Clinical Study Protocol

NCT Number: NCT03943446

Title: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase 2a Study to Evaluate the Safety, Tolerability, and Early Proof of Concept of TAK-018 for the Prevention of Postoperative Crohn's Disease Recurrence

Study Number: TAK-018-2001

Document Version and Date: Version 5 (08-October-2021)

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

TAKEDA PHARMACEUTICALS

PROTOCOL

A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase 2a Study to Evaluate the Safety, Tolerability, and Early Proof of Concept of TAK-018 for the Prevention of Postoperative Crohn's Disease Recurrence

TAK-018 for Prevention of the Recurrence of Postoperative Crohn's Disease

Sponsor: Takeda Development Center Americas, Inc.
95 Hayden Avenue
Lexington, MA USA 02421

Study Number: TAK-018-2001

IND Number: 137694 **EudraCT Number:** 2019-000886-19

Compound: TAK-018 (Sibofimloc)

Date: 08 October 2021 **Amendment Number:** 05

Amendment History:

Date	Amendment Number	Amendment Type	Region
01 March 2019	Initial Protocol	Not applicable	Global
02 July 2019	Amendment 01	Substantial	Global
05 December 2019	Amendment 02	Nonsubstantial	France
14 January 2020	Amendment 03	Substantial	Global
30 July 2020	Amendment 04	Substantial	Global
08 October 2021	Amendment 05	Substantial	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Serious adverse event and pregnancy reporting information is presented in Section 10.0.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

The names and contact information for the medical monitor and responsible medical officer are in the study manual.

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer and other signatories can be found on the signature page.

Electronic Signatures are provided on the last page of this document.

[redacted], PhD Date

Statistical and Quantitative Sciences
(or designee)

[redacted], MS Date

Quantitative Clinical Pharmacology
(or designee)

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[redacted], MD, PhD Date
[redacted]
Clinical Science
(or designee)

[redacted] Date
[redacted]
Statistical and Quantitative Sciences
(or designee)

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[redacted]
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[redacted], MD, PhD Date
[redacted].
Clinical Science
(or designee)

[redacted], PhD Date
Statistical and Quantitative Sciences
(or designee)

[redacted] Date
Quantitative Clinical Pharmacology
(or designee)

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, prescribing information, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator. (Appendix G)

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix I of this protocol.

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Provence)

_____

Location of Facility (Country)

1.3 Protocol Amendment No. 05 Summary and Rationale

This section describes the changes to the protocol incorporating Amendment 05. The primary reason for this amendment is to update the legal entity to Takeda Development Center Americas, Inc. and to update its address. In addition, study signatories have been updated to align with changes in study personnel, and the International Nonproprietary Name (INN) "sibofimloc" has been added.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 05			
Summary of Changes Compared With TAK-018-2001 Amendment 04			
Description of Each Change and Rationale			
Description		***Rationale***	***Section(s) Affected by Change***
1	Identification of the legal entity.	To clarify that the legal entity has changed.	Title page, Sponsor
2	Updates to the study signatories.	To identify changes in study personnel.	Section 1.2 Approval
3	Addition of the INN: sibofimloc.	To include the INN nomenclature.	Title page, Compound Section 2.0 STUDY SUMMARY
4	Changes in Appendix J	To be compliant with process, updated this appendix to accurately capture and reflect protocol history.	Appendix J, Protocol History

