study. All other patients will return to the site for a follow-up visit (day 127 [±~~14~~ ***3*** days]). For those patients who enter the long-term extension study, adverse events and concomitant medication	… Randomization: Patients satisfying the eligibility criteria at the end of the screening period will be randomized in a 1:1:1 ratio (stratified by diagnosis [UC or CD] and previous exposure to advanced therapy for IBD (yes/no) (biologics, JAK inhibitors, and S1P receptor modulators) to 1 of 3 treatment groups for the double-blind treatment period (Table 3). … Patients randomized prior to Amendment 03 with Revision 01 will continue to receive the same dose, volume, and rate of administration of the IMP to which they were initially randomized and will remain blinded. … Treatment and Follow-Up Period: During the 14-week treatment period, patients will visit the site Q2W on days 1, 15, 29, 43, 57, 71, and 85 (±3 days) for IMP administration (7 visits), as well as an end-of-treatment visit on day 99 (±3 days; week 14) (Table14). After the end of the 14-week treatment period, all patients may be offered the option to enter a long-term extension study, which is described in a separate protocol (TV48574-IMM-20038). If they choose to enter (sign the extension study informed consent form [ICF]) and will subsequently be randomized into the long-term extension study, they will not need to complete the follow-up visit in this study. All other patients will return to the site for a follow-up visit (day 127 [±3 days]). For those patients who enter the long-term extension study, adverse events and concomitant medication	Clarification. • Patients randomized prior to Amendment 03 with Revision 01 will continue to receive the dose (including volume, rate, and duration) of IMP to which they were initially randomized to not disrupt potential response to treatment and maintain the integrity of the study (eg, blinding concerns and data analysis). • All patients randomized in this study may be eligible for enrollment in the long-term extension study.

Original text with changes shown	New wording	Reason/Justification for change
data will be recorded in the dose-ranging study case report form (CRF) up until the date of extension study randomization (defined as the study completion date for the dose-ranging study). For those patients who screen fail the long-term extension study, adverse events and concomitant medication data will be recorded in the dose-ranging study up until the follow-up visit (day 127 [±~~14~~ ***3*** days]) CRF. Patients who complete the last scheduled visit will be considered to have completed the study. … The end of study is defined as the last visit of the last patient. ***The total duration of patient participation in the study is planned to be up to 24 weeks for each individual patient.*** The study duration will be approximately 24 months, from Q3 2022 until approximately Q3 2024. …	data will be recorded in the dose-ranging study case report form (CRF) up until the date of extension study randomization (defined as the study completion date for the dose-ranging study). For those patients who screen fail the long-term extension study, adverse events and concomitant medication data will be recorded in the dose-ranging study up until the follow-up visit (day 127 [±~~14~~ ***3*** days]) CRF. Patients who complete the last scheduled visit will be considered to have completed the study. … The end of study is defined as the last visit of the last patient. The total duration of patient participation in the study is planned to be up to 24 weeks for each individual patient. The study duration will be approximately 24 months, from Q3 2022 until approximately Q3 2024. …	• Added the total duration of patient participation.
Figure 2 Overall Study Schematic Diagram		
See new wording column.	Figure 2 was modified as described below. • Added a note to indicate the figure only applies to patients randomized as of Amendment 03 with Revision 01. Patients randomized prior to Amendment 03 with Revision 01 will continue to receive the same dose, volume, and rate of administration of the IMP to which they were initially randomized and will remain blinded. • Clarified that all patients randomized in this study may enroll in the long-term extension study. • Revised the duration of follow-up window from ±14 days to ±3 days.	• Clarification. - Patients randomized prior to Amendment 03 with Revision 01 will continue to receive the dose (including volume, rate, and duration) of IMP to which they were initially randomized to not disrupt potential response to treatment and maintain the integrity of the study (eg, blinding

Original text with changes shown	New wording	Reason/Justification for change
		concerns and data analysis). - All patients randomized in this study may be eligible for enrollment in the long-term extension study. • To provide a uniform variation of visits throughout the study, the follow-up window duration was updated to ±3 days.
Section 3.2 Planned Number of Patients and Countries		
Approximately 480 patients will be screened to achieve approximately 240 randomized patients (approximately 120 patients with UC and 120 patients with CD). ***The sample size does not include patients that were randomized to the 1800 mg treatment group prior to Amendment 03 with Revision 01.*** The study is planned to be conducted in ***North America*** ~~the United States of America (USA)~~, Europe, ***Africa,*** and Asia in approximately ~~100~~ ***200*** investigational centers. The study is expected to start in Q3 2022 and last until approximately Q3 2024.	Approximately 480 patients will be screened to achieve approximately 240 randomized patients (approximately 120 patients with UC and 120 patients with CD). The sample size does not include patients that were randomized to the 1800 mg treatment group prior to Amendment 03 with Revision 01. The study is planned to be conducted in North America, Europe, Africa, and Asia in approximately 200 investigational centers. The study is expected to start in Q3 2022 and last until approximately Q3 2024.	Clarification. • The planned total study sample size does not include patients randomized to the 1800 mg treatment group. • Revised USA to North America for consistency of continental regions. • Added Africa to the list of regions where the study is being conducted. • Updated the estimated number of investigational

Original text with changes shown	New wording	Reason/Justification for change
		centers participating in this study from 100 to 200.
Section 3.5 Schedule of Study Procedures and Assessments		
Study procedures and assessments with their time points are presented in Table14. Detailed descriptions of each method of procedures and assessments are provided in Section 6 (efficacy assessments), Section 7 (safety assessments), and Section 8 (pharmacokinetic and other assessments). Study procedures and assessments by visit are listed in Appendix B. ***Exclusionary laboratory values can be retested once during the screening period. If the retested laboratory value(s) remain(s) exclusionary, the subject will be considered a screen failure. Redrawing samples if previous samples were unable to be analyzed would not count as a retest since previous result was never obtained.***	Study procedures and assessments with their time points are presented in Table14. Detailed descriptions of each method of procedures and assessments are provided in Section 6 (efficacy assessments), Section 7 (safety assessments), and Section 8 (pharmacokinetic and other assessments). Study procedures and assessments by visit are listed in Appendix B. Exclusionary laboratory values can be retested once during the screening period. If the retested laboratory value(s) remain(s) exclusionary, the subject will be considered a screen failure. Redrawing samples if previous samples were unable to be analyzed would not count as a retest since previous result was never obtained.	Clarification.
Section 3.5 Schedule of Study Procedures and Assessments, Table 1		
See new wording column.	Table 1 Study Procedures and Assessments was modified as follows: • Added biomarker [redacted] collections at weeks 0, 2, 8, 14, and early termination. • Revised the duration of follow-up window from ±14 days to ±3 days. • Removed the assessment of COVID-19 symptoms inquiry from all visits. • Specified stool samples may be collected for other stool-derived markers at weeks 0, 2, 4, 8, 14, 18 and early termination. • Added urine pregnancy testing at weeks 2, 6, and 10. • Footnote a updated to clarify all patients in this study may enroll in the long-term extension study and to revise the duration of the follow-up window from ±14	• [redacted] collection added for better evaluation of target engagement, PD, and mechanism of action. • To provide a uniform variation of visits throughout the study, the follow-up window duration was updated to ±3 days. • Experience of the current stage of the pandemic does not

Original text with changes shown	New wording	Reason/Justification for change
	days to ±3 days. • Footnote e was deleted since assessment of COVID-19 symptoms inquiry removed from all visits; subsequent footnotes were renumbered. • Footnote h updated to define baseline (ie, last screening visit prior to randomization) for PRO2, rectal bleeding and stool frequency for UC and stool frequency and abdominal pain for CD. • Footnote l updated to clarify the hematocrit value measured at screening will be used to calculate the baseline CDAI score. • Footnote s updated to revise the duration of the follow-up window from ±14 days to ±3 days. • Footnote t updated to revise the duration of the follow-up window from ±14 days to ±3 days.	support the contingent restrictions of COVID-19. • Clarification. - All patients randomized in this study may be eligible for enrollment in the long-term extension study. - Specified the definition of baseline for PRO2. - Specified the hematocrit value measured at screening will be used to calculate the baseline CDAI score. • Other fecal biomarkers may be investigated to study the treatment effect of TEV-48574. • Urine pregnancy test added to visits 2, 4, and 6 to align with IMP administration every 2 weeks.

Original text with changes shown	New wording	Reason/Justification for change
Section 4.2 Patient Exclusion Criteria		
Criterion l Absolute neutrophil count <1.5x10^9/L or Hemoglobin <~~8~~***9*** g/dL or lymphocyte count <0.8x10^9/L or platelet count <100,000/mL	Criterion l Absolute neutrophil count <1.5x10^9/L or Hemoglobin <9 g/dL or lymphocyte count <0.8x10^9/L or platelet count <100,000/mL	Correction.
Criterion n ~~Patients with confirmed infection with COVID-19 within 6 weeks prior to the screening visit, or with residual COVID-19 symptoms ("long COVID-19"). Patients with active documented or suspected COVID-19 infection within 4 weeks of randomization or asymptomatic positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) test within 2 weeks of randomization are excluded.~~ ***Any acute infection which in the opinion of the investigator compromises the safety of the patient.***	Criterion n Any acute infection which in the opinion of the investigator compromises the safety of the patient.	Experience of the current stage of the pandemic does not support the contingent restrictions of COVID-19.
Section 4.6 Screening Failure		
Screen failure occurs when a patient who consents to participate in the clinical study is not subsequently randomized into the study because that patient did not meet the inclusion criteria or did meet the exclusion criteria. ~~Patients will be allowed to screen fail twice before no longer being considered for enrollment in the clinical study.~~ …	Screen failure occurs when a patient who consents to participate in the clinical study is not subsequently randomized into the study because that patient did not meet the inclusion criteria or did meet the exclusion criteria. …	Correction.
Section 5.1 Investigational Medicinal Products Used in the Study		
An IMP is defined as the test IMP (TEV-48574) and matching placebo IMP to the test IMP. ***For patients randomized prior to Amendment 03 with Revision 01:*** ***The volume of the solution of each IMP (TEV-48574 and placebo) will be constant (15 mL loading dose volume and 12 mL induction dose volume) and will be administered as single sc administrations.***	An IMP is defined as the test IMP (TEV-48574) and matching placebo IMP to the test IMP. For patients randomized prior to Amendment 03 with Revision 01: The volume of the solution of each IMP (TEV-48574 and placebo) will be constant (15 mL loading dose volume and 12 mL induction dose volume) and will be administered as single sc administrations.	Clarification. • Twelve (12) mL is the induction dose volume associated with the 1800 mg dose and has a 24-minute infusion duration; therefore, all patients

Original text with changes shown	New wording	Reason/Justification for change
Active IMP will be diluted with placebo to achieve the final delivered concentrations. Patients will receive the following regimens as a single sc administration Q2W using the [redacted] • ***TEV-48574 2250 mg (single loading dose)/1800 mg (6 induction doses)*** • ***TEV-48574 2250 mg (single loading dose)/900 mg (6 induction doses)*** • ***TEV-48574 2250 mg (single loading dose)/450 mg (6 induction doses)*** • ***Placebo to match TEV-48574 (single loading dose)/(Induction doses)*** ***For patients randomized as of Amendment 03 03 with Revision 01:*** The volume of the solution of each IMP (TEV-48574 and placebo) will be constant (15 mL loading dose volume and 6 mL induction dose volume) and will be administered as single sc administrations. …	Active IMP will be diluted with placebo to achieve the final delivered concentrations. Patients will receive the following regimens as a single sc administration Q2W using the [redacted] • TEV-48574 2250 mg (single loading dose)/1800 mg (6 induction doses) • TEV-48574 2250 mg (single loading dose)/900 mg (6 induction doses) • TEV-48574 2250 mg (single loading dose)/450 mg (6 induction doses) • Placebo to match TEV-48574 (single loading dose)/(Induction doses) For patients randomized as of Amendment 03 with Revision 01: The volume of the solution of each IMP (TEV-48574 and placebo) will be constant (15 mL loading dose volume and 6 mL induction dose volume) and will be administered as single sc administrations. …	randomized prior to Amendment 03 with Revision 01 (doses of 2250/1800 mg, 2250/900 mg, 2250/450 mg, or placebo) will continue to receive the 12 mL induction volume over 24 minutes to maintain study blind. • Six (6) mL is the induction dose volume associated with the 900 mg dose and has a 12-minute infusion duration; therefore, all patients randomized as of Amendment 03 with Revision 01 will receive the 6 mL induction volume over 12 minutes to maintain study blind.
Section 5.1.3 Test and Placebo Investigational Medicinal Product Administration		
… The infusion rate is fixed at 30 mL/hr for all sc infusions. ***For patients randomized prior to Amendment 03 03 with***	… The infusion rate is fixed at 30 mL/hr for all sc infusions. For patients randomized prior to Amendment 03 with Revision	Clarification. • Twelve (12) mL is the induction dose volume associated

Original text with changes shown	New wording	Reason/Justification for change
Revision 01: ***The expected infusion durations will therefore be 30 minutes for the 15 mL loading dose and 24 minutes for the 12 mL induction doses.*** ***For patients randomized as of Amendment 03 03 with Revision 01:*** The expected infusion durations will therefore be 30 minutes for the 15 mL loading dose and 12 minutes for the 6 mL induction doses. …	01: The expected infusion durations will therefore be 30 minutes for the 15 mL loading dose and 24 minutes for the 12 mL induction doses. For patients randomized as of Amendment 03 with Revision 01: The expected infusion durations will therefore be 30 minutes for the 15 mL loading dose and 12 minutes for the 6 mL induction doses. …	with the 1800 mg dose and has a 24-minute infusion duration; therefore, all patients randomized prior to Amendment 03 with Revision 01 (doses of 2250/1800 mg, 2250/900 mg, 2250/450 mg, or placebo) will continue to receive the 12 mL induction volume over 24 minutes to maintain study blind. • Six (6) mL is the induction dose volume associated with the 900 mg dose and has a 12-minute infusion duration; therefore, all patients randomized as of Amendment 03 with Revision 01 will receive the 6 mL induction volume over 12 minutes to maintain study blind.

Original text with changes shown	New wording	Reason/Justification for change
Section 5.3.1 Justification for Dose of Test Investigational Medicinal Product		
See new wording column.	This text in this section was deleted and replaced as follows: The justification listed herein refers to the study doses introduced in Amendment 03 with Revision 01 of the study protocol. In this study as of Amendment 03 with Revision 01, TEV-48574 will be administered as a single loading dose of 2250 mg followed by induction doses of 450 or 900 mg sc Q2W, for a total of 7 doses. Patients randomized prior to Amendment 03 with Revision 01 will continue to receive the dose (including volume, rate, and duration) of IMP to which they were initially randomized to not disrupt potential response to treatment and maintain the integrity of the study (eg, blinding concerns and data analysis). …	Removal of the 1800 mg Q2W treatment arm.
Section 5.4 Treatment After the End of the Study		
After the end of the 14-week treatment period, ***all*** patients may be offered the option to enter a long-term extension study (to be described in a separate protocol ***[TV48574-IMM-20038]***).	After the end of the 14-week treatment period, all patients may be offered the option to enter a long-term extension study (to be described in a separate protocol [TV48574-IMM-20038]).	Clarification. All patients randomized in this study may be eligible for enrollment in the long-term extension study.
Section 5.6.1 Prior Medications		
All prior medications for IBD will be recorded in the source documentation and in the CRF. Any ***other*** prior ~~or concomitant~~ therapy, medication (including nonprescription drugs, vitamins, and dietary or herbal supplements), or procedure a patient has had 4 weeks before screening through the end of the study will be recorded in the source documentation and in the CRF. …	All prior medications for IBD will be recorded in the source documentation and in the CRF. Any other prior therapy, medication (including nonprescription drugs, vitamins, and dietary or herbal supplements), or procedure a patient has had 4 weeks before screening through the end of the study will be recorded in the source documentation and in the CRF. …	Clarification. All prior medications for IBD will be captured in the source documentation and CRF.
Section 5.8 Randomization and Blinding		
This is a randomized, double-blind, placebo-controlled study. Patients who meet all the inclusion criteria and none of the	This is a randomized, double-blind, placebo-controlled study. Patients who meet all the inclusion criteria and none of the	Clarification. • Patients

Original text with changes shown	New wording	Reason/Justification for change
exclusion criteria will be randomly assigned to receive TEV-48574 (single loading dose/6 induction doses): 2250/900 mg, 2250/450 mg, or placebo to match TEV-48574, in a 1:1:1 ratio, stratified by diagnosis (UC or CD) and previous exposure to advanced therapy for IBD (yes/no) (biologics, JAK inhibitors, and S1P receptor modulators). ***Prior to Amendment 03 with Revision 01, patients were randomly assigned to receive 1 of 4 treatment regimens (2250/1800 mg, 2250/900 mg, 2250/450 mg, or placebo to match TEV-48574); these patients will continue to receive the same dose, volume, and rate of administration of the IMP to which they were initially randomized and will remain blinded.*** Approximately 120 UC patients and 120 CD patients will be randomly assigned to the treatment groups by means of a computer-generated randomization list using interactive-response technology. The specifications for randomization will be under the responsibility and oversight of Teva Global Statistics. ~~The patients and the site will be blinded until all patients complete the study, and the database is locked for final analysis for both indications. The sponsor will be blinded to treatment assignment until the database is locked for analysis of each indication. Prior to unblinding, the sponsor will establish a separate blinded study team supporting the conduct of the study until the database is locked for final analysis for both indications.~~ …	exclusion criteria will be randomly assigned to receive TEV-48574 (single loading dose/6 induction doses): 2250/900 mg, 2250/450 mg, or placebo to match TEV-48574, in a 1:1:1 ratio, stratified by diagnosis (UC or CD) and previous exposure to advanced therapy for IBD (yes/no) (biologics, JAK inhibitors, and S1P receptor modulators). Prior to Amendment 03 with Revision 01, patients were randomly assigned to receive 1 of 4 treatment regimens (2250/1800 mg, 2250/900 mg, 2250/450 mg, or placebo to match TEV-48574); these patients will continue to receive the same dose, volume, and rate of administration of the IMP to which they were initially randomized and will remain blinded. Approximately 120 UC patients and 120 CD patients will be randomly assigned to the treatment groups by means of a computer-generated randomization list using interactive-response technology. The specifications for randomization will be under the responsibility and oversight of Teva Global Statistics. …	randomized prior to Amendment 03 with Revision 01 will continue to receive the dose (including volume, rate, and duration) of IMP to which they were initially randomized to not disrupt potential response to treatment and maintain the integrity of the study (eg, blinding concerns and data analysis). • Specifications of blinding moved to Section 5.9.2 (Blinding and Unblinding).
Section 5.9.1 Maintenance of Randomization		
Patient randomization codes will be ***securely*** maintained ~~in a secure location at~~ ***by*** the service provider contracted to generate the codes. At the time of analysis (interim analysis and after the end of study), after receiving unblinding request from Teva statistician, the service provider will provide the unblinded IMP assignment according to the processes defined in the relevant Standard Operating Procedure (SOP).	Patient randomization codes will be securely maintained by the service provider contracted to generate the codes. At the time of analysis (interim analysis and after the end of study), after receiving unblinding request from Teva statistician, the service provider will provide the unblinded IMP assignment according to the processes defined in the relevant Standard Operating Procedure (SOP).	Clarification.

Original text with changes shown	New wording	Reason/Justification for change
Section 5.9.2 Blinding and Unblinding		
~~For information about p~~***P***ersonnel who may be aware of IMP assignments~~, see Section 5.8. These individuals~~ will not be involved in the conduct of any study procedures or assessment of any adverse events. ***The patients and the site will be blinded until all patients complete the study, and the database is locked for final analysis for both indications. The sponsor study team will be blinded to treatment assignment until the database is locked for analysis of each indication.*** Details regarding unblinding of ***an independent*** Teva team while maintaining the blind of the study, ~~in case efficacy threshold is met at the interim analysis, and~~ in case the final analysis is conducted for one indication while the other indication is ongoing, will be provided in a separate unblinding charter. …	Personnel who may be aware of IMP assignments will not be involved in the conduct of any study procedures or assessment of any adverse events. The patients and the site will be blinded until all patients complete the study, and the database is locked for final analysis for both indications. The sponsor study team will be blinded to treatment assignment until the database is locked for analysis of each indication. Details regarding unblinding of an independent Teva team while maintaining the blind of the study, in case the final analysis is conducted for one indication while the other indication is ongoing, will be provided in a separate unblinding charter. …	Consolidated blinding procedures in a single section of the protocol.
Section 5.9.3 Independent Data Monitoring Committee		
A single review committee (IDMC) will be established to monitor the study while it is ongoing, including periodic reviews of safety data, and pre-specified analyses of efficacy data, as described below. • The IDMC will include 2 Clinicians (external to Teva) with expertise in IBD and 1 external Statistician. The names of the external IDMC members will be included in the IDMC charter. ~~In addition to the IDMC, there will be an independent (external to the sponsor and the study team) statistical reporting team that will perform the planned unblinded analyses of interim efficacy and safety data for the IDMC to review.~~ • The role of the IDMC will be to periodically monitor unblinded safety data to ensure the safety of study patients ***as well as efficacy data for pre-specified interim analysis,*** and make recommendations on study	A single review committee (IDMC) will be established to monitor the study while it is ongoing, including periodic reviews of safety data, and pre-specified analyses of efficacy data, as described below. • The IDMC will include 2 Clinicians (external to Teva) with expertise in IBD and 1 external Statistician. The names of the external IDMC members will be included in the IDMC charter. • The role of the IDMC will be to periodically monitor unblinded safety data to ensure the safety of study patients as well as efficacy data for pre-specified interim analysis, and make recommendations on study conduct. • There will be an independent (external to the sponsor and the study team) statistical reporting team that will	Clarification.

Original text with changes shown	New wording	Reason/Justification for change
conduct. ~~In addition, the IDMC will review pre-specified analyses of efficacy data to make recommendations to the sponsor regarding futility or the possible acceleration of Phase 3 planning.~~ • ***There will be an independent (external to the sponsor and the study team) statistical reporting team that will perform the planned unblinded analyses of interim efficacy and safety data for the IDMC to review.*** …	perform the planned unblinded analyses of interim efficacy and safety data for the IDMC to review. …	
Section 5.10 Total Blood Volume		
The estimated maximum blood volume to be collected ~~for each patient~~ in this study is approximately ~~20 mL per visit and approximately 240~~ ***280*** mL for each patient during the entire study. Details on blood volumes to be collected during the study are provided in the ICF and the Laboratory Manual.	The estimated maximum blood volume to be collected in this study is approximately 280 mL for each patient during the entire study. Details on blood volumes to be collected during the study are provided in the ICF and the Laboratory Manual.	Total blood volume was increased to account for the added biomarker [redacted] collections.
Section 6.1.2.1 Biopsy Collection		
For patients with CD, an ileo-colonoscopy will be performed at screening and week 14. During each endoscopy, a total of 16 to 18 mucosal biopsies ~~will be collected and handled as outlined below. Mucosal biopsies~~ will be obtained from the area with the greatest inflammation in each segment ***at screening and at the same location at week 14 or early termination***. If ulceration is present, biopsies should be taken from the edge of the largest ulcer. If no ulceration is present, then biopsies should be taken from the most affected area of the segment. If the mucosa appears normal (eg, at follow-up), then random biopsies of the segment should be obtained. … ~~Ileal (for CD) and multiple colonic tissue sampling will be obtained by e~~***E***ndoscopic biopsies and will be evaluated by microscopic and histologic analyses, as well as for exploratory measures involving established and novel biomarkers of intestinal inflammation and fibrosis. There are several different approaches for obtaining these endoscopic biopsy samples, and	For patients with CD, an ileo-colonoscopy will be performed at screening and week 14. During each endoscopy, a total of 16 to 18 mucosal biopsies will be obtained from the area with the greatest inflammation in each segment at screening and at the same location at week 14 or early termination. If ulceration is present, biopsies should be taken from the edge of the largest ulcer. If no ulceration is present, then biopsies should be taken from the most affected area of the segment. If the mucosa appears normal (eg, at follow-up), then random biopsies of the segment should be obtained. … Endoscopic biopsies and will be evaluated by microscopic and histologic analyses, as well as for exploratory measures involving established and novel biomarkers of intestinal inflammation and fibrosis. There are several different approaches for obtaining these endoscopic biopsy samples, and the preferred procedures are described in the Laboratory Manual and Quick Reference Card.	Clarification. To describe the time of obtaining biopsy and its location in patients with CD.

Original text with changes shown	New wording	Reason/Justification for change
the preferred procedures are described in the Laboratory Manual and Quick Reference Card. …	…	
Section 7.3 Pregnancy		
… If the pregnancy in the woman participating in the study and/or the female partners of men participating in the study does not continue to term, 1 of the following actions will be taken: • For a spontaneous abortion, report as a serious adverse event ***(in addition to the pregnancy form)***. • For an elective abortion due to developmental anomalies, report as a serious adverse event ***(in addition to the pregnancy form)***. …	… If the pregnancy in the woman participating in the study and/or the female partners of men participating in the study does not continue to term, 1 of the following actions will be taken: • For a spontaneous abortion, report as a serious adverse event (in addition to the pregnancy form). • For an elective abortion due to developmental anomalies, report as a serious adverse event (in addition to the pregnancy form). …	Clarification.
Section 7.5.1 Serum Chemistry, Hematology, and Urinalysis		
… Screening laboratory test abnormalities, if considered by the Investigator to be transient and inconsistent with the patient's clinical condition, may be repeated once during the screening period for confirmation. ***Redrawing samples if previous samples were unable to be analyzed would not count as a retest since previous result was never obtained.***	… Screening laboratory test abnormalities, if considered by the Investigator to be transient and inconsistent with the patient's clinical condition, may be repeated once during the screening period for confirmation. Redrawing samples if previous samples were unable to be analyzed would not count as a retest since previous result was never obtained.	Clarification.
Section 7.5.2 Other Clinical Laboratory Tests		
… ~~At screening, patients with clinical symptoms that may indicate COVID-19 infection and/or patients who, in the investigator's opinion, were at high risk of exposure to COVID-19 within 6 weeks before screening or during screening will be tested for active COVID-19 infection. Patients who test positive will be excluded. COVID-19 testing will be available at the central laboratory. Locally performed COVID-19 testing results will also be accepted.~~	… Not applicable; text was deleted. ""	Experience of the current stage of the pandemic does not support the contingent restrictions of COVID-19.

Original text with changes shown	New wording	Reason/Justification for change
…		
Section 8.4 Assessment of Exploratory Biomarkers		
Potential exploratory biomarker objectives include characterization of TEV-48574 responders, identification of tissue-***, fecal-,*** and ~~serum~~ ***blood-based-***resident proteomic or transcriptomic biomarkers indicative of TEV-48574 mechanism of action and ~~pharmacodynamics~~ ***PD***, development of scalable tools to identify likely responders in future studies, and elucidation of TL1A-mediated pathway(s) that drive IBD in responders within the target patient population. The following exploratory biomarker assessments will be pursued from samples collected at indicated time points (Table 1): • Serum free and total TL1A levels will be measured using qualified***/validated*** assay methods. Tissue TL1A protein expression will also be assessed. • Serum proteomic markers assertive of ~~pharmacodynamics~~ ***PD*** and mechanism of action effects will be pursued by ***singleplex or*** multiplex assays. [redacted] ***will be collected and may be analyzed for evaluation of target engagement, PD, and mechanism of action.*** … • Fecal calprotectin ***or other stool-derived markers*** as a tissue proximal marker of GI inflammation … Residual biopsy, fecal, and ~~serum~~ ***blood*** samples, after appropriate analysis to support this study, may be stored at a Teva-secured facility for up to 15 years towards future analysis related to TEV-48574 or IBD if permitted by the ICF and local regulations. …	Potential exploratory biomarker objectives include characterization of TEV-48574 responders, identification of tissue-, fecal-, and blood-based**-**resident proteomic or transcriptomic biomarkers indicative of TEV-48574 mechanism of action and PD, development of scalable tools to identify likely responders in future studies, and elucidation of TL1A-mediated pathway(s) that drive IBD in responders within the target patient population. The following exploratory biomarker assessments will be pursued from samples collected at indicated time points (Table 1): • Serum free and total TL1A levels will be measured using qualified/validated assay methods. Tissue TL1A protein expression will also be assessed. • Serum proteomic markers assertive of PD and mechanism of action effects will be pursued by singleplex or multiplex assays. [redacted] will be collected and may be analyzed for evaluation of target engagement, PD, and mechanism of action. … • Fecal calprotectin or other stool-derived markers as a tissue proximal marker of GI inflammation … Residual biopsy, fecal, and blood samples, after appropriate analysis to support this study, may be stored at a Teva-secured facility for up to 15 years towards future analysis related to TEV-48574 or IBD if permitted by the ICF and local regulations. …	• The biomarker [redacted] was added for better evaluation of target engagement, PD, and mechanism of action. • Other fecal biomarkers may be investigated to study the treatment effect of TEV48574.

Original text with changes shown	New wording	Reason/Justification for change
Section 9.1 Sample Size and Power Calculations		
A total study sample size of 240 patients is planned, with 120 patients (40 patients per dose arm) each for the 2 indications of UC and CD. ***The sample size does not include patients that were randomized to the 1800 mg treatment group prior to Amendment 03 with Revision 01.*** … Simulation-based operating characteristics for the analysis of the primary efficacy variable using a Bayesian Beta Binomial model are presented in Table 10. This model uses a posterior probability cutoff of ~~<0.55~~ ***<0.30*** for the assessment of futility at the interim analysis and a posterior probability cutoff of ≥0.90 to declare success at the final analysis. For UC, the family-wise false-positive rate (ie, probability of making at least 1 false-positive conclusion under the null assumption for both doses) is 13%, and the probability of declaring success for at least 1 dose group is ~~97%~~ ***98%***, under the assumptions above. For CD, the family-wise false-positive rate is ~~15%~~ ***16%***, and the probability of declaring success for at least 1 dose is 95%, under the assumptions above. … Under a less optimistic scenario where the placebo response rates remain the same while the clinical remission rate in the UC indication is reduced to 20% for both doses, and the endoscopic response rate in the CD indication is reduced to 25% for both doses, the probability of declaring success in at least 1 dose is ~~75%~~ ***77%*** for UC and ~~74%~~ 7***6%*** for CD. …	A total study sample size of 240 patients is planned, with 120 patients (40 patients per dose arm) each for the 2 indications of UC and CD. The sample size does not include patients that were randomized to the 1800 mg treatment group prior to Amendment 03 with Revision 01. … Simulation-based operating characteristics for the analysis of the primary efficacy variable using a Bayesian Beta Binomial model are presented in Table 10. This model uses a posterior probability cutoff of <0.30 for the assessment of futility at the interim analysis and a posterior probability cutoff of ≥0.90 to declare success at the final analysis. For UC, the family-wise false-positive rate (ie, probability of making at least 1 false-positive conclusion under the null assumption for both doses) is 13%, and the probability of declaring success for at least 1 dose group is 98%, under the assumptions above. For CD, the family-wise false-positive rate is 16%, and the probability of declaring success for at least 1 dose is 95%, under the assumptions above. … Under a less optimistic scenario where the placebo response rates remain the same while the clinical remission rate in the UC indication is reduced to 20% for both doses, and the endoscopic response rate in the CD indication is reduced to 25% for both doses, the probability of declaring success in at least 1 dose is 77% for UC and 76% for CD. …	• Clarification. The planned total study sample size does not include patients randomized to the 1800 mg treatment group. • The cutoff for the interim assessment of futility was reduced to align with priorities of the business to minimize the risk of falsely stopping an effective compound at the interim analysis.
Table 10 (Operating Characteristics of Interim and Final Analysis) See new wording column.	Table 10 (Operating Characteristics of Interim and Final Analysis) was revised as described below: • Simulations updated based on updated futility cutoff and number of expected evaluable patients for the	The operating characteristics were revised based on the updated futility cutoff of <0.30 and the

Original text with changes shown	New wording	Reason/Justification for change
	interim analysis • Modified the futility cutoff in the footnotes	assumed number of evaluable patients to be included in the interim analysis.
Section 9.5.4 Planned Method of Analysis		
The mITT analysis set (Section 9.2.2) will be used ***as the primary analysis set*** for all efficacy analyses. Summaries will be presented by treatment group, underlying disease, and for all patients. ***Note that patients that were randomized to the 1800 mg treatment group are excluded from the mITT analysis set. Efficacy endpoints for these patients will be analyzed using descriptive statistics, in separate summary tables.***	The mITT analysis set (Section 9.2.2) will be used as the primary analysis set for all efficacy analyses. Summaries will be presented by treatment group, underlying disease, and for all patients. Note that patients that were randomized to the 1800 mg treatment group are excluded from the mITT analysis set. Efficacy endpoints for these patients will be analyzed using descriptive statistics, in separate summary tables.	A small number of patients had been randomized to the 1800 mg Q2W treatment arm at the time of sponsor decision to discontinue development of this dose. As this number of patients will not provide sufficient data to test the study hypotheses, the 1800 mg Q2W treatment arm will be summarized descriptively and not contribute to the primary analysis results of the study.
Section 9.11 Biomarker Analysis		
Exploratory analyses may be undertaken to study the treatment effects of TEV-48574 on hsCRP, fecal calprotectin, autoantibodies, and other potential TL1A-mediated ~~serum~~ ***blood-based*** biomarkers. … Other potential emerging ***fecal,*** ~~serum~~ ***blood-based-resident*** proteomic***,*** and tissue transcriptomic biomarkers reflective of ~~pharmacodynamic~~ ***PD, mechanism of action,*** and GI tissue condition may also be assessed. [redacted] ***will be collected and may be analyzed.*** …	Exploratory analyses may be undertaken to study the treatment effects of TEV-48574 on hsCRP, fecal calprotectin, autoantibodies, and other potential TL1A-mediated blood-based biomarkers. … Other potential emerging fecal, blood-based-resident proteomic, and tissue transcriptomic biomarkers reflective of PD, mechanism of action, and GI tissue condition may also be assessed. [redacted] will be collected and may be analyzed. …	• Clarification. Other potential exploratory fecal biomarkers may be assessed. • [redacted] collection added for better evaluation of target engagement, PD, and mechanism of action.
Section 9.13. Planned Interim Analysis		

Original text with changes shown	New wording	Reason/Justification for change
Interim analyses for safety and efficacy are planned for this study. An interim efficacy/futility analysis is planned in each indication (UC and CD) when ~~at least~~ ***approximately*** 50% of patients in the indication have completed the 14-week primary efficacy readout ***time point*** or had the opportunity to do so. ***This is expected to yield approximately 20 evaluable patients per treatment group for each indication in the interim analysis.*** In the interim analysis, the same Bayesian Beta-Binomial model described in the primary analysis model will be used to analyze the primary efficacy response variable for each dose within each indication. The futility criterion for each dose is: Posterior probability (TEV-48574 response rate – placebo response rate >-0) ~~<0.55~~ ***<0.30*** … In addition to futility, efficacy criteria***, which is nonbinding,*** will be incorporated for the purpose of internal decision making ~~and planning purposes~~ ***for further development planning***. ~~The criteria are non-binding, purely for purposes of accelerating planning for subsequent trials, and will not trigger any recommendations on trial conduct~~. Details of the efficacy criteria will be provided in the Statistical Analysis Plan. …	Interim analyses for safety and efficacy are planned for this study. An interim efficacy/futility analysis is planned in each indication (UC and CD) when approximately 50% of patients in the indication have completed the 14-week primary efficacy readout time point or had the opportunity to do so. This is expected to yield approximately 20 evaluable patients per treatment group for each indication in the interim analysis. In the interim analysis, the same Bayesian Beta-Binomial model described in the primary analysis model will be used to analyze the primary efficacy response variable for each dose within each indication. The futility criterion for each dose is: Posterior probability (TEV-48574 response rate – placebo response rate >0) <0.30 … In addition to futility, efficacy criteria, which is nonbinding, will be incorporated for the purpose of internal decision making for further development planning. Details of the efficacy criteria will be provided in the Statistical Analysis Plan. …	• Clarification. - The timing of the interim efficacy/futility analysis is at approximately 50% for each indication. - The interim efficacy criteria are considered nonbinding. • The cutoff for the interim assessment of futility was reduced to align with priorities of the business to minimize the risk of falsely stopping an effective compound at the interim analysis.
Section 15 References		
See new wording column.	The following references were added: • Sands B, Peyrin-Biroulet L, Danese S, Rubin DT, Vermeire S, Laurent O, et al. PRA03 Demonstrated Efficacy and Favorable Safety as Induction Therapy for Moderately to Severely Active UC: Phase 2 ARTEMIS-UC Study Results [abstract]. J Crohns Colitis 2023;17:i56-i59. • Wenxiu J, Mingyue Y, Fei H, Yuxin L, Mengyao W, Chenyang L, et al. Effect and Mechanism of TL1A Expression on Epithelial-Mesenchymal Transition during Chronic Colitis-Related Intestinal Fibrosis.	• Added references as used source of information in support of the proposed study. • Deleted literature references that are no longer applicable to support the study.

Original text with changes shown	New wording	Reason/Justification for change
	Mediators Inflamm 2021;5927064. The following references were deleted: • Back I, Marcon S, Gaino N, Vulcano D, Dorna M, Sassaki L. Body composition in patients with Crohn's disease and ulcerative colitis. Arq Gastroenterol 2017;54(2):109-114. • Dirks N, Meibohm B. Population pharmacokinetics of therapeutic monoclonal antibodies. Clin Pharmacokinet 2010;49:633-59. • Dong J, Chen Y, Tang Y, Xu F, Yu C, Li Y et al. Body mass index is associated with inflammatory bowel disease: a systematic review and meta-analysis. PLoS ONE 2015;10(12): e0144872. • Fasanmade AA, Adedokun OJ, Ford J, Hernandez D, Johanns J, Hu C, et al. Population pharmacokinetic analysis of infliximab in patients with ulcerative colitis. Eur J Clin Pharmacol 2009;65:1211–28. • Flores A, Burstein E, Cipher DJ, Feagins LA. Obesity in inflammatory bowel disease: a marker of less severe disease. Dig Dis Sci 2015;60:2436–45. • Johnson AM, Harmsen WS, Aniwan S, Tremaine WJ, Abu Dayyeh BK, Loftus EV. Prevalence and impact of obesity on disease-specific outcomes in a population-based cohort of patients with ulcerative colitis. J Crohn's Colitis 2021;15(11):1816-23.. • Kapel N, Meillet D, Favennec L, Magne D, Raichvarg D, Gobert JG. Evaluation of intestinal clearance and faecal excretion of alpha 1-antiproteinase and immunoglobulins during Crohn's disease and ulcerative colitis. Eur J Clin Chem Clin 1992;30:197–202. • Lobo ED, Hansen RJ, Balthasar JP. Antibody pharmacokinetics and pharmacodynamics. J Pharm Sci 2004;93(11):2645-68.	

Original text with changes shown	New wording	Reason/Justification for change
	• Mascelli MA, Zhou H, Sweet R, Getsy J, Davis HM, Graham M, et al. Molecular, biologic, and pharmacokinetic properties of monoclonal antibodies: impact of these parameters on early clinical development. J Clin Pharmacol 2007;47(5):553-65. • Neelakantan S, Martin SW, Li G, Hung K, Chandra DE, Rath N, et al. Population pharmacokinetic/pharmacodynamic modeling of PF-06480605, an anti-TL1A antibody, in healthy subjects and ulcerative colitis patients [poster abstract]. Presented at Population Approach Group Europe (PAGE) 2019 meeting; June 11-14, 2019; Stockholm, Sweden [Abstract published online]. • Nic Suibhne T, Raftery TC, McMahon O, Walsh C, O'Morain C, O'Sullivan M. High prevalence of overweight and obesity in adults with Crohn's disease: associations with disease and lifestyle factors. J Crohn's Colitis 2013;7(7):e241–e248. • Singh S, Dulai PS, Zarrinpar A, Ramamoorthy S, Sandborn WJ. Obesity in IBD: epidemiology, pathogenesis, disease course and treatment outcomes. Nat Rev Gastroenterol Hepatol 2017;14:110–21. • GUIDANCE ON THE MANAGEMENT OF CLINICAL TRIALS DURING THE COVID-19 (CORONAVIRUS) PANDEMIC Version 4, 04/02/2021. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf	
Appendix B. Study Procedures and Assessments by Visit		
1. Procedures for Screening (week -6 to week -1, days -42 to -1) • ~~coronavirus disease 2019 (COVID-19) symptoms inquiry~~ 2. Procedures During Administration of Investigational	1. Procedures for Screening (week -6 to week -1, days -42 to -1) • NA; text for COVID-19 inquiry was deleted 2. Procedures During Administration of Investigational	• Experience of the current stage of the pandemic does not support the contingent restrictions of

Original text with changes shown	New wording	Reason/Justification for change
Medicinal Product (Double-Blind Treatment Period) a. Visit 1 (week 0, day 1) • ~~COVID-19 symptoms inquiry~~ • Stool sample for fecal calprotectin (FeCal) ***or other stool-derived markers*** • ***biomarker*** [redacted] b. Visits 2, 4, and 6 (weeks 2, 6, and 10, days 15, 43, 71 ([±3 days based on previous visit]) • ~~COVID-19 symptoms inquiry~~ • ***pregnancy test (urine) in women of childbearing potential)*** • stool sample for fecal calprotectin (FeCal) ***or other stool-derived markers*** **(visit 2 only)** • ***biomarker*** [redacted] ***(visit 2 only)*** c. Visits 3, 5, and 7 (weeks 4, 8, and 12, days 29, 57, 85 ([±3 days based on previous visit]) • ~~COVID-19 symptoms inquiry~~ • stool sample for fecal calprotectin (FeCal) ***or other stool-derived markers*** **(visits 3 and 5 only)** • ***biomarker*** [redacted] ***(visit 5 only)*** d. Visit 8 (week 14, day 99 [±3 days based on previous visit]) • ~~COVID-19 symptoms inquiry~~ • stool sample for fecal calprotectin (FeCal) ***or other stool-derived markers*** • ***biomarker*** [redacted] 3. Follow-up (visit 9, week 18, day 127 [±~~14~~ ***3*** days based on previous visit])	Medicinal Product (Double-Blind Treatment Period) a. Visit 1 (week 0, day 1) • NA; text for COVID-19 inquiry was deleted • Stool sample for fecal calprotectin (FeCal) or other stool-derived markers • biomarker [redacted] b. Visits 2, 4, and 6 (weeks 2, 6, and 10, days 15, 43, 71 ([±3 days based on previous visit]) • NA; text for COVID-19 inquiry was deleted • pregnancy test (urine) in women of childbearing potential) • stool sample for fecal calprotectin (FeCal) or other stool-derived markers **(visit 2 only)** • biomarker [redacted] **(visit 2 only)** c. Visits 3, 5, and 7 (weeks 4, 8, and 12, days 29, 57, 85 ([±3 days based on previous visit]) • NA; text for COVID-19 inquiry was deleted • stool sample for fecal calprotectin (FeCal) or other stool-derived markers **(visits 3 and 5 only)** • biomarker [redacted] **(visit 5 only)** d. Visit 8 (week 14, day 99 [±3 days based on previous visit]) • NA; text for COVID-19 inquiry was deleted • stool sample for fecal calprotectin (FeCal) or other stool-derived markers • biomarker [redacted] 3. Follow-up (visit 9, week 18, day 127 [±3 days based on previous visit])	COVID19. • Urine pregnancy test added to visits 2, 4, and 6 to align with IMP administration every 2 weeks. • [redacted] collection added for better evaluation of target engagement, PD, and mechanism of action. • Other fecal biomarkers may be investigated to study the treatment effect of TEV48574. • To provide a uniform variation of visits throughout the study, the followup window duration was updated to ±3 days.

Original text with changes shown	New wording	Reason/Justification for change
• ~~COVID-19 symptoms inquiry~~ • stool sample for fecal calprotectin (FeCal) ***or other stool-derived markers***	• NA; text for COVID-19 inquiry was deleted • stool sample for fecal calprotectin (FeCal) or other stool-derived markers	
Appendix C. Quality Control and Quality Assurance		
… Study Monitoring … In case of an emergency situation (eg, the COVID-19 pandemic), where trial monitors may not be able to access the investigational centers for on-site visits, investigational centers will be monitored remotely, where allowed, and in accordance with global and/or local regulations. … Audit and Inspection … The investigator must accept that competent authorities and sponsor representatives may conduct inspections and audits to verify compliance with GCP guidelines. ***In case of an emergency situation (eg, the COVID-19 pandemic), where auditors may not be able to access the investigational centers for on-site visits, investigational centers will be audited remotely, where allowed, and in accordance with global and/or local regulations.***	… Study Monitoring … In case of an emergency situation (eg, the COVID-19 pandemic), where trial monitors may not be able to access the investigational centers for on-site visits, investigational centers will be monitored remotely, where allowed, and in accordance with global and/or local regulations. … Audit and Inspection … The investigator must accept that competent authorities and sponsor representatives may conduct inspections and audits to verify compliance with GCP guidelines. In case of an emergency situation (eg, the COVID-19 pandemic), where auditors may not be able to access the investigational centers for on-site visits, investigational centers will be audited remotely, where allowed, and in accordance with global and/or local regulations.	Clarification. The procedures related to emergency situations of monitoring and site audits were originally included in Appendix K. With the deletion of Appendix K, these details were moved to Appendix C.
Appendix K. Management of Study Activities During COVID-19 Outbreaks		
See new wording column.	Not applicable. Appendix K was deleted and subsequent appendices were renumbered, as applicable.	Experience of the current stage of the pandemic does not support the contingent restrictions of COVID-19.
Appendix M. Operating Characteristics and Assumptions for Final and Interim Analysis		
… <u>Number of Patients at the Interim Analysis:</u>	… <u>Number of Patients at the Interim Analysis:</u>	• Clarification. The timing of the

Original text with changes shown	New wording	Reason/Justification for change
The interim analysis for each indication is planned when ~~at least~~ ***approximately*** 50% of patients in the indication have completed the 14-week primary efficacy readout or had the opportunity to do so. Operating characteristics were obtained from simulations assuming that exactly ~~21~~ ***20*** patients per arm in the corresponding indication will be included in the interim analysis. Since the analysis is separate for each indication, no assumptions on the expected difference in recruitment rate between UC and CD are required. … <u>Statistical Futility Cutoff – Interim Analysis:</u> The same Bayesian Beta-Binomial model described in the primary analysis model will be used for the interim futility analysis for each dose within each indication. A TEV-48574 dose will be declared futile at the interim analysis if the posterior probability that the response rate in the TEV-48574 dose is higher than the response rate in the placebo arm is ~~<0.55~~ ***<0.30***, ie, the futility criterion for each dose within indication is: Posterior Probability (TEV-48574 response rate – placebo response rate >0) ~~<0.55~~ ***<0.30*** … These simulations demonstrate that the probability of a false positive result is ≤~~15~~***16***% for each indication, while the probability of declaring success for at least 1 dose within each indication under the efficacy assumption for both doses is ≥95%. The futility threshold was selected to control the probability to declare an effective dose to be futile at a maximum of ~~7~~***1***%, while making the correct decision in the null with a probability of ~~at least 60~~***approximately 25***%.	The interim analysis for each indication is planned when approximately 50% of patients in the indication have completed the 14-week primary efficacy readout or had the opportunity to do so. Operating characteristics were obtained from simulations assuming that exactly 20 patients per arm in the corresponding indication will be included in the interim analysis. Since the analysis is separate for each indication, no assumptions on the expected difference in recruitment rate between UC and CD are required. … <u>Statistical Futility Cutoff – Interim Analysis:</u> The same Bayesian Beta-Binomial model described in the primary analysis model will be used for the interim futility analysis for each dose within each indication. A TEV-48574 dose will be declared futile at the interim analysis if the posterior probability that the response rate in the TEV-48574 dose is higher than the response rate in the placebo arm is <0.30, ie, the futility criterion for each dose within indication is: Posterior Probability (TEV-48574 response rate – placebo response rate >0) <0.30 … These simulations demonstrate that the probability of a false positive result is ≤16% for each indication, while the probability of declaring success for at least 1 dose within each indication under the efficacy assumption for both doses is ≥95%. The futility threshold was selected to control the probability to declare an effective dose to be futile at a maximum of 1%, while making the correct decision in the null with a probability of approximately 25%.	interim efficacy/futility analysis is at approximately 50% for each indication. • The cutoff for the interim assessment of futility was reduced to align with priorities of the business to minimize the risk of falsely stopping an effective compound at the interim analysis.
Table 12 (Operating Characteristics of Interim and Final Analysis – All Scenarios) See new wording column	Table 12 (Operating Characteristics of Interim and Final Analysis – All Scenarios) was revised as described below: • Simulations updated based on updated futility cutoff and number of expected evaluable patients for the	The operating characteristics were revised based on the updated futility cutoff of <0.30 and the

Original text with changes shown	New wording	Reason/Justification for change
	interim analysis • Modified the futility cutoff in the footnotes	assumed number of evaluable patients to be included in the interim analysis.

17.5. Amendment 03 Dated 28 June 2023

The protocol was amended for the following reasons:

- To remove the 1800 mg Q2W treatment arm. Based on recent PD data along with pharmacokinetic predictions, the induction dose of 1800 mg Q2W is projected to exceed the exposure needed to demonstrate clinical effect and as such is being removed.
  - This reduces the total number of treatment groups to 3 (2 doses of TEV-48574 [450 and 900 mg Q2W] and placebo).
  - This reduces the induction volume of solution for each IMP dose from 12 mL to 6 mL, and adjusts the duration time of the 6 mL infusion to 12 minutes.
- To change the timing of the planned interim analysis to at least 50% of patients per indication and add non-binding analysis of efficacy.
- To amend the primary and secondary objectives to characterize the efficacy instead of dose response of TEV-48574 since there are only 2 active treatment arms.
- To update the primary and supplementary estimands, and the statistical methods and analysis sections of the protocol to address revisions to the primary analysis model, sample size and operating characteristics.
- To revise the definition of endoscopic response for the primary CD endpoint as a reduction from baseline in SES-CD from “>50%” to “of at least 50%”.
- To remove the CDAI assessments and analysis at weeks 2, 6, and 10.
- To clarify the stratification factors for randomization are diagnosis (UC and CD) and previous exposure to advanced therapy for IBD.
- To modify clinical laboratory sample collection as follows:
  - Added a clinical laboratory sample collection at week 12.
  - Clarified screening laboratory tests may be repeated once during the screening period at the discretion of the Investigator.
  - Removed lymphocytes atypical as an analyte for clinical laboratory testing.
  - Added local laboratory testing can be used under extenuating circumstances and only following agreement with the sponsor.
- Added a weight measurement at week 14.
- To correct the total blood volume collected per patient from 200 mL to 240 mL.

- To revise study entry criteria as follows:
  - Inclusion criterion g: Amended definition of inadequate response, loss of response, or intolerance to treatment to include at least 1 therapy for IBD and no more than 3 locally approved classes of biologics; included IL-23 class therapy as a locally approved classes and biologics; aligned permitted doses of AZA, 6-MP, and methotrexate with regional standard of care.
  - Exclusion criterion c: Clarified dysplasia on a completely excised adenomatous polyp (not a sessile one) is permitted.
  - Exclusion criterion f: Clarified Hepatitis B and Hepatitis C virus testing procedures at screening.
  - Exclusion criterion g: Clarified patients with a positive TB test at screening are eligible to participate if documentation of prior TB treatment is available.
  - Exclusion criterion i: Modified to 2 episodes of herpes zoster episodes in the last 5 years as exclusionary instead of a history of 1 episode.
  - Exclusion criterion k: Clarified that screening or baseline clinical laboratory value for ALT or AST should not exceed 2x ULN.
  - Exclusion criterion n: Clarified patients will be excluded from participation into the study if confirmed COVID-19 infection within 6 weeks before the screening visit or has residual symptoms (“long COVID-19”), within 4 weeks before randomization, or within 2 weeks before randomization if asymptomatic PCR test positive.
  - Exclusion criterion r: Included curatively resected papillary thyroid cancer as an exception for history of malignancy within the last 5 years.
  - Exclusion criterion s: Added anti-IL-23 as a prohibited biologic if administered within 3 half-lives prior to randomization
  - Exclusion criterion u: Clarified informed consent must be provided in written form.
  - Exclusion criterion v: Removed restriction that patients cannot be an employee or an immediate relative of an employee of the sponsor or of any of the clinical investigational centers participating in the study.
- To remove COVID-19 infection as a criterion for withdrawal of IMP.

All major changes to the protocol body are listed below in the table, and are reflected in the synopsis, as applicable. Minor editorial changes (typos, punctuation, etc.) have been made to the protocol (and protocol synopsis, as appropriate). Table 1 (Study Procedures and Assessments) and Figure 1 (Overall Study Schematic Diagram) have been revised to reflect changes described below.

Original text with changes shown	New wording	Reason/Justification for change
Document History		
Amendment 02 (JP 02) (ES 01) 27 March 2023 20 patients screened and ~~10~~ ***04*** patients randomized to date	Amendment 02 (JP 02) (ES 01) 27 March 2023 20 patients screened and 04 patients randomized to date	Correction to number of patients enrolled as of 27 March 2023.
Sponsor Protocol Approval		
Sponsor's Authorized Representative [redacted] Teva Branded Pharmaceutical Products R&D, Inc.	Sponsor's Authorized Representative [redacted] Teva Branded Pharmaceutical Products R&D, Inc.	Transfer of sponsor responsibility.
Section 1.1.3 TEV-48574 and Inflammatory Bowel Disease		
In ~~both asthma and~~ colitis animal models, TEV-48574 has shown anti-inflammatory and anti-fibrotic effects during nonclinical studies.	In colitis animal models, TEV-48574 has shown anti-inflammatory and anti-fibrotic effects during nonclinical studies.	Removed reference of asthma findings in nonclinical rat models as it is not relevant for this study in IBD.
Section 1.1.4 Purpose of Current Study		
The purpose of the study is to determine the pharmacokinetics, efficacy, safety**,** and tolerability of ~~3~~ **2** different dose**s** ~~regimens~~ of TEV-48574 subcutaneously (sc) administered every 2 weeks (Q2W) in adult patients with moderate to severe UC or CD	The purpose of the study is to determine the pharmacokinetics, efficacy, safety, and tolerability of 2 different doses of TEV-48574 subcutaneously (sc) administered every 2 weeks (Q2W) in adult patients with moderate to severe UC or CD	Removal of the 1800 mg Q2W treatment arm.
Section 1.3.2 Overall Benefit and Risk Assessment for This Study		
… ~~The basket design of this study allows a lower number of patients to be studied (as compared to 2 parallel, independent studies of UC and CD), further reducing the total exposure in this population.~~ …	Not applicable; text was deleted.	Deleted description of basket design as it is not relevant for the overall assessment of benefit and risk of the study or of TEV-48574 in patients with IBD.

Original text with changes shown	New wording	Reason/Justification for change
Section 2.1 Primary and Secondary Study Objectives and Endpoints		
The **primary objective** of the study is to characterize the ~~dose response~~ ***efficacy*** of TEV-48574 sc administered Q2W ~~and to evaluate the efficacy~~ in adult patients with IBD (IBD with moderate to severe UC or CD), as assessed by induction of clinical remission (UC) and endoscopic response (CD) at week 14.	The **primary objective** of the study is to characterize the efficacy of TEV-48574 sc administered Q2W in adult patients with IBD (IBD with moderate to severe UC or CD), as assessed by induction of clinical remission (UC) and endoscopic response (CD) at week 14.	Removal of the 1800 mg Q2W treatment arm.
Primary endpoint: CD Endoscopic response at week 14 in patients with moderate to severe CD, defined as a reduction in Simple Endoscopic Score for Crohn's Disease (SES-CD) of ~~>~~ ***at least*** 50% from baseline	Primary endpoint: CD Endoscopic response at week 14 in patients with moderate to severe CD, defined as a reduction in Simple Endoscopic Score for Crohn's Disease (SES-CD) of at least 50% from baseline	To align with FDA 2022 draft guidance "Crohn's Disease: Developing Drugs for Treatment" (Apr 2022).
A **secondary objective** of the study is to evaluate the efficacy ~~and dose response~~ of ~~3~~ ***2*** different dose***s*** ~~regimens~~ of TEV-48574 sc administered Q2W in adult patients with IBD (moderate to severe UC or CD) as assessed by multiple standard measures at week 14.	A **secondary objective** of the study is to evaluate the efficacy of 2 different doses of TEV-48574 sc administered Q2W in adult patients with IBD (moderate to severe UC or CD) as assessed by multiple standard measures at week 14.	Removal of the 1800 mg Q2W treatment arm.
Secondary endpoint: CD Clinical response defined as a ≥100-point decrease in Crohn's Disease Activity Index (CDAI) score from baseline at weeks ~~2,~~ 4, ~~6,~~ 8, ~~10~~, 12 and 14	Secondary endpoint: CD Clinical response defined as a ≥100-point decrease in Crohn's Disease Activity Index (CDAI) score from baseline at weeks 4, 8, 12 and 14	To reduce patient burden associated with additional blood draws for the hematocrit component of CDAI.
A **secondary objective** of the study is to evaluate the safety and tolerability of ~~3~~ ***2*** different dose***s*** ~~regimens~~ of TEV-48574 sc administered Q2W in adult patients with IBD (moderate to severe UC or CD).	A **secondary objective** of the study is to evaluate the safety and tolerability of 2 different doses of TEV-48574 sc administered Q2W in adult patients with IBD (moderate to severe UC or CD).	Removal of the 1800 mg Q2W treatment arm.
A **secondary objective** of the study is to evaluate the immunogenicity of ~~3~~ ***2*** different dose***s*** ~~regimens~~ of TEV-48574 sc administered Q2W in adult patients with IBD (moderate to severe UC or CD).	A **secondary objective** of the study is to evaluate the immunogenicity of 2 different doses of TEV-48574 sc administered Q2W in adult patients with IBD (moderate to severe UC or CD).	Removal of the 1800 mg Q2W treatment arm.
Section 2.1.1 Justification of Primary Endpoints		
…	…	To align with FDA 2022 draft

Original text with changes shown	New wording	Reason/Justification for change
The selected primary endpoint for patients with moderate to severe CD is endoscopic response, defined as a reduction in Simple Endoscopic Score for Crohn's Disease (SES-CD) of ~~>~~ ***at least*** 50% from baseline. …	The selected primary endpoint for patients with moderate to severe CD is endoscopic response, defined as a reduction in Simple Endoscopic Score for Crohn's Disease (SES-CD) of at least 50% from baseline. …	guidance "Crohn's Disease: Developing Drugs for Treatment" (Apr 2022).
Section 2.2 Primary Estimand		
• **Treatment:** In both UC and CD ~~groups~~ ***indications***, patients will be randomly assigned to receive any one of the study treatment regimens shown below, in a 1:1:1~~:1~~ ratio: ~~- TEV-48574 2250 mg (single loading dose)/1800 mg (6 induction doses)~~ - TEV-48574 2250 mg (single loading dose)/900 mg (6 induction doses) - TEV-48574 2250 mg (single loading dose)/450 mg (6 induction doses) - Matching placebo	• **Treatment:** In both UC and CD indications, patients will be randomly assigned to receive any one of the study treatment regimens shown below, in a 1:1:1 ratio: - TEV-48574 2250 mg (single loading dose)/900 mg (6 induction doses) - TEV-48574 2250 mg (single loading dose)/450 mg (6 induction doses) - Matching placebo	Removal of the 1800 mg Q2W treatment arm.
• **Handling of intercurrent events:** Intercurrent events addressed here are (a) use of rescue medication; (b) important protocol deviations; (c) UC or CD related surgery; and (d) treatment discontinuation. These intercurrent events will be addressed as follows: (a) Patients who used rescue medications prior to their week 14 evaluation of response (clinical remission in the UC ~~group~~ ***indication*** ~~and prior to the week 14 evaluation of~~ ***or*** endoscopic response in the CD ~~group~~ ***indication***) will be reported as non-responders, ie, the composite variable strategy; (b) Patients experiencing any important protocol deviations, namely, use or changes in other medications, will be analyzed as if the deviation had not occurred, ie, treatment policy strategy; (c) Patients undergoing UC or CD related surgery will be treated as non-responders, ie, the composite strategy; and (d) Patients discontinuing	• **Handling of intercurrent events:** Intercurrent events addressed here are (a) use of rescue medication; (b) important protocol deviations; (c) UC or CD related surgery; and (d) treatment discontinuation. These intercurrent events will be addressed as follows: (a) Patients who used rescue medications prior to their week 14 evaluation of response (clinical remission in the UC indication or endoscopic response in the CD indication) will be reported as non-responders, ie, the composite variable strategy; (b) Patients experiencing any important protocol deviations, namely, use or changes in other medications, will be analyzed as if the deviation had not occurred, ie, treatment policy strategy; (c) Patients undergoing UC or CD related surgery will be treated as non-responders, ie, the	Correction.

Original text with changes shown	New wording	Reason/Justification for change
treatment, regardless of the reason, will be treated as non-responders, ie, the composite strategy	composite strategy; and (d) Patients discontinuing treatment, regardless of the reason, will be treated as non-responders, ie, the composite strategy	
… • **Population-level summary:** The population-level summary of interest is the quantity Posterior Probability ($p_{d,i}$-$p_{0,i}$>0) estimated from a ***Bayesian Beta-Binomial model for the response rate (clinical remission rate for UC, or endoscopic response rate for CD),*** $p_{d,i}$, ***where i=UC, CD and d=0,1,2 represent placebo, TEV-48574 low dose (450 mg Q2W), and TEV-48574 high dose (900 mg Q2W), respectively.*** ~~hierarchical 3-parameter Emax model (with E_(0,i),ED_(50,i) and E_(max,i),i=1,2 for UC,CD) for the logit of response rate. p_(d,i) denotes either the clinical remission (for UC) or endoscopic response rate (for CD) and doses d =0,1,2,3 represent placebo, low, mid, and high doses of TEV-48574~~.	… • **Population-level summary:** The population-level summary of interest is the quantity Posterior Probability ($p_{d,i}$-$p_{0,i}$>0) estimated from a Bayesian Beta-Binomial model for the response rate (clinical remission rate for UC, or endoscopic response rate for CD), $p_{d,i}$, where i=UC, CD and d=0,1,2 represent placebo, TEV-48574 low dose (450 mg Q2W), and TEV-48574 high dose (900 mg Q2W), respectively.	Updated definition of primary estimand and corresponding analysis methods following the removal of the 1800 mg Q2W treatment arm and change in the primary analysis.
Section 2.2.1 Supplementary Estimand		
~~A supplementary analysis using a frequentist logistic regression dose-response model that incorporates separate dose-response lines for each patient population (UC and CD) will be used in support of the supplementary estimand below.~~ The supplementary estimand is defined by the following attributes: • **Treatment**: same as for the Primary Estimand. • **Target population**: same as for the Primary Estimand. • **Variable**: same as for the Primary Estimand. • **Handling of intercurrent events**: same as for the Primary Estimand. • **Population-level summary**: ***The population-level summary is difference in response rates of each TEV-48574 dose compared to placebo obtained from a logistic regression model fit separately to each***	The supplementary estimand is defined by the following attributes: • **Treatment**: same as for the Primary Estimand. • **Target population**: same as for the Primary Estimand. • **Variable**: same as for the Primary Estimand. • **Handling of intercurrent events**: same as for the Primary Estimand. • **Population-level summary**: The population-level summary is difference in response rates of each TEV-48574 dose compared to placebo obtained from a logistic regression model fit separately to each indication, with dose as categorical variable.	Updated definition of supplementary estimand and corresponding analysis methods following the removal of the 1800 mg Q2W treatment arm and change in the primary analysis.

Original text with changes shown	New wording	Reason/Justification for change
indication, with dose as categorical variable. ~~A logistic regression analysis of response at week 14 will be performed. The population-level summary will be provided by the estimated slope terms specific to each patient population from this model~~.		
Section 2.3 Exploratory Objectives and Endpoints		
An **exploratory objective** of the study is to obtain trough serum TEV-48574 concentrations, to compare major pharmacokinetic ~~(PK)~~ characteristics between UC and CD patients with healthy volunteers and asthma patients, and, if data allows, to evaluate the pharmacokinetics/pharmacodynamics and/or exposure-response relationship of ~~3~~ ***2*** different dose***s*** ~~regimens~~ of TEV-48574 sc.	An **exploratory objective** of the study is to obtain trough serum TEV-48574 concentrations, to compare major pharmacokinetic characteristics between UC and CD patients with healthy volunteers and asthma patients, and, if data allows, to evaluate the pharmacokinetics/pharmacodynamics and/or exposure-response relationship of 2 different doses of TEV-48574 sc.	Removal of the 1800 mg Q2W treatment arm.
Section 3.1 General Study Design and Study Schematic Diagram		
This is a Phase 2b, randomized, double-blind, dose-ranging study to determine the pharmacokinetics, efficacy, safety, and tolerability of TEV-48574 in adult patients with moderate to severe UC or CD. The study will enroll adult patients (18 to 75 years of age, inclusive) of male and female sex (without restrictions on gender) with moderate to severe active UC or CD and who have demonstrated an inadequate response to, loss of response to, or intolerance ~~of~~ ***to*** at least 1 of the following ***therapies***: ~~agents~~ ***corticosteroids, immunosuppressants, or an advanced therapy for IBD including biologics (anti-TNF, anti-integrins, anti-IL-12/23 or anti-IL-23), JAK inhibitors, or sphingosine-1-phosphate (S1P) receptor modulators; and no more than 3 locally approved classes of biologics.*** ~~and no more than 2 classes of biologics: corticosteroids, immunosuppressant drugs, and/or tumor necrosis factor alpha (TNF α) antagonist therapy, anti-integrins, anti-IL-12/23, JAK inhibitors, and/or sphingosine-1-phosphate (S1P) receptor modulators (see Section 4.1 for definitions of these terms).~~	This is a Phase 2b, randomized, double-blind, dose-ranging study to determine the pharmacokinetics, efficacy, safety, and tolerability of TEV-48574 in adult patients with moderate to severe UC or CD. The study will enroll adult patients (18 to 75 years of age, inclusive) of male and female sex (without restrictions on gender) with moderate to severe active UC or CD and who have demonstrated an inadequate response to, loss of response to, or intolerance to at least 1 of the following therapies: corticosteroids, immunosuppressants, or an advanced therapy for IBD including biologics (anti-TNF, anti-integrins, anti-IL-12/23) or anti-IL-23, JAK inhibitors, or sphingosine-1-phosphate (S1P) receptor modulators; and no more than 3 locally approved classes of biologics.	• Included IL-23 as it is a newly approved class for treatment for IBD and will be considered a similar class as the IL-12/23. • Updated to no more than 3 classes of biologics to potentially increase the patient pool for enrollment.

Original text with changes shown	**New wording**	**Reason/Justification for change**
Randomization: Patients satisfying the eligibility criteria at the end of the screening period will be randomized in a 1:1:1~~:1~~ ratio (stratified by diagnosis [UC or CD] and previous exposure to ***advanced therapy for IBD (yes/no)***~~,~~ ~~failure of~~ (biologics~~, and small molecules including~~ JAK inhibitors**,** and S1P receptor modulators ~~for UC~~) ~~or naive to biologics and small molecule therapy~~) to 1 of ~~4~~ ***3*** treatment groups for the double-blind treatment period (Table 3).	Randomization: Patients satisfying the eligibility criteria at the end of the screening period will be randomized in a 1:1:1 ratio (stratified by diagnosis [UC or CD] and previous exposure to advanced therapy for IBD (yes/no) (biologics, JAK inhibitors, and S1P receptor modulators) to 1 of 3 treatment groups for the double-blind treatment period (Table 3).	Clarification.
Table 3: Randomization Scheme See new wording column.	Table 3 Randomization Scheme was modified as follows: • Row removed for 1800 mg treatment arm. • Number of patients to be randomized modified from 35 to 40 for each indication (UC and CD) for the remaining 3 treatments arms.	Updated the sample size following the removal of the 1800 mg Q2W treatment arm.
Figure 2 Overall Study Schematic Diagram		
See new wording column.	Figure 2 was modified as described below. • Removed 1800 mg treatment arm from the UC and CD patient groups • Changed the sample size for each treatment arm from 35 to 40 and total sample size for each indication from 140 to 120 patients • Changed screening estimate from 570 to 480 patients • Removed description of analysis model	Modified Figure 2 to include updates to the sample size and primary analysis following the removal of the 1800 mg Q2W treatment arm.
Section 3.2 Planned Number of Patients and Countries		
Approximately ~~570~~ ***480*** patients will be screened to achieve approximately~~280~~ ***240*** randomized patients (approximately	Approximately 480 patients will be screened to achieve approximately 240 randomized patients (approximately	Updated the sample size following the removal of the 1800

Original text with changes shown	New wording	Reason/Justification for change
~~140~~ ***120*** patients with UC and ~~140~~ ***120*** patients with CD). …	120 patients with UC and 120 patients with CD). …	mg Q2W treatment arm.
Section 3.3 Justification for Study Design and Selection of Population		
… The basket DRF design offers the following efficiencies: … ~~• Enable information sharing between UC and CD doses, thereby enhancing the inferential quotient in a single trial as compared with independent analyses/trials for UC and CD.~~ ~~• Allow a lower number of patients to be studied (as compared to 2 parallel, independent studies of UC and CD), further reducing the total exposure in this population.~~ Basket studies are prospectively designed studies typically conducted in Phase 2 to allow effective evaluation of therapeutic benefit of a single investigational treatment in multiple diseases or disease subtypes. In some instances, these designs have served as a basis for regulatory approval (Hyman et al 2015, Subbiah et al 2018). ~~Bayesian hierarchical models are used to analyze the data and generally demonstrate a robust control of the family-wise (type 1) error rate (Kaizer et al 2019) when compared to a simple pooling or an independence approach for analysis of a range of outcomes. The operating characteristics for various scenarios (ie, treatment effect for doses, indications) can be explored using simulation studies. Further, such designs permit interim evaluations (efficacy and/or futility) of the accumulating data.~~ ~~An overall primary efficacy analysis incorporating all data from both indications will be performed using a Bayesian hierarchical model. .~~ ~~In this Phase 2 dose-range study, a functional relationship (namely E_{max} model) between the doses is assumed. While there are many options for specifying these relationships (ie,~~	… The basket DRF design offers the following efficiencies: … Basket studies are prospectively designed studies typically conducted in Phase 2 to allow effective evaluation of therapeutic benefit of a single investigational treatment in multiple diseases or disease subtypes. In some instances, these designs have served as a basis for regulatory approval (Hyman et al 2015, Subbiah et al 2018). In summary, the commonality of the anti-TL1A mechanism of action in patients with UC and CD, the approved mAbs that have similar dose regimens for both UC and CD, and the opportunities for operational efficiencies make a basket design well suited for the planned study. …	Removed description of the E_{max} analysis since no longer applicable following removal of the 1800 mg Q2W treatment arm and change in the primary analysis model.