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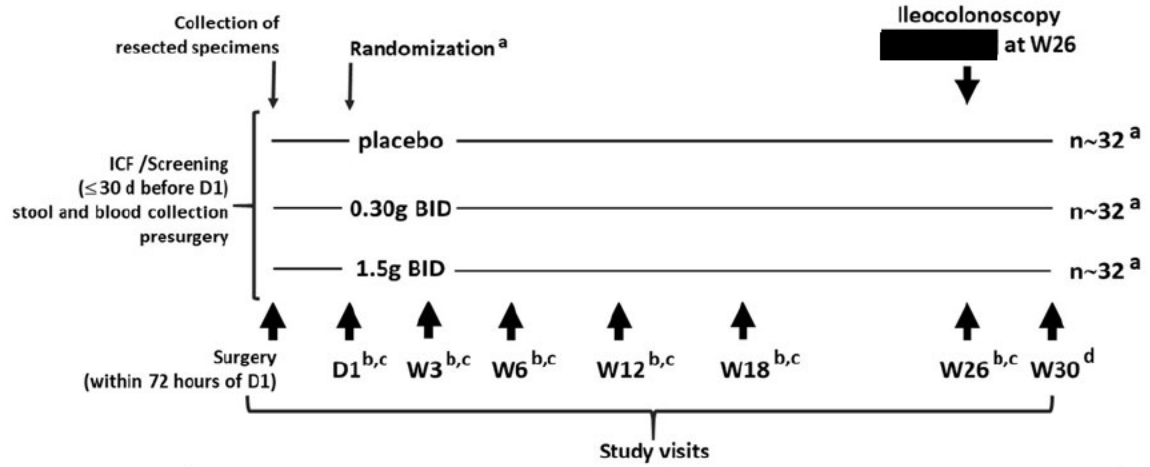
2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc.	**Compound:** TAK-018 (Sibofimloc)	
Title of Protocol: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase 2a Study to Evaluate the Safety, Tolerability, and Early Proof of Concept of TAK-018 for the Prevention of Postoperative Crohn's Disease Recurrence	**IND No.:** 137694	*EudraCT No.:* 2019-000886-19
Study Number: TAK-018-2001	**Phase:** 2a	

Study Design:

This is a randomized, placebo-controlled, double-blind study of TAK-018 (INN: sibofimloc; previously known as EB8018) in approximately 96 postoperative subjects with Crohn's disease (CD) who are undergoing a planned laparoscopic ileocecal resection with primary anastomosis. Of note, the laparoscopic ileocecal resection is not considered a study procedure and should be completed per institutional standard of care. All eligible subjects will be randomized 1:1:1 to either TAK-018 low dose (0.30 g taken twice daily [BID]), TAK-018 high dose (1.5 g taken BID), or placebo (BID) for a 26-week treatment period. Randomization will be stratified by smoking status (active smoker vs nonsmoker/previous smoker). Subjects will receive the first dose of study drug on Day 1 (D1, within 72 hours after surgery) administered twice daily immediately after a meal (ie, breakfast and dinner) with water, approximately 8 to 12 hours apart. Subjects will have study visits at Week 3 (W3), Week 6 (W6), Week 12 (W12), Week 18 (W18), and Week 26 (W26), with a final study visit at Week 30 (W30), 30 days after the W26 endoscopy. Study visits at D1 and W26 are clinic visits; study visits at screening, W3, W6, W12, W18, and W30 may be conducted as clinic or home health care (HHC) visits to provide flexibility to subjects.

Blood samples will be collected presurgery and at all scheduled study visits after dosing starts to characterize disease progression, response to study drug, safety parameters, and the pharmacokinetics (PK) of TAK-018. Subjects will also provide stool samples before surgery during the screening period and at W3, W6, W12, W18, W26, and W30. Fecal calprotectin will be measured before surgery during the screening period and in every stool collection. Endoscopic assessments will be performed at the end of the 26-week treatment period (ie, W26 clinic visit). Intestinal resection tissue will be collected at surgery and biopsies of the neoterminal ileum will be performed at W26. Subjects who relapse clinically or endoscopically (Rutgeerts score ≥i2) during the study will discontinue study drug, receive institutional standard of care, attend an early termination visit 30 days after their last dose of study drug, and be discontinued from the study. The end of study visit will occur at W30 or, for subjects who discontinue early, will occur 30 days after their last dose of study drug.



a Approximately (~) 96 subjects randomized 1:1:1 among treatment arms, stratified by smoking status
b PK sampling: collection times as specified in Appendix B
c D1 and W26 are clinic visits; visits at W3, W6, W12, W18, and W30 may be clinic or HHC visits
d The final study visit (End of Study) occurs at W30, 30-days after the W26 endoscopy

TAK-018 therapy is expected to block the adhesin portion of type 1 fimbriae on FimH-expressing bacteria in the gut lumen, thereby decreasing bacterial penetration of the mucus layer and invasion of the gastrointestinal tissue. The clinical hypothesis is that these collective actions of TAK-018 will lead to a decrease in local inflammatory cytokine production and a corresponding decrease in disease recurrence as diagnosed by endoscopy [redacted].

Primary Objective: To evaluate the efficacy of TAK-018 in reducing endoscopic recurrence of intestinal inflammation in postoperative subjects with CD after planned laparoscopic ileocecal resection with primary anastomosis.

Safety Objective: To assess the safety and tolerability of TAK-018 in postoperative subjects with CD after planned laparoscopic ileocecal resection with primary anastomosis.

Secondary Objectives:

- To evaluate the effect of TAK-018 on intestinal inflammation based on serial fecal calprotectin measures.
- To characterize the PK of TAK-018 in postoperative subjects with CD after planned laparoscopic ileocecal resection with primary anastomosis.

Exploratory Objectives:

[redacted].

Subject Population: Subjects with an endoscopic diagnosis of CD aged ≥18 years or of local legal age who are scheduled to undergo a planned laparoscopic ileocecal resection with primary anastomosis.

Number of Subjects:	**Number of Sites:**
Estimated total approximately (~) 96 subjects: Placebo: ~32 subjects TAK-018 low dose: ~32 subjects TAK-018 high dose: ~32 subjects	Approximately 40 sites globally.
Dose Level(s):	**Route of Administration:**
TAK-018 at 2 doses: Low: 0.30 g per dose taken BID High: 1.5 g per dose taken BID Placebo BID	TAK-018: oral Placebo: oral
Duration of Treatment:	**Period of Evaluation:**
26 weeks of BID dosing	30 day screening period, 26 weeks of treatment with study visits on W3, W6, W12; W18, W26, and W30.

Total Duration of Study:

An individual subject's participation is up to 34 weeks (4-week screening period, 26-week treatment period, 4-week safety follow-up) with the global study duration of approximately 2 to 3 years.

Main Criteria for Inclusion:

1. Male or female subject aged ≥18 years or local legal age at signing of informed consent
2. Subject has a documented diagnosis of CD confirmed by endoscopic biopsy before resection or by tissue obtained at resection.
3. Subject is planned to undergo laparoscopic ileocecal resection with primary anastomosis within 72 hours before randomization (D1). Confirmation that no active disease has been left behind after resection will be based on the surgeon's documentation in the operative report.
4. Subject with postoperative discontinuation of all concomitant medications related specifically to the treatment of CD. This includes anti-tumor necrosis factor and anti-integrin therapy, anti-IL 12/23, thiopurines and other immunomodulators, steroids, 5-aminosalicylates, and prophylactic use of antibiotics for the prevention of postoperative recurrence such as metronidazole.
5. Subject has resumed oral intake and is capable of swallowing tablets within 72 hours after surgery.
6. If female of child-bearing potential, subject must agree to comply with the contraception requirements.
7. A male subject who is nonsterilized and sexually active with a female partner of child-bearing potential must agree to comply with protocol-defined contraception requirements.

Main Criteria for Exclusion:

1. Subject has active perianal CD.
2. Subject has had >3 previous surgical procedures for CD.
3. Subject has macroscopically active CD that was not resected at the time of surgery as documented in the surgeon's operative report.
4. Subject with small bowel resection that exceeds 100 cm or a subject who is considered at risk for short bowel syndrome.
5. Subject has any significant intraoperative or postoperative complications such as anastomotic leak, surgical site infection, or inability to tolerate oral intake.
6. Subject is unable or unwilling to undergo or has contraindications to ileocolonoscopic procedures as assessed by the investigator.
7. Subject has inadequate renal or hepatic function postsurgery and before the first dose of study drug on the basis of one of the following laboratory parameters: total bilirubin >1.5× the institutional upper limit of normal (ULN) unless subject has known Gilbert's syndrome that can explain the elevation of bilirubin, serum alanine aminotransferase >3× the institutional ULN, creatinine >1.5× the institutional ULN or estimated creatinine clearance <50 mL/minute/1.73 m^2 for subjects with serum creatinine concentrations above institutional limits.