Original text with changes shown	New wording	Reason/Justification for change
~~E_{max}, logistic, exponential etc.), the E_{max} model (with Hill parameter close to 1) has been shown to provide a good fit across a range of pharmaceutical studies (Thomas et al 2014). Additionally, as demonstrated in Gajewski et al (2019), the E_{max} model performs adequately when non-monotonicity is not expected, thereby resulting in a higher likelihood of identifying the correct dose. Further, previously conducted phase 2 trial for Tofacitinib (Sandborn et al 2013) has implemented such an approach to characterize the dose response and to identify efficacious doses via E_{max} models.~~ In summary, the commonality of the anti-TL1A mechanism of action in patients with UC and CD, the approved mAbs that have similar dose regimens for both UC and CD, and the opportunities for operational ~~and inferential~~ efficiencies make a basket design well suited for the planned study. …		
Section 3.4.1.1 Permanent Individual Withdrawn from IMP		
… • ~~The patient experiences coronavirus disease 2019 (COVID-19) infection.~~ …	Not applicable; event of COVID-19 was deleted as a criterion for withdrawal from IMP.	Experience of the current stage of the pandemic does not support the contingent restrictions of COVID-19.
Section 3.5 Schedule of Study Procedures and Assessments, Table 1		
See new wording column.	Table 1 Study Procedures and Assessments was modified as follows: • CDAI assessments removed at weeks 2, 6, and 10 • Weight measurement added at week 14 • Clinical laboratory assessments added at week 12	• Removed specified assessment of CDAI to reduce patient burden associated with additional blood draws for the hematocrit component of CDAI. • Correction to include weight as a measurement for CDAI at week 14. • Correction to add the

Original text with changes shown	New wording	Reason/Justification for change
		collection of laboratory assessments at week 12.
Footnote e At screening, patients with clinical symptoms that may indicate COVID-19 infection, and/or patients who, in the investigator's opinion, were at high risk of exposure to COVID-19 within 6 weeks before screening or during screening, will be tested for active COVID-19 infection. Patients who test positive will be excluded. ~~After day 1, if a patient exhibits clinical symptoms during the study that may indicate COVID-19 infection, the patient will be tested for active COVID-19 infection. If the patient tests positive, the patient will be discontinued from IMP and will need to visit the clinical site again for an early termination visit after recovery.~~	Footnote e At screening, patients with clinical symptoms that may indicate COVID-19 infection, and/or patients who, in the investigator's opinion, were at high risk of exposure to COVID-19 within 6 weeks before screening or during screening, will be tested for active COVID-19 infection. Patients who test positive will be excluded.	Experience of the current stage of the pandemic does not support the contingent restrictions of COVID-19.
Footnote g For UC patients, endoscopy will include a ***flexible*** sigmoidoscopy only ***(colonoscopy may be performed instead for baseline endoscopy if not done in the prior 12 months)***. For CD patients, endoscopy will include ileo-colonoscopy.	Footnote g For UC patients, endoscopy will include a flexible sigmoidoscopy only (colonoscopy may be performed instead for baseline endoscopy if not done in the prior 12 months). For CD patients, endoscopy will include ileo-colonoscopy.	Clarification.

Original text with changes shown	New wording	Reason/Justification for change
Footnote k Serology includes hepatitis B core antibody and surface antigen, hepatitis C virus, and human immunodeficiency virus types 1 or 2. ***Patients with HBcAb positive and HBsAg negative serology and undetectable Hepatitis B viral DNA at screening may have follow-up Hepatitis B viral DNA testing throughout their participation in the study***.	Footnote k Serology includes hepatitis B core antibody and surface antigen, hepatitis C virus, and human immunodeficiency virus types 1 or 2. Patients with HBcAb positive and HBsAg negative serology and undetectable Hepatitis B viral DNA at screening may have follow-up Hepatitis B viral DNA testing throughout their participation in the study.	Clarification.
Footnote m Clinical laboratory tests includ***ing***~~e~~ serum chemistry and ***complete blood count (***hematology***)***. Patients should be fasting for at least 8 hours prior to safety laboratory assessments only at the screening, week 14, and early termination visits (ie, visits at which low density lipoprotein, high density lipoprotein, and triglycerides will be measured). Coagulation tests (PT/PTT/INR) will be performed at screening only or in case of suspected liver injury (see Appendix M). ***Screening laboratory test abnormalities, if considered by the Investigator to be transient and inconsistent with the patient's clinical condition, may be repeated once during the screening period for confirmation.***	Footnote m Clinical laboratory tests including serum chemistry and complete blood count (hematology). Patients should be fasting for at least 8 hours prior to safety laboratory assessments only at the screening, week 14, and early termination visits (ie, visits at which low density lipoprotein, high density lipoprotein, and triglycerides will be measured). Coagulation tests (PT/PTT/INR) will be performed at screening only or in case of suspected liver injury (see Appendix M). Screening laboratory test abnormalities, if considered by the Investigator to be transient and inconsistent with the patient's clinical condition, may be repeated once during the screening period for confirmation.	To confirm validity of out of range laboratory result(s).
Section 4.1 Patient Inclusion Criteria		
Criterion g. Patient must have inadequate response to, loss of response to, or intolerance ~~of~~ ***to***: - ~~a~~***A***t least 1 of the following ***therapies*** ~~agents~~***: corticosteroids, immunosuppressants, or an approved advanced therapy for IBD including biologics (anti-TNF, anti-integrins, anti-IL-12/23, or anti-IL-23), JAK inhibitors, or S1P receptor modulators.*** ~~and n~~***N***o more than ~~2~~ 3 ***locally approved*** classes of	Criterion g. Patient must have inadequate response to, loss of response to, or intolerance to: - At least 1 of the following therapies: corticosteroids, immunosuppressants, or an approved advanced therapy for IBD including biologics (anti-TNF, anti-integrins, anti-IL-12/23, or anti-IL-23), JAK inhibitors, or S1P receptor modulators. No more than 3 locally approved	• Included IL-23 as it is a newly approved class for treatment for IBD and will be considered a similar class as the IL-12/23. • Removed doses of AZA,

Original text with changes shown	New wording	Reason/Justification for change
biologics~~: corticosteroids, immunosuppressant drugs, and/or TNF-α antagonist therapy, anti-integrins, anti-IL-12/23, JAK inhibitors, and/or S1P receptor modulators.~~ … • Inadequate response to, loss of response to, or intolerance to prior immunosuppressant treatment is defined by 1 or more of the following: - Persistent signs and symptoms of active disease despite a history of at least ~~one~~ ~~12-week~~ 1 regimen of oral AZA ~~(≥2 to 2.5 mg/kg/day)~~ or 6-MP ~~(≥1 to 1.5 mg/kg/day)~~ and/or methotrexate ~~(≥25 mg/week)~~ ***consistent with the regional standard of care;*** … Inadequate response to, loss of response to, or intolerance to prior ***advanced therapy for IBD*** (biologics***, JAK inhibitors, and S1P receptor modulators)*** ~~or small molecules~~ defined as 1 or more of the following: - Loss of response: Persistent signs and symptoms of active disease despite at least one induction and one maintenance regimen of the locally approved regimen of anti-TNF~~-inhibitors~~, anti-integrins, anti-IL-12/23 ***or anti-IL-23*** ~~monoclonal antibodies~~***mAbs***, JAK inhibitors, or S1P receptor modulators. - Inadequate response (primary non-response): Persistent signs and symptoms of active disease despite at least one induction regimen of the locally approved highest dosing regimen of anti-TNF~~-inhibitors~~, anti-integrins, anti-IL-12/23 ***or anti-IL-23*** mAbs, JAK inhibitors, or S1P receptor modulators. - Intolerance: Discontinuation of anti-TNF ~~inhibitors~~, anti-integrins, anti-IL-12/23 ***or anti-IL-23*** ~~monoclonal antibodies~~ ***mAbs***, JAK	classes of biologics. … • Inadequate response to, loss of response to, or intolerance to prior immunosuppressant treatment is defined by 1 or more of the following: - Persistent signs and symptoms of active disease despite a history of at least 1 regimen of oral AZA or 6-MP and/or methotrexate consistent with the regional standard of care; … Inadequate response to, loss of response to, or intolerance to prior advanced therapy for IBD (biologics, JAK inhibitors, and S1P receptor modulators) defined as 1 or more of the following: - Loss of response: Persistent signs and symptoms of active disease despite at least one induction and one maintenance regimen of the locally approved regimen of anti-TNF, anti-integrins, anti-IL-12/23 or anti-IL-23 mAbs, JAK inhibitors, or S1P receptor modulators. - Inadequate response (primary non-response): Persistent signs and symptoms of active disease despite at least one induction regimen of the locally approved highest dosing regimen of anti-TNF, anti-integrins, anti-IL-12/23 or anti-IL-23 mAbs, JAK inhibitors, or S1P receptor modulators. - Intolerance: Discontinuation of anti-TNF, anti-integrins, anti-IL-12/23 or anti-IL-23 mAbs, JAK inhibitors, or S1P receptor modulators due to an adverse drug reaction as determined by treating physician. Such	6-MP, and methotrexate to align with regional standards of care. • Updated to no more than 3 classes to potentially increase the patient pool for enrollment.

Original text with changes shown	New wording	Reason/Justification for change
inhibitors, or S1P receptor modulators due to an adverse drug reaction as determined by treating physician. Such adverse drug reactions include, but are not limited to, nausea/vomiting, abdominal pain, pancreatitis, liver function testing abnormalities, lymphopenia, and infections.	adverse drug reactions include, but are not limited to, nausea/vomiting, abdominal pain, pancreatitis, liver function testing abnormalities, lymphopenia, and infections.	
Section 4.2 Patient Exclusion Criteria		
Criterion c. Patient has colonic dysplasia or neoplasia ***(with exception of dysplasia on a completely excised adenomatous polyp [not a sessile one]),*** toxic megacolon, primary sclerosing cholangitis, known non-passable colonic stricture, presence of colonic or small bowel stoma, presence of non-passable colonic or small bowel obstruction or resection preventing the endoscopy procedure, or fulminant colitis.	Criterion c. Patient has colonic dysplasia or neoplasia (with exception of dysplasia on a completely excised adenomatous polyp [not a sessile one]), toxic megacolon, primary sclerosing cholangitis, known non-passable colonic stricture, presence of colonic or small bowel stoma, presence of non-passable colonic or small bowel obstruction or resection preventing the endoscopy procedure, or fulminant colitis.	Clarification. If dysplasia or neoplasm on an adenomatous polyp can be demonstrated to have been completely resected by polypectomy, and wide tissue margins are shown to be free of any dysplastic or neoplastic tissue, then the excision can therefore be considered to have been curative and the patient does not need to be excluded from study participation.
Criterion f. ~~A patient is~~ Hepatitis B core antibody ***(HBcAb)*** or surface antigen ***(HBsAg)*** positive~~,~~. ~~and/or~~ ***If HBcAb is positive and HBsAg negative, Hepatitis B viral deoxyribonucleic acid (DNA) will be done as reflective test, and, if undetectable, then not exclusionary.*** Hepatitis C antibody positive with detectable ribonucleic acids ***(RNAs)***~~,~~. ~~or p~~***P***ositive human immunodeficiency virus types 1 or 2 at screening.	Criterion f. Hepatitis B core antibody (HBcAb) or surface antigen (HBsAg) positive. If HBcAb is positive and HBsAg negative, Hepatitis B viral deoxyribonucleic acid (DNA) will be done as reflective test, and, if undetectable, then not exclusionary. Hepatitis C antibody positive with detectable ribonucleic acids (RNAs). Positive human immunodeficiency virus types 1 or 2 at screening.	Clarification.
Criterion g. Tested positive for TB at screening by the QuantiFERON® TB Gold Test ***(unless documentation of prior TB treatment is available)*** or had a history of untreated latent or active TB.	Criterion g. Tested positive for TB at screening by the QuantiFERON® TB Gold Test (unless documentation of prior TB treatment is available) or had a history of untreated latent or active TB.	Clarification.
Criterion i. A history of more than ~~1~~***2*** herpes zoster episode***s in the last***	Criterion i. A history of more than 2 herpes zoster episodes in the	The mechanism of action of aTL1A is involved in

Original text with changes shown	New wording	Reason/Justification for change
5 years or multimetameric herpes zoster.	last 5 years or multimetameric herpes zoster.	amplification of immune response; therefore, does not require such a rigid restriction.
Criterion k. Current or history of chronic liver or biliary disease (with the exception of Gilbert's syndrome, asymptomatic gallstones or uncomplicated fatty liver disease) ***at screening or baseline*** ~~or alanine aminotransferase (~~ALT~~)~~ ***or AST*** >2x ~~upper limit of normal (~~ULN~~)~~ ~~and~~ ***or*** bilirubin >1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at screening.	Criterion k. Current or history of chronic liver or biliary disease (with the exception of Gilbert's syndrome, asymptomatic gallstones or uncomplicated fatty liver disease) at screening or baseline ALT or AST >2x ULN or bilirubin >1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at screening.	Clarification.
Criterion n. Patients with ~~clinical symptoms that may indicate~~ ***confirmed infection with*** ~~coronavirus disease 2019 (~~COVID-19~~) infection, and/or patients who, in the investigator's opinion, were at high risk of exposure to COVID-19~~ within 6 weeks ~~before~~ ***prior to the*** screening ~~or during screening~~ ***visit***, ~~will be tested for active COVID-19 infection and will be excluded if they test positive for COVID-19. Patients who were admitted to an intensive care unit during a prior COVID-19 infection, patients who contracted or recovered from COVID-19 less than 6 weeks prior to screening, or patients~~ ***or*** with ***residual COVID-19 symptoms (“***long~~-term~~-COVID-19***”). Patients with active documented or suspected COVID-19 infection within 4 weeks of randomization or asymptomatic positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) test within 2 weeks of randomization*** ~~symptoms~~ are excluded ~~from the study~~.	Criterion n. Patients with confirmed infection with COVID-19 within 6 weeks prior to the screening visit, or with residual COVID-19 symptoms (“long COVID-19”). Patients with active documented or suspected COVID-19 infection within 4 weeks of randomization or asymptomatic positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) test within 2 weeks of randomization are excluded.	Experience of the current stage of the pandemic does not support the contingent restrictions of COVID-19.
Criterion r. A history of malignancy within the last 5 years (exception: basal cell carcinoma or in situ carcinoma of the cervix if successful curative therapy occurred at least 12 months prior to screening ***or curatively resected papillary thyroid cancer***).	Criterion r. A history of malignancy within the last 5 years (exception: basal cell carcinoma or in situ carcinoma of the cervix if successful curative therapy occurred at least 12 months prior to screening or curatively resected papillary thyroid cancer).	Clarification.
Criterion s.	Criterion s.	Included IL-23 as it is a newly

Original text with changes shown	**New wording**	**Reason/Justification for change**
Patient is receiving any of the following therapies within the designated time period: … - Biologics including anti-TNF ~~inhibitors~~, anti-integrin***s*** ~~inhibitors~~, ~~and~~ anti-IL-12/23***, or anti-IL-23*** ~~inhibitors~~ within 3 half-lives prior to randomization. …	Patient is receiving any of the following therapies within the designated time period: … - Biologics including anti-TNF, anti-integrins, anti-IL-12/23, ***or anti-IL-23*** within 3 half-lives prior to randomization. …	approved class for treatment for IBD and will be considered a similar class as the IL-12/23.
Criterion u. Patients with incurable diseases, persons in nursing homes, and patients incapable of giving ***written*** informed consent	Criterion u. Patients with incurable diseases, persons in nursing homes, and patients incapable of giving written informed consent	Clarification.

Original text with changes shown	New wording	Reason/Justification for change
Criterion v. ~~The patient is either an employee or an immediate relative of an employee of the sponsor or of any of the clinical investigational centers participating in the study.~~	Criterion v. Not applicable; exclusion criterion was deleted.	Criterion is an unlikely restriction for this study.
Section 5.1 Investigational Medicinal Products Used in the Study		
… The volume of the solution of each IMP (TEV-48574 and placebo) will be constant (15 mL loading dose volume and ~~12~~ ***6*** mL induction dose volume) and will be administered as single sc administrations. … Patients will receive the following regimens as a single sc administration Q2W using the [redacted] • ~~TEV-48574 2250 mg (single loading dose)/1800 mg (6 induction doses)~~ • TEV-48574 2250 mg (single loading dose)/900 mg (6 induction doses) • TEV-48574 2250 mg (single loading dose)/450 mg (6 induction doses) • Placebo to match TEV-48574 (single loading dose)/(~~I~~*i*nduction doses)	… The volume of the solution of each IMP (TEV-48574 and placebo) will be constant (15 mL loading dose volume and 6 mL induction dose volume) and will be administered as single sc administrations. … Patients will receive the following regimens as a single sc administration Q2W using the [redacted] • TEV-48574 2250 mg (single loading dose)/900 mg (6 induction doses) • TEV-48574 2250 mg (single loading dose)/450 mg (6 induction doses) • Placebo to match TEV-48574 (single loading dose)/(induction doses)	• 12 mL is the volume associated with the 1800 mg dose. The highest dose is now 900 mg and is associated with 6 mL induction volume. • Removal of the 1800 mg Q2W treatment arm.
Section 5.1.3 Test and Placebo Investigational Medicinal Product Administration		
… The infusion rate is fixed at 30 mL/hr for all sc infusions. The expected infusion durations will therefore be 30 minutes for the 15 mL loading dose and ~~24~~ ***12*** minutes for the ~~12~~ ***6*** mL induction doses.	… The infusion rate is fixed at 30 mL/hr for all sc infusions. The expected infusion durations will therefore be 30 minutes for the 15 mL loading dose and 12 minutes for the 6 mL induction doses.	12 mL is the volume associated with the 1800 mg dose. The highest dose is now 900 mg and is associated with 6 mL induction volume.

Original text with changes shown	New wording	Reason/Justification for change
…	…	
Section 5.3.1 Justification for Dose of Test Investigational Medicinal Product		
In this study, TEV-48574 will be administered as a single loading dose of 2250 mg followed by induction doses of 450 ***or,*** ~~900, or 1800~~ mg sc Q2W, for a total of 7 doses. … Furthermore, in preclinical rat models of ~~asthma and~~ colitis, ~~good efficacy~~ ***improvement in disease outcomes, including fibrosis,*** was observed at TEV-48574 doses of 3 mg/kg and above~~, with reductions in efficacy at doses below 1 mg/kg. This suggests that TEV-48574 would have a similar range of efficacious doses in asthma and IBDs~~. … The ~~3~~ ***2*** induction dose strengths in this study were selected based on a combination of safety, preclinical evidence, and pharmacokinetic considerations and will enable ~~an identification of a minimal potential efficacy dose and a comprehensive exposure-response relationship characterization to support dose~~ selection for the next stage of clinical development. ~~As wide a range of~~ ***The 2*** doses ***are*** ~~as is~~ compatible with practicality and patient safety ~~was~~ ***and were*** selected to discern clinically meaningful differences as currently there are no pharmacologic or biomarker data to give sufficient guidance as to dose. With regard to safety, TEV-48574 exposure in patients with UC or CD is not expected to exceed that of asthma patients and HV, and therefore, the suggested [redacted] level [redacted] and the highest [redacted] level [redacted] are supported by both nonclinical and available clinical safety data. ~~The dose of [redacted] is 12.5% higher than the top repeated dose [redacted] previously safely administered in Study TV48574-SAD-10126 and administered in Study TV48574-AS-20031 in patients with asthma. This change is driven by the change in IMP formulation from 100 mg/mL to 150 mg/mL, resulting in overall lower volumes of~~	In this study, TEV-48574 will be administered as a single loading dose of 2250 mg followed by induction doses of 450 or 900 mg sc Q2W, for a total of 7 doses. … Furthermore, in preclinical rat models of colitis, improvement in disease outcomes, including fibrosis, was observed at TEV-48574 doses of 3 mg/kg and above. … The 2 induction dose strengths in this study were selected based on a combination of safety, preclinical evidence, and pharmacokinetic considerations and will enable selection for the next stage of clinical development. The 2 doses are compatible with practicality and patient safety and were selected to discern clinically meaningful differences as currently there are no pharmacologic or biomarker data to give sufficient guidance as to dose. With regard to safety, TEV-48574 exposure in patients with UC or CD is not expected to exceed that of asthma patients and HV, and therefore, the suggested [redacted] level [redacted] and the highest [redacted] level [redacted] are supported by both nonclinical and available clinical safety data. … Selection of [redacted] as the highest dose provides an opportunity to maximize exposure within the safe range in case such increased clearance phenomenon materializes for TEV-48574. … In addition, it was established that the pharmacokinetics of TEV-48574 was linear at doses ≥400 mg. Based on these considerations, the low dose of [redacted] is used in the current study to optimize the safety profile, exposure,	• Removal of the 1800 mg Q2W treatment arm. • Removed reference of asthma findings in preclinical rat models as it is not relevant for this study in IBD.

Original text with changes shown	New wording	Reason/Justification for change
~~administration but risking the accuracy of administration of the [redacted] dose, which would result in a volume of 10.667 mL. Therefore, a dose of [redacted] (12 mL administration volume) is selected. The sponsor considers this difference to be marginal in the context of the inherent pharmacokinetic variability of TEV-48574 of ≥40% for different pharmacokinetic parameters and still contained well within the nonclinical safety margins. Based on dose-linear pharmacokinetics and a simple equivalence calculation, the safety margins for the [redacted] dose versus exposure parameters retrieved from the 100 mg/kg sc dose in cynomolgus monkeys (highest NOAEL reported) are 9.8 and 10.4 for C_{max} and area under the concentration-time curve (AUC), respectively.~~ ~~Predictions obtained from the established population pharmacokinetic model based on the observed data from Study TV48574-SAD-10126 suggest the steady-state median value of 145.8 µg/mL (with 62.9 µg/mL and 299.6 µg/mL being the 5th and 95th percentile, respectively) for C_{max}, and median value of 1372 days*µg/mL (with 562.6 days*µg/mL and 2936.5 days*µg/mL being the 5th and 95th percentile, respectively) for AUCτ for the simulated [redacted] The safety margins for the [redacted] dose based on population pharmacokinetic simulation exposure are 9.5 and 4.9 for C_{max} and AUC, respectively.~~ … Selection of [redacted] as the highest dose provides an opportunity to maximize exposure within the safe range in case such increased clearance phenomenon materializes for TEV-48574. … In addition, it was established that the pharmacokinetics of TEV-48574 was linear at doses ≥400 mg. Based on these considerations, the low~~est~~ dose of [redacted] is used in the current study to optimize the safety profile, exposure, and future pharmacokinetic/pharmacodynamic relationship	and future pharmacokinetic/ pharmacodynamic relationship characterization of TEV-48574. … For drugs with high pharmacokinetic variability, a greater spread of exposures could be chosen. Therefore, the 2 doses were selected to provide sufficient exposure separation between the highest and the lowest potentially therapeutic dose. Additional supportive evidence is provided by the findings of a completed Phase 2b study in patients with UC that evaluated another anti-TL1A mAb (RVT-3101, previously known as PF--06480605). Neelakantan and colleagues analyzed the totality of observed pharmacokinetic data from RVT-3101 studies in HV (Phase 1) and patients with UC (Phase 2a) (Neelakantan et al 2019). The available data included various dose levels from both iv and sc administrations. Their results suggest that the pharmacokinetics of RVT-3101 displayed the typical attributes of a mAb, with a half-life of around 20 days, approximately 67% bioavailability, and with no observable differences between the subject populations. Weight at baseline was the only identifiable factor that influenced the drug exposure, and its influence was incorporated as a covariate on drug elimination rate. The exposure comparison between TEV-48574 and RVT-3101 using population pharmacokinetic modelling and simulation approaches was performed. The suggested TEV-48574 [redacted] were benchmarked with those reported to be administered in the Phase 2b study of RVT-3101, and the analyses suggest comparable concentrations for the 2 dose levels. Due to the differences in half-lives between the 2 compounds, average drug exposure over time was used as a comparative metric. …	

Original text with changes shown	New wording	Reason/Justification for change
characterization of TEV-48574 ~~in this study~~. … For drugs with high pharmacokinetic variability, a greater spread of ~~doses~~ ***exposures*** could be chosen. Therefore, ***the 2 doses were*** ~~an intermediate dose of 900 mg providing 2-fold difference between the tested dose strengths that is considered reasonable for proper exposure-response characterization was~~ selected to provide sufficient exposure separation between the highest and the lowest potentially therapeutic dose. Additional supportive evidence is provided by ***the findings of a completed Phase 2b study in patients with UC that evaluated another anti-TL1A mAb*** (***RVT-3101, previously known as*** PF-06480605~~), an anti-TL1A mAb currently under investigation in a Phase 2b study in patients with UC~~. Neelakantan and colleagues analyzed the totality of observed pharmacokinetic data from ***RVT-3101*** ~~PF-06480605~~ studies in HV (Phase 1) and patients with UC (Phase 2a) (Neelakantan et al 2019). The available data included various dose levels from both iv and sc administrations. Their results suggest that the pharmacokinetics of ***RVT-3101*** ~~PF-06480605~~ displayed the typical attributes of a mAb, with a half-life of around 20 days, approximately 67% bioavailability, and with no observable differences between the subject populations. Weight at baseline was the only identifiable factor that influenced the drug exposure, and its influence was incorporated as a covariate on drug elimination rate. The exposure comparison between TEV-48574 and ***RVT-3101*** ~~PF-06480605~~ using population pharmacokinetic modelling and simulation approaches was performed. The suggested TEV-48574 [redacted] were benchmarked with those reported to be administered in the Phase 2b study of ***RVT-3101*** ~~PF-06480605~~, and the analyses suggest comparable concentrations for ***the*** ~~all 3~~ ***2*** dose levels. Due to the differences in half-lives between the 2 compounds, average drug exposure over time was used as a comparative metric~~s~~. …		

Original text with changes shown	New wording	Reason/Justification for change
Section 5.6.3 Permitted Inflammatory Bowel Disease Medications and Rescue Medications		
… Patients will be allowed to use the following medications as detailed below: … A stable dose of immunosuppressant drugs (methotrexate, ~~≤25 mg intramuscular or sc once weekly or ≤15 mg per os once weekly;~~ 6-MP, ~~≤1.5 mg/kg/day~~; or AZA ~~≤2.5 mg/kg/day~~ **consistent with regional standard of care**) for 4 weeks prior to endoscopy and through week 14. Decreases due to adverse events are permitted.	… Patients will be allowed to use the following medications as detailed below: … A stable dose of immunosuppressant drugs (methotrexate, 6-MP, or AZA consistent with regional standard of care) for 4 weeks prior to endoscopy and through week 14. Decreases due to adverse events are permitted.	Removed doses of AZA, 6-MP, and methotrexate to align with regional standards of care.
Section 5.6.4 Prohibited Medications and Therapies		
The following medications will be prohibited during this study: … • Biologics including anti-TNF ~~inhibitors~~, anti-integrin***s*** ~~inhibitors,~~ ~~and~~ anti-IL-12/23***, or anti-IL-23*** ~~inhibitors~~ within 3 half-lives prior to randomization. …	The following medications will be prohibited during this study: … • Biologics including anti-TNF, anti-integrins, anti-IL-12/23, or anti-IL-23 within 3 half-lives prior to randomization. …	Included IL-23 as it is a newly approved class for treatment for IBD and will be considered a similar class as the IL-12/23.
Section 5.8 Randomization and Blinding		
This is a randomized, double-blind, placebo-controlled study. Patients who meet all the inclusion criteria and none of the exclusion criteria will be randomly assigned to receive TEV-48574 (single loading dose/6 induction doses): ~~2250/1800 mg,~~ 2250/900 mg, 2250/450 mg, or placebo to match TEV-48574, in a 1:1:1~~:1~~ ratio, stratified by diagnosis (UC or CD) and previous exposure ***to advanced therapy for IBD (yes/no)***~~, failure of~~ (biologics~~, and small molecules,~~ ~~including~~ JAK inhibitors***,*** and S1P receptor modulators ~~for UC~~) ~~or naive to biologics and small molecule therapy~~. Approximately ~~140~~ ***120*** UC patients and ~~140~~ ***120*** CD patients will be randomly assigned to the treatment groups by means of	This is a randomized, double-blind, placebo-controlled study. Patients who meet all the inclusion criteria and none of the exclusion criteria will be randomly assigned to receive TEV-48574 (single loading dose/6 induction doses): 2250/900 mg, 2250/450 mg, or placebo to match TEV-48574, in a 1:1:1 ratio, stratified by diagnosis (UC or CD) and previous exposure to advanced therapy for IBD (yes/no) (biologics, JAK inhibitors, and S1P receptor modulators). Approximately 120 UC patients and 120 CD patients will be randomly assigned to the treatment groups by means of a computer-generated randomization list using	• Clarification. • Updated the sample size following the removal of the 1800 mg Q2W treatment arm.

Original text with changes shown	New wording	Reason/Justification for change
a computer-generated randomization list using interactive-response technology. … ~~The study~~ patients, ~~sponsor, and the clinical team at the site will be blinded to treatment assignment until the database is locked for analysis~~ ***and the site will be blinded until all patients complete the study, and the database is locked for final analysis for both indications. The sponsor will be blinded to treatment assignment until the database is locked for analysis of each indication. Prior to unblinding, the sponsor will establish a separate blinded study team supporting the conduct of the study until the database is locked for final analysis for both indications***. …	interactive-response technology. … The patients and the site will be blinded until all patients complete the study, and the database is locked for final analysis for both indications. The sponsor will be blinded to treatment assignment until the database is locked for analysis of each indication. Prior to unblinding, the sponsor will establish a separate blinded study team supporting the conduct of the study until the database is locked for final analysis for both indications. …	
Section 5.9.2 Blinding and Unblinding		
… ***Details regarding unblinding of Teva team while maintaining the blind of the study, in case efficacy threshold is met at the interim analysis, and in case the final analysis is conducted for one indication while the other indication is ongoing, will be provided in a separate unblinding charter.*** …	… Details regarding unblinding of Teva team while maintaining the blind of the study, in case efficacy threshold is met at the interim analysis, and in case the final analysis is conducted for one indication while the other indication is ongoing, will be provided in a separate unblinding charter. …	Clarification.
Section 5.9.3 Independent Data Monitoring Committee		
A single review committee (IDMC) will be established to ~~assess futility and~~ monitor ~~safety data~~***the study*** while ~~the study~~***it*** is ongoing, ***including periodic reviews of safety data, and pre-specified analyses of efficacy data,*** as described below. … • The role of the IDMC will be to periodically monitor unblinded safety data ***to ensure the safety of study patients,*** ~~review the planned interim futility analysis,~~ and make recommendations on study conduct. ***In***	A single review committee (IDMC) will be established to monitor the study while it is ongoing, including periodic reviews of safety data, and pre-specified analyses of efficacy data, as described below. … • The role of the IDMC will be to periodically monitor unblinded safety data to ensure the safety of study patients, and make recommendations on study conduct. In addition, the IDMC will review pre-specified analyses of	Modification to accommodate the change in the interim analysis to include non-binding analysis of high efficacy.

Original text with changes shown	New wording	Reason/Justification for change
addition, the IDMC will review pre-specified analyses of efficacy data to make recommendations to the sponsor regarding futility or the possible acceleration of Phase 3 planning. The IDMC charter will provide details regarding procedures to protect the scientific integrity of ***the*** trial, conduct of the interim analysis, dissemination of results, and decision criteria ~~based on the futility analysis~~ in addition to pre-specified study stopping rules for safety. ….	efficacy data to make recommendations to the sponsor regarding futility or the possible acceleration of Phase 3 planning. The IDMC charter will provide details regarding procedures to protect the scientific integrity of the trial, conduct of the interim analysis, dissemination of results, and decision criteria in addition to pre-specified study stopping rules for safety. ….	
Section 5.10 Total Blood Volume		
The estimated maximum blood volume to be collected for each patient in this study is approximately 20 mL per visit and approximately ~~200~~ ***240*** mL for each patient during the entire study.	The estimated maximum blood volume to be collected for each patient in this study is approximately 20 mL per visit and approximately 240 mL for each patient during the entire study.	Correction to include serum measures of tissue condition in the calculation of total blood volume.
Section 6.1.2.1 Biopsy Collection		
… ~~Biopsies will be used for measures of histologic disease and exploratory biomarker assays.~~ ***Ileal (for CD) and multiple colonic tissue sampling will be obtained by endoscopic biopsies and will be evaluated by microscopic and histologic analyses, as well as for exploratory measures involving established and novel biomarkers of intestinal inflammation and fibrosis. There are several different approaches for obtaining these endoscopic biopsy samples, and the preferred procedures are described in the Laboratory Manual and Quick Reference Card.*** …	… Ileal (for CD) and multiple colonic tissue sampling will be obtained by endoscopic biopsies and will be evaluated by microscopic and histologic analyses, as well as for exploratory measures involving established and novel biomarkers of intestinal inflammation and fibrosis. There are several different approaches for obtaining these endoscopic biopsy samples, and the preferred procedures are described in the Laboratory Manual and Quick Reference Card. …	Clarification.
Section 7.5 Clinical Laboratory Tests, Table 9		
See new wording column.	Table 9 Clinical Laboratory Tests was updated as follows: • Hematology and Coagulation	Laboratory does not measure this analyte.

Original text with changes shown	New wording	Reason/Justification for change
	– Lymphocytes atypical was removed as a laboratory test.	
Section 7.5.1 Serum Chemistry, Hematology, and Urinalysis		
… Clinical laboratory tests will be performed using the central laboratory***. Local laboratory testing can be used under extenuating circumstances and only following agreement with the sponsor.*** ***Screening laboratory test abnormalities, if considered by the Investigator to be transient and inconsistent with the patient's clinical condition, may be repeated once during the screening period for confirmation.***	… Clinical laboratory tests will be performed using the central laboratory. Local laboratory testing can be used under extenuating circumstances and only following agreement with the sponsor. Screening laboratory test abnormalities, if considered by the Investigator to be transient and inconsistent with the patient's clinical condition, may be repeated once during the screening period for confirmation**.**	Clarification.
Section 7.5.2 Other Clinical Laboratory Tests		
At screening, patients will be tested for HBcAb and HBsAg, antibodies to hepatitis C virus ***(reflex viral RNA testing if hepatitis C antibodies present)***, human immunodeficiency virus types 1 or 2, and enteric pathogens (including stool culture and Clostridium difficile toxin assay; additional testing [eg, ova and parasites] may be performed at the investigator's clinical discretion). ***If HBcAb is positive and HBsAg negative, hepatitis B viral DNA will be done as reflective test, and, if undetectable, then not exclusionary.*** Patients will also be tested for TB at screening (QuantiFERON® TB Gold Test). Patients with confirmed positive results will not be eligible to participate in the study ***(unless documentation of prior TB treatment is available)***. …	At screening, patients will be tested for HBcAb and HBsAg, antibodies to hepatitis C virus (reflex viral RNA testing if hepatitis C antibodies present), human immunodeficiency virus types 1 or 2, and enteric pathogens (including stool culture and Clostridium difficile toxin assay; additional testing [eg, ova and parasites] may be performed at the investigator's clinical discretion). If HBcAb is positive and HBsAg negative, hepatitis B viral DNA will be done as reflective test, and, if undetectable, then not exclusionary. Patients will also be tested for TB at screening (QuantiFERON® TB Gold Test). Patients with confirmed positive results will not be eligible to participate in the study (unless documentation of prior TB treatment is available). …	Clarification.
… At screening, patients with clinical symptoms that may indicate	… At screening, patients with clinical symptoms that may indicate COVID-19 infection and/or patients who, in the	Experience of the current stage of the pandemic does not support the contingent restrictions of COVID-

Original text with changes shown	New wording	Reason/Justification for change
COVID-19 infection and/or patients who, in the investigator's opinion, were at high risk of exposure to COVID-19 within 6 weeks before screening or during screening will be tested for active COVID-19 infection. Patients who test positive will be excluded. ~~After day 1, if a patient exhibits clinical symptoms during the study that may indicate COVID-19 infection, the patient will be tested for active COVID-19 infection. If the patient tests positive, the patient will be discontinued from IMP and will need to visit the clinical site again for an early termination visit after recovery.~~ …	investigator's opinion, were at high risk of exposure to COVID-19 within 6 weeks before screening or during screening will be tested for active COVID-19 infection. Patients who test positive will be excluded. …	19.
Section 8.4 Assessment of Exploratory Biomarkers		
… Details of the specimen collection, processing, and handling requirements are provided in the ~~study reference~~ ~~m~~ ***Laboratory Manual***. ~~All biopsy and fecal samples collected in this study will be utilized to support study-specific endpoints, and any residual samples will be destroyed.~~ Residual ***biopsy, fecal, and*** serum samples, after appropriate analysis to support this study, may be stored at a Teva-secured facility for up to ***15*** ~~5~~ years towards future analysis related to TEV-48574 or IBD if permitted by the ICF and local regulations. …	… Details of the specimen collection, processing, and handling requirements are provided in the Laboratory Manual. Residual biopsy, fecal, and serum samples, after appropriate analysis to support this study, may be stored at a Teva-secured facility for up to 15 years towards future analysis related to TEV-48574 or IBD if permitted by the ICF and local regulations. …	Correction.
Section 9.1 Sample Size and Power Considerations		
A total study sample size of ~~280~~ ***240*** patients is planned, with ~~140~~ ***120*** patients (~~35~~***40*** patients per dose arm) each for the 2 ~~disease~~ ~~groups~~ ***indications*** of UC and CD. Assumptions: The clinical remission and endoscopic response rates assumed in the sample size and related operating characteristics computations are as follows:	A total study sample size of 240 patients is planned, with 120 patients (40 patients per dose arm) each for the 2 indications of UC and CD. Assumptions: The clinical remission and endoscopic response rates assumed in the sample size and related operating characteristics computations are as follows:	Updated the sample size calculation following the removal of the 1800 mg Q2W treatment arm.