Main Criteria for Evaluation and Analyses:

The primary endpoint for this study is the percentage of subjects with endoscopic recurrence of CD at W26. Endoscopic recurrence is defined as Rutgeerts score ≥i2 (i2, i3, i4).

Safety endpoints are measured from the administration of the first dose of study drug through 30 days after the last dose of study drug. Safety endpoints will include the percentage of subjects who experience treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and/or clinically significant changes in vital signs, standard laboratory tests and procedures (eg, clinical chemistry, hematology, urinalysis).

Secondary endpoints for this study are: fecal calprotectin (FCP) >135 µg/g at W3, W6, W12, W18, W26, and W30; and observed plasma trough concentrations of TAK-018 at W3.

Statistical Considerations:

The study endpoints will be analyzed using the full analysis set (FAS) that contains all randomized subjects who receive at least 1 dose of study treatment.

Primary Efficacy Analysis: The proportion of subjects with endoscopic recurrence of CD at W26 in each of the 2 TAK-018 dose arms will be compared to placebo using the Cochran-Mantel-Haenszel (CMH) test stratified by smoking status at randomization. The point estimates for the treatment difference (TAK-018 – placebo) for each of the 2 dose levels, along with the 80% and 95% confidence intervals (CI) will be presented.

Secondary [redacted] Analyses: Continuous longitudinal endpoints will be analyzed using a mixed-effect model repeated measures (MMRM) model to compare each dose of the TAK-018 arms to the placebo arm. Continuous endpoints measured at a single time point will be analyzed using an ANCOVA model. Binary endpoints will be analyzed using the methodology used for the primary efficacy endpoint.

Safety Analysis: The percentage of subjects with TEAEs and/or SAEs will be summarized descriptively by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms, by severity, and by relationship to study drug for each treatment arm.

Change from baseline in clinical laboratory tests and vital signs will be summarized descriptively by treatment arm and by visit. Subjects with markedly abnormal values for laboratory tests and vital signs will be summarized and listed.

Sample Size Justification:

This study is planned to randomize approximately 96 subjects in a 1:1:1 ratio to each of the 3 treatment arms (2 active, 1 placebo, approximately 32 subjects per arm).

Assuming the true recurrence rate in the placebo arm to be 50%, a total of 81 subjects will provide at least 75% power to detect a 25% or larger difference in recurrence rates between treatment and placebo arms for a 2-sided chi-squared test at a 0.2 level of significance. To account for an assumed dropout rate of 15%, approximately 96 subjects will be randomized in this study.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the clinical study supplier list or equivalent. The vendors identified in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol and the study drug, their expertise in the therapeutic area and the conduct of clinical research, and study participation. The signatory coordinating investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

Acronym	Definition
AE	adverse event
AIEC	adherent-invasive *Escherichia coli*
ALT	alanine aminotransferase
anti-TNF-α	anti-tumor necrosis factor-alpha
AST	aspartate aminotransferase
AUC_t	plasma area under the concentration-time curve from administration to last observed concentration at time t
BID	twice daily
CD	Crohn's disease
CEACAM6	carcinoembryonic antigen-related cell-adhesion molecule 6
CFR	Code of Federal Regulations
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease 2019
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
D1	Day 1
EB8018	former name of the investigational agent also known as TAK-018
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
ET	early termination
FCP	fecal calprotectin
FDA	Food and Drug Administration
FAS	full analysis set
FimH	adhesin portion of type 1 fimbriae (mediates attachment to mucosal epithelial surfaces)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GP2	glycoprotein
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HED	human equivalent dose
HHC	home health care
[redacted]	[redacted]
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	identification
IEC	independent ethics committee
IL	interleukin

Acronym	Definition
IMP	investigational medicinal product
INN	International Nonproprietary Name
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology system
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	mixed-effect model repeated measures
MOA	mechanism of action
NOEL	no-observed effect level
NOAEL	no-observed adverse effect level
PI	principal investigator
PK	pharmacokinetics
PO	orally
[redacted]	[redacted]
QD	once daily
[redacted]	[redacted]
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SOE	schedule of events
TEAE	treatment-emergent adverse event
TNF-α	tumor necrosis factor-alpha
ULN	upper limit of normal
UK	United Kingdom
US	United States
VAS	visual analog score
W3	Week 3
W6	Week 6
W12	Week 12
W18	Week 18
W26	Week 26
W30	Week 30

3.4 Corporate Identification

TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

4.1.1 Disease Under Study

Crohn's disease (CD) is a chronic, relapsing inflammatory disease of the gastrointestinal tract with no known cure. Its incidence globally is on the rise, reaching 20 per 100,000 person-years in Western countries [1]. A third of patients with CD will require a major abdominal resection within 5 years after diagnosis, and up to 60% of patients within a decade [2,3]. Up to 70% of patients who undergo resection develop postoperative endoscopic recurrence within 1 year, and one third need repeat surgery within 10 years [4-6].

The pathophysiology of CD relies on a complex interaction of host genetics, the microbiome and inflammatory responses [7,8]. Significant human gut commensal community functional breakdown or dysbiosis is observed in CD [9,10]. Genome-wide association study (GWAS) results in CD underscore the theme of aberrant host-microbiome interactions, specifically ineffective pathogen clearance from the mucosa because of genetic defects in bacterial pattern recognition (Nod2) and in autophagy [11]. Chronic immune stimulation by bacterial antigens is well established as patients with CD have detectable antibodies to bacterial cell constituents such as OmpC and Flagellin, with higher titers of antibodies being associated with a more severe "complicated" disease phenotype [12]. The question that arises is whether immune recognition of proteobacteria is causative for inflammation in CD or is it a secondary phenomenon due to mucosal barrier disruption? Recent evidence shows that antibacterial antibodies can be detected in serum of patients with CD several years before clinical symptoms and diagnosis, supporting the hypothesis of an initial bacterial insult that triggers inflammation [13]. In addition, metagenomic approaches coupled with classic culture microbiology from mucosal biopsies from the terminal ileum of patients with Crohn's ileitis support the case for proteobacteria as pathobionts in CD [10].

The specific association of *Escherichia coli* with invasive properties, termed adherent-invasive Escherichia coli (AIEC), with CD was first reported by Darfeuille-Michaud et al [14,15]. Since then, AIEC have been isolated from multiple independent studies involving adult and pediatric patients with CD. Using the multi-component definition of Darfeuille-Michaud et al [16], the reported prevalence of AIEC in the literature varies from approximately 36% to over 90% in patients with CD when evaluating mucosa-associated and intracellular *E coli* [17].

AIEC are distinct from other strains of *E coli* because they show non-classic virulence factors of adherence and invasion. In particular, AIEC are able to survive and replicate in intestinal epithelial cells and macrophages, thereby stimulating the production of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) [18]. The interaction between AIEC and the intestinal epithelial cells is primarily mediated by the FimH adhesin located at the tip of type 1 pili present on the bacterial surface [19].

Although type 1 pili genes are present in the genomes of all *E coli*, AIEC strains specifically express FimH adhesin and variants that allow them to more efficiently bind to mannose [20].