Original text with changes shown	New wording	Reason/Justification for change
• Clinical remission rates in UC ~~group~~ ***indication***: 8% for placebo ~~and low-dose~~; 30% for ***TEV-48574 low~~mid-*** and high-dose groups, respectively • Endoscopic response rates in CD ~~group~~ ***indication***: 12% for placebo ~~and low-dose~~; 34% for ***TEV-48574 low*** ~~mid-~~ and high-dose groups, respectively Simulation-based operating characteristics for the analysis of the primary efficacy variable using a Bayesian ***Beta Binomial*** ~~hierarchical 3-parameter E_{max}~~ model ~~for the interim and final analysis~~ ***are presented in Table 10~~.~~ ***. This model uses*** ~~with~~ a posterior probability ~~futility~~ cutoff of <0.55 for ***the assessment of futility at the interim analysis*** ~~each disease group~~, and ~~final success~~ ***a*** posterior probability cutoff of ≥0.~~86~~ ***90~~, are presented in Table 10*** ***to declare success at the final analysis***. ***For UC,*** ~~Tf~~***he*** family-wise false-positive rate (ie, probability of ***making*** at least 1 false-positive conclusion under the ~~global~~ null assumption ***for both doses***) is ~~no more than 12%~~***13%,*** and the probability of declaring success for ***at least 1 dose group is 97%***~~both UC and CD groups is 94%,~~ under the assumptions ~~stated~~ above. ***For CD, the family-wise false-positive rate is 15%, and the probability of declaring success for at least 1 dose is 95%, under the assumptions above.*** **…** Under a less optimistic scenario ~~for mid- and high-dose groups, when~~ ***where the placebo response rates remain the same while*** the clinical remission rate in the UC ~~group~~ ***indication*** is reduced to 20% ~~(from 30%)~~ ***for both doses***, and ***the*** endoscopic response rate in the CD ~~group~~ ***indication*** is reduced to 25% ~~(from 34%)~~ ***for both doses***, ~~while maintaining the identical response rates for placebo and low-dose (in both UC and CD groups),~~ the probability of declaring success in ***at least 1 dose*** ~~both UC~~ ***is 75% for UC*** and ~~CD groups is about 69~~***74***% ***for CD***.	• Clinical remission rates in UC indication: 8% for placebo; 30% for TEV-48574 low- and high-dose groups, respectively • Endoscopic response rates in CD indication: 12% for placebo; 34% for TEV-48574 low- and high-dose groups, respectively Simulation-based operating characteristics for the analysis of the primary efficacy variable using a Bayesian Beta Binomial model are presented in Table 10. This model uses a posterior probability futility cutoff of <0.55 for the assessment of futility at the interim analysis and a posterior probability cutoff of ≥0.90 to declare success at the final analysis. For UC, the family-wise false-positive rate (ie, probability of making at least 1 false-positive conclusion under the null assumption for both doses) is 13%, and the probability of declaring success for at least 1 dose group is 97%, under the assumptions above. For CD, the family-wise false-positive rate is 15%, and the probability of declaring success for at least 1 dose is 95%, under the assumptions above. … Under a less optimistic scenario where the placebo response rates remain the same while the clinical remission rate in the UC indication is reduced to 20% for both doses, and the endoscopic response rate in the CD indication is reduced to 25% for both doses, the probability of declaring success in at least 1 dose is 75% for UC and 74% for CD. Details regarding the statistical decision criteria and Bayesian model, as well as operating characteristics in case only 1 active dose is effective are provided in Appendix N. For comparison, a frequentist logistic regression analysis	

Original text with changes shown	New wording	Reason/Justification for change
Details regarding the statistical decision criteria and Bayesian ~~hierarchical~~ model, ***as well as*** operating characteristics ~~including priors and hyper-priors used in the computation of the operating characteristics,~~ ***in case only 1 active dose is effective*** are provided in Appendix N. ~~The operating characteristics under additional scenarios, including discordant scenarios where the treatment is effective only in one disease group, are presented in Appendix N~~. For ***comparison,*** ~~an independent (by UC, CD indication)~~***a*** frequentist logistic regression analysis, ~~140~~ ***with 40*** patients per ***dose per*** indication ***would*** provide~~s~~ at least 90% power ***using a Mantel-Haenszel test*** with ***a 1-sided*** Type I error rate of 10% ~~as determined by 1-sided Cochran-Armitage trend~~ test ~~with~~ ***and the*** assumptions ~~of the true clinical remission and endoscopic~~ about response rate~~s~~ specified ~~under "Assumptions"~~ above. ***This power does not take into account the planned futility analysis.***	with 40 patients per dose per indication would provide at least 90% power using a Mantel-Haenszel test with a 1-sided Type 1 error rate of 10% and the assumptions about response rate specified above. This power does not take into account the planned futility analysis.	
Table 10 (Operating Characteristics of Interim and Final Analysis See new wording column.	Table 10 was revised as described below: • Simulations updated based on Beta-Binomial model • Modified the futility cutoffs in the footnotes	The interim and final analysis rules with a corresponding update to the operating characteristics were revised following the removal of the 1800 mg Q2W treatment arm and change in the primary analysis model.

Original text with changes shown	New wording	Reason/Justification for change
Section 9.2.2 Modified Intent-to-Treat Analysis Set		
The modified intent-to-treat (mITT) analysis set for each indication (UC or CD) is a subset of the ITT analysis set including only patients who receive at least 1 dose of ***placebo, TEV-48574 450 mg (low dose), or TEV-48574 900 mg (high dose)*** ~~IMP~~. …	The modified intent-to-treat (mITT) analysis set for each indication (UC or CD) is a subset of the ITT analysis set including only patients who receive at least 1 dose of placebo, TEV-48574 450 mg (low dose), or TEV-48574 900 mg (high dose). …	Removal of the 1800 mg Q2W treatment arm.
Section 9.2.4 Per-Protocol Analysis Set		
~~The per-protocol (PP) analysis set for each indication (UC or CD) is a subset of the mITT analysis set including only patients without important protocol deviations.~~ ~~In the PP analysis set, patients will be categorized by treatment patients actually received, regardless of the treatment to which they were randomized.~~	Not applicable; the analysis set was deleted.	No longer applicable for the study design.
Section 9.4 Study Population		
The ~~m~~ITT analysis set (Section 9.2.1) will be used for all ~~efficacy~~ ***study population*** summaries ~~unless otherwise specified~~. ***Summaries will be presented by treatment group, pooled TEV-48574, and all patients, separately by indication (UC or CD) and pooled (UC and CD).*** ~~Efficacy summaries will be presented separately by indication (UC or CD). The safety analysis set will be used for all safety summaries unless otherwise specified. Safety summaries will be presented separately by indication (UC or CD) and pooled (UC and CD).~~	The ITT analysis set (Section 9.2.1) will be used for all study population summaries. Summaries will be presented by treatment group, pooled TEV-48574, and all patients, separately by indication (UC or CD) and pooled (UC and CD).	Correction to describe analysis of study population.
Section 9.5.4.1 Primary Efficacy Analysis		
A Beta-binomial model with a non-informative Beta(1,1) prior will be used to analyze the primary response endpoint, clinical remission (for UC) or endoscopic response (for CD), hereafter denoted as "response". The model will be fit separately for each dose within each indication. ~~An E_{max} dose-response model will be used to analyze the primary efficacy variable (defined in the primary estimand). Notation and distributional assumptions are as follows:~~	A Beta-binomial model with a non-informative Beta(1,1) prior will be used to analyze the primary response endpoint, clinical remission (for UC) or endoscopic response (for CD), hereafter denoted as "response". The model will be fit separately for each dose within each indication. Inference will be based on posterior distribution of the response rates. A TEV-48574 dose will be declared	The previous Bayesian hierarchical E_{max} dose-response model is not applicable following the removal of the 1800 mg Q2W treatment arm. The simple beta-binomial model fit separately to each dose within each indication, with a final cutoff of

Original text with changes shown	New wording	Reason/Justification for change
~~• Y represents response~~ ~~• $\theta_{d,i}$ denotes the log-odds of response~~ ~~– d = 0, 1, 2, 3 denote placebo, low, medium, and high doses~~ ~~– i = 1, 2 correspond to UC, CD~~ ~~• $Y \sim$ Ber $(antilogit(\theta_{d,i}))$~~ ~~The 3-parameter E_{max} model for dose response is given by:~~ $$\theta_{d,i} = E_{0,i} + \frac{(E_{max,i} \cdot d)}{(ED_{50,i} + d)}$$ ~~For each $i = 1,2$, the parameters are as follows:~~ ~~• $E_{0,i}$ is the average placebo response~~ ~~• $E_{max,i}$ represents the maximum effect of the drug~~ ~~• $ED_{50,i}$ is the dose corresponding to half the effect of $E_{max,i}$~~ ~~A Bayesian hierarchical model will be employed to model the data and estimate these parameters. A common underlying prior distribution is assumed for the same parameters across the 2 models for UC and CD. The hierarchical model borrows information across disease groups (UC, CD), shrinking the estimates of the model parameters for the 2 disease groups towards a common mean. The borrowing of information improves precision associated with the estimates of the parameters. A smaller variance (ie, 1/precision) in the common prior increases information borrowed, whereas a larger variance would mean that the estimates are largely impacted by the data within the disease group.~~ Inference will be based on posterior distribution of ***the response rates. A TEV-48574 dose will be declared successful***	successful at the final analysis if the posterior probability that the response rate in the TEV-48574 dose is higher than the response rate in the placebo arm is ≥0.90. Put another way, the success criterion for each dose within indication can be written as: Posterior Probability (TEV-48574 response rate – placebo response rate > 0) ≥0.90 The following quantities will be presented: • Posterior means of the response rates for TEV-48574 high dose (900 mg Q2W), TEV-48574 low dose (450 mg Q2W) and placebo • 95% credible intervals for difference in response rates (TEV-48574 doses – placebo) • For each TEV-48574 dose, Posterior Probability (TEV-48574 dose – placebo response rate >0) For further details, see Appendix N.	≥0.90, was selected based on operating characteristics.

Original text with changes shown	New wording	Reason/Justification for change
at the final analysis if the posterior probability that the response rate in the TEV-48574 dose is higher than the response rate in the placebo arm is ≥0.90. Put another way, the success criterion for each dose within indication can be written as~~:these parameters and summarized as follows for each indication (UC, CD):~~ ***Posterior Probability (TEV-48574 response rate – placebo response rate > 0) ≥0.90*** ***The following quantities will be presented:*** • Posterior means ~~and/or medians~~ of the response rates for TEV-48574 ***high dose (900 mg Q2W),*** ***TEV-48574 low dose (450 mg Q2W)*** ~~doses~~,***and*** placebo • 95% credible intervals for difference in response rates (TEV-48574 doses – placebo) • For each TEV-48574 dose, Posterior Probability (TEV-48574 dose – placebo response rate > 0) ~~• Posterior Probability (E_{max} > 0)~~ ***For further details, see*** Appendix N.~~ provides details regarding prior and hyper-prior distributions for the Bayesian hierarchical (E_{max}) model in addition to operating characteristics under various assumptions of remission (UC), response rates (CD).~~		
Section 9.5.4.2 Sensitivity Analysis		
Tipping point analysis will be performed to test the robustness of the primary analysis to the imputation of patients that discontinue the study or have missing week 14 modified Mayo score (UC patients) or SES-CD (CD patients) data as non-responders. ~~The following sensitivity analyses will be performed for the primary efficacy analysis: (a) replication of the primary~~	Tipping point analysis will be performed to test the robustness of the primary analysis to the imputation of patients that discontinue the study or have missing week 14 modified Mayo score (UC patients) or SES-CD (CD patients) data as non-responders.	Updated sensitivity analysis.

Original text with changes shown	New wording	Reason/Justification for change
~~analysis using the PP analysis set and (b) an analysis to test the robustness of the missing at random assumption (made in the primary analysis) by using an alternate approach (ie, different from non-responder imputation) to handle missing data. Details will be provided in the Statistical Analysis Plan.~~		
Section 9.5.4.3 Supplementary Analysis		
A supplementary analysis for the ***primary*** efficacy variable (defined in the supplementary estimand) will be performed using a logistic regression model ***fit separately to each indication*** with the following fixed effects: dose ***(as categorical variable)***, ~~indication, dose-by-indication interaction, randomization stratification factors,~~ ***previous exposure to advanced IBD therapy (yes/no),*** and baseline ***modified Mayo score (UC patients) or SES-CD (CD patients).*** ~~response. Separate dose-response lines will be derived for each of the 2 disease groups. The (slope) coefficient corresponding to dose within an indication will be estimated and~~ ***Each comparison of TEV-48574 dose versus placebo will be*** tested (one-sided) ~~for statistical significance~~ at a n***ominal significance level of α***=~~alpha of~~0.1. ~~The following additional analyses will be undertaken to examine the robustness of the primary efficacy analysis results:~~ ***In addition, a*** Cochran-Mantel-Haenszel (CMH) test for pairwise comparisons between the active dose groups and placebo ***will be performed*** separately for UC and CD. Nominal p-values will be presented for each of the comparisons. ~~• Bayesian E_{max} dose-response model fit separately (ie, no borrowing) for UC and CD. Inferences presented for the primary efficacy analysis will be re-produced for this approach.~~ ~~• Frequentist E_{max} dose-response model fit separately for UC and CD. Response rates of TEV-48574 doses, placebo and 95% confidence intervals for difference~~	A supplementary analysis for the primary efficacy variable (defined in the supplementary estimand) will be performed using a logistic regression model fit separately to each indication with the following fixed effects: dose (as categorical variable), previous exposure to advanced IBD therapy (yes/no), and baseline modified Mayo score (UC patients) or SES-CD (CD patients).-Each comparison of TEV-48574 dose versus placebo will be tested (one-sided) at a nominal significance level of α=0.1. In addition, a Cochran-Mantel-Haenszel (CMH) test for pairwise comparisons between the active dose groups and placebo will be performed separately for UC and CD. Nominal p-values will be presented for each of the comparisons.	Updated supplementary analyses following the removal of the 1800 mg Q2W treatment arm and change in the primary analysis.

Original text with changes shown	New wording	Reason/Justification for change
~~in response rates (TEV-48574 doses – placebo), along with summaries of model parameters will be presented~~ • ~~Logistic regression model with fixed effects for dose, randomization stratification factors and baseline response fit separately for UC and CD.~~		
Section 9.5.4.4 Secondary Efficacy Analysis		
All secondary efficacy endpoints will be analyzed separately for the UC and CD ~~disease groups~~ ***indications***. ***For each binary endpoint,*** ~~A~~***a*** logistic regression model ***similar to the supplementary model described in Section 9.5.4.3*** ~~will be used with the following fixed effects: dose, randomization stratification factors, and~~ ***with*** the respective baseline measurement ***will be used. For each comparison of TEV-48574 dose versus placebo, the differences in proportions,*** ~~O~~***o***dds ratios ~~(for each of the TV48574 doses versus placebo)~~***,*** associated 95% CIs, and nominal p-value~~s~~ will be reported.	All secondary efficacy endpoints will be analyzed separately for the UC and CD indications. For each binary endpoint, a logistic regression model similar to the supplementary model described in Section 9.5.4.3 with the respective baseline measurement will be used. For each comparison of TEV-48574 dose versus placebo, the differences in proportions, odds ratios, associated 95% CIs, and nominal p-value will be reported.	Clarification.
Section 9.13 Planned Interim Analysis		
Interim analyses for safety and efficacy are planned for this study. An interim efficacy***/futility*** analysis ~~for futility~~ is planned in each ~~disease group~~ ***indication*** (UC and CD) when at least ~~44~~ ***50% of*** patients ~~(approximately 30%)~~ in ~~that group~~ ***the indication*** have completed the 14-week primary efficacy readout or had the opportunity to do so. In the interim analysis, the same Bayesian ***Beta-Binomial*** ~~hierarchical E_{max} dose-response~~ model ~~used as~~ ***described in*** the primary analysis model will be used to analyze the primary efficacy ***response*** variable ~~(clinical remission for UC and endoscopic response for CD, hereafter denoted as "response")~~ for each ***dose within each*** ~~disease group~~ ***indication***. The futility criterion for each ~~disease group~~ ***dose*** is:	Interim analyses for safety and efficacy are planned for this study. An interim efficacy/futility analysis is planned in each indication (UC and CD) when at least 50% of patients in the indication have completed the 14-week primary efficacy readout or had the opportunity to do so. In the interim analysis, the same Bayesian Beta-Binomial model described in the primary analysis model will be used to analyze the primary efficacy response variable for each dose within each indication. The futility criterion for each dose is: • Posterior probability (TEV-48574 response rate – placebo response rate > 0) <0.55 Refer to Table 12 and Appendix N for operating	• The interim analysis timing, method, and cutoff were updated following the change in the primary analysis model and the corresponding operating characteristics. • Efficacy analysis added to allow the sponsor timely assessment for futility and efficacy.

Original text with changes shown	New wording	Reason/Justification for change
• ~~If the~~ ***~~p~~Posterior*** probability $P(E_{max,i} > 0 \mid interim\ data)$ ~~for disease group *i* is <0.55, then the corresponding disease group is futile.~~***(TEV-48574 response rate – placebo response rate > 0) < 0.55*** ~~An analysis of each disease group independently will be performed at the interim analysis for the disease group as a supporting analysis, as follows:~~ • ~~A Beta-Binomial model with a non-informative prior *Beta(1,1)* will be fitted to the response rate π in each treatment group *d* in the disease group *i*, and the posterior probability that the response rate in each active group is higher than the response rate in the placebo group, $P(\pi_{a,i} > \pi_{0,i})$, will be calculated.~~ Refer to Table 12 and Appendix N for operating characteristics of the interim and final analysis. ***In addition to futility, an efficacy criteria will be incorporated for the purpose of internal decision making and planning purposes. The criteria are non-binding, purely for purposes of accelerating planning for subsequent trials, and will not trigger any recommendations on trial conduct. Details of the efficacy criteria will be provided in the Statistical Analysis Plan.*** **…** All interim analyses will be performed by an external, independent, unblinded reporting team. The results ***of all interim analyses*** will be reviewed by an IDMC comprised of external medical and statistical experts. The IDMC will make ~~a~~ recommendation***s regarding study conduct*** after evaluation of the totality of ~~available safety~~ ***the*** data. ***Recommendations include, but are not limited to, dropping of a dose arm, termination of an indication, or termination of the study.*** The details regarding the statistical analysis methods will be	characteristics of the interim and final analysis. In addition to futility, efficacy criteria will be incorporated for the purpose of internal decision making and planning purposes. The criteria are non-binding, purely for purposes of accelerating planning for subsequent trials, and will not trigger any recommendations on trial conduct. Details of the efficacy guideline will be provided in the Statistical Analysis Plan. … All interim analyses will be performed by an external, independent, unblinded reporting team.The results of all interim analyses will be reviewed by an IDMC comprised of external medical and statistical experts. The IDMC will make recommendations regarding study conduct after evaluation of the totality of the data. Recommendations include, but are not limited to, dropping of a dose arm, termination of an indication, or termination of the study. The details regarding the statistical analysis methods will be provided in the Statistical Analysis Plan. The IDMC charter will provide details regarding procedures to protect the scientific integrity of the study, conduct of the interim analysis, dissemination of results, and decision criteria. … Additional Analyses: As part of the interim analysis for efficacy/futility, additional analyses may be provided to the IDMC upon request or as deemed necessary by the sponsor.	

Original text with changes shown	New wording	Reason/Justification for change
provided in the Statistical Analysis Plan. The IDMC charter will provide details regarding procedures to protect the scientific integrity of the study, conduct of the interim analysis, dissemination of results, and decision criteria ~~based on the futility analysis~~. … ***Additional Analyses:*** As part of the interim analysis for ***efficacy/***futility, ***additional analyses may be provided to the IDMC upon request or as deemed necessary by the sponsor***. ~~the primary efficacy endpoints may be analyzed by the presence of TEV-48574 ligand or other relevant biomarkers.~~ ~~Additional endpoints may also be provided to the IDMC as part of the interim analyses for futility.~~		
Section 15 References		
… • ~~Gajewski BJ, Meinzer C, Berry SM, et al. Bayesian hierarchical EMAX model for dose-response in early phase efficacy clinical trials. Stat Med.~~ 2019;38(17):3123-3138. ... • ~~Kaizer A, Koopmeiners J, Kane M, Roychoudhury S, Hong D, Hobbs B, et al. Basket designs: statistical considerations for oncology trials. JCO Precision Oncology 2019;3:1-9.~~ … • Sand~~born WJ, Ghosh S, Panes J, et al. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis.~~	Not applicable; the 3 references were deleted:	References were removed as they are no longer applicable to support the study, including the statistical analysis methods due to removal of the 1800 mg Q2W treatment arm.

Original text with changes shown	New wording	Reason/Justification for change
~~N Engl J Med. 2012;367(7):616-624.~~ … • ~~Thomas N, Sweeney K, & Somayaji V Meta-analysis of clinical dose-response in a large drug development portfolio. Statistics in~~ ---		
Appendix A. Departments and Institutions		
Sponsor's Authorized Representative [redacted] ~~Teva Branded Pharmaceutical Products R&D, Inc.~~ [redacted] ***Teva Branded Pharmaceutical Products R&D, Inc.*** [redacted]	Sponsor's Authorized Representative [redacted] Teva Branded Pharmaceutical Products R&D, Inc. [redacted]	Transfer of sponsor responsibilities.
Appendix B. Study Procedures and Assessments by Visit		
2. Procedures During Administration of Investigational Medicinal Product (Double-Blind Treatment Period) b. Visits 2, 4, and 6 (weeks 2, 6, and 10, days 15, 43, 71 ([±3 days based on previous visit]) • ~~CDAI score (CD only)~~ c. Visits 3, 5, and 7 (weeks 4, 8, and 12, days 29, 57, 85 ([±3	2. Procedures During Administration of Investigational Medicinal Product (Double-Blind Treatment Period) b. Visits 2, 4, and 6 (weeks 2, 6, and 10, days 15, 43, 71 ([±3 days based on previous visit]) Not applicable; CDAI assessment was deleted at weeks 2, 6, and 10. c. Visits 3, 5, and 7 (weeks 4, 8, and 12, days 29, 57, 85	• To reduce patient burden associated with additional blood draws for the hematocrit component of CDAI. • CDAI is being collected at week 12; therefore, a clinical laboratory collection was

Original text with changes shown	New wording	Reason/Justification for change
days based on **previous visit**]) • clinical laboratory tests ~~**(visits 3 and 5 only)**~~ d. Visit 8 (week 14, day 99 [±3 days based on previous visit]) • ***weight measurement***	([±3 days based on **previous visit**]) Clinical laboratory test added at visit 7; performed at visits 3, 5, and 7 d. Visit 8 (week 14, day 99 [±3 days based on previous visit]) Weight measurement added at visit 8.	added at visit 7. • CDAI is being collected at week 14; therefore, weight measurement was added at visit 8.
4. Early Termination The procedures and assessments performed at the early termination visit are identical to those performed at the visit 8 (week 14 visit; see item "d" above), except that weight is measured as well. ***If a patient develops COVID-19 during the course of the trial this is not an indication for early termination.***	4. Early Termination The procedures and assessments performed at the early termination visit are identical to those performed at the visit 8 (week 14 visit; see item "d" above), except that weight is measured as well. If a patient develops COVID-19 during the course of the trial this is not an indication for early termination.	Experience of the current stage of the pandemic does not support the contingent restrictions of COVID-19.
Appendix K. Management of Study Activities During COVID-19 Outbreaks		
Section 1.3. Known and Potential Benefits and Risks to Patients … It should be noted that patients diagnosed with active or residual COVID-19 or who were hospitalized in the intensive care unit during COVID-19 infection would not be included in the study as they would meet exclusion criteri***on*** ~~a~~ "a" ***and did not meet inclusion criterion*** "k". … ~~If a patient exhibits clinical symptoms during the study that may indicate COVID-19 infection, the patient will be tested for active COVID-19 infection. If the patient tests positive, the patient will be discontinued from the IMP and will attend an early termination visit once recovered. Remote assessment of safety via teleconference (TC) and/or videoconference (VC), with VC being the preferred method, is recommended until the patient attends for the early termination visit.~~ ~~Section 3.1. General Study Design and Study Schematic~~	Section 1.3. Known and Potential Benefits and Risks to Patients … It should be noted that patients diagnosed with active or residual COVID-19 or who were hospitalized in the intensive care unit during COVID-19 infection would not be included in the study as they would meet exclusion criterion "a" and did not meet inclusion criterion "k". …	• Correction to denote eligibility criterion "a" as part of the inclusion criteria. • Experience of the current stage of the pandemic does not support the contingent restrictions of COVID-19.

Original text with changes shown	New wording	Reason/Justification for change
~~Diagram; Section 3.5. Schedule of Study Procedures and Assessments~~ ~~In the event of an emergency situation (eg, COVID-19 outbreaks), in case a patient cannot return to the clinic for the scheduled visits (eg, due to quarantine, isolation, patient's concern, active COVID-19 infection, or closure of the site clinic), the patient will be discontinued from the IMP, scheduled adverse event and concomitant medication monitoring will be continued, and the patient will attend an early termination visit when that becomes possible. Remote assessment of safety via TC and/or VC, with VC being the preferred method, is recommended until the patient attends the early termination visit. All other tests (including safety labs, pharmacokinetics, anti-drug antibody, and biomarkers [if applicable and only in patients who do not have active COVID-19 infection]) are to be conducted once the patient can return to the study center for the early termination visit.~~ ~~In the event that a patient completes the screening procedures but cannot come to the site for visit 1 (eg, due to quarantine, isolation, patient's concern, or closure of the site clinic), it may be possible to extend the duration of the screening period on a case-by-case basis, following discussion between the investigator and the sponsor study physician. Rescreening of the patient will also be allowed.~~ ~~These measures will be implemented on a case-by-case basis, and only when and where they are warranted due to the emergency situation. Preferably, the full protocol instructions will be followed whenever the modified instructions are not required~~. … ~~Section 4.4. Replacement of Patients~~ ~~In the event of an emergency situation (eg, COVID-19 outbreaks), the number of patients to be randomized may be increased to ensure the targeted number of completers per arm.~~ ~~Section 6. Assessment of Efficacy~~ ~~In the event of an emergency situation (eg, COVID-19~~		

Original text with changes shown	New wording	Reason/Justification for change
~~outbreaks), in case a patient cannot return to the clinic for the scheduled visits (eg, due to quarantine, isolation, patient's concern, active COVID-19 infection, or closure of the site clinic), the patient will be discontinued from IMP, remote monitoring will continue, and the patient will attend for an early termination visit when that becomes possible.~~ ~~These measures will be implemented on a case-by-case basis, and only when and where they are warranted due to the emergency situation. Preferably, the full protocol instructions will be followed whenever the modified instructions are not required.~~ … ~~Section 7.5. Clinical Laboratory Tests~~ ~~For early termination patients (patients who cannot be administered the IMP), all required samples scheduled for early termination will be collected once the patient can return to the study center.~~ ~~Section 9.5.5. Planned Method of Analysis~~ ~~Sensitivity and supplementary analyses will be conducted to evaluate the impact of the change to remote monitoring (TC/VC visits) and the impact of COVID-19 on primary efficacy measurements. The analysis will include subgroup analysis (eg, pre-, during, and post-COVID-19 outbreak, where each patient will be classified into 1 of the levels), a multivariate model (eg, Cox regression with time-dependent covariates for COVID-19 and/or use of remote monitoring), and/or imputation methodology for patients' attrition due to the COVID-19, as appropriate and if data permit. Details of the supplementary and sensitivity analyses will be presented in the Statistical Analysis Plan or addendum thereof, following a blinded review meeting prior to database lock.~~ …		
Appendix N. Operating Characteristics and Assumptions for Final and Interim Analysis		
Final Analysis and Interim Futility Analysis	Final Analysis and Interim Futility Analysis	Operating characteristics

Original text with changes shown	New wording	Reason/Justification for change
A Beta-binomial model with a non-informative Beta(1,1) prior will be used to analyze the primary response endpoint, clinical remission (for UC) or endoscopic response (for CD), hereafter denoted as "response". The model will be fit separately for each dose within each indication. ~~Primary analysis will be based on the 3-parameter E_{max} model for dose response, as explained in Section 9.5 (where d = 0, 1, 2, 3 for placebo, low, mid, and high doses and i = 1, 2 for UC, CD).~~ ~~$\theta_{d,i} = E_{0,i} + \frac{(E_{max,i} \cdot d)}{ED_{50,i} + d}$~~ Assumptions: ~~The priors used in the Bayesian hierarchical (E_{max}) model are given by:~~ ~~$E_{0,i} \sim N(\mu_{E_0}, \sigma^2_{E_0})$,~~ ~~$E_{max,i} \sim N(\mu_{E_{max}}, \sigma^2_{E_{max}})$,~~ ~~$ED_{50,i} \sim half\ Cauchy\ (0, 5)$~~ ~~Also assume the following hyper-prior distributions:~~ ~~$\mu_{E_0} \sim N(0, 10^2)$, $\mu_{E_{max}} \sim N(0, 10^2)$,~~ ~~$\sigma^2_{E_0} \sim half\ Cauchy\ (0, 2)$, $\sigma^2_{E_{max}} \sim half\ Cauchy\ (0, 2)$~~ ~~Given the lack of information on dose response of TEV-48574 in UC and CD indications, the prior distributions are non-informative and are chosen to encompass the range of plausible values for the model parameters and to optimize the power under various scenarios while controlling the type I error rate.~~ Various scenarios for remission (UC), response rates (CD) are assumed as outlined in Table 11 to investigate the operating characteristics.	A Beta-binomial model with a non-informative Beta(1,1) prior will be used to analyze the primary response endpoint, clinical remission (for UC) or endoscopic response (for CD), hereafter denoted as "response". The model will be fit separately for each dose within each indication. Assumptions: Various scenarios for remission (UC), response rates (CD) are assumed as outlined in Table 11 to investigate the operating characteristics.	throughout Appendix N were revised following the removal of the 1800 mg Q2W treatment arm and change in the primary analysis model.
Final Analysis and Interim Futility Analysis Table 11 (Remission (UC), Response (CD) Rates Scenarios for Clinical Trial Simulations)	Final Analysis and Interim Futility Analysis Table 11 was revised as described below: • Remove the low dose • Remove the scenarios low efficacy; efficacy	Operating characteristics throughout Appendix N were revised following the removal of the 1800 mg Q2W treatment arm

Original text with changes shown	New wording	Reason/Justification for change
	UC, Null CD; and Null UC, Efficacy CD • Removed footnote ”a” and note to table describing the deleted scenarios noted above	and change in the primary analysis model.
Number of Patients at the Interim Analysis: The interim analysis for each indication is planned when at least ~~44~~ ***50% of*** patients ~~(approximately 30%)~~ in ~~that group~~ ***the indication*** have completed the 14-week primary efficacy readout or had the opportunity to do so. Operating characteristics were obtained from simulations assuming that exactly ~~11~~ ***21*** patients per arm in the corresponding ~~disease group~~ ***indication*** will be included in the interim analysis. ***Since the analysis is separate for each indication, no assumptions on*** ~~Due to~~ the expected difference in recruitment rate between UC and CD ***are required***~~., it is assumed that at the time of the interim analysis for UC, data from ~20 patients (5 patients per arm) in CD will be available; at the time of the interim analysis for CD, data from ~96 patients (24 patients per arm) in UC will be available if UC was not stopped for futility at the UC interim analysis.~~ Statistical Decision Criteria – Final Analysis: ***A TEV-48574 dose will be declared successful at the final analysis if the posterior probability that the response rate in the TEV-48574 dose is higher than the response rate in the placebo arm is ≥0.90, ie, the success criterion for each dose within indication is:*** ***Posterior Probability (TEV-48574 response rate – placebo response rate > 0) ≥0.90*** ~~The trial will be deemed positive if at least 1 dose of TEV-48574 is demonstrated to be better than placebo in the primary efficacy analysis for UC, CD. The corresponding statistical decision criteria translate to:~~ ~~• $p_{a,t} > p_{0,t}$, (where $p_{a,t}$ denotes the probability of response for dose d)~~	Number of Patients at the Interim Analysis: The interim analysis for each indication is planned when at least 50% of patients in the indication have completed the 14-week primary efficacy readout or had the opportunity to do so. Operating characteristics were obtained from simulations assuming that exactly 21 patients per arm in the corresponding indication will be included in the interim analysis. Since the analysis is separate for each indication, no assumptions on the expected difference in recruitment rate between UC and CD are required. Statistical Decision Criteria – Final Analysis: A TEV-48574 dose will be declared successful at the final analysis if the posterior probability that the response rate in the TEV-48574 dose is higher than the response rate in the placebo arm is ≥0.90, ie, the success criterion for each dose within indication is: Posterior Probability (TEV-48574 response rate – placebo response rate > 0) ≥0.90 Statistical Futility Cutoff – Interim Analysis: The same Bayesian Beta-Binomial model described in the primary analysis model will be used for the interim futility analysis for each dose within each indication. A TEV-48574 dose will be declared futile at the interim analysis if the posterior probability that the response rate in the TEV-48574 dose is higher than the response rate in the placebo arm is <0.55, ie, the futility criterion for each dose within indication is: • Posterior Probability (TEV-48574 response rate – placebo response rate > 0) <0.55 Operating Characteristics:	Operating characteristics throughout Appendix N were revised following the removal of the 1800 mg Q2W treatment arm and change in the primary analysis model.

Original text with changes shown	New wording	Reason/Justification for change
~~• This occurs if and only if $\theta_{d,t} > \theta_{0,t}$~~ ~~• This will occur if and only if $E_{max,t} > 0$.~~ ~~To elaborate,~~ ~~$\theta_{d,t} - \theta_{0,t}$ measures the difference in log-odds of response between TEV-48574 doses and placebo. In particular for any dose d = 1, 2, 3:~~ ~~• $\theta_{d,t} - \theta_{0,t} > 0$ if and only if $\frac{(E_{max,t} \cdot d)}{ED_{50,t}+d} > 0$,~~ ~~which equates to $E_{max,t} > 0$~~ ~~• $p_{d,t}$ is uniquely identified by a corresponding value of the log odds, $\theta_{d,t}$ ($p_{d,t} = \exp(\theta_{d,t})/(1+\exp(\theta_{d,t}))$~~ ~~Thus, if the Posterior Probability P ($E_{max,t} > 0 \mid full\ data$) exceeds the pre-specified threshold of 0.86, the study will have met the criterion for success. The threshold was selected to achieve optimal operating characteristics for the assumed scenarios.~~ Statistical Futility Cutoff – Interim Analysis: ***The same Bayesian Beta-Binomial model described in the primary analysis model will be used for the interim futility analysis for each dose within each indication. A TEV-48574 dose will be declared futile at the interim analysis if the posterior probability that the response rate in the TEV-48574 dose is higher than the response rate in the placebo arm is <0.55, ie, the futility criterion for each dose within indication is:*** • ***Posterior Probability (TEV-48574 response rate – placebo response rate > 0) <0.55*** ~~The Bayesian hierarchical E_{max} model will be used in the futility analysis of each disease group (UC and CD). For each interim analysis, the available data from the patients that completed 14 weeks or early terminated, in both treatment groups, will be used. However, the futility decision will be for~~	Clinical trial simulations were performed under the assumptions for the interim and primary analysis to generate the operating characteristics (presented in Table 12), for a target sample size of 40 patients per arm in each indication, and an interim analysis for futility for each indication at 21 patients per arm in the indication. The posterior probability futility cutoff is <0.55 for each indication and final success posterior probability cutoff is ≥0.90.	