These mechanisms set the stage for a selective over-colonization of the epithelium by AIEC and subsequent biofilm formation [21]. The type 1 pili interact with glycoproteins such as carcinoembryonic antigen-related cell-adhesion molecule 6 (CEACAM6) on intestinal epithelial cells [22,23], TLR4 on immune cells [24], and glycoprotein (GP2) on intestinal M cells [25,26] in a mannose-dependent manner. CEACAM6 and TLR4 receptors are upregulated by inflammatory cytokines in patients with CD with ileal disease [27]. The binding of FimH to TLR4 induces the production of TNF-α, interleukin (IL)-6 and IL-8 in the gut, independently of lipopolysaccharide (LPS). Additionally, FimH binding to GP2 on the surface of M cells in the Peyer's patches allow AIEC to enter into the lamina propria. The subsequent phagocytosis of the AIEC by the macrophages further contributes to the chronic production of TNF-α. A vicious cycle of proinflammatory cytokine release is produced by the TNFα-driven overexpression of CEACAM6 and increase in M-cell development [28]. Thus, FimH appears as a critical factor both in the production of pro-inflammatory cytokines from the gut epithelium and in the invasion of the lamina propria [25,29,30].

4.1.2 Investigational Medicinal Product (Study Drug)

TAK-018
(1-(2,7-bis(((2*R*,3*S*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxylmethyl)tetrahydro-2*H*-pyran-2-yl) ethynyl)spiro[fluorene-9,4′-piperidin]-1′-yl)ethan-1-one), previously known as EB8018, is a first-in-class FimH blocker being developed for the treatment of CD that blocks FimH-mediated binding to mannose and can aggregate FimH-expressing bacteria and facilitate their clearance. TAK-018 is comprised of 2 mannoside residues held together by a chemically inert linker. These mannosides efficiently compete for binding with mannose residues such as those found on glycosylated proteins like CEACAM6 and GP2. Furthermore, because of its "bi-valent" nature, TAK-018 can bind a FimH receptor on 1 bacterial cell, and another FimH on a different bacterial cell at the same time resulting in the enchaining of several bacterial cells together [31]. This leads to the "clumping" of the bacteria within the lumen, enabling their clearance from the gut lumen [32]. In addition to facilitating clearance, the clumping process may significantly slow or prevent the penetration of FimH-expressing bacteria into the mucus layer and the intestinal epithelium. As a result, binding and activation of receptors such as TLR4, CEACAM6 and GP2, that contribute to the inflammation in the gut of patients with CD, are attenuated. Enterome's translational MOBIDIC study (clinicaltrials.gov/ct/show/NCT02882841; accessed 07January 2019) showed that a majority (61%, 74 of 111) of patients with CD with ileitis had invasive/adherent proteobacteria that could be cultured from mucosal biopsies and aggregated in the presence of TAK-018 [33].

4.2 Rationale for the Proposed Study

As most patients with CD eventually require an intestinal resection, postoperative recurrence poses a significant burden to the CD population. Disease recurrence on the histological level is observed within days after ileocolonic anastomosis [34]. Most CD therapies, such as probiotics, aminosalicylates, thiopurines, steroids, antibiotics, and biologics, have yielded either negative or equivocal results in terms of preventing relapse. Because of its unique mechanism of action

(MOA), TAK-018 should block the pathobiont entry underlying chronic inflammation and bowel wall damage observed in patients with CD. This MOA is distinct from the conventional approach of neutralizing inflammatory mediators such as TNF-α and IL-23, thereby allowing patients with CD to maintain remission without lifelong immune suppression.

The purpose of this phase 2a, randomized, multicenter, double-blind study is to evaluate the safety, tolerability, and early proof of concept of TAK-018 for the prevention of postoperative CD recurrence.

4.3 Benefit/Risk Profile

TAK-018 is a first-in-class investigational medical product (IMP) and has no known class effects.

Nonclinical studies with TAK-018 have been conducted in rats, rabbits, and dogs. In the 14-day toxicity study in rats, TAK-018 was administered subcutaneously (SC) for 14 days at 40, 100, 400 mg/kg/day. Transient clinical signs (skin swelling of head/ears/limbs likely related to histamine release; reddish discoloration of extremities), observed during the first 3 days of treatment and intermittently up to Day 8 in males at 100 and 400 mg/kg/day and in females at 400 mg/kg/day, resolved despite continued dosing. Increased histamine levels were also reported in the 400 mg/kg/day treatment group that indicated a possible pseudo-allergic reaction. These clinical signs were not observed in rabbits or dogs.