Original text with changes shown	New wording	Reason/Justification for change
~~the disease group under investigation, ie, at the UC interim analysis only futility of UC will be tested, and vice versa.~~ ~~The futility decision rule is:~~ ~~If the posterior probability $P(E_{max,i} > 0 \mid interim\ data)$ for disease group i is <0.55, then the corresponding disease group is futile. The threshold was selected to achieve optimal operating characteristics for the null and efficacy scenarios.~~ Operating Characteristics: Clinical trial simulations were performed under the assumptions for the interim and primary analysis to generate the operating characteristics (presented in Table 12), for a target sample size of ~~35~~ ***40*** patients per arm in each indication, and an interim analysis for futility for each indication at ~~11~~ ***21*** patients per ~~group~~ ***arm*** in the indication. The posterior probability futility cutoff is <0.55 for each ~~disease group~~ ***indication*** and final success posterior probability cutoff is ~~0.86~~ ***≥0.90***. ~~For all scenarios presented in Table 12, it is assumed that the E_{max} model is used for decision making in the interim analysis.~~		
Operating Characteristics: Table 12 (~~Simulation based~~ Operating Characteristics for Interim and Final Analysis All Scenarios) See new wording column.	Operating Characteristics: Table 12 (Operating Characteristics for Interim and Final Analysis – All Scenarios) was revised as described below: • Simulations updated based on Beta-Binomial model • Removed the scenarios low efficacy; efficacy UC, Null CD; and Null UC, Efficacy CD • Updated the number of simulations performed in the footnote	Operating characteristics throughout Appendix N were revised following the removal of the 1800 mg Q2W treatment arm and change in the primary analysis model.
Operating Characteristics: These simulations demonstrate that the probability of a false positive ***result*** is ***≤15%***~~no more than 12%~~ for ~~the trial~~ ***each indication***, ~~with~~ ***while*** the probability of declaring success for ***at least 1 dose within each indication*** ~~both UC and CD disease~~	Operating Characteristics: These simulations demonstrate that the probability of a false positive result is ≤15% for each indication, while the probability of declaring success for at least 1 dose within each indication under the efficacy assumption for	Operating characteristics throughout Appendix N were revised following the removal of the 1800 mg Q2W treatment arm and change in the primary

Original text with changes shown	New wording	Reason/Justification for change
~~groups~~ under the ~~high~~ efficacy assumption ***for both doses is*** ~~≥at 94~~**95**%. ***The futility threshold was selected to control the probability to declare an effective dose to be futile at a maximum of 7%, while making the correct decision in the null with a probability of at least 60%.*** ***Since the analysis is done separately for each dose and each indication, the probability to demonstrate efficacy in one dose is not affected by the other dose. Moreover, no inflation of the Type 1 error rate is expected in hypothetical*** ~~The~~ discordant scenarios ***where TEV-48574 is effective in 1 indication but not in the other*** ~~of Efficacy-UC, Null-CD and Null-UC, Efficacy-CD result in a higher rate of positive trials for the null indication as compared to the other relevant concordant scenarios~~. ~~Clinical trial simulations were also performed under these assumptions for the primary analysis only (without interim analysis) to generate the operating characteristics (shown in Table 13) with a posterior probability threshold of 0.86 and 35 patients per (dose) arm for each of UC, CD disease groups.~~	both doses is ≥95%. The futility threshold was selected to control the probability to declare an effective dose to be futile at a maximum of 7%, while making the correct decision in the null with a probability of at least 60%. Since the analysis is done separately for each dose and each indication, the probability to demonstrate efficacy in one dose is not affected by the other dose. Moreover, no inflation of the Type 1 error rate is expected in hypothetical discordant scenarios where TEV-48574 is effective in 1 indication but not in the other.	analysis model.
Table 13 (Simulation-based Operating Characteristics for Primary Analysis with n = 35/arm for UC, CD: Success Criterion*Posterior Probability* ($E_{max,i} > 0 \mid full\ data) > 0.86, i = 1{,}2\ for\ UC, CD$) was deleted	Not applicable; Table 13 was deleted and subsequent in-text tables were renumbered, as applicable.	Operating characteristics throughout Appendix N were revised following the removal of the 1800 mg Q2W treatment arm and change in the primary analysis model.
<u>Operating Characteristics:</u> ~~These simulations demonstrate that the probability of a false positive is no more than 15% for the trial, with the probability of declaring success for both UC and CD groups at about 99%.~~ ~~Further simulations to assess the impact of varying degrees of borrowing (shrinkage) on the same dose response scenarios are tabulated below in Table 14. These simulations are for the final analysis only, without an interim analysis.~~	<u>Operating Characteristics:</u> Not applicable; this section was deleted.	Operating characteristics throughout Appendix N were revised following the removal of the 1800 mg Q2W treatment arm and change in the primary analysis model.

Original text with changes shown	New wording	Reason/Justification for change
Table 14 (Additional Simulation-based Operating Characteristics for Primary Analysis with n = 35/arm for UC, CD: Success Criterion Posterior Probability ($\boldsymbol{E_{max,i} > 0 \,|full\ data) > 0.86, i = 1,2\ for\ UC, CD}$) was deleted.	Not applicable; Table 14 was deleted.	Operating characteristics throughout Appendix N were revised following the removal of the 1800 mg Q2W treatment arm and change in the primary analysis model.
Operating Characteristics: ~~These additional simulations demonstrate that:~~ • ~~The family-wise error rate remains close to 15% in instances of increased borrowing (ie, half Cauchy(0, 0.5)) or low borrowing (ie, under half Cauchy(0, 6)).~~ • ~~Under increased borrowing, the discordant scenarios result in a higher rates of positive results for CD as compared to lower borrowing (ie, under half Cauchy (0, 6) or under half Cauchy (0, 2) in Table 13).~~ ~~Further simulations provided below involve independent (ie, by UC, CD) analyses using:~~ • ~~Bayesian E_{max} model – no borrowing between UC and CD with same posterior probability threshold~~ – ~~Success criteria (applied separately to each population): posterior Prob(Difference in Response proportions for TEV-48574 dose – Placebo > 0|data) > 0.86~~ • ~~Response Proportion Difference between active dose groups and placebo (frequentist framework)~~ – ~~Success Criterion: at least one Agresti-Caffo 90% CI for difference in proportions (relative to placebo) has lower limit > 0~~ • ~~Cochran-Armitage Trend test (one-sided increasing at~~	Operating Characteristics: Not applicable; this section was deleted.	Operating characteristics throughout Appendix N were revised following the removal of the 1800 mg Q2W treatment arm and change in the primary analysis model.

Original text with changes shown	New wording	Reason/Justification for change
~~type I error rate = 0.15).~~ ~~Success Criterion: p-value for 1-sided Cochran-Armitage test of increasing trend is < 0.15~~ ~~These simulations are for the final analysis only, without an interim analysis (Table 15).~~		
Table 15 (Operating Characteristics with n=35/group for Separate Analysis of UC and CD [ie, No Borrowing]) was deleted.	Not applicable; Table 15 was deleted.	Operating characteristics throughout Appendix N were revised following the removal of the 1800 mg Q2W treatment arm and change in the primary analysis model.
Operating Characteristics: ~~Comparing these simulations with the primary analysis, it can be noted that~~ • ~~In the complete null case, the proposed primary analysis (hierarchical E_{max} with borrowing) provides stronger control of the family-wise type I error rate (<14%) than the independent (by indication) analyses~~ • ~~In the scenario #2 (employed in powering the study), the proposed primary analysis (hierarchical E_{max} with borrowing) gains a small amount in power relative to the separate (by UC, CD) Bayesian E_{max} model and Cochran-Armitage trend test, and a measurable advantage in power over the analysis of difference in proportions~~ • ~~In the discordant scenario #3, as expected, the separate (ie, by UC, CD) analyses for all three models result in a lower false positive rate for CD relative to the primary analysis.~~	Operating Characteristics: Not applicable; this section was deleted	Operating characteristics throughout Appendix N were revised following the removal of the 1800 mg Q2W treatment arm and change in the primary analysis model.

Original text with changes shown	New wording	Reason/Justification for change
• ~~Regardless of the scenarios considered, one observes that the E_{max} model provides consistent operating characteristics as compared to Difference in proportions or Cochran-Armitage test, thus increasing the likelihood of identifying the dose correctly for Phase 3 confirmatory trials.~~		

17.6. Amendment 02 Dated 13 January 2023

The protocol was amended for the following reasons:

- Revise the definition of endoscopic response for the primary CD endpoint as a reduction in Simple Endoscopic Score for Crohn's Disease (SES-CD) of >50% from baseline
- Amend the primary estimand to include the same strategy to handle the intercurrent event of treatment discontinuation regardless of the reason
- Amend the primary estimand to include the intercurrent event of CD surgery
- Clarify collection procedures for adverse events and concomitant medication for patients rolling over into the long-term extension study
- Add serious infections to the list of protocol-defined adverse events of special interest
- Redefine the patient population cut-off point for the futility analysis from "at least 50%" to "at least 44 patients (approximately 30%)"
- Revise the futility analysis and futility rule with a corresponding update to the operating characteristics in Appendix N
- Update the safety stopping rules to be based on totality of safety data rather than solely on the proposed study stopping rules

All major changes to the protocol body are listed below in the table, and are reflected in the synopsis, as applicable. Minor editorial changes (typos, punctuation, etc.) have been made to the protocol (and protocol synopsis, as appropriate). Table 1 (Study Procedures and Assessments) has been revised to reflect changes described below.

Original text with changes shown	New wording	Reason/Justification for change
Section 2.1 Primary and Secondary Study Objectives and Endpoints		
Primary endpoint: CD Endoscopic response at week 14 in patients with moderate to severe CD, defined as a reduction ~~from baseline~~ in Simple Endoscopic Score for Crohn's Disease (SES-CD) of ~~at least~~ >50% ***from baseline***	Primary Endpoint: CD Endoscopic response at week 14 in patients with moderate to severe CD, defined as a reduction in Simple Endoscopic Score for Crohn's Disease (SES-CD) of >50% from baseline	Health authority (FDA) advice and information request dated 29Nov2022 – update to >50% reduction from baseline in SES-CD as primary CD endpoint.
Section 2.1.1 Justification of Primary Endpoints		
… The selected primary endpoint for patients with moderate to severe CD is endoscopic response, defined as a reduction ~~from baseline~~ in Simple Endoscopic Score for Crohn's Disease (SES-CD) of ***~~at least~~ >50% from baseline***.	… The selected primary endpoint for patients with moderate to severe CD is endoscopic response, defined as a reduction in Simple Endoscopic Score for Crohn's Disease (SES-CD) of >50% from baseline.	Health authority (FDA) advice and information request dated 29Nov2022 – update to >50% reduction from baseline in SES-CD as primary CD endpoint.
Section 2.2 Primary Estimand		
… Handling of intercurrent events: Intercurrent events addressed here are (a) use of rescue medication***;*** ~~and~~ (b) important protocol deviations***;*** (c) UC ~~only:~~ ***or CD*** related surgery***; and*** (d) ***treatment*** discontinuation ~~due to lack of efficacy or adverse events~~. These intercurrent events will be addressed as follows: (a) Patients who used rescue medications prior to their week 14 evaluation of response (clinical remission in the UC group and prior to the week 14 evaluation of endoscopic response in the CD group) will be reported as non-responders, ie, the composite variable strategy; ~~and~~ (b) Patients experiencing any important protocol deviations, namely, use or changes in other medications, will be analyzed as if the deviation had not occurred, ie, treatment policy strategy***;*** (c) ~~UC only:~~ Patients undergoing UC or CD related surgery will be treated as non-responders, ie, the composite strategy***; and*** (d) Patients discontinuing treatment ~~due to lack of efficacy or adverse events~~***, regardless of the reason,*** will be treated as non-responders, ie, the composite strategy**.**	… Handling of intercurrent events: Intercurrent events addressed here are (a) use of rescue medication; (b) important protocol deviations; (c) UC or CD related surgery; and (d) treatment discontinuation. These intercurrent events will be addressed as follows: (a) Patients who used rescue medications prior to their week 14 evaluation of response (clinical remission in the UC group and prior to the week 14 evaluation of endoscopic response in the CD group) will be reported as non-responders, ie, the composite variable strategy; (b) Patients experiencing any important protocol deviations, namely, use or changes in other medications, will be analyzed as if the deviation had not occurred, ie, treatment policy strategy; (c) Patients undergoing UC or CD related surgery will be treated as non-responders, ie, the composite strategy; and (d) Patients discontinuing treatment, regardless of the reason, will be treated as non-responders, ie, the composite strategy.	Treatment discontinuation: Health authority (FDA) advice and information request dated 29Nov2022 – use the same strategy to handle the intercurrent event of treatment discontinuation regardless of the reason. CD-related surgery: Correction as surgery is applicable to both disease groups.

Original text with changes shown	New wording	Reason/Justification for change
Section 3.1 General Study Design and Study Schematic Diagram		
… Treatment and Follow-Up Period: During the 14-week treatment period, patients will visit the site Q2W on days 1, 15, 29, 43, 57, 71, and 85 (±3 days) for IMP administration (7 visits), as well as an end-of-treatment visit on day 99 (±3 days; week 14) (Table 1). After the end of the 14-week treatment period, patients may be offered the option to enter a long-term extension study (to be described in a separate protocol). If they choose to enter ***(sign the extension study informed consent form [ICF]) and will subsequently be randomized into*** the ***long-term*** extension study, they will not need to complete the follow-up visit in this study. All other patients will return to the site for a follow-up visit (day 127 [±14 days]). ***For those patients who enter the long-term extension study, adverse events and concomitant medication data will be recorded in the dose-ranging study case report form (CRF) up until the date of extension study randomization (defined as the study completion date for the dose-ranging study). For those patients who screen fail the long-term extension study, adverse events and concomitant medication data will be recorded in the dose-ranging study up until the follow-up visit (day 127 [±14 days]) CRF***. Patients who complete the ***last scheduled*** ~~follow up~~ visit will be considered to have completed the study.	… Treatment and Follow-Up Period: During the 14-week treatment period, patients will visit the site Q2W on days 1, 15, 29, 43, 57, 71, and 85 (±3 days) for IMP administration (7 visits), as well as an end-of-treatment visit on day 99 (±3 days; week 14) (Table 1). After the end of the 14-week treatment period, patients may be offered the option to enter a long-term extension study (to be described in a separate protocol). If they choose to enter (sign the extension study informed consent form [ICF]) and will subsequently be randomized into the long-term extension study, they will not need to complete the follow-up visit in this study. All other patients will return to the site for a follow-up visit (day 127 [±14 days]). For those patients who enter the long-term extension study, adverse events and concomitant medication data will be recorded in the dose-ranging study case report form (CRF) up until the date of extension study randomization (defined as the study completion date for the dose-ranging study). For those patients who screen fail the long-term extension study, adverse events and concomitant medication data will be recorded in the dose-ranging study up until the follow-up visit (day 127 [±14 days]) CRF. Patients who complete the last scheduled visit will be considered to have completed the study.	Clarification of data collection procedures for patients rolling into the long-term extension study.
Section 3.1 General Study Design and Study Schematic Diagram, Figure 2		
Note: After the end of the 14-week treatment period, patients may be offered the option to enter a long-term extension study (to be described in a separate protocol). If they choose to enter ***(sign the extension study ICF) and will subsequently be randomized into*** the ***long-term*** extension study, they will not need to complete the follow-up visit in this study. All other patients will return to the site for a follow-up visit (day 127 [±14 days]).	Note: After the end of the 14-week treatment period, patients may be offered the option to enter a long-term extension study (to be described in a separate protocol). If they choose to enter (sign the extension study ICF) and will subsequently be randomized into the long-term extension study, they will not need to complete the follow-up visit in this study. All other patients will return to the site for a follow-up visit (day 127 [±14 days]).	Clarification of data collection procedures for patients rolling into the long-term extension study.

Original text with changes shown	New wording	Reason/Justification for change
Section 3.5, Schedule of Study Procedures and Assessments, Table 1		
Footnote a: After the end of the 14-week treatment period, patients may be offered the option to enter a long-term extension study (to be described in a separate protocol). If they choose to enter ***(sign the extension study ICF) and will subsequently be randomized into*** the ***long-term*** extension study, they will not need to complete the follow-up visit in this study. All other patients will return to the site for a follow-up visit (day 127 [±14 days]).	Footnote a: After the end of the 14-week treatment period, patients may be offered the option to enter a long-term extension study (to be described in a separate protocol). If they choose to enter (sign the extension study ICF) and will subsequently be randomized into the long-term extension study, they will not need to complete the follow-up visit in this study. All other patients will return to the site for a follow-up visit (day 127 [±14 days]).	Clarification of data collection procedures for patients rolling into the long-term extension study.
Footnote t: For each patient, adverse events will be captured from signature of the ICF to the end of study (ie, patient's last visit). ***For those patients who enter the long-term extension study, adverse events will be recorded in the dose-ranging study CRF up until the date of extension study randomization (defined as the study completion date for the dose-ranging study). For those patients who screen fail the long-term extension study, adverse events will be recorded in the dose-ranging study up until the follow-up visit (day 127 [±14 days]) CRF.***	Footnote t: For each patient, adverse events will be captured from signature of the ICF to the end of study (ie, patient's last visit). For those patients who enter the long-term extension study, adverse events will be recorded in the dose-ranging study CRF up until the date of extension study randomization (defined as the study completion date for the dose-ranging study). For those patients who screen fail the long-term extension study, adverse events will be recorded in the dose-ranging study up until the follow-up visit (day 127 [±14 days]) CRF.	Clarification of adverse event collection procedures for patients rolling into the long-term extension study.
See new wording column	Footnote u was added as described below: [u] For each patient, concomitant medication data will be captured from signature of the ICF to the end of study (ie, patient's last visit). For those patients who enter the long-term extension study, concomitant medication data will be recorded in the dose-ranging study CRF up until the date of extension study randomization (defined as the study completion date for the dose-ranging study). For those patients who screen fail the long-term extension study, concomitant medication data will be recorded in the dose-ranging study up until the follow-up visit (day 127 [±14 days]) CRF. Subsequent footnotes were re-lettered.	Added footnote to clarify concomitant medication collection procedures for patients rolling into the long-term extension study.

Original text with changes shown	New wording	Reason/Justification for change
Section 7.1.10.1 Protocol-Defined Adverse Events of Special Interest that Require Reporting to Sponsor's Global Patient Safety and Pharmacovigilance		
… • opportunistic or severe ***and/or serious*** infections … <u>Opportunistic or severe ***and/or serious***</u> infections	… • opportunistic or severe and/or serious infections … • <u>Opportunistic or severe and/or serious infections</u>	Health authority (FDA) advice and information request dated 29Nov2022 – include serious infections as protocol-defined adverse events of special interest.
Section 9.1 Sample Size and Power Considerations		
A total study sample size of 280 patients is planned, with 140 patients (35 patients per dose arm) each for the 2 ~~indications~~ ***disease groups*** of UC and CD.	A total study sample size of 280 patients is planned, with 140 patients (35 patients per dose arm) each for the 2 disease groups of UC and CD.	Correction.
Simulation-based operating characteristics for the analysis of the primary efficacy variable using a Bayesian hierarchical 3-parameter E_{max} model ***for the interim and final analysis, with a posterior probability futility cutoff of 0.55 for each disease group and final success posterior probability cutoff of 0.86, are presented in Table 10. The*** ~~indicate a~~ family-wise false-positive rate (ie, probability of at least 1 false-positive conclusion ***under the global null assumption***) ~~of~~ ***is*** no more than ~~15%~~ ***12%,*** and the probability of declaring success for both UC and CD groups ~~at about 99%~~ ***is 94%,*** under the assumptions stated above.	Simulation-based operating characteristics for the analysis of the primary efficacy variable using a Bayesian hierarchical 3-parameter E_{max} model for the interim and final analysis, with a posterior probability futility cutoff of 0.55 for each disease group and final success posterior probability cutoff of 0.86, are presented in Table 10. The family-wise false-positive rate (ie, probability of at least 1 false-positive conclusion under the global null assumption) is no more than 12%, and the probability of declaring success for both UC and CD groups is 94%, under the assumptions stated above.	The futility analysis and futility rules with a corresponding update to the operating characteristics were revised to allow the Sponsor to offset any potential adverse impacts of uncertainty associated with patient accrual on a timely assessment of futility.
See new wording column.	Table 10 (Operating Characteristics of Interim and Final Analysis) was added to Section 9.1 to provide additional details on the operating characteristics of the interim and final analyses (ie, the probability to stop for futility or be successful at final). Subsequent in-text tables were renumbered.	The futility analysis and futility rules with a corresponding update to the operating characteristics were revised to allow the Sponsor to offset any potential adverse impacts of uncertainty associated with patient accrual on a timely assessment of futility.
Under a less optimistic scenario for mid- and high-dose groups, when the clinical remission rate in the UC group is reduced to 20% (from 30%) and endoscopic response rate in the CD group is	Under a less optimistic scenario for mid- and high-dose groups, when the clinical remission rate in the UC group is reduced to 20% (from 30%) and endoscopic response rate in	The futility analysis and futility rules with a corresponding update to the operating characteristics were

Original text with changes shown	New wording	Reason/Justification for change
reduced to 25% (from 34%), while maintaining the identical response rates for placebo and low-dose (in both UC and CD groups), the probability of declaring success in both UC and CD groups is about ~~83%~~***69%.*** ~~Note that in the computation of operating characteristics summarized above, study success is defined as a posterior probability threshold of 0.86 for the population-level summary (defined in the primary estimand).~~ Details regarding the statistical decision criteria and Bayesian hierarchical model, including priors and hyper-priors used in the computation of the operating characteristics, are provided in Appendix N***. The operating characteristics under additional scenarios, including discordant scenarios where the treatment is effective only in one disease group, are presented in Appendix N.***	the CD group is reduced to 25% (from 34%), while maintaining the identical response rates for placebo and low-dose (in both UC and CD groups), the probability of declaring success in both UC and CD groups is about 69%. Details regarding the statistical decision criteria and Bayesian hierarchical model, including priors and hyper-priors used in the computation of the operating characteristics, are provided in Appendix N. The operating characteristics under additional scenarios, including discordant scenarios where the treatment is effective only in one disease group, are presented in Appendix N.	revised to allow the Sponsor to offset any potential adverse impacts of uncertainty associated with patient accrual on a timely assessment of futility.
Section 9.13 Planned Interim Analysis		
Interim analyses for safety and efficacy are planned for this study. An interim efficacy analysis for futility is planned in each disease group (UC and CD) when at least ~~50% of~~ ***44 patients (approximately 30%)*** in that group ~~has~~ ***have*** completed the 14-week primary efficacy readout or had the opportunity to do so. ~~Interim analysis futility criterion is defined by $Posterior\ Probability\ (p_{d,i} > p_{0,i} \mid Interim\ data) < 0.45\ for\ i = 1\ and\ 2$ ($p_{d,i}$ denotes the probability of response for dose d = 0, 1, 2, 3 for placebo, low, mid, and high doses).~~ ~~Simulation-based operating characteristics indicate the probability of incorrectly stopping the study for futility is about 0.1%, whereas the probability of correctly stopping the study at the interim analysis is about 13.8%. Further details regarding the assumptions and futility decision criteria are provided in Appendix N.~~ ***In the interim analysis, the same Bayesian hierarchical E_{max} dose-response model used as the primary analysis model will be used to analyze the primary efficacy variable (clinical remission for UC and endoscopic response for CD, hereafter denoted as***	Interim analyses for safety and efficacy are planned for this study. An interim efficacy analysis for futility is planned in each disease group (UC and CD) when at least 44 patients (approximately 30%) in that group have completed the 14-week primary efficacy readout or had the opportunity to do so. In the interim analysis, the same Bayesian hierarchical E_{max} dose-response model used as the primary analysis model will be used to analyze the primary efficacy variable (clinical remission for UC and endoscopic response for CD, hereafter denoted as "response") for each disease group. The futility criterion for each disease group is: • If the posterior probability $P(E_{max,i} > 0 \mid interim\ data)$ for disease group i is <0.55, then the corresponding disease group is futile. An analysis of each disease group independently will be performed at the interim analysis for the disease group as a supporting analysis, as follows:	The interim analysis timing, method, and cutoff were updated to allow the Sponsor to offset any potential adverse impacts of uncertainty associated with patient accrual on a timely assessment of futility.

Original text with changes shown	New wording	Reason/Justification for change
"response") for each disease group. The futility criterion for each disease group is: • ***If the posterior probability $P(E_{max,i} > 0 \mid interim\ data)$ for disease group i is <0.55, then the corresponding disease group is futile.*** ***An analysis of each disease group independently will be performed at the interim analysis for the disease group as a supporting analysis, as follows:*** • ***A Beta-Binomial model with a non-informative prior Beta(1,1) will be fitted to the response rate π in each treatment group d in the disease group i, and the posterior probability that the response rate in each active group is higher than the response rate in the placebo group, $P(\pi_{d,i} > \pi_{0,i})$, will be calculated.*** ***Refer to Table 12 and Appendix N for operating characteristics of the interim and final analysis.***	• A Beta-Binomial model with a non-informative prior *Beta(1,1)* will be fitted to the response rate π in each treatment group *d* in the disease group *i*, and the posterior probability that the response rate in each active group is higher than the response rate in the placebo group, $P(\pi_{d,i} > \pi_{0,i})$, will be calculated. Refer to Table 12 and Appendix N for operating characteristics of the interim and final analysis.	
Additionally periodic analysis of safety data will also be done during the study. Analyses will focus on the following events: • Incidence of serious adverse events • Incidence of ***CTCAE*** grade 3 or grade 4 events • Incidence of opportunistic infections and severe ***and/or serious*** infections • Incidence of anaphylaxis … The results will be reviewed by an IDMC comprised of external medical and statistical experts. ***The IDMC will make a recommendation after evaluation of the totality of available safety data.*** The details regarding the statistical analysis methods will be provided in the Statistical Analysis Plan. The IDMC charter will provide details regarding procedures to protect the scientific integrity of the study, conduct of the interim analysis, dissemination of results, and decision criteria based on the futility analysis.	Additionally periodic analysis of safety data will also be done during the study. Analyses will focus on the following events: • Incidence of serious adverse events • Incidence of CTCAE grade 3 or grade 4 events • Incidence of opportunistic infections and severe and/or serious infections • Incidence of anaphylaxis ... The results will be reviewed by an IDMC comprised of external medical and statistical experts. The IDMC will make a recommendation after evaluation of the totality of available safety data. The details regarding the statistical analysis methods will be provided in the Statistical Analysis Plan. The IDMC charter will provide details regarding procedures to protect the scientific integrity of the study, conduct of the interim analysis, dissemination of results, and decision criteria based on the futility analysis.	CTCAE: Correction. And/or serious infections: Health authority (FDA) advice and information request dated 29Nov2022 – include serious infections as protocol-defined adverse events of special interest.
Additional Analyses:	Additional Analyses:	Clarification.

Original text with changes shown	New wording	Reason/Justification for change
As part of the interim analysis for futility, ***the*** primary efficacy ***endpoints*** may be analyzed by the presence of TEV-48574 ligand or other relevant biomarkers. Additional endpoints~~, including PK and PD analysis,~~ may also be provided to the IDMC as part of the interim analyses ***for futility*** ~~or as requested by the IDMC~~. ***Pharmacokinetic (PK) and PD analysis may be provided to the IDMC upon request***. Population PK and PD analysis will be performed by an external analysis group independent of the study team. The process to ensure the study integrity, the maintenance of the double blind, and the responsibilities of the external members~~,~~ ***and*** relevant study personnel will be described in the IDMC charter. The details regarding the population PK or PD analysis will be described in the pharmacometric analysis plan.	As part of the interim analysis for futility, the primary efficacy endpoints may be analyzed by the presence of TEV-48574 ligand or other relevant biomarkers. Additional endpoints may also be provided to the IDMC as part of the interim analyses for futility. Pharmacokinetic (PK) and PD analysis may be provided to the IDMC upon request. Population PK and PD analysis will be performed by an external analysis group independent of the study team. The process to ensure the study integrity, the maintenance of the double blind, and the responsibilities of the external members and relevant study personnel will be described in the IDMC charter. The details regarding the population PK or PD analysis will be described in the pharmacometric analysis plan.	
Appendix N. Operating Characteristics and Assumptions for Final and Interim Analysis		
Final Analysis ***and Interim Futility Analysis***	Final Analysis and Interim Futility Analysis	Clarification of subheading title.
See new wording column.	A new row was added to Table 11 as described below: • Added the scenario Null-UC, Efficacy CD	The futility analysis and futility rules with a corresponding update to the operating characteristics were revised to allow the Sponsor to offset any potential adverse impacts of uncertainty associated with patient accrual on a timely assessment of futility.
See new wording column.	A new section of Appendix N was added as described below: <u>Number of Patients at the Interim Analysis:</u> The interim analysis for each indication is planned when at least 44 patients (approximately 30%) in that group have completed the 14-week primary efficacy readout or had the opportunity to do so. Operating characteristics were obtained from simulations assuming that exactly 11 patients per arm in the corresponding disease group will be included in the interim analysis. Due to the expected difference in	The interim analysis timing, method, and cutoff were updated to allow the Sponsor to offset any potential adverse impacts of uncertainty associated with patient accrual on a timely assessment of futility.

Original text with changes shown	New wording	Reason/Justification for change
	recruitment rate between UC and CD, it is assumed that at the time of the interim analysis for UC, data from ~20 patients (5 patients per arm) in CD will be available; at the time of the interim analysis for CD, data from ~96 patients (24 patients per arm) in UC will be available if UC was not stopped for futility at the UC interim analysis.	
Statistical Decision Criteria – ***Final Analysis*** … Thus**,** if the *Posterior Probability* ***P*** $(E_{max,i} > 0 \mid full\ data)$ exceeds ~~a~~ ***the*** pre-specified threshold ***of 0.86***, the study will have met the criterion for success. The threshold ~~is~~ ***was*** selected to achieve optimal operating characteristics for the assumed scenarios.	Statistical Decision Criteria – Final Analysis … Thus, if the *Posterior Probability P* $(E_{max,i} > 0 \mid full\ data)$ exceeds the pre-specified threshold of 0.86, the study will have met the criterion for success. The threshold was selected to achieve optimal operating characteristics for the assumed scenarios.	Clarification.
See new wording column.	A new section of Appendix N was added as described below: <u>Statistical Futility Cutoff – Interim Analysis:</u> The Bayesian hierarchical E_{max} model will be used in the futility analysis of each disease group (UC and CD). For each interim analysis, the available data from the patients that completed 14 weeks or early terminated, in both treatment groups, will be used. However, the futility decision will be for the disease group under investigation, ie, at the UC interim analysis only futility of UC will be tested, and vice versa. The futility decision rule is: If the posterior probability $P(E_{max,i} > 0 \mid interim\ data)$ for disease group *i* is <0.55, then the corresponding disease group is futile. The threshold was selected to achieve optimal operating characteristics for the null and efficacy scenarios.	The interim analysis timing, method, and cutoff were updated to allow the Sponsor to offset any potential adverse impacts of uncertainty associated with patient accrual on a timely assessment of futility.
See new wording column.	New text was added to the Operating Characteristics of Appendix N as described below: Clinical trial simulations were performed under assumptions for the interim and primary analysis to generate the	The futility analysis and futility rules with a corresponding update to the operating characteristics were revised to allow the Sponsor to

Original text with changes shown	New wording	Reason/Justification for change
	operating characteristics (presented in Table 12), for a target sample size of 35 patients per arm in each indication, and an interim analysis for futility for each indication at 11 patients per group in the indication. The posterior probability futility cutoff is 0.55 for each disease group and final success posterior probability cutoff is 0.86. For all scenarios presented in Table 12, it is assumed that the E_{max} model is used for decision making in the interim analysis. These simulations demonstrate that the probability of a false positive is no more than 12% for the trial, with the probability of declaring success for both UC and CD disease groups under the high efficacy assumption at 94%. The discordant scenarios of Efficacy-UC, Null-CD and Null-UC, Efficacy-CD result in a higher rate of positive trials for the null indication as compared to the other relevant concordant scenarios.	offset any potential adverse impacts of uncertainty associated with patient accrual on a timely assessment of futility.
See new wording column.	Table 12 (Simulation-based Operating Characteristics for Interim and Final Analysis – All Scenarios) was added to the Operating Characteristics section of Appendix N as described below: • Simulations performed to generate the operating characteristics for a sample size of 35 patients per arm in the final analysis and 11 patients per group in each indication for the interim analysis • Probability to stop at interim analysis or to be successful at final analysis is presented Subsequent in-text tables were renumbered.	The futility analysis and futility rules with a corresponding update to the operating characteristics were revised to allow the Sponsor to offset any potential adverse impacts of uncertainty associated with patient accrual on a timely assessment of futility.
Operating Characteristics: … Clinical trial simulations were ***also*** performed under these assumptions for the primary analysis ***only (without interim analysis)*** to generate the operating characteristics (shown in Table ~~11~~ ***13***) with a posterior probability threshold of 0.86 and 35	Operating Characteristics: … Clinical trial simulations were also performed under these assumptions for the primary analysis only (without interim analysis) to generate the operating characteristics (shown in Table 13) with a posterior probability threshold of 0.86 and 35 patients per (dose) arm for each of UC, CD disease	Clarification.

Original text with changes shown	New wording	Reason/Justification for change
patients per (dose) arm for each of UC, CD disease groups.	groups.	
Operating Characteristics: Further simulations to assess the impact of varying degrees of borrowing (shrinkage) on the same dose response scenarios are tabulated below ***in Table 14***. ***These simulations are for the final analysis only, without an interim analysis.***	Operating Characteristics: Further simulations to assess the impact of varying degrees of borrowing (shrinkage) on the same dose response scenarios are tabulated below in Table 14. These simulations are for the final analysis only, without an interim analysis.	Clarification.
Operating Characteristics: Further simulations provided below involve independent (***ie***., by UC, CD) analyses using: … ***These simulations are for the final analysis only, without an interim analysis (Table 15)***.	Operating Characteristics: Further simulations provided below involve independent (ie, by UC, CD) analyses using: … These simulations are for the final analysis only, without an interim analysis (Table 15).	Clarification.
~~Interim Futility Analysis~~ ~~An interim efficacy analysis for futility is planned for each indication (UC and CD) when at least 50% of patients (in each indication) complete the 14-week primary efficacy readout or withdrawn from the study. The futility analysis may result in either:~~ • ~~stopping the study or~~ • ~~stopping enrolment within a dose or an indication~~ ~~Notation and Assumptions:~~ ~~The following notations and distributional assumptions are used in evaluating the operating characteristics of the interim futility analysis:~~ ~~Let~~ • $p_{d,i}$ ~~denote the probability of response for dose~~ d, ~~where~~ d ~~= 0, 1, 2, 3 for placebo, low, mid, and high doses, and~~ i ~~= 1, 2 for UC, CD.~~ • $n_{d,i}$ ~~and~~ $x_{d,i}$ ~~denote the sample size and number of responses at interim analysis~~ ~~Assuming a~~ $Bernoulli(p_{d,i})$ ~~distribution for response (= Yes, No), and a~~ $Beta(1,1)$ ~~prior, the posterior distribution for~~ $p_{d,i}$ ~~is given~~	Not applicable; this section (Interim Futility Analysis) and its corresponding table were deleted. Subsequent in-text tables were renumbered.	The interim analysis timing, method, and cutoff were updated to allow the Sponsor to offset any potential adverse impacts of uncertainty associated with patient accrual on a timely assessment of futility; therefore, this section was deleted and applicable text was added throughout Appendix N.

Original text with changes shown	New wording	Reason/Justification for change
~~by $Beta(1 + x_{a,t}, 1 + n_{a,t} - x_{a,t})$.~~ ~~Statistical Decision Criteria:~~ • ~~The trial will be deemed futile if interim results indicate: $Posterior\ Probability\ (p_{3,t} > p_{0,t} \mid Interim\ data) < threshold\ for\ i = 1\ and\ 2$.~~ • ~~Individual indications may be deemed futile if this criterion is achieved for either $i = 1\ or\ 2$.~~ ~~The threshold is selected to achieve optimal operating characteristics for the assumed scenarios.~~ ~~Operating Characteristics:~~ ~~With a posterior probability threshold of 0.45 and 18 patients per (dose) arm for each of UC, CD indications, the simulation-based operating characteristics for high dose are provided in the Table 14 below.~~		
See new wording column.	Table 16 (Posterior Probability of Adverse Events) of Appendix N was renumbered based on table additions/deletions explained above and revised as described below: • Classified grade 3 and 4 adverse events as CTCAE • Added serious infections to AE type	Clarification.
Safety Stopping Rules … • The DMC will review in detail any safety signal that meets the safety stopping rule, ~~taking~~ ***and take*** into account the totality of safety ~~and efficacy~~ data. Additional analyses, eg, SAEs in the same HLT, may be performed. • The DMC will make a recommendation if the safety signal ***and the totality of the safety data*** warrants stopping the dose/indication/study.	Safety Stopping Rules … • The DMC will review in detail any safety signal that meets the safety stopping rule, and take into account the totality of safety data. Additional analyses, eg, SAEs in the same HLT, may be performed. • The DMC will make a recommendation if the safety signal and the totality of the safety data warrants stopping the dose/indication/study.	Health authority (FDA) advice and information request dated 29Nov2022 – stopping the study for safety should be based on totality of safety data.

17.7. Amendment 01 Dated 13 June 2022

The protocol was amended for the following reasons:

- Clarification of the objectives and endpoints
- Inclusion of additional efficacy assessments using non-invasive measures
- Change in the grading method for AE severity
- Inclusion of subject (individual) and study stopping rules
- Inclusion of severe infections to the list of adverse events of special interest
- Additional scenarios for operating characteristics and revisions to the description of the interim analyses including establishing an IDMC for unblinded data monitoring
- Updates to the inclusion and exclusion criteria
- Updates for the estimand
- Inclusion of information on the SC infusion method/device, infusion duration, and infusion rate
- Addition of a description of the proposed time and storage conditions between study drug dilution and administration

All major changes to the protocol body are listed below in the table, and are reflected in the synopsis, as applicable. Minor editorial changes (typos, punctuation, etc) have been made to the protocol (and protocol synopsis, as appropriate). Table 1 (Study Procedures and Assessments) has been revised to reflect changes described below.

Original text with changes shown	New wording	Reason/Justification for change
Section 2.1. Primary and Secondary Study Objectives and Endpoints		
The primary objective of the study is to ~~evaluate~~ characterize the ~~efficacy and~~ dose response of ~~3 different dose regimens of~~ TEV-48574 sc administered ~~every 2 weeks~~ ~~(~~Q2W~~)~~ and to evaluate the efficacy in adult patients with inflammatory bowel disease ~~(~~IBD~~;~~ (IBD with ~~moderate to severe ulcerative colitis~~ ~~[~~UC] or ~~Crohn's disease~~ [CD~~]~~)), as assessed by induction of clinical remission (UC) and endoscopic response (CD) at week 14.	The **primary objective** of the study is to characterize the dose response of TEV-48574 sc administered Q2W and to evaluate the efficacy in adult patients with IBD (IBD with moderate to severe UC or CD), as assessed by induction of clinical remission (UC) and endoscopic response (CD) at week 14.	Clarification. Objective updated to remove dose response of 3 different doses.
Endoscopic response at week 14 in patients with moderate to severe CD, defined as a reduction from baseline in Simple Endoscopic Score for Crohn's Disease (SES-CD) of ~~>~~ at least 50%	Endoscopic response at week 14 in patients with moderate to severe CD, defined as a reduction from baseline in Simple Endoscopic Score for Crohn's Disease (SES-CD) of at least 50%	Clarification. Reduction from baseline in Simple Endoscopic Score for Crohn's Disease (SES-CD) updated.
The secondary efficacy endpoints to be measured in patients with moderate to severe UC are as follows: • Clinical response defined as decrease from baseline of at least 50% in 2-item patient-reported outcome (PRO2; rectal bleeding and stool frequency) at weeks 2, 4, 6, 8, 10, 12 and 14 • Clinical remission defined as score of rectal bleeding = 0 and stool frequency = 0 on the PRO2 scale at weeks 2, 4, 6, 8, 10, 12 and 14 The secondary efficacy endpoints to be measured in patients with moderate to severe CD are as follows: • Clinical response defined as a ≥100-point decrease in Crohn's Disease Activity Index (CDAI) score from baseline at ~~week 14~~ weeks 2, 4, 6, 8, 10, 12 and 14 • Clinical remission defined as a CDAI score ≤<150 at week 14 • Endoscopic remission defined as SES- CD: ~~<3 points or the absence~~ score of ~~ulcerations (~~0-2, or SES- CD ~~ulceration subscore = 0)~~ score of 0-4, with no individual sub score >1 at week 14 • Clinical response defined as a decrease from baseline	The secondary efficacy endpoints to be measured in patients with moderate to severe UC are as follows: • Clinical response defined as decrease from baseline of at least 50% in 2-item patient-reported outcome (PRO2; rectal bleeding and stool frequency) at weeks 2, 4, 6, 8, 10, 12 and 14 • Clinical remission defined as score of rectal bleeding = 0 and stool frequency = 0 on the PRO2 scale at weeks 2, 4, 6, 8, 10, 12 and 14 The secondary efficacy endpoints to be measured in patients with moderate to severe CD are as follows: • Clinical response defined as a ≥100-point decrease in Crohn's Disease Activity Index (CDAI) score from baseline at weeks 2, 4, 6, 8, 10, 12 and 14 • Clinical remission defined as a CDAI score <150 at week 14 • Endoscopic remission defined as SES CD	Update. The secondary efficacy endpoints updated to include more assessment times.

Original text with changes shown	New wording	Reason/Justification for change
of at least 50% in PRO2 (PRO2 is defined as having 2 components, abdominal pain and stool frequency) at weeks 2, 4, 6, 8, 10, 12 and 14 • Clinical remission defined as abdominal pain ≤1 and stool frequency ≤3 on the PRO2 scale at weeks 2, 4, 6, 8, 10, 12 and 14 • Endoscopic response defined as a decrease in modified multiplier (MM)-SES-CD of >50% from baseline at week 14 • Histologic response defined as a ≥50% decrease in Global Histologic Activity Score from baseline at week 14	score of 0-2, or SES CD score of 0-4, with no individual sub score >1 at week 14 • Clinical response defined as a decrease from baseline of at least 50% in PRO2 (PRO2 is defined as having 2 components, abdominal pain and stool frequency) at weeks 2, 4, 6, 8, 10, 12 and 14 • Clinical remission defined as abdominal pain ≤1 and stool frequency ≤3 on the PRO2 scale at weeks 2, 4, 6, 8, 10, 12 and 14 • Endoscopic response defined as a decrease in modified multiplier (MM)-SES-CD of >50% from baseline at week 14 • Histologic response defined as a ≥50% decrease in Global Histologic Activity Score from baseline at week 14	
Section 2.1.1.Justification of Primary Endpoints		
The selected primary endpoint for patients with moderate to severe CD is endoscopic response, defined as a reduction from baseline in Simple Endoscopic Score for Crohn's Disease (SES CD) of ~~≥~~ at least 50%.	The selected primary endpoint for patients with moderate to severe CD is endoscopic response, defined as a reduction from baseline in Simple Endoscopic Score for Crohn's Disease (SES CD) of at least 50%.	Update. Text updated to include revised primary endpoint.
Section 2.2. Primary Estimand		
Variable: Response for the primary efficacy analysis is defined as clinical remission status at week 14 for UC patients or endoscopic response status at week 14 for CD patients~~, when not receiving rescue medications prior to the week 14 assessment~~.	**Variable:** Response for the primary efficacy analysis is defined as clinical remission status at week 14 for UC patients or endoscopic response status at week 14 for CD patients.	Clarification. Response variable updated.
• Handling of intercurrent events: Intercurrent events addressed here are (a) use of rescue medication and (b) ~~other~~ important	Handling of intercurrent events: Intercurrent events addressed here are (a) use of rescue	Update. Primary estimand updated to reflect the latest guidance documents for

Original text with changes shown	New wording	Reason/Justification for change
protocol deviations (c) UC only: UC related surgery (d) discontinuation due to lack of efficacy or adverse events. These intercurrent events will be addressed as follows: (a) Patients who used rescue medications prior to their week 14 evaluation of response (clinical remission in the UC group and prior to the week 14 evaluation of endoscopic response in the CD group) will be reported as non responders, ie, the composite variable strategy; and (b) Patients experiencing any ~~other~~ important protocol deviations, ~~including~~ namely, use or changes in other medications, will be analyzed as if the deviation had not occurred, ie, treatment policy strategy. (c) UC only: Patients undergoing UC related surgery will be treated as non-responders, ie, the composite strategy (d) Patients discontinuing treatment due to lack of efficacy or adverse events will be treated as non-responders, ie, the composite strategy	medication and (b) important protocol deviations (c) UC only: UC related surgery (d) discontinuation due to lack of efficacy or adverse events. These intercurrent events will be addressed as follows: (a) Patients who used rescue medications prior to their week 14 evaluation of response (clinical remission in the UC group and prior to the week 14 evaluation of endoscopic response in the CD group) will be reported as non-responders, ie, the composite variable strategy; and (b) Patients experiencing any important protocol deviations, namely, use or changes in other medications, will be analyzed as if the deviation had not occurred, ie, treatment policy strategy (c) UC only: Patients undergoing UC related surgery will be treated as non-responders, ie, the composite strategy (d) Patients discontinuing treatment due to lack of efficacy or adverse events will be treated as non-responders, ie, the composite strategy	developing treatments for UC and CD.
The population-level summary of interest is the quantity *Posterior Probability* ($p_{d,i} - p_{0,i} > 0$) ~~($E_{max,i} > 0$)~~ estimated from a Bayesian hierarchical 3-parameter E_{max} model (with $E_{0,i}, ED_{50,i}$ and $E_{max,i}, i = 1,2\ for\ UC, CD$) for the logit of response rate. $p_{d,i}$ denotes either the clinical remission (for UC) or endoscopic response rate (for CD) and doses d =0,1,2,3 represent placebo, low, mid, and high doses of TEV-48574.	The population-level summary of interest is the quantity *Posterior Probability* ($p_{d,i} - p_{0,i} > 0$) estimated from a Bayesian hierarchical 3-parameter E_{max} model (with $E_{0,i}, ED_{50,i}$ and $E_{max,i}, i = 1,2\ for\ UC, CD$) for the logit of response rate. $p_{d,i}$ denotes either the clinical remission (for UC) or endoscopic response rate (for CD) and doses d =0,1,2,3 represent placebo, low, mid, and high doses of TEV-48574.	Update. Population level summary updated.
Section 2.3.Exploratory Objectives and Endpoints		
An exploratory objective of the study is to obtain trough serum TEV 48574 concentrations, to ~~evaluate population pharmacokinetics~~ compare major pharmacokinetic (PK) characteristics between UC and CD patients with healthy volunteers and asthma patients, and, if data allows, to evaluate	An **exploratory objective** of the study is to obtain trough serum TEV-48574 concentrations, to compare major PK characteristics between UC and CD patients with healthy volunteers and asthma patients, and, if data allows, to evaluate the pharmacokinetics/pharmacodynamics and/or	Update. Exploratory objective revised.

Original text with changes shown	New wording	Reason/Justification for change
the pharmacokinetics/pharmacodynamics and/or exposure-response relationship of 3 different dose regimens of TEV-48574 sc.	exposure-response relationship of 3 different dose regimens of TEV-48574 sc.	
• Population pharmacokinetic-pharmacodynamic parameters • Exposure-response parameters	• Population pharmacokinetic-pharmacodynamic parameters • Exposure-response parameters	Update. Exploratory endpoint added.
Section 3.3 Justification for Study Design and Selection of Population		
~~In this study, an~~ An overall primary efficacy analysis incorporating all data from both indications will be performed using a Bayesian hierarchical model. ~~The estimated treatment effects and corresponding estimated standard errors for UC and for CD derived from separate per-indication analyses will be input to a hierarchical model to re-estimate the treatment effects using empirical Bayes shrinkage estimators, as described in Section 9.5.4.1.~~ In this Phase 2 dose-range study, a functional relationship (namely E_{max} model) between the doses is assumed. While there are many options for specifying these relationships (i.e., E_{max}, logistic, exponential etc.), the E_{max} model (with Hill parameter close to 1) has been shown to provide a good fit across a range of pharmaceutical studies (Thomas et al 2014). Additionally, as demonstrated in Gajewski et al (2019), the E_{max} model performs adequately when non-monotonicity is not expected, thereby resulting in a higher likelihood of identifying the correct dose. Further, previously conducted phase 2 trial for Tofacitinib (Sandborn et al 2013) has implemented such an approach to characterize the dose response and to identify efficacious doses via E_{max} models.	An overall primary efficacy analysis incorporating all data from both indications will be performed using a Bayesian hierarchical model. In this Phase 2 dose-range study, a functional relationship (namely E_{max} model) between the doses is assumed. While there are many options for specifying these relationships (i.e., E_{max}, logistic, exponential etc.), the E_{max} model (with Hill parameter close to 1) has been shown to provide a good fit across a range of pharmaceutical studies (Thomas et al 2014). Additionally, as demonstrated in Gajewski et al (2019), the E_{max} model performs adequately when non-monotonicity is not expected, thereby resulting in a higher likelihood of identifying the correct dose. Further, previously conducted phase 2 trial for Tofacitinib (Sandborn et al 2013) has implemented such an approach to characterize the dose response and to identify efficacious doses via E_{max} models.	Addition. Text added to justify study design.

Original text with changes shown	New wording	Reason/Justification for change
Section 3.4. Stopping Rules for the Study		
3.4.1. Individual Stopping Criteria	**3.4.1. Individual Stopping Criteria**	Addition. Section describing the stopping criteria for individual patients added.
3.4.2. Study Stopping Criteria	**3.4.2. Study Stopping Criteria**	Addition. Section describing stopping criteria for the study added.
Table 1 ±3 days based on ~~day 1~~ previous visit	**Table 1** ±3 days based on previous visit	Update. Timing for visits during the induction period updated.
Table 1 ±14 days based on ~~day 1~~ previous visit	**Table 1** ±14 days based on previous visit	Update. Timing of the follow-up visit updated.
Table 1 Row: Stool frequency and Rectal bleeding Mayo sub-scores (PRO2 UC) [i] Assessments added at Visits 2 to 8	**Table 1** Row: Stool frequency and Rectal bleeding Mayo sub-scores (PRO2 UC) [i] Assessments added at Visits 2 to 8	Addition. PRO2 split across two rows and additional assessments included.
Table 1 Row: CDAI score (CD only) Assessments added at Visits 2 to 7	**Table 1** Row: CDAI score (CD only) Assessments at Visits 2 to 7	Addition. Additional assessments added.
Table 1 Row: Stool frequency and Abdominal pain (PRO2 CD) [i] Assessments added at Visits 2 to 8	**Table 1** Stool frequency and Abdominal pain (PRO2 CD) [i] Assessments added at Visits 2 to 8	Addition. PRO2 split across two rows and additional assessments included.
Table 1 Row: ~~PRO2 (UC and CD)~~[d]	**Table 1** **Row removed**	Update. PRO2 split across two rows.

Original text with changes shown	New wording	Reason/Justification for change
[m]Clinical laboratory tests include serum chemistry and hematology. Patients should be fasting for at least 8 hours prior to safety laboratory assessments only at the screening, week 14, and early termination visits (ie, visits at which low density lipoprotein, high density lipoprotein, and triglycerides will be measured). Coagulation tests (PT/PTT/INR) will be performed at screening only~~.~~ or in case of suspected liver injury (see Appendix M).	[m]Clinical laboratory tests include serum chemistry and hematology. Patients should be fasting for at least 8 hours prior to safety laboratory assessments only at the screening, week 14, and early termination visits (ie, visits at which low density lipoprotein, high density lipoprotein, and triglycerides will be measured). Coagulation tests (PT/PTT/INR) will be performed at screening only or in case of suspected liver injury (see Appendix M).	Update. Footnote updated to state when coagulation tests will be performed.
Section 4.1. Patient Inclusion Criteria		
c. UC patients only: Patient with moderate to severe active UC as defined by the 3 component modified Mayo score of 5 to 9, inclusive, with an endoscopic subscore of ≥2 (from central reading)~~, and a rectal bleeding subscore of ≥1.)~~	c. UC patients only: Patient with moderate to severe active UC as defined by the 3 component modified Mayo score of 5 to 9, inclusive, with an endoscopic subscore of ≥2 (from central reading)	Update. Rectal bleeding subscore removed.
e. CD patients only: SES-CD score of ~~>~~≥6 ~~or >~~ (≥4 for isolated ileal disease).	e. CD patients only: SES-CD score of ≥6 (≥4 for isolated ileal disease).	Update. Inclusion criteria revised.

• Inadequate response to, loss of response to, or intolerance to prior biologics or small molecules defined as 1 or more of the following:
  • Loss of response: Persistent signs and symptoms of active disease despite at least one ~~8-week~~ induction and one maintenance regimen of the locally approved ~~highest dosing~~ regimen of anti-TNF inhibitors, anti-integrins, anti-IL-12/23 ~~mAbs~~ monoclonal antibodies, JAK inhibitors, or ~~S1P receptor~~ S1Preceptor modulators.
  • ~~Discontinuation~~ Inadequate response (primary non-response): Persistent signs and symptoms of active disease despite at least one induction regimen of the locally approved highest dosing regimen of anti-TNF inhibitors, anti-integrins, anti-IL-12/23 mAbs, JAK inhibitors, or S1P receptor modulators ~~due to an adverse drug reaction as determined by the~~
	• Inadequate response to, loss of response to, or intolerance to prior biologics or small molecules defined as 1 or more of the following:
	  • Loss of response: Persistent signs and symptoms of active disease despite at least one induction and one maintenance regimen of the locally approved regimen of anti-TNF inhibitors, anti-integrins, anti-IL-12/23 monoclonal antibodies, JAK inhibitors, or S1Preceptor modulators.
	  • Inadequate response (primary non-response): Persistent signs and symptoms of active disease despite at least one induction regimen of the locally approved highest dosing regimen of anti-TNF inhibitors, anti-integrins, anti-IL-12/23
		Update. Text updated to describe inadequate response to biologics and small molecules.

Original text with changes shown	New wording	Reason/Justification for change
~~investigator.~~ • Intolerance: Discontinuation of anti-TNF inhibitors, anti-integrins, anti-IL-12/23 monoclonal antibodies, JAK inhibitors, or S1P receptor modulators due to an adverse drug reaction as determined by treating physician. Such adverse drug reactions include, but are not limited to, nausea/vomiting, abdominal pain, pancreatitis, liver function testing abnormalities, lymphopenia, and infections.	mAbs, JAK inhibitors, or S1P receptor modulators • Intolerance: Discontinuation of anti-TNF inhibitors, anti-integrins, anti-IL-12/23 monoclonal antibodies, JAK inhibitors, or S1P receptor modulators due to an adverse drug reaction as determined by treating physician. Such adverse drug reactions include, but are not limited to, nausea/vomiting, abdominal pain, pancreatitis, liver function testing abnormalities, lymphopenia, and infections.	
Section 4.2. Patient Exclusion Criteria		
k. Current or history of chronic liver or biliary disease (with the exception of Gilbert's syndrome, asymptomatic gallstones or uncomplicated fatty liver disease) or ALT >2x ULN and bilirubin >1.5x ULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at screening. l. Absolute neutrophil count <1.5x10^9/L or Hemoglobin <8 g/dL or lymphocyte count <0.8x10^9/L or platelet count <100,000/mL	k. Current or history of chronic liver or biliary disease (with the exception of Gilbert's syndrome, asymptomatic gallstones or uncomplicated fatty liver disease) or ALT >2x ULN and bilirubin >1.5x ULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at screening. l. Absolute neutrophil count <1.5x10^9/L or Hemoglobin <8 g/dL or lymphocyte count <0.8x10^9/L or platelet count <100,000/mL	Addition. Text added to include liver and biliary disease as exclusion criteria. Absolute neutrophil count, hemoglobin, lymphocyte count and platelet count added to exclusion criteria.
m. The patient has QTc>480 ms	m. The patient has QTc>480 ms	Addition. QT_C exclusion criteria added.
~~p.~~ s. Patient is receiving any of the following therapies within the designated time period: – The patient is currently using any systemic immunosuppressant or immunomodulatory biologic or nonbiologic (other than those listed in inclusion criterion "h" and those that are used for IBD) within 30 days or 5 half-lives (whichever is longer) prior to	p. s. Patient is receiving any of the following therapies within the designated time period: – The patient is currently using any systemic immunosuppressant or immunomodulatory biologic or nonbiologic (other than those listed in inclusion criterion "h" and those that are used for IBD) within 30 days or 5	Update. Text updated to include the number of half-lives needed to wash out certain small molecules and biologics.

Original text with changes shown	New wording	Reason/Justification for change
the endoscopy. – >9 mg/day of oral budesonide or >20 mg/day prednisone or equivalent within 2 weeks prior to the endoscopy. – Topical (rectal) treatment of 5-ASA or intravenous, intramuscular (parenteral), or enema/suppository administration of corticosteroids within 2 weeks prior to the endoscopy. – Biologics ~~or small molecules,~~ including anti-TNF inhibitors, anti-integrin inhibitors, anti-IL-12/23 inhibitors~~, JAK inhibitors, or S1P receptor modulators,~~ within ~~4 weeks~~ 3 half-lives prior to ~~the endoscopy~~ randomization. – Small molecules including JAK inhibitors, or S1P receptor modulators, within 5 half-lives or shorter washout duration if undetectable drug levels can be demonstrated prior to ~~the endoscopy~~ randomization – Other investigational procedures or products, within 30 days or 5 half-lives of investigational product prior to the endoscopy, whichever is longer – Live vaccine within 14 days prior to the first screening visit. Inactivated vaccines (including approved inactivated COVID-19 vaccines) should preferably be completed 14 days before first IMP dosing. If administered during the study, it is recommended to be at least 3 days before and after IMP administration, or as required by local country regulations.	half-lives (whichever is longer) prior to the endoscopy. – >9 mg/day of oral budesonide or >20 mg/day prednisone or equivalent within 2 weeks prior to the endoscopy. – Topical (rectal) treatment of 5-ASA or intravenous, intramuscular (parenteral), or enema/suppository administration of corticosteroids within 2 weeks prior to the endoscopy. – Biologics including anti-TNF inhibitors, anti-integrin inhibitors, anti-IL-12/23 inhibitors within 3 half-lives prior to randomization. – Small molecules including JAK inhibitors, or S1P receptor modulators, within 5 half-lives or shorter washout duration if undetectable drug levels can be demonstrated prior to randomization – Other investigational procedures or products, within 30 days or 5 half-lives of investigational product prior to the endoscopy, whichever is longer. – Live vaccine within 14 days prior to the first screening visit. Inactivated vaccines (including approved inactivated COVID-19 vaccines) should preferably be completed 14 days before first IMP dosing. If administered during the study, it is recommended to be at least 3 days before and after IMP administration, or as required by local country regulations.	
Section 4.3.Withdrawal Criteria and Assessments/Procedures for the Patient		
• in the event of intercurrent illness, adverse events, pregnancy, or any other reason concerning the health or well-	• in the event of intercurrent illness, adverse events, pregnancy, or any other reason concerning	Update. Cross reference added for

Original text with changes shown	New wording	Reason/Justification for change
being of the patient that indicates to the investigator that continued participation is not in the best interest of the patient (see also Individual Stopping Rules can be found in Section 3.4.1);	the health or well-being of the patient that indicates to the investigator that continued participation is not in the best interest of the patient (see also Individual Stopping Rules can be found in Section 3.4.1);	Stopping Rules.
Section 5.1.Investigational Medicinal Products Used in the Study		
The volume of the solution of each IMP (TEV-48574 and placebo) will be constant (15 mL loading dose volume and 12 mL induction dose volume~~).~~) and will be administered as single sc administrations. Active IMP will be diluted with placebo to achieve the final delivered concentrations. Patients will receive the following regimens as a single sc Q2W using ~~a commercial sc infusion system:~~ the [redacted]. • TEV-48574 2250 mg (single loading dose)/1800 mg (6 induction doses) • TEV-48574 2250 mg (single loading dose)/900 mg (6 induction doses) • TEV-48574 2250 mg (single loading dose)/450 mg (6 induction doses) • Placebo to match TEV-48574 (single loading dose)/(Induction doses)	The volume of the solution of each IMP (TEV-48574 and placebo) will be constant (15 mL loading dose volume and 12 mL induction dose volume) and will be administered as single sc administrations. Active IMP will be diluted with placebo to achieve the final delivered concentrations. Patients will receive the following regimens as a single sc Q2W using the [redacted]. • TEV-48574 2250 mg (single loading dose)/1800 mg (6 induction doses) • TEV-48574 2250 mg (single loading dose)/900 mg (6 induction doses) • TEV-48574 2250 mg (single loading dose)/450 mg (6 induction doses) • Placebo to match TEV-48574 (single loading dose)/(Induction doses)	Update. IMP dilution information included.
Section 5.1.3.Test and Placebo Investigational Medicinal Product Administration		
TEV-48574 or placebo IMP will be administered using a commercial sc infusion system. ~~The~~ For this study, the [redacted] will be utilized. This syringe infusion system ~~will be CE marked and~~ is cleared for use in the US under a ~~current~~ 510(k~~).~~) K092313 and CE marked for use in the EU. This infusion system ~~will be~~ is indicated for the iv or sc infusion of medications and fluids in	TEV-48574 or placebo IMP will be administered using a commercial sc infusion system. For this study, the [redacted] will be utilized. This syringe infusion system is cleared for use in the US under a 510(k) K092313 and CE marked for use in the EU. This infusion system is indicated for the iv or sc infusion of	Update. Dosing details included.

Original text with changes shown	New wording	Reason/Justification for change
the hospital and clinics where the use of the pump can be supervised by a clinician.	medications and fluids in the hospital and clinics where the use of the pump can be supervised by a clinician.	
This system safely enables single-site sc administration of large volumes to avoid the need for multiple injections from individual syringes. ~~The commercial syringe infusion systems are~~ and is capable of ~~sc drug~~ administration of up to 60 mL syringe using a sc safety needle set. The system controls the rate of drug entry into the tissues surrounding the sc infusion site as well as the duration of infusion. The syringe infusion system is a mechanical or electromechanical syringe pump that pushes the syringe plunger at a constant rate throughout the infusion to infuse drug. ~~The sponsor has evaluated the suitability of these types of syringe infusion system~~	This system safely enables single-site sc administration of large volumes to avoid the need for multiple injections from individual syringes and is capable of administration of up to 60 mL syringe using a sc safety needle set. The system controls the rate of drug entry into the tissues surrounding the sc infusion site as well as the duration of infusion. The syringe infusion system is a mechanical or electromechanical syringe pump that pushes the syringe plunger at a constant rate throughout the infusion to infuse drug.	Update. [redacted] details included
A sterile disposable 20 mL syringe is utilized with the infusion systems and is connected to a subcutaneous needle set, via a luer lock connector, which has a 6mm needle length and delivers the IMP to the subcutaneous tissue. The subcutaneous needle set, which is used in conjunction with the pump and 20 mL syringe, is the KORU (RMS 12606) 26G 6mm single needle infusion set that is cleared under 510k (K102512) and is also CE marked. The infusion rate is fixed at 30 mL/hr for all sc infusions. The expected infusion durations will therefore be 30 minutes for the 15 mL loading dose and 24 minutes for the 12 mL induction doses.	A sterile disposable 20 mL syringe is utilized with the infusion systems and is connected to a subcutaneous needle set, via a luer lock connector, which has a 6mm needle length and delivers the IMP to the subcutaneous tissue. The subcutaneous needle set, which is used in conjunction with the pump and 20 mL syringe, is the KORU (RMS 12606) 26G 6mm single needle infusion set that is cleared under 510k (K102512) and is also CE marked. The infusion rate is fixed at 30 mL/hr for all sc infusions. The expected infusion durations will therefore be 30 minutes for the 15 mL loading dose and 24 minutes for the 12 mL induction doses.	Update. Syringe and infusion rate details included.
The sponsor has evaluated the suitability of these types of syringe infusion systems to deliver TEV-48574 and the compatibility of TEV-48574 with the appropriate syringe and tubing sets (drug fluid path) that ~~would~~ will be used for sc delivery of TEV-48574.	The sponsor has evaluated the suitability of these types of syringe infusion systems to deliver TEV-48574 and the compatibility of TEV-48574 with the appropriate syringe and tubing sets (drug fluid path) that will be used for sc delivery of TEV-48574.	Update. Infusion system suitability statement added.

Original text with changes shown	New wording	Reason/Justification for change
Section 5.2.1. Preparation, Storage and Security		
Prepared doses of TEV-48574 and placebo IMP will be kept for no more than 4 hours at 25ºC from time of opening the first vial, to completion of dose administration. Additional preparation details may be found in the Pharmacy Manual.	Prepared doses of TEV-48574 and placebo IMP will be kept for no more than 4 hours at 25ºC from time of opening the first vial, to completion of dose administration. Additional preparation details may be found in the Pharmacy Manual.	Update. Addition of a description of the proposed time and storage conditions between study drug dilution and administration
Section 5.3.1. Justification for Dose of Test Investigational Medicinal Product		
In line with this concept, a single loading dose of 2250 mg is used in this study. This dose level is within the range of doses safely administered to patients with asthma in the MAD portion of Study TV48574-SAD-10126 and in Study TV48574-AS-20031. The loading dose as part of the induction dose regimen has been selected to rapidly achieve steady-state concentration and address the significant over-production of TL1A in the colon (Jia Wenxiu et al 2021) within the first weeks of induction. The TEV-48574 dosing regimen is designed to achieve steady state-concentration fast, whereas PF-06480605 achieves steady state at approximately 8 weeks (Danese et al 2021). TEV-48574 has linear PK for the dose range of 200 to 2300 mg, as described in FIH TV48574-SAD-10126 study, with elimination half-life of 7-9 days. In MAD portion of TV48574-SAD-10126 trial, a 2300 mg loading dose followed by 1600 mg doses reached steady-state after 2 weeks and no accumulation was observed. Using population PK approaches, we described TEV-48574 PK characteristics and used the model subsequently to simulate the proposed loading and induction doses in study TV48574-IMM-20036 and therefore predict resulting exposures.	In line with this concept, a single loading dose of 2250 mg is used in this study. This dose level is within the range of doses safely administered to patients with asthma in the MAD portion of Study TV48574-SAD-10126 and in Study TV48574-AS-20031. The loading dose as part of the induction dose regimen has been selected to rapidly achieve steady-state concentration and address the significant over-production of TL1A in the colon (Jia Wenxiu et al 2021) within the first weeks of induction. The TEV-48574 dosing regimen is designed to achieve steady state-concentration fast, whereas PF-06480605 achieves steady state at approximately 8 weeks (Danese et al 2021). TEV-48574 has linear PK for the dose range of 200 to 2300 mg, as described in FIH TV48574-SAD-10126 study, with elimination half-life of 7-9 days. In MAD portion of TV48574-SAD-10126 trial, a 2300 mg loading dose followed by 1600 mg doses reached steady-state after 2 weeks and no accumulation was observed. Using population PK approaches, we described TEV-48574 PK characteristics and used the model subsequently to simulate the proposed loading and induction doses in study TV48574-IMM-20036 and therefore	Clarification. Addition text included to justify dose.

Original text with changes shown	New wording	Reason/Justification for change
	predict resulting exposures.	
Section 5.6.4. Prohibited Medications and Therapies		
• ~~Any investigational drug or biologic or small molecule~~ The patient is currently using any systemic immunosuppressant or immunomodulatory ~~treatments~~ biologic or nonbiologic (other than those listed in inclusion criterion "h~~)~~" and those that are used for IBD) within 30 days or 5 half-lives ~~of the drug~~ (whichever is ~~greater),~~ longer) prior to the endoscopy ~~and/~~ . • Biologics including anti-TNF inhibitors, anti-integrin inhibitors, and anti-IL-12/23 inhibitors within 3 half-lives prior to randomization. • Small molecules including JAK inhibitors, or S1P receptor modulators, within 5 half-lives or ~~during study participation~~ shorter washout duration if undetectable drug levels can be demonstrated prior to randomization. • Oral budesonide of >9 mg/day or equivalent from 2 weeks prior to endoscopy through week 14. • Patients requiring a surgical intervention for UC or CD will be discontinued from the study	• The patient is currently using any systemic immunosuppressant or immunomodulatory biologic or nonbiologic (other than those listed in inclusion criterion "h" and those that are used for IBD) within 30 days or 5 half-lives (whichever is longer) prior to the endoscopy. • Biologics including anti-TNF inhibitors, anti-integrin inhibitors, and anti-IL-12/23 inhibitors within 3 half-lives prior to randomization. • Small molecules including JAK inhibitors, or S1P receptor modulators, within 5 half-lives or shorter washout duration if undetectable drug levels can be demonstrated prior to randomization. • Oral budesonide of >9 mg/day or equivalent from 2 weeks prior to endoscopy through week 14. • Patients requiring a surgical intervention for UC or CD will be discontinued from the study	Update. Section updated to state that surgical interventions for UC and CD are prohibited during the study.
Section 5.8. Randomization and Blinding		
~~Patients~~ Approximately 140 UC patients and 140 CD patients	Approximately 140 UC patients and 140 CD	Clarification. Additional details

Original text with changes shown	New wording	Reason/Justification for change
will be randomly assigned to the treatment groups by means of a computer-generated randomization list using interactive-response technology. The specifications for randomization will be under the responsibility and oversight of Teva Global Statistics. The study patients, sponsor, and the clinical team at the site will be blinded to treatment assignment until the database is locked for analysis. ~~Individuals who may not be blinded include (but are not limited to) the bioanalytical scientists, pharmacokineticists, and biostatisticians who are not directly involved in study conduct.~~	patients will be randomly assigned to the treatment groups by means of a computer-generated randomization list using interactive-response technology. The specifications for randomization will be under the responsibility and oversight of Teva Global Statistics. The study patients, sponsor, and the clinical team at the site will be blinded to treatment assignment until the database is locked for analysis.	describing the randomization process added.
Section 5.9.2. Blinding and Unblinding		
~~Blinded pharmacokinetic~~ Pharmacokinetic, pharmacodynamics and immunogenicity ~~data may~~ samples will be ~~assessed~~ collected for bioanalysis during the study. ~~For patients who have pharmacokinetic or immunogenicity sample bioanalysis or data analysis conducted, the individuals~~ Individuals responsible for sample bioanalysis and other responsible personnel ~~will~~ may know who received test IMP and who received placebo IMP during the study ~~(of those patients only).~~. Personnel responsible for bioanalysis will be provided with the randomization code to facilitate the analysis. However, the personnel responsible for bioanalysis ~~and pharmacokinetic data analysis~~ will not have access to clinical safety and efficacy data and will provide concentration data to other personnel in a manner that will not identify individual patients (ie, a dummy patient identifier will be linked to the concentration data of an individual patient). ~~The process to ensure study integrity, maintenance of the double blind, and~~	Pharmacokinetic, pharmacodynamics and immunogenicity samples will be collected for bioanalysis during the study. Individuals responsible for sample bioanalysis and other responsible personnel may know who received test IMP and who received placebo IMP during the study. Personnel responsible for bioanalysis will be provided with the randomization code to facilitate the analysis. However, the personnel responsible for bioanalysis will not have access to clinical safety and efficacy data and will provide concentration data to other personnel in a manner that will not identify individual patients (ie, a dummy patient identifier will be linked to the concentration data of an individual patient).	Clarification. Blinding procedure updated.