TAK-018 showed no evidence effects on embryo-fetal development studies in rats or rabbits dosed SC from Gestation Days 6 to 17 at doses up to 1000 mg/kg, with the exception of maternal toxicity in rabbits where the no-observed-adverse-effect level (NOAEL) was 300 mg/kg. There was no evidence or potential for teratogenicity.

In addition, TAK-018 showed no stimulatory effect on human mucosal mast cells in an in vitro study. Therefore, the swelling and discoloration observed in the 14-day rat study are likely related to rodent-specific histamine release resulting from high local concentration after SC administration.

TAK-018 was administered SC (50, 150, 300 mg/kg/day) and orally ([PO]; 200, 600, and 2000 mg/kg/day) and SC (400 mg/kg/day) in the 12-week and 13-week rat toxicity studies, respectively. Similar transient clinical signs (ie, pseudo-allergic reactions) were observed after SC administration in the 12-week study and in the 13-week study (400 mg/kg/day SC group only) as were noted in the 14-day rat toxicity study. The NOAEL was established at 300 mg/kg/day for SC and 2000 mg/kg/day for PO.

In the 400 mg/kg/day SC group, minimal to moderate tubular degeneration in the kidneys of male rats was observed that was considered to be adverse. This finding showed no correlation to clinical laboratory values and was not observed in any other species or in any other rat study at any other dose and is therefore considered to be likely of low toxicologic significance. The male-only occurrence suggests that this could be part of spontaneous rat nephropathy that is more frequently seen in male rats. These findings are likely to be of low clinical significance. Urinalysis will be done at baseline and each study visit and abnormalities will be treated per routine standard of care.

In the 14-day toxicity study in dogs, TAK-018 administered PO twice daily ([BID]; 100, 300, 1000 mg/kg) was well tolerated and did not result in any signs of overt toxicity. The no-observed effect level (NOEL) for TAK-018 was 2000 mg/kg/day.

The NOEL, derived from 14-day rat SC (most sensitive species), was 40 mg/kg for males and 100 mg/kg for females. The estimated human equivalent dose (HED) was 387 mg (40 mg/kg [NOEL in 14-day rat SC] /6.2 [rat conversion factor] = 6.45 mg/kg × 60 kg human = 387 mg). A 10-fold safety factor was applied to the HED to obtain the maximum starting dose of 38.7 mg. Considering the expected lower bioavailability in humans compared to rats used in the HED calculation, 50 mg was used as the starting dose in the single ascending dose (SAD) part of the first study in healthy volunteers.

The phase 1a study EBFIM116 in healthy volunteers included 2 parts: SAD of 50, 250, 750, 1500, and 3000 mg or placebo, and multiple ascending doses of 750 and 1500 mg, or placebo administered PO BID for 14 days. The safety data suggested that oral TAK-018 up to 1500 mg BID for 14-days was well-tolerated: no subjects discontinued treatment, adverse events (AEs) were of mild intensity, and no serious adverse events (SAEs) were reported. Consistent with nonclinical data, there was low plasma exposure in phase 1a, suggesting low bioavailability of TAK-018 in healthy volunteers when administered capsules PO. The geometric mean terminal half-life ranged from 12.63 to 45.63 hours over the SAD range of 50 to 3000 mg.

In the 12-week toxicity study in dogs (TAK-018 dosed PO [300 and 1000 mg/kg/day] and SC [10, 20, and 40 mg/kg/day]), the NOAEL was identified as 40 mg/kg once daily (QD) SC with a corresponding average plasma area under the concentration-time curve from time 0 to 24 hours ($AUC_{0\text{-}24hr}$) at the end of treatment of 102,739 ng*h/mL. Using this value from the dog toxicity study (the higher species), the estimated safety margin exceeded 100-fold the plasma exposure in healthy volunteers.