Original text with changes shown	New wording	Reason/Justification for change
~~the responsibilities of the relevant study personnel will be described in a pharmacokinetic analysis plan that will be approved prior to any data transfer, per the sponsor's relevant SOPs (Section .)~~**9.13**		
~~An interim efficacy analysis for futility will be performed separately in each indication (UC and CD) by an independent, unblinded statistician. An Internal Review Committee Charter defining the procedures for the unblinding and decision making will be finalized prior to interim unblinding. The charter will specify the sponsor personnel who are to be unblinded.~~ Interim analyses as described in Section 9.13 will be performed throughout the study by unblinded analysis groups external to Teva and will be reviewed by an independent data monitoring committee.	Interim analyses as described in Section 9.13 will be performed throughout the study by unblinded analysis groups external to Teva and will be reviewed by an independent data monitoring committee.	Update. Additional text added to describe interim analysis.
Section 5.9.3. Independent Data Monitoring Committee		
Text describing the Internal Review Committee removed and text added to describe the Independent Data Monitoring Committee.	Description of the Independent Data Monitoring Committee.	Update. Description of the Internal Review Committee removed.
Section 6.1.2.1. Biopsy Collection		
Biopsies will be used for measures of histologic disease, ~~pharmacokinetic assessments,~~ and exploratory biomarker assays.	Biopsies will be used for measures of histologic disease and exploratory biomarker assays.	Update. Text revised to state that biopsy drug concentrations will not be collected.

Original text with changes shown	New wording	Reason/Justification for change
Section 7. Assessment of Safety		
There will be an I~~SR~~DMC to monitor safety in this study (Section .)5.9.3	There will be an IDMC to monitor safety in this study (Section .)5.9.3	Update. The ISRC committee updated with IDMC.
Section 7.1.5. Severity of an Adverse Event		
~~The severity of each adverse event must be recorded as 1 of the following:~~ ~~**Mild:** No limitation of usual activities~~ ~~**Moderate:** Some limitation of usual activities~~ ~~**Severe:** Inability to carry out usual activities~~ The severity of each adverse event must be recorded. The adverse event severity grading scale for the current version of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; version 5) will be used for assessing adverse event severity. Table 6 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.	The severity of each adverse event must be recorded. The adverse event severity grading scale for the current version of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; version 5) will be used for assessing adverse event severity. Table 6 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.	Update. Change in the grading method for AE severity presented in section.
Table 6: Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE	Table 6: Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE	Addition. Adverse Event Severity Grading Scale table added.
Section 7.1.10. Protocol-Defined Adverse Events of Special Interest		
Adverse events of special interest (AESIs)—which are not necessarily adverse drug reactions (ADRs) but are of special interest based on standard drug registration topics, safety findings from previous studies, potential risks associated with biologic immunomodulators, are listed below.	Adverse events of special interest (AESIs)—which are not necessarily adverse drug reactions (ADRs) but are of special interest based on standard drug registration topics, safety findings from previous studies, potential risks associated with biologic immunomodulators, are listed below.	Addition. Text describing adverse events of special interest included.
Section 7.1.10.1. Protocol-Defined Adverse Events of Special Interest that Require Reporting to Sponsor's Global Patient Safety and Pharmacovigilance		
For purposes of this protocol, the following are considered protocol-defined adverse events of special interest to be sent to	For purposes of this protocol, the following are considered protocol-defined adverse events of	Update. Text updated to include severe infections, liver injury and severe

Original text with changes shown	New wording	Reason/Justification for change
the sponsor's GPSP for evaluation: • systemic severe reactions (including anaphylaxis) • opportunistic or severe infections • malignancies (including non-melanoma skin cancer) • liver injury • severe hematology abnormalities	special interest to be sent to the sponsor's GPSP for evaluation: • systemic severe reactions (including anaphylaxis) • opportunistic or severe infections • malignancies (including non-melanoma skin cancer) • liver injury • severe hematology abnormalities	hematology abnormalities as protocol-defined adverse events of special interest to be sent to the sponsor's GPSP for evaluation.
As a precaution, each site should have a resuscitation medication/equipment nearby. If a patient has symptoms of anaphylaxis or severe hypersensitivity, the administration of study drug must be discontinued permanently. In addition, information about all suspected anaphylaxis and hypersensitivity events will be recorded on the Suspected Anaphylaxis CRF, which is based on the 2006 Joint National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network Second Symposium on Anaphylaxis (Sampson et al 2006). Investigators should report these events immediately to the Sponsor as adverse events of special interest and as serious adverse events, if appropriate. ~~A list of opportunistic infections is included in .Appendix L~~	As a precaution, each site should have a resuscitation medication/equipment nearby. If a patient has symptoms of anaphylaxis or severe hypersensitivity, the administration of study drug must be discontinued permanently. In addition, information about all suspected anaphylaxis and hypersensitivity events will be recorded on the Suspected Anaphylaxis CRF, which is based on the 2006 Joint National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network Second Symposium on Anaphylaxis (Sampson et al 2006). Investigators should report these events immediately to the Sponsor as adverse events of special interest and as serious adverse events, if appropriate.	Update. Text updated to describe steps to be taken if a patient experiences anaphylaxis or severe hypersensitivity.
Opportunistic or severe infections In the event of opportunistic or severe infections (CTCAE grade 3 to 4), the patient should not receive further study drug until the event has completely resolved. Study drug will be permanently stopped in case of infections following stopping criteria (see section 3.4.1). Study drug may be restarted following consultation with the Medical Monitor. Treatment of infections should be initiated promptly according to standard of care and all efforts should be made to identify the infectious agent. Events should be reported to the Sponsor immediately (ie, no more than 24 hours after learning of the event), either as	Opportunistic or severe infections In the event of opportunistic or severe infections (CTCAE grade 3 to 4), the patient should not receive further study drug until the event has completely resolved. Study drug will be permanently stopped in case of infections following stopping criteria (see section 3.4.1). Study drug may be restarted following consultation with the Medical Monitor. Treatment of infections should be initiated promptly according to standard of care and all efforts should	Update. Text updated to describe steps to be taken if a patient experiences opportunistic or severe infections.

Original text with changes shown	New wording	Reason/Justification for change
a serious adverse event or an adverse event of special interest. Examples for opportunistic infections are included in Appendix L.	be made to identify the infectious agent. Events should be reported to the Sponsor immediately (ie, no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest. Examples for opportunistic infections are included in Appendix L.	
Malignancies Any signs or symptoms that could be suggestive of malignancy should be promptly and aggressively evaluated. Patients who develop a malignancy (with the exception of an appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix) should be withdrawn from study drug and must not receive additional doses of study drug. Malignancies should be reported to the Sponsor immediately (ie, no more than 24 hours after learning of the event).	Malignancies Any signs or symptoms that could be suggestive of malignancy should be promptly and aggressively evaluated. Patients who develop a malignancy (with the exception of an appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix) should be withdrawn from study drug and must not receive additional doses of study drug. Malignancies should be reported to the Sponsor immediately (ie, no more than 24 hours after learning of the event).	Update. Text updated to describe steps to be taken if a patient experiences malignancies.
Liver injury If any of the following criteria occur, study drug should be withheld and additional monitoring and follow-up assessment will be required (as detailed in the Liver Safety Required Actions and Follow-up Assessments section in Appendix M): • Alanine transaminase (ALT) or aspartate aminotransferase (AST) ≥5x upper limit of normal (ULN) • ALT or AST ≥3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) • AST and/or ALT ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample or in combination with clinical jaundice or INR>1.5 (not applicable for patients on anticoagulants) The additional information will be recorded on the Liver Event	Liver injury If any of the following criteria occur, study drug should be withheld and additional monitoring and follow-up assessment will be required (as detailed in the Liver Safety Required Actions and Follow-up Assessments section in Appendix M): • Alanine transaminase (ALT) or aspartate aminotransferase (AST) ≥5x upper limit of normal (ULN) • ALT or AST ≥3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) • AST and/or ALT ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample or in combination with clinical	Update. Text updated to describe steps to be taken if a patient experiences liver injury.

Original text with changes shown	New wording	Reason/Justification for change
CRF. 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 7.1.3) and reported to the Sponsor immediately (ie, no more than 24 hours after learning of the event), either as a serious adverse event (ie, a possible Hy's Law case: ALT≥3xULN and Bilirubin≥2xULN or INR>1.5) or an adverse event of special interest.	jaundice or INR>1.5 (not applicable for patients on anticoagulants) The additional information will be recorded on the Liver Event CRF. 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 7.1.3) and reported to the Sponsor immediately (ie, no more than 24 hours after learning of the event), either as a serious adverse event (ie, a possible Hy's Law case: ALT≥3xULN and Bilirubin≥2xULN or INR>1.5) or an adverse event of special interest.	
Severe hematology abnormalities Predefined confirmed hematology stopping criteria (see section 3.4.1) should be re-tested every 3 to 5 days until values have returned to above the hematological exclusion criteria threshold, at which point dosing can be resumed (however, two consecutive doses of IMP, should never be given less than 7 days apart).	Severe hematology abnormalities Predefined confirmed hematology stopping criteria (see section 3.4.1) should be re-tested every 3 to 5 days until values have returned to above the hematological exclusion criteria threshold, at which point dosing can be resumed (however, two consecutive doses of IMP, should never be given less than 7 days apart).	Update. Text updated to describe steps to be taken if a patient experiences severe hematology abnormalities.
Section 7.1.10.2. Protocol-Defined Adverse Events of Special Interest that Do Not Require Reporting to Sponsor's Global Patient Safety and Pharmacovigilance		
The following are considered protocol-defined adverse events of special interest that do not need to be sent to the sponsor's GPSP department (unless assessed as serious) and will be recorded only in the clinical database ~~as described in Section 7.2:~~: • administration site reactions (as described in Section 7.2)	The following are considered protocol-defined adverse events of special interest that do not need to be sent to the sponsor's GPSP department (unless assessed as serious) and will be recorded only in the clinical database: • administration site reactions (as described in Section 7.2)	Updated. Text updated to state that hematology abnormalities do not need to be sent to the sponsor's GPSP department.
Section 7.5.2. Other Clinical Laboratory Tests		
In case of a suspected liver injury, additional laboratory tests	In case of a suspected liver injury, additional	Addition. Text added to state that

Original text with changes shown	New wording	Reason/Justification for change
will be required (see Appendix M).	laboratory tests will be required (see Appendix M).	additional clinical laboratory assessments should be performed if a patient experiences liver injury.
Section 9.5.4.1. Primary Efficacy Analysis		
~~Inference will be based on posterior distribution of these parameters, along with summaries presented as posterior means and/or medians and the corresponding 95% credible intervals for UC and CD disease groups.~~ Inference will be based on posterior distribution of these parameters and summarized as follows for each indication (UC, CD): •Posterior means and/or medians of the response rates for TEV-48574 doses, placebo •95% credible intervals for difference in response rates (TEV-48574 doses – placebo) •For each TEV-48574 dose, Posterior Probability (TEV-48574 dose – placebo response rate > 0) •Posterior Probability (E_{max} > 0)	Inference will be based on posterior distribution of these parameters and summarized as follows for each indication (UC, CD): •Posterior means and/or medians of the response rates for TEV-48574 doses, placebo •95% credible intervals for difference in response rates (TEV-48574 doses – placebo) •For each TEV-48574 dose, Posterior Probability (TEV-48574 dose – placebo response rate > 0) •Posterior Probability (E_{max} > 0)	Update. Primary efficacy analysis methods updated.
Section 9.5.4.3. Supplementary Analysis		
The following additional analyses will be undertaken to examine the robustness of the primary efficacy analysis results: • Cochran-Mantel-Haenszel (CMH) test for pairwise comparisons between the active dose groups and placebo separately for UC and CD. Nominal p-values will be presented for each of the comparisons. • Bayesian E_{max} dose-response model fit separately (i.e., no borrowing) for UC and CD. Inferences presented for the primary efficacy analysis will be re-produced for this approach. • Frequentist E_{max} dose-response model fit separately for UC and CD. Response rates of TEV-48574 doses, placebo and 95% confidence intervals for difference in response rates (TEV-48574 doses – placebo), along with summaries of model	The following additional analyses will be undertaken to examine the robustness of the primary efficacy analysis results: • Cochran-Mantel-Haenszel (CMH) test for pairwise comparisons between the active dose groups and placebo separately for UC and CD. Nominal p-values will be presented for each of the comparisons. • Bayesian E_{max} dose-response model fit separately (i.e., no borrowing) for UC and CD. Inferences presented for the primary efficacy analysis will be re-produced for this approach. • Frequentist E_{max} dose-response model fit separately for UC and CD. Response rates of TEV-	Update. Supplementary analysis described.

Original text with changes shown	New wording	Reason/Justification for change
parameters will be presented • Logistic regression model with fixed effects for dose, randomization stratification factors and baseline response fit separately for UC and CD.	48574 doses, placebo and 95% confidence intervals for difference in response rates (TEV-48574 doses – placebo), along with summaries of model parameters will be presented • Logistic regression model with fixed effects for dose, randomization stratification factors and baseline response fit separately for UC and CD.	
Section 9.13. Planned Interim Analysis		
Section revised to describe interim analysis and who will be blinded to the analysis.	Section updated to describe interim analysis.	Update. Section updated to detail interim analysis.
APPENDIX A. Departments And Institutions		
[redacted] ~~Teva Branded Pharmaceutical Products R&D, Inc.~~ [redacted] Teva Branded Pharmaceutical Products R&D, Inc. [redacted]	[redacted] Teva Branded Pharmaceutical Products R&D, Inc. [redacted]	Update. Staff change.
APPENDIX B. Study Procedures And Assessments By Visit		
b. Visits 2, 4, and 6 (weeks 2, 6, and 10, days 15, 43, 71 ([±3 days based on ~~day 1~~ previous visit]) •CDAI score (CD only) •Stool frequency and Abdominal pain (PRO2 CD) •Stool frequency and Rectal bleeding Mayo sub-scores (PRO2 UC)	b. Visits 2, 4, and 6 (weeks 2, 6, and 10, days 15, 43, 71 ([±3 days based on previous visit]) •CDAI score (CD only) •Stool frequency and Abdominal pain (PRO2 CD) •Stool frequency and Rectal bleeding Mayo sub-scores (PRO2 UC)	Update. Additional assessments added to visits and timing of visits updated.

Original text with changes shown	New wording	Reason/Justification for change
c. Visits 3, 5, and 7 (weeks 4, 8, and 12, days 29, 57, 85 ([±3 days based on ~~day 1~~ previous visit]) •CDAI score (CD only) •Stool frequency and Abdominal pain (PRO2 CD) •Stool frequency and Rectal bleeding Mayo sub-scores (PRO2 UC)	c. Visits 3, 5, and 7 (weeks 4, 8, and 12, days 29, 57, 85 ([±3 days based on previous visit]) •CDAI score (CD only) •Stool frequency and Abdominal pain (PRO2 CD) •Stool frequency and Rectal bleeding Mayo sub-scores (PRO2 UC)	Update. Additional assessments added to visits and timing of visits updated.
d. Visit 8 (week 14, day 99 [±3 days based on ~~day 1~~ previous visit])	d. Visit 8 (week 14, day 99 [±3 days based on previous visit])	Update. Timing of visit updated.
3. Follow-up (visit 9, week 18, day 127 [±14 days based on ~~day 1~~ previous visit])	3. Follow-up (visit 9, week 18, day 127 [±14 days based on previous visit])	Update. Timing of follow-up visit updated.
Appendix K. Management Of Study Activities During Covid-19 Outbreaks		
Section 4.4. Replacement of Patients In the event of an emergency situation (eg, COVID-19 outbreaks), the number of patients to be randomized may be increased to ensure the targeted number of completers per arm. ~~Section 5.9. Maintenance of Randomization and Blinding~~ ~~Unblinded data review of COVID-19 patients by member(s) not part of the blinded study team may be conducted upon Internal Safety Review Committee recommendations and Teva's discretion.~~ ~~Active COVID-19 cases will be monitored throughout the study. If a total of number COVID-19 infections are confirmed and related to a serious adverse event to reach a minimum threshold (based on total randomized patients, detailed in the medical monitoring plan) the pharmacovigilance physician in consultation with the clinical study physician will determine if an unblinded review of the cases is warranted to ensure patient safety. Any unblinded review will be conducted by appropriate personnel that are not connected with the study.~~	Section 4.4. Replacement of Patients In the event of an emergency situation (eg, COVID-19 outbreaks), the number of patients to be randomized may be increased to ensure the targeted number of completers per arm.	Update. Description of the maintenance of the randomization and blinding of COVID-19 patients removed from appendix.

Original text with changes shown	New wording	Reason/Justification for change
APPENDIX M. Liver Safety: Required Actions And Follow-Up Assessments Guidelines		
Appendix M added.	Appendix M.	Addition. Appendix added to detail the liver stopping and increased monitoring criteria.
Appendix N. Operating Characteristics And Assumptions For Final And Interim Analysis		
Appendix updated to include additional simulations and Safety Stopping Rules.	Appendix updated.	Update. Appendix updated.

APPENDIX A. STUDY PROCEDURES AND ASSESSMENTS BY VISIT

1. **Procedures for Screening (week -6 to week -1, days -42 to -1)**

   The screening visit will take place not more than 6 weeks before the baseline visit (visit 1). The following procedures will be performed at the screening visit:

   - obtain written informed consent before any study-related procedures are performed (a separate informed consent form will be provided for pharmacogenetics samples)
   - review inclusion and exclusion criteria
   - review demographics and medical history
   - vital signs measurements
   - weight and height measurements
   - full physical examination
   - electrocardiography
   - endoscopy
   - Modified Mayo score (ulcerative colitis [UC] only)
   - Robarts Histopathology Index (UC only)
   - Crohn's Disease Activity Index (CDAI) score (Crohn's disease [CD] only)
   - Simple Endoscopic Score for Crohn's Disease (SES-CD) (CD only)
   - modified multiplier (MM)-SES-CD (CD only)
   - 2-item patient-reported outcome (PRO2)
   - stool sample tests for enteric pathogens (including stool culture and *Clostridium difficile* toxin assay)
   - infectious serologies
   - tuberculosis (TB) screening (QuantiFERON® TB Gold Test)
   - follicle-stimulating hormone testing (to confirm postmenopausal status)
   - pregnancy test (serum) in women of childbearing potential
   - clinical laboratory tests
   - urinalysis
   - biopsy towards tissue transcriptomics
   - adverse event monitoring
   - review prior and concomitant medication and treatments

2. **Procedures During Administration of Investigational Medicinal Product (Double-Blind Treatment Period)**

a. **Visit 1 (week 0, day 1)**

The following procedures and assessments will be performed at visit 1:

- review inclusion and exclusion criteria
- vital signs measurements
- weight measurement
- pregnancy test (urine) in women of childbearing potential
- clinical laboratory tests
- urinalysis
- retained pharmacogenetic sample
- biomarker high sensitivity C-reactive protein (hsCRP)
- serum free and total tumor necrosis factor (ligand) 1A (TL1A)
- stool sample for fecal calprotectin (FeCal) or other stool-derived markers
- serum measure of PD
- biomarker [redacted]
- serum measures of tissue condition
- serum TEV-48574 concentration
- anti-drug antibody (ADA) and neutralizing ADA
- randomization (after all screening procedures complete and eligibility confirmed)
- investigational medicinal product (IMP) administration
- adverse event monitoring
- review prior and concomitant medication and treatments
- local tolerability assessment

b. Visits 2, 4, and 6 (weeks 2, 6, and 10, days 15, 43, 71 ([±3 days based on previous visit])

The following procedures and assessments will be performed at visits 2, 4, and 6:

- vital signs measurements
- Stool frequency and Abdominal pain (PRO2 CD)
- Stool frequency and Rectal bleeding Mayo sub-scores (PRO2 UC)
- pregnancy test (urine) in women of childbearing potential)
- biomarker hsCRP **(visit 2 only)**
- serum free and total TL1A **(visit 2 only)**
- stool sample for fecal calprotectin (FeCal) or other stool-derived markers **(visit 2 only)**

- serum measure of PD **(visit 2 only)**
- biomarker [redacted] (**visit 2 only**)
- serum measures of tissue condition **(visit 2 only)**
- serum TEV-48574 concentration **(visit 2 only)**
- ADA and neutralizing ADA **(visit 2 only)**
- IMP administration
- adverse event monitoring
- review prior and concomitant medication and treatments
- local tolerability assessment

c. Visits 3, 5, and 7 (weeks 4, 8, and 12, days 29, 57, 85 ([±3 days based on **previous visit**])

The following procedures and assessments will be performed at visits 3, 5, and 7:

- vital signs measurements
- weight measurement
- brief physical exam
- electrocardiography **(visits 3 and 5 only)**
- CDAI score (CD only)
- Stool frequency and Abdominal pain (PRO2 CD)
- Stool frequency and Rectal bleeding Mayo sub-scores (PRO2 UC)
- pregnancy test (urine) in women of childbearing potential)
- clinical laboratory tests
- urinalysis **(visits 3 and 5 only)**
- biomarker hsCRP **(visits 3 and 5 only)**
- serum free and total TL1A **(visits 3 and 5 only)**
- stool sample for fecal calprotectin (FeCal) or other stool-derived markers **(visits 3 and 5 only)**
- serum measure of PD **(visits 3 and 5 only)**
- biomarker [redacted] (**visit 5 only**)
- serum measures of tissue condition **(visits 3 and 5 only)**
- serum TEV-48574 concentration **(visits 3 and 5 only)**
- ADA and neutralizing ADA **(visits 3 and 5 only)**
- IMP administration
- adverse event monitoring

- review prior and concomitant medication and treatments
- local tolerability assessment

d. **Visit 8 (week 14, day 99 [±3 days based on previous visit])**

The following procedures and assessments will be performed at visit 8:

- vital signs measurements
- weight measurement
- full physical exam
- electrocardiography
- endoscopy
- Modified Mayo score (UC only)
- Robarts Histopathology Index (UC only)
- CDAI score (CD only)
- Stool frequency and Abdominal pain (PRO2 CD)
- Stool frequency and Rectal bleeding Mayo sub-scores (PRO2 UC)
- SES-CD (CD only)
- MM-SES-CD (CD only)
- pregnancy test (urine) in women of childbearing potential)
- clinical laboratory tests
- urinalysis
- biomarker hsCRP
- serum free and total TL1A
- stool sample for fecal calprotectin (FeCal) or other stool-derived markers
- biopsy towards tissue transcriptomics
- serum measure of PD
- biomarker [redacted]
- serum measures of tissue condition
- serum TEV-48574 concentration
- ADA and neutralizing ADA
- adverse event monitoring
- review prior and concomitant medication and treatments

3. **Follow-up (visit 9, week 18, day 127 [±3 days based on previous visit])**

   The following procedures and assessments will be performed at the follow-up visit:

   - vital signs measurements
   - weight measurement
   - full physical exam
   - pregnancy test (urine) in women of childbearing potential
   - clinical laboratory tests
   - urinalysis
   - biomarker hsCRP
   - serum free and total TL1A
   - stool sample for fecal calprotectin (FeCal) or other stool-derived markers
   - serum measure of PD
   - serum measures of tissue condition
   - serum TEV-48574 concentration
   - ADA and neutralizing ADA
   - adverse event monitoring
   - review prior and concomitant medication and treatments

4. **Early Termination**

   The procedures and assessments performed at the early termination visit are identical to those performed at the visit 8 (week 14 visit; see item “d” above), except that weight is measured as well. If a patient develops COVID-19 during the course of the trial this is not an indication for early termination.

5. **Unscheduled Visits**

   The investigator may schedule unplanned visits in addition to those listed in the Schedule of Study Procedures and Assessments, in order to conduct evaluations or assessments required to protect the well-being of the patient. The date and reason for the unscheduled visit will be recorded on the CRF as well as any other data obtained from procedures and assessments.

APPENDIX B. QUALITY CONTROL AND QUALITY ASSURANCE

Protocol Amendments and Protocol Deviations

Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and national and local competent authorities, as applicable, except when necessary to address immediate safety concerns to the patients or when the change involves only nonsubstantial logistics or administration. The principal investigator at each investigational center, the coordinating investigator (if applicable), and the sponsor will sign the protocol amendment.

Important Protocol Deviations

Any deviation from the protocol that affects, to a significant degree, (a) the safety, physical, or mental integrity of the patients in the study and/or (b) the scientific value of the study will be considered an important protocol deviation. Important protocol deviations may include non-adherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion and exclusion criteria, primary objective variable criteria, or Good Clinical Practice (GCP) guidelines; noncompliance to investigational medicinal product administration; use of prohibited medications. Important protocol deviations will be documented by investigational center personnel. All important protocol deviations will be reported to the responsible IEC/IRB, as required.

When an important protocol deviation is reported, the sponsor will determine whether to withdraw the patient from the study or permit the patient to continue in the study, with documented approval from the medical expert. The decision will be based on ensuring the safety of the patient and preserving the integrity of the study.

Changes in the inclusion and exclusion criteria of the protocol are **not** prospectively granted by the sponsor. If investigational center personnel learn that a patient who did not meet protocol inclusion and exclusion criteria was entered in a study, they must immediately inform the sponsor of the important protocol deviation. If such patient has already completed the study or has withdrawn early, no action will be taken but the deviation will be recorded.

Information to Study Personnel

The investigator is responsible for giving information about the study to all personnel members involved in the study or in any element of patient management, both before starting the study and during the course of the study (eg, when new personnel become involved). The investigator must ensure that all study personnel are qualified by education, experience, and training to perform their specific task. These study personnel members must be listed on the investigational center authorization form, which includes a clear description of each personnel member’s responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study personnel, including the investigator, and for ensuring they comply with the protocol.

Study Monitoring

To ensure compliance with GCP guidelines, the study monitor or representative is responsible for ensuring that patients have signed the informed consent form and the study is conducted according to applicable Standard Operating Procedures (SOPs), the protocol, and other written instructions and regulatory guidelines.

The study monitor is the primary association between the sponsor and the investigator. The main responsibilities of the study monitor(s) are to visit the investigator before, during, and after the study to ensure adherence to the protocol, that all data are correctly and completely recorded and reported, and that informed consent is obtained and recorded for all patients before they participate in the study and when changes to the consent form are warranted, in accordance with IEC/IRB approvals.

The study monitor(s) will contact the investigator and visit the investigational center according to the monitoring plan. The study monitor will be permitted to review and verify the various records (CRFs and other pertinent source data records, including specific electronic source document relating to the study) to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded.

As part of the supervision of study progress, other sponsor personnel may, on request, accompany the study monitor on visits to the investigational center. The investigator and assisting personnel must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected during the course of these monitoring visits or provided in follow-up written communication.

In case of an emergency situation (eg, the COVID-19 pandemic), where trial monitors may not be able to access the investigational centers for on-site visits, investigational centers will be monitored remotely, where allowed, and in accordance with global and/or local regulations.

Audit and Inspection

The sponsor may audit the investigational center to evaluate study conduct and compliance with protocols, SOPs, GCP guidelines, and applicable regulatory requirements. The sponsor’s Global Clinical Quality Assurance, independent of Global Specialty Development, is responsible for determining the need for (and timing of) an investigational center audit.

The investigator must accept that competent authorities and sponsor representatives may conduct inspections and audits to verify compliance with GCP guidelines.

In case of an emergency situation (eg, the COVID-19 pandemic), where auditors may not be able to access the investigational centers for on-site visits, investigational centers will be audited remotely, where allowed, and in accordance with global and/or local regulations.

APPENDIX C. ETHICS

Informed Consent

The investigator, or a qualified person designated by the investigator, should fully inform the patient of all pertinent aspects of the study, including the written information approved by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB). All written and oral information about the study will be provided in a language as nontechnical as practical to be understood by the patient. The patient should be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. The above should be detailed in the source documents.

Written informed consent will be obtained from each patient before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The patient's willingness to participate in the study will be documented in the informed consent form (ICF), which will be signed and personally dated by the patient and by the person who conducted the informed consent discussion. The investigator will keep the original ICFs, and copies will be given to the patients. It will also be explained to the patients that the patient is free to refuse participation in the study and free to withdraw from the study at any time without prejudice to future treatment.

Competent Authorities and Independent Ethics Committees/Institutional Review Boards

Before this study starts, the protocol will be submitted to the national competent authority and to the respective IEC/IRB for review. As required, the study will not start before the IEC/IRB and competent authority (as applicable) for the investigational center give written approval or a favorable opinion.

Confidentiality Regarding Study Patients

The investigator must ensure that the privacy of the patients, including their identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the sponsor, patients will be identified not by their names, but by an identification number.

Personal medical information may be reviewed for the purpose of patient safety or for verifying data in the source and the CRF. This review may be conducted by the study monitor, properly authorized persons on behalf of the sponsor, Global Quality Assurance, or competent authorities. Personal medical information will always be treated as confidential.

Registration of the Clinical Study

In compliance with national and local regulations and in accordance with Teva standard procedures, this clinical study will be registered on clinical trial registries if applicable.

APPENDIX D. BIRTH CONTROL METHODS

Only highly effective birth control methods (methods that can achieve a failure rate of less than 1% per year when used consistently and correctly) may be used. Such methods include the following:

- Combined estrogen and progestogen hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation; these should be initiated at least 14 days before the first dose of investigational medicinal product (IMP)
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation; these should be initiated at least 14 days before the first dose of IMP
- Intrauterine device and intrauterine hormone-releasing system need to be in place at least 2 months before screening
- Bilateral tubal occlusion, except for hysteroscopic bi-tubal ligation (Essure®), for which a hysterosalpingogram is required 3 months post procedure to assess surgical success
- Vasectomized partner, provided he is the sole sexual partner and has received medical assessment of the surgical process
- Heterosexual abstinence is **only** considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Minimum time adherence prior to first dosing is 6 months.

Male patients (including vasectomized) with women of childbearing potential partners (whether pregnant or not) must use condoms after the first IMP administration and throughout the study or until 50 days after the last IMP dose, whichever is longer.

APPENDIX E. LOST TO FOLLOW-UP

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the investigational center.

The following actions must be taken if a patient fails to return to the investigational center for a required study visit:

- The investigational center must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- In cases in which the patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls [preferably on different days] and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of "lost to follow-up."

APPENDIX F. PHARMACOGENETIC ASSESSMENTS

Blood samples (2.5 mL) for pharmacogenetic assessments will be collected from all patients in the study who signed the informed consent form (ICF) for the pharmacogenetic assessments at the time point detailed in Table 1. Genetic assessments will be conducted only as part of an ancillary study. Each patient will sign a separate ICF for genetic assessment. Patients who do not wish to participate in the genetic research may still participate in the study.

Pharmacogenetic assessment potentially includes the association of DNA variations with clinical responses (eg, efficacy, pharmacokinetics, tolerability, and safety features or disease susceptibility and severity features). The final list of genes that might be investigated will be selected at a later stage before the analysis to allow updating with new scientific information.

APPENDIX G. PRODUCT COMPLAINTS

I. Clinical Product Complaints/Device Deficiency

A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical investigational medicinal product (IMP) supplies or clinical device supplies used in a clinical research study sponsored by Teva. Examples of a product complaint include but are not limited to:

- suspected contamination
- questionable stability (eg, color change, flaking, crumbling, etc)
- defective components
- missing or extra units (eg, primary container is received at the investigational center with more or less than the designated number of units inside)
- incorrect packaging, or incorrect or missing labeling/labels
- unexpected or unanticipated taste or odor, or both
- device not working correctly or appears defective in some manner

Each investigational center will be responsible for reporting a possible clinical product complaint by completing the product complaint form provided by Teva and emailing it to clinical.productcomplaints@tevapharm.com within 48 hours of becoming aware of the issue.

For complaints involving a device/combination product or other retrievable item, it is required that the device/combination product (or item) be sent back to the sponsor for investigative testing whenever possible. For complaints involving an IMP, all relevant samples (eg, the remainder of the patient's IMP supply) should be sent back to the sponsor for investigative testing whenever possible.

1. Product Complaint Information Needed from the Investigational Center

In the event that the product complaint form cannot be completed, the investigator will provide the following information, as available:

- investigational center number and principal investigator name
- name, phone number, and address of the source of the complaint
- clinical protocol number
- patient identifier (patient study number) and corresponding visit numbers, if applicable
- product name and strength for open-label studies
- patient number, bottle, and kit numbers (if applicable) for double-blind or open-label studies
- product available for return Yes/No
- product was taken or used according to protocol Yes/No

- description or nature of complaint
- device deficiency associated with adverse event Yes/No
- device deficiency associated with serious adverse event Yes/No
- device deficiency that could lead to a serious adverse event Yes/No
- clinical supplies unblinded (for blinded studies) Yes/No
- date and name of person receiving the complaint

Note: Reporting a product complaint must not be delayed even if not all the required information can be obtained immediately. Known information must be reported immediately. The sponsor will collaborate with the investigator to obtain any outstanding information.

2. **Handling of Investigational Medicinal Product(s)/Devices at the Investigational Center(s)**

The investigator is responsible for retaining the product in question in a location separate from the investigator's clinical study supplies. The sponsor may request that the investigator return the product for further evaluation and/or analysis. If this is necessary, the clinical study monitor or designee will provide the information needed for returning the IMP or device.

If it is determined that the investigational center must return all IMP or devices, the sponsor will provide the information needed to handle the return.

The integrity of the randomization code and corresponding blinded clinical supplies will be maintained whenever possible. A serious adverse event or the potential for a product quality problem existing beyond the scope of the complaint may be a reason to unblind the clinical supplies for an affected patient, if applicable.

3. **Adverse Events or Serious Adverse Events Associated with a Product Complaint**

If there is an adverse event or serious adverse event due to product complaint, the protocol should be followed for recording and reporting (Section 8.1.3 and Section 8.1.8, respectively).

4. **Documenting a Product Complaint**

The investigator will record in the source documentation a description of the product complaint, the initial determination whether the deficiency could have led to a serious adverse event (Section II), and any actions taken to resolve the complaint and to preserve the safety of the patient. Once the complaint has been investigated by the sponsor and the investigator, if necessary, an event closure letter may be sent to the investigational center where the complaint originated or to all investigational centers using the product.

Medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study.

II. Assessment of Device Performance

Device performance will be assessed by device deficiencies and product complaints.

A device deficiency is defined as any inadequacy of an investigational medical device or combination product with respect to its identity, quality, durability, reliability, usability, safety, or performance (Figure 4). This definition includes malfunctions, use errors, inadequate labeling

(eg, unintelligible label, incorrect expiry date), and product complaints that are related to the device.

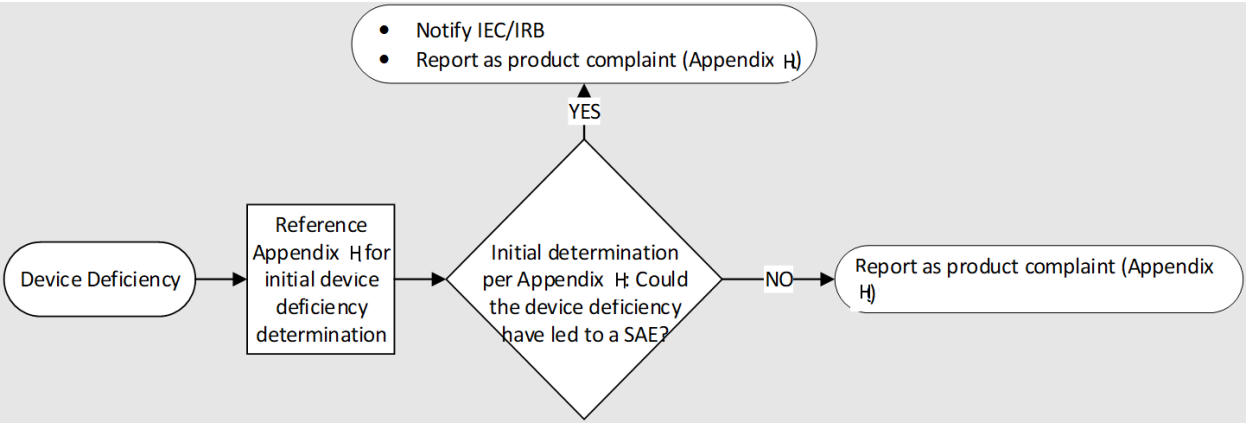
The investigator should make an initial determination whether the device deficiency could have led to a serious adverse event and notify the sponsor by completing the product complaint form provided by Teva and emailing it to clinical.productcomplaints@tevapharm.com.

Device deficiencies with potential serious adverse device effect are defined as deficiencies that might have led to a serious adverse device effect if (Figure 4):

- suitable action had not been taken (or)
- intervention had not been made (or)
- if circumstances had been less fortunate

These device deficiencies shall be reported to the sponsor and the Independent Ethics Committee/Institutional Review Board by the investigator, and to the regulatory authorities by the sponsor according to the national and local regulations. Device complaints related to potential device malfunctions will be initially assessed by the sponsor to determine the root cause of the complaint. Device complaints that are assessed to be caused specifically by device deficiencies will be reported to the device manufacturer for evaluation and further reporting according to national and local regulations.

Figure 4: Decision Tree for Device Deficiencies



IEC=Independent Ethics Committee; IRB=Institutional Review Board; SAE=serious adverse event.

Appendix H. DATA MANAGEMENT AND RECORD KEEPING

Direct Access to Source Data and Documents

All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the case report form (CRF). Data may not be recorded directly on the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the CRF.

If data are processed from other institutions or by other means (eg, clinical laboratory, central image center, or electronic diary data) the results will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management).

The medical experts, study monitors, auditors, Independent Ethics Committee (IEC)/Institutional Review Board (IRB), and inspectors from competent authority (or their agents) will be given direct access to source data and documents (eg, medical charts/records, laboratory test results, printouts, videotapes) for source data verification, provided that patient confidentiality is maintained in accordance with national and local requirements.

The investigator must maintain the original records (ie, source documents) of each patient's data at all times. The investigator must maintain a confidential patient identification list that allows the unambiguous identification of each patient.

Data Collection

Data will be collected using CRFs that are specifically designed for this study. The data collected on the CRFs will be captured in a clinical data management system (CDMS) that meets the technical requirements described in Title 21 Code of Federal Regulation Part 11 (United States of America) and documents of other concerned competent authorities. Before using the CDMS, it will be fully validated and all users will receive training on the system and study-specific training. After they are trained, users will be provided with individual system access rights.

Data will be collected at the investigational center by appropriately designated and trained personnel, and CRFs must be completed for each patient who provided informed consent. Patient identity should not be discernible from the data provided on the CRF.

If data are processed from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary data, or electronic patient-reported outcome tablet), these data will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management). All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the CRF. Data may not be recorded directly on the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the CRF.

For patients who enter a study but do not meet entry criteria, at a minimum, data for screening failure reason, demography, and adverse events from the time of informed consent will be entered in the CRF.

Data Quality Control

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Oversight will be carried out as described in the sponsor's Standard Operating Procedures (SOPs) for clinical studies. Day-to-day data management tasks for this study are delegated to a contract organization, and these functions may be carried out as described in the SOPs for clinical studies at that organization. These SOPs will be reviewed by the sponsor before the start of data management activities.

Data will be verified by the study monitor using the data source, and reviewed by Data Management using both automated logical checks and manual review. Data identified as erroneous, or data that are missing, will be referred to the investigational center for resolution through data queries. Any necessary changes will be made in the clinical database, and data review and validation procedures will be repeated as needed. Data from external sources will be compared with the information available in the CDMS, and any discrepancies will be queried.

Applicable terms will be coded according to the coding conventions for this study.

At the conclusion of the study, the CDMS and all other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate. All data collected will be approved by the investigator at the investigational center. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

Archiving of Case Report Forms and Source Documents

Sponsor Responsibilities

The original CRFs will be archived by the sponsor. Investigational center-specific CRFs will be provided to the respective investigational centers for archiving.

Investigator Responsibilities

The investigator must maintain all written and electronic records, accounts, notes, reports, and data related to the study and any additional records required to be maintained under country, state/province, or national and local laws, including, but not limited to:

- full case histories
- signed informed consent forms
- patient identification lists
- CRFs for each patient on a per-visit basis
- data from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary)
- safety reports
- financial disclosure reports/forms

- reports of receipt, use, and disposition of the IMPs
- copies of all correspondence with sponsor, the IEC/IRB, and any competent authority

The investigator will retain all records related to the study and any additional records required, as indicated by the protocol and according to applicable laws and regulations, until the contract research organization or sponsor notifies the institution in writing that records may be destroyed. If, after 25 years from study completion, or earlier in the case of the investigational center closing or going out of business, the investigator reasonably determines that study record retention has become unduly burdensome, and sponsor has not provided written notification of destruction, then the investigator may submit a written request to sponsor at least 60 days before any planned disposition of study records. After receipt of such request, the sponsor may make arrangements for appropriate archival or disposition, including requiring that the investigator deliver such records to the sponsor. The investigator shall notify the sponsor of any accidental loss or destruction of study records.

APPENDIX I. PUBLICATION POLICY

All unpublished information given to the investigator by the sponsor shall not be published or disclosed to a third party without the prior written consent of the sponsor.

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: "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" (www.ICMJE.org). Publication of the results will occur in a timely manner according to applicable regulations. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual investigational center data. In this case, a coordinating investigator will be designated by mutual agreement.

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

- substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work
- drafting the work or revising it critically for important intellectual content
- final approval of the version to be published
- agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

The publications committee established by the sponsor will oversee this process. Additional publications may follow. Policies regarding the publication of the study results are defined in the financial agreement.

No patent applications based on the results of the study may be made by the investigator nor may assistance be given to any third party to make such an application without the written authorization of the sponsor.

Appendix J. LIST OF EXAMPLES OF OPPORTUNISTIC INFECTIONS

- Bacterial enteric infections
- Bartonellosis
- Candidiasis (excluding vulvovaginal candidiasis)
- Chagas disease
- Coccidioidomycosis
- Community-acquired pneumonia
- Cryptococcosis
- Cryptosporidiosis
- Cystoisosporiasis (Formerly Isosporiasis)
- Cytomegalovirus Disease
- Hepatitis B Virus Infection
- Hepatitis C Virus Infection
- Herpes Simplex Virus
- Histoplasmosis
- Human Herpesvirus-8
- Human Papillomavirus
- Leishmaniasis
- Malaria
- Microsporidiosis
- Mycobacterium avium
- Mycobacterium tuberculosis
- Pneumocystis Pneumonia
- Progressive Multifocal Leukoencephalopathy/JC Virus Infection
- Syphilis
- Talaromycosis (Formerly Penicilliosis)
- *Toxoplasma gondii*
- Varicella-Zoster Virus

Any suspected opportunistic infections (ie, infections that are not listed above [eg, *Clostridium difficile*, aspergillosis, etc] and/or infections that occur more frequently and are more severe than expected) are to be reported.

Further details are available in "Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents." Available at: https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/0). Accessed 18 August 2021. Vulvovaginal candidiasis was removed from the list above as it may be expected in the study patient population.

APPENDIX K. LIVER SAFETY: REQUIRED ACTIONS AND FOLLOW-UP ASSESSMENTS GUIDELINES

The liver chemistry stopping and increased monitoring criteria (see Section 4.4.1) have been designed to assure patient safety and evaluate liver event etiology and require follow up assessments as detailed below:

Required Actions and Follow up Assessments	
Actions	Follow up Assessment
○ Withhold study drug. ○ Report the event to Sponsor within 24 hours ○ Complete the liver event CRF and complete an SAE/PDAESI form. ○ Perform liver chemistry event follow-up assessments. ○ Monitor the patient and repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) weekly (if bilirubin >2x ULN or INR>1.5, twice weekly) until liver chemistries resolve, stabilize or return to within baseline ○ Do not restart/patient with study drug unless allowed per protocol and Sponsor approval is granted. ○ If restart is not allowed per protocol or not granted, permanently discontinue study treatment and complete the assessments for the early termination visit and the follow-up period in the study.	○ Viral hepatitis serology[1] ○ Obtain INR. ○ Obtain blood sample for pharmacokinetic analysis, as soon as possible, and at least within 7 days. ○ Obtain complete blood count with differential to assess eosinophilia. ○ Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form. ○ Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. ○ Record alcohol use on the liver event CRF ○ If bilirubin and/or INR are elevated: ▪ Test Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-live kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. ▪ Check serum acetaminophen levels if definite or likely acetaminophen use in the preceding week: ▪ Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy. ▪ Consider a specialist or hepatology consultation.

[1]Includes: Hepatitis A immunoglobulin M (IgM) antibody; HBsAg and HBcAb; Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody.

APPENDIX L. OPERATING CHARACTERISTICS AND ASSUMPTIONS FOR FINAL AND INTERIM ANALYSIS

Final Analysis and Interim Futility Analysis

A Beta-binomial model with a non-informative Beta (1,1) prior will be used to analyze the primary response endpoint, clinical remission (for UC) or endoscopic response (for CD), hereafter denoted as "response". The model will be fit separately for each dose within each indication.

Assumptions:

Various scenarios for remission (UC), response rates (CD) are assumed as outlined in Table 9 to investigate the operating characteristics.

Table 9: Remission (UC), Response (CD) Rates Scenarios for Clinical Trial Simulations

Scenario	Indication	Placebo (%)	Low Dose 450 mg Q2W (%)	High Dose 900 mg Q2W (%)
Null	UC	8	8	8
	CD	12	12	12
Intermediate Efficacy	UC	8	20	20
	CD	12	25	25
Efficacy	UC	8	30	30
	CD	12	34	34
Efficacy-high dose only	UC	8	8	30
	CD	12	12	34

CD=Crohn's disease; Q2W=every 2 weeks; UC=ulcerative colitis.

Number of Patients at the Interim Analysis:

The interim analysis for each indication is planned when approximately 50% of patients in the indication have completed the 14-week primary efficacy readout or had the opportunity to do so. Operating characteristics were obtained from simulations assuming that exactly 20 patients per arm in the corresponding indication will be included in the interim analysis. Since the analysis is separate for each indication, no assumptions on the expected difference in recruitment rate between UC and CD are required.

Statistical Decision Criteria – Final Analysis:

A TEV-48574 dose will be declared successful at the final analysis if the posterior probability that the response rate in the TEV-48574 dose is higher than the response rate in the placebo arm is ≥0.90, ie, the success criterion for each dose within indication is:

- Posterior Probability (TEV-48574 response rate – placebo response rate >0) ≥0.90

Statistical Futility Cutoff – Interim Analysis:

The same Bayesian Beta-Binomial model described in the primary analysis model will be used for the interim futility analysis for each dose within each indication. A TEV-48574 dose will be declared futile at the interim analysis if the posterior probability that the response rate in the TEV-48574 dose is higher than the response rate in the placebo arm is <0.30, ie, the futility criterion for each dose within indication is:

- Posterior Probability (TEV-48574 response rate – placebo response rate >0) <0.30

Operating Characteristics:

Clinical trial simulations were performed under the assumptions for the interim and primary analysis to generate the operating characteristics (presented in Table 10), for a target sample size of 40 patients per arm in each indication, and an interim analysis for futility for each indication at 21 patients per arm in the indication. The posterior probability futility cutoff is <0.30 for each indication and final success posterior probability cutoff is ≥0.90.

Table 10: Operating Characteristics for Interim and Final Analysis – All Scenarios

	UC						CD					
	% Futile at interim analysis			% Successful at end of trial			% Futile at interim analysis			% Successful at end of trial		
	TEV-48574 doses											
	450 mg Q2W	900 mg Q2W	Both Doses	450 mg Q2W	900 mg Q2W	At least 1 dose	450 mg Q2W	900 mg Q2W	Both Doses	450 mg Q2W	900 mg Q2W	At least 1 dose
Null	25%	24%	11%	8%	8%	13%	24%	24%	12%	9%	10%	16%
Intermediate efficacy both doses	4%	4%	1%	61%	61%	77%	4%	4%	1%	59%	59%	76%
Efficacy both doses	1%	1%	<1%	91%	91%	98%	1%	1%	<1%	87%	87%	95%
Efficacy high dose only	24%	1%	<1%	8%	91%	91%	25%	1%	1%	10%	87%	87%

CD=Crohn's disease; Q2W=every 2 weeks; UC=ulcerative colitis.
Note: Beta-Binomial model with non-informative prior; posterior probability futility cutoff: <0.30; final analysis posterior probability cutoff of ≥0.90.
Note: Operating characteristics based on 500,000 simulations.

These simulations demonstrate that the probability of a false positive result is ≤16% for each indication, while the probability of declaring success for at least 1 dose within each indication under the efficacy assumption for both doses is ≥95%.

The futility threshold was selected to control the probability to declare an effective dose to be futile at a maximum of 1%, while making the correct decision in the null with a probability of approximately 25%.

Since the analysis is done separately for each dose and each indication, the probability to demonstrate efficacy in one dose is not affected by the other dose. Moreover, no inflation of the Type 1 error rate is expected in hypothetical discordant scenarios where TEV-48574 is effective in 1 indication but not in the other.

Safety Stopping Rules

- For each of the 4 types of AEs listed below (Table 11), a Bayesian analysis using the Beta-binomial model with a non-informative Beta(1,1) prior will be conducted. The posterior probability of each type of AE will be compared for each dose and the 3 dose levels combined versus placebo. If the posterior probability that the AE rate in the active group is larger than the AE rate in the placebo group with a posterior probability cutoff defined below, the stopping rule will be triggered. The analyses and evaluation will be conducted for UC and CD separately and across the entire study population.

Table 11: Posterior Probability of Adverse Events

AE type	Posterior probability cutoff
Serious adverse events (aggregated)	90%
CTCAE grade 3/4 adverse events (aggregated)	90%
Opportunistic and severe and/or serious infections	85%
Anaphylaxis	85%

AE=adverse event; CTCAE= Common Terminology Criteria for Adverse Events.

- The DMC will review in detail any safety signal that meets the safety stopping rule, and take into account the totality of safety data. Additional analyses, eg, SAEs in the same HLT, may be performed.
- The DMC will make a recommendation if the safety signal and the totality of the safety data warrants stopping the dose/indication/study.

APPENDIX M. COUNTRY-SPECIFIC REQUIREMENTS

Country-Specific Requirements: France

The following country specific requirements are applicable to all subjects enrolled at study centers in France.

Amendment 04 (JP 05) (ES 01) (FR 01): Local Administrative Letter 01 Dated 11 March 2024

LOCAL ADMINISTRATIVE LETTER 01 FOR FRANCE

Study number: TV48574-IMM-20036

Clinical Study Protocol with Protocol Am 03 with Rev 01 (JP 03) (ES 01)

A 14-Week Phase 2b, Randomized, Double-Blind, Dose-Ranging Study to Determine the Pharmacokinetics, Efficacy, Safety, and Tolerability of TEV-48574 in Adult Patients with Moderate to Severe Ulcerative Colitis or Crohn's Disease (RELIEVE UCCD)

15 August 2023

IND number: **157634**; NDA number: **Not applicable**; EudraCT number: **2021-006881-19**

11 MAR 2024

Dear Investigator:

The purpose of this letter is to provide clarification that patients enrolled in France will not be offered the option to enter in the long-term extension study (TV48574-IMM-20038). Therefore, the statement "After the end of the 14-week treatment period, all patients may be offered the option to enter a long-term extension study (to be described in a separate protocol [TV48574-IMM-20038])", which is noted in the protocol sections below, is not applicable for patients enrolled in France.

- Protocol Synopsis: "Treatment and Follow-Up Period" and "Plans for Treatment or Care after the Patient Has Ended Participation in the Study"
- Section 3.1. General Study Design and Study Schematic Diagram: "Treatment and Follow-Up Period
- Figure 2: Overall Study Schematic Diagram
- Table 4: Study Procedures and Assessments
- Section 5.4 Treatment After the End of the Study

After the end of the 14-week treatment period, those patients enrolled in France will return to the site for a follow-up visit at week 18 (day 127 [±3 days]) as specified in Table 4 (Study Procedures and Assessments) of the protocol.

These changes will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

Please feel free to contact [redacted] if you have any questions or concerns regarding this letter.

Teva Pharmaceuticals 145 Brandywine Parkway | West Chester, PA 19380 | Tel. 610.344.0200 |www.tevapharm.com

Sincerely,

[redacted]

11-Mar-2024 | 23:02 GMT

[redacted]

Teva Pharmaceuticals 145 Brandywine Parkway | West Chester, PA 19380 | Tel. 610.344.0200 |www.tevapharm.com

Country-Specific Requirements: Japan

The following country-specific requirements are applicable to all subjects enrolled at study centers in Japan.

Revised Text is captured in the format strikethrough=deleted text; underline=new text.

Amendment 04 (JP 05) (ES 01) (FR 01): Local Administrative Letter 01 Dated 12 March 2024

LOCAL ADMINISTRATIVE LETTER 01 FOR JAPAN (JP)

Study number: TV48574-IMM-20036

Clinical Study Protocol TV48574-IMM-20036 Protocol Am 03 with Rev 01 (JP 04) (ES 01)

A 14-Week Phase 2b, RandomizEd, Double-BLind, Dose-Ranging Study to Determine the PharmacokInetics, Efficacy, Safety, and Tolerability of TEV-48574 in Adult PatiEnts with Moderate to Severe Ulcerative Colitis or Crohn's Disease (RELIEVE UCCD) 1

21 September 2023

IND number: **157634**; NDA number: **Not applicable**; EudraCT number: **2021-006881-19**.

12 MAR 2024

Dear Investigator:

The intent of this letter is to provide clarification that the following inclusion criterion, which was implemented for participants enrolled in Japan as of Amendment 03 (JP 03) dated 28 June 2023, is to be used in conjunction with global inclusion criterion "h" and is designated as "h (JP)" for database purposes.

Section 4.1 Patient Inclusion Criteria:

h (JP) Concomitant use of Chinese herbal medicines/Chinese herbal supplements (except Seitai and other indigo supplements) is allowed for patients who have been taking Chinese herbal medicines/Chinese herbal supplements prior to the start of the study, except that the dosage of Chinese herbal medicines/Chinese herbal supplements will not be changed during the study period.

As for Seitai (Indigo naturalis)[1)] , the Ministry of Health, Labour and Welfare (MHLW) issued an alert to the relevant academic societies on 27 December 2016 to use Sentai for IBD treatment. Because it was found that there were several cases of pulmonary arterial hypertension (PAH) in patients with ulcerative colitis who took Seitai)(Indigo naturalis) or health foods containing Seitai (Indigo naturalis), PAH causality could not be denied. With that, concomitant use of Seitai (Indigo naturalis) is not allowed.

1): Seitai (Indigo naturalis [IN]): IN is a herbal medicine extracted from leaves and stems of plants such as Indigofera tinctoria, Strobilanthes cusia O Kuntze, and Polygonum tinctorium Lour. In China, IN is quality controlled as an herbal medicine containing more than 2.0% indigo and more than 0.13% indirubin. IN made from Fujian is regarded as being of the highest quality. IN is usually used as a raw material in Japan, and is classified as a dye, rather than a medicine. IN is considered an anti-inflammatory agent in Chinese textbooks from the tenth century

Reference: Naganuma M. Treatment with indigo naturalis for inflammatory bowel disease and other immune diseases. Immunol Med 2019;42(1):16-21

The above inclusion criteria itself remains unchanged.

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This change will be incorporated into the protocol during the next amendment, as applicable. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

Please feel free to contact [redacted] if you have any questions or concerns regarding this letter.

Sincerely,

[redacted]

[redacted]

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Amendment 03 (JP 04): Dated 21 September 2023

Original text with changes shown	New wording	Reason/justification for change
Section 6.1.2.1 Biopsy Collection		
For patients with CD, an ileo-colonoscopy will be performed at screening and week 14. During each endoscopy, a total of ~~16 to 18~~ ***8*** mucosal biopsies will be obtained from the area with the greatest inflammation in each segment at screening and at the same location at week 14 or early termination. If ulceration is present, biopsies should be taken from the edge of the largest ulcer. If no ulceration is present, then biopsies should be taken from the most affected area of the segment. If the mucosa appears normal (eg, at follow-up), then random biopsies of the segment should be obtained. For patients with UC, a flexible sigmoidoscopy will be performed at screening and week 14 (colonoscopy may be performed instead for baseline endoscopy if not done in the prior 12 months). During each endoscopy, a total of ~~8 to 12~~ ***7*** biopsies will be obtained from the area with the worst disease 15 to 25 cm from the anal verge.	For patients with CD, an ileo-colonoscopy will be performed at screening and week 14. During each endoscopy, a total of 8 mucosal biopsies will be obtained from the area with the greatest inflammation in each segment at screening and at the same location at week 14 or early termination. If ulceration is present, biopsies should be taken from the edge of the largest ulcer. If no ulceration is present, then biopsies should be taken from the most affected area of the segment. If the mucosa appears normal (eg, at follow-up), then random biopsies of the segment should be obtained. For patients with UC, a flexible sigmoidoscopy will be performed at screening and week 14 (colonoscopy may be performed instead for baseline endoscopy if not done in the prior 12 months). During each endoscopy, a total of 7 biopsies will be obtained from the area with the worst disease 15 to 25 cm from the anal verge.	To specify the number of total biopsies for each endoscopy procedure in Japan as follows: • For CD: 8 mucosal biopsies • For UC: 7 mucosal biopsies

Amendment 03 (JP 03): Dated 28 June 2023

Original text with changes shown	New wording	Reason/justification for change
Section 4.1 Patient Inclusion Criteria		
	Concomitant use of Chinese herbal medicines/Chinese herbal supplements (except Seitai and other indigo supplements) is allowed for patients who have been taking Chinese herbal medicines/Chinese herbal supplements prior to the start of the study, except that the dosage of Chinese herbal medicines/Chinese herbal	Adding inclusion criteria as standard Japanese medical practice in IBD.

Original text with changes shown	New wording	Reason/justification for change
	supplements will not be changed during the study period. As for Seitai (Indigo naturalis)[1)] , the Ministry of Health, Labour and Welfare (MHLW) issued an alert to the relevant academic societies on 27 December 2016 to use Sentai for IBD treatment. Because it was found that there were several cases of pulmonary arterial hypertension (PAH) in patients with ulcerative colitis who took Seitai)(Indigo naturalis) or health foods containing Seitai (Indigo naturalis), PAH causality could not be denied. With that, concomitant use of Seitai (Indigo naturalis) is not allowed. 1): Seitai (Indigo naturalis [IN]): IN is a herbal medicine extracted from leaves and stems of plants such as Indigofera tinctoria, Strobilanthes cusia O Kuntze, and Polygonum tinctorium Lour. In China, IN is quality controlled as an herbal medicine containing more than 2.0% indigo and more than 0.13% indirubin. IN made from Fujian is regarded as being of the highest quality. IN is usually used as a raw material in Japan, and is classified as a dye, rather than a medicine. IN is considered an anti-inflammatory agent in Chinese textbooks from the tenth century Reference: Naganuma M. Treatment with indigo naturalis for inflammatory bowel disease and other immune diseases. Immunol Med 2019;42(1):16-21	
Section 5.6.4 Prohibited Medications and Therapies		
See new wording column	Any Chinese herbal medicine/Chinese herbal supplement is prohibited during the study unless taken prior to the start of the study and the dosage will remain unchanged during the study period.	Adding these prohibited medications as standard Japanese medical practice in IBD

Amendment 01 (JP 02): Dated 03 October 2022

Original text with changes shown	New wording	Reason/justification for change
TEV-48574 and Inflammatory Bowel Disease (Section 1.1.3)		
TEV-48574 is a highly potent, fully human immunoglobulin G (IgG) subclass 1 (lambda) monoclonal antibody (mAb) with a molecular weight of 146 kDA that targets TL1A, encoded by the TNF superfamily member 15 (*TNFSF15*) gene. TEV-48574 is a recombinant drug product that is manufactured using a cell line derived from Chinese hamster ovaries.	TEV-48574 is a highly potent, fully human immunoglobulin G (IgG) subclass 1 (lambda) monoclonal antibody (mAb) with a molecular weight of 146 kDA that targets TL1A, encoded by the TNF superfamily member 15 (*TNFSF15*) gene. TEV-48574 is a recombinant drug product that is manufactured using a cell line derived from Chinese hamster ovaries.	Clarification of cell line used to manufacture IMP.

Amendment 01 (JP 01): Dated 15 August 2022

Original text with changes shown	New wording	Reason/justification for change
Patient Inclusion Criteria: item 'g' (Section 4.1 and in Synopsis)		
Patient must have inadequate response to, loss of response to, or intolerance of at least 1 of the following agents and no more than 2 classes of biologics: corticosteroids, immunosuppressant drugs, and/or TNF-α antagonist therapy, anti-integrins, anti-IL-12/23, JAK inhibitors, and/or S1P receptor modulators. • Inadequate response to, loss of response to, or intolerance to corticosteroid treatment is defined as 1 or more of the following: – Steroid refractory: persistent symptoms of active disease despite treatment with at least one 4-week induction regimen that included a dose of ≥30 mg prednisone* (oral) daily for at least 2 weeks or intravenous (iv) for at least 1 week within the	Patient must have inadequate response to, loss of response to, or intolerance of at least 1 of the following agents and no more than 2 classes of biologics: corticosteroids, immunosuppressant drugs, and/or TNF-α antagonist therapy, anti-integrins, anti-IL-12/23, JAK inhibitors, and/or S1P receptor modulators. • Inadequate response to, loss of response to, or intolerance to corticosteroid treatment is defined as 1 or more of the following: – Steroid refractory: persistent symptoms of active disease despite treatment with at least one 4-week induction regimen that included a dose of ≥30 mg prednisone* (oral) daily for at least 2 weeks or intravenous (iv) for at least 1 week within the	Adding a note to indicate prednisone is not licensed in Japan

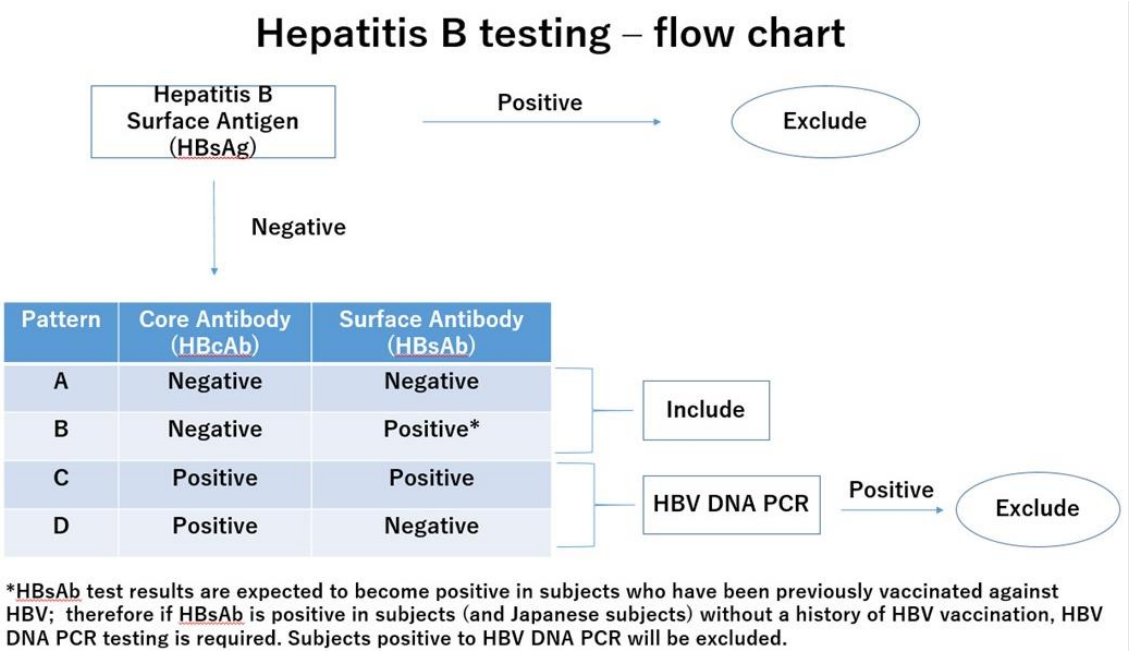
Original text with changes shown	New wording	Reason/justification for change
previous 5 years; – Steroid dependent: 2 failed attempts to taper steroids below a dose equivalent to 10 mg prednisone* (oral) daily within the previous year; * Prednisone is not licensed in Japan.	previous 5 years; – Steroid dependent: 2 failed attempts to taper steroids below a dose equivalent to 10 mg prednisone* (oral) daily within the previous year; * Prednisone is not licensed in Japan.	
Patient Exclusion Criteria: item 'f' (Section 4.2 and Synopsis)		
A patient is Hepatitis B core antibody (HBcAb), ~~or~~ surface antigen (HBsAg), surface antibody (HBsAb; in line with the HBV testing flow chart in Figure 5), and/or Hepatitis C antibody positive with detectable ribonucleic acids, or positive human immunodeficiency virus types 1 or 2 at screening.	A patient is Hepatitis B core antibody (HBcAb), surface antigen (HBsAg), surface antibody (HBsAb; in line with the HBV testing flow chart in Figure 5), and/or Hepatitis C antibody positive with detectable ribonucleic acids, or positive human immunodeficiency virus types 1 or 2 at screening.	Adding HBsAb to serology test (in line with the HBV testing flow chart) as standard Japanese medical practice
Patient Exclusion Criteria: item 's' (Section 4.2 and Synopsis)		
Patient is receiving any of the following therapies within the designated time period: – >9 mg/day of oral budesonide or >20 mg/day prednisone* or equivalent within 2 weeks prior to the endoscopy. * Prednisone is not licensed in Japan.	Patient is receiving any of the following therapies within the designated time period: – >9 mg/day of oral budesonide or >20 mg/day prednisone* or equivalent within 2 weeks prior to the endoscopy. * Prednisone is not licensed in Japan.	Adding a note to indicate prednisone is not licensed in Japan.
Patient Exclusion Criteria: item w (Section 4.2 and Synopsis)		
See new wording column	Patient is receiving any of the following therapies within the designated time period: • The patient (UC or CD) had received cytapheresis therapy within 27 days before the first dose of IMP administration. • For CD patients only - The patient had received central intravenous nutrition therapy or complete enteral nutrition therapy, or had fasted	Adding these exclusion criteria as standard Japanese medical practice in IBD

Original text with changes shown	New wording	Reason/justification for change
	within 20 days before the first dose of IMP administration. - The patient had received over 900 kcal/day of enteral nutrition therapy, or had started enteral nutrition at 900 kcal/day or less within 20 days before the first dose of IMP administration. - The patient had started enteral nutritional supplements of 900 kcal/day or less 21 days or more before the start of administration of the investigational drug, and those who had changed or discontinued the dose within 20 days before the first dose of IMP administration.	
Investigational Medicinal Products Used in the Study (Section 5.1)		
See new wording column	'Drug Used in Clinical Trial' is defined as approved or non-approved drugs (including test drugs that are used for efficacy and safety evaluation of test drugs in clinical trial. 'Drug Used in Clinical Trial' includes test drugs, comparators, concomitant drugs, rescue drugs, pre-medication drugs, and the like. Drugs that are not specified in protocol or are not used for efficacy and safety evaluation of test drugs are excluded from 'Drug Used in Clinical Trial'. The regulation/guidance stipulated in Japan GCP is also applied for medical devices ('Device Used in Clinical Trial') and regenerative products ('Regenerative Medical Product Used in Clinical Trial') used for efficacy and safety evaluation of test drugs. In this study, 'Drug Used in Clinical Trial' is defined as below: • TEV-48574 and placebo In this study, 'Device Used in Clinical Trial' is defined as below: • [redacted] and accessories	By JGCP guidelines, identifying and describing drug and device to be used in the current study in Japan
Permitted Inflammatory Bowel Disease Medications and Rescue Medications (bullet 2 in Section 5.6.3)		
• A stable dose of oral corticosteroids (prednisone* equivalent of up to 20 mg/day; budesonide of up to 9 mg/day) for at	• A stable dose of oral corticosteroids (prednisone* equivalent of up to 20 mg/day; budesonide of up to 9 mg/day) for at	Adding a note to indicate prednisone is not licensed in Japan.

Original text with changes shown	New wording	Reason/justification for change
least 2 weeks prior to endoscopy and through week 14. If oral corticosteroids have been recently discontinued, they must have been stopped at least 2 weeks prior to endoscopy. Decreases in steroid use due to adverse events are allowed. * Prednisone is not licensed in Japan.	least 2 weeks prior to endoscopy and through week 14. If oral corticosteroids have been recently discontinued, they must have been stopped at least 2 weeks prior to endoscopy. Decreases in steroid use due to adverse events are allowed. * Prednisone is not licensed in Japan.	
Prohibited Medications and Therapies (bullet 3 in Section 5.6.4)		
• Prednisone* dose of >20 mg/day or equivalent oral systemic corticosteroid from 2 weeks prior to endoscopy through week 14. * Prednisone is not licensed in Japan.	• Prednisone* dose of >20 mg/day or equivalent oral systemic corticosteroid from 2 weeks prior to endoscopy through week 14. * Prednisone is not licensed in Japan.	Adding a note to indicate prednisone is not licensed in Japan.
Prohibited Medications and Therapies (Section 5.6.4)		
See new wording column	• Cytapheresis therapy within 27 days before the first dose of IMP administration. • For CD patients only: - Central intravenous nutrition therapy or complete enteral nutrition therapy, or had fasted within 20 days before the first dose of IMP administration. - Over 900 kcal/day of enteral nutrition therapy, or had started enteral nutrition at 900 kcal/day or less within 20 days before the first dose of IMP administration. - Enteral nutritional supplements of 900 kcal/day or less 21 days or more before the start of administration of the investigational drug, and those who had changed or discontinued the dose within 20 days before the first dose of IMP administration.	Meeting JGCP requirement
Appendix E (item 1 & item2): Birth Control Methods		
• Combined estrogen and progestogen hormonal	• Combined estrogen and progestogen hormonal contraception (oral, intravaginal*, transdermal*) associated	Adding a note to indicate these methods

Original text with changes shown	New wording	Reason/justification for change
contraception (oral, intravaginal*, transdermal*) associated with inhibition of ovulation*; these should be initiated at least 14 days before the first dose of ~~investigational medicinal product (~~IMP~~)~~ • Progestogen-only hormonal contraception* (oral, injectable, implantable) associated with inhibition of ovulation*; these should be initiated at least 14 days before the first dose of IMP *Not approved in Japan	with inhibition of ovulation*; these should be initiated at least 14 days before the first dose of IMP • Progestogen-only hormonal contraception* (oral, injectable, implantable) associated with inhibition of ovulation*; these should be initiated at least 14 days before the first dose of IMP *Not approved in Japan.	are not approved in Japan
Appendix I: Data Management and Record Keeping Archiving of Case Report Forms and Source Documents		
See new wording column	The institution, IRB, and sponsor are required by the JGCP ordinance, etc. to preserve the records. In accordance with the JGCP ordinance, etc., a person responsible for the preservation of various records (including data) related to this clinical trial must be designated for each, and these records must be preserved under appropriate conditions. The storage period must comply with Appendix I.	Adding the statements of responsibilities for various perspectives
Appendix M (footnote): Liver Safety: Required Actions and Follow-Up Assessments Guidelines		
Includes: Hepatitis A immunoglobulin M (IgM) antibody; HBsAg, HBcAb, and HBsAb; Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody.	Includes: Hepatitis A immunoglobulin M (IgM) antibody; HBsAg, HBcAb, and HBsAb; Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody.	Adding HBsAb to serology test (in line with the HBV testing flow chart, Figure 5) as standard Japanese medical practice

Figure 5: Hepatitis B Testing Flow Chart



Country-Specific Requirements: Spain

The following country-specific requirements are applicable to all subjects enrolled at study centers in Spain.

Revised text is captured in the format strikethrough=deleted text; underline=new text.

Amendment 02 (JP 02) (ES 01): Dated 27 March 2023

Original text with changes shown	New wording	Reason/justification for change
Patient Inclusion Criteria: item 'g' (Section 4.1 and in Synopsis)		
Patient must have inadequate response to, loss of response to, or intolerance ~~of at least 1 of the following agents and no more than 2 classes of biologies: corticosteroids, immunosuppressant drugs, and/or~~ to anti-TNF~~-α antagonist therapy~~ inhibitors~~., anti-integrins, anti-IL-12/23, JAK inhibitors, and/or S1P receptor modulators~~	Patient must have inadequate response to, loss of response to, or intolerance to anti-TNF inhibitors.	The local Spanish Health Authority and Ethics Committee requested modifications.