In the chronic 39-week toxicity study in dogs (TAK-018 dosed PO [600 and 2000 mg/kg/day] and SC [10, 20, and 40 mg/kg/day]), the NOAEL was identified as 40 mg/kg QD SC with a corresponding average plasma area under the concentration-time curve from administration to last observed concentration at time t (AUC_t) at the end of treatment (Week 39) of 115,044 ng*h/mL. In addition, in the chronic 26-week toxicity study in rats (TAK-018 dosed PO [600 and 2000 mg/kg/day] and SC [50, 150, and 300 mg/kg/day]), the NOAEL was identified as 300 mg/kg QD SC with a corresponding average plasma AUC_t at the end of treatment (Week 26) of 112,313 ng*h/mL. These exposure values in the chronic studies (dog and rat) support the previously estimated safety margins in healthy volunteers.

In the phase 1b study EBFIM117 in subjects with active CD, TAK-018 tablets are administered PO (1.5 g BID) for 13 days. Preliminary observations from the first 6 subjects confirmed that the study drug is well tolerated with no SAEs reported nor study drug discontinuations. The preliminary exposure data from the first 4 subjects in this study suggested that the average systemic exposure of TAK-018 in subjects with active CD was approximately 2 to 5-fold higher with more variability than that observed in healthy subjects. Safety margins, re-evaluated based on the exposure data in subjects with active CD, still exceed 10-fold, supporting the highest dose of 3.0 g daily to be administered in the current study.

As a first-in-class IMP and because TAK-018 has been administered to only a small number of human subjects, the types of AEs that may be observed in this phase 2a study are not known. The phase 2a study will include routine monitoring for AEs and SAEs. Currently there are no identified or potential risks associated with TAK-018 treatment based on the evidence from two phase 1 clinical studies and toxicology studies.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

- To evaluate the efficacy of TAK-018 in reducing endoscopic recurrence of intestinal inflammation in postoperative subjects with CD after planned laparoscopic ileocecal resection with primary anastomosis.

5.1.2 Safety Objective

- To assess the safety and tolerability of TAK-018 in postoperative subjects with CD after planned laparoscopic ileocecal resection with primary anastomosis.

5.1.3 Secondary Objectives

- To evaluate the effect of TAK-018 on intestinal inflammation based on serial fecal calprotectin measures.
- To characterize the pharmacokinetics (PK) of TAK-018 in postoperative subjects with CD after planned laparoscopic ileocecal resection with primary anastomosis.

5.1.4 Exploratory Objectives

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoint

The percentage of subjects with endoscopic recurrence of CD at Week 26 (W26). Endoscopic recurrence is defined as Rutgeerts score ≥i2 (i2, i3, i4; Appendix C).

5.2.2 Safety Endpoint

The percentage of subjects who experience treatment-emergent adverse events (TEAEs), defined as AEs that begin or worsen after the first dose of study treatment regardless of relationship to

study drug, SAEs, and/or clinically significant changes in vital signs, standard laboratory tests and procedures (eg, clinical chemistry, hematology, urinalysis).

5.2.3 Secondary Endpoints

- The percentage of subjects with fecal calprotectin (FCP) >135 µg/g at Week 3 (W3), Week 6 (W6), Week 12 (W12), Week 18 (W18), W26, and Week 30 (W30).
- Observed plasma trough concentrations of TAK-018 at W3.

5.2.4 Exploratory Endpoints

[redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Overview of Study Design

This is a randomized, double-blind, placebo-controlled, multicenter, phase 2a study to evaluate the safety, tolerability, and efficacy of TAK-018 administered postoperatively to subjects with CD who have undergone a planned laparoscopic ileocecal resection with primary anastomosis to prevent postoperative recurrence of their disease. Of note, the laparoscopic ileocecal resection is *not* considered a study procedure and should be completed per institutional standard of care.

Initial eligibility will be determined during the screening period. Subjects will provide written informed consent at screening. Subjects who meet all eligibility criteria on D1, defined as the day within 72 hours after surgery on which the first dose of study drug is administered, will be randomized into this study. Randomization will be stratified by smoking status (Section 9.3.2) Approximately 96 subjects will be randomized in a 1:1:1 ratio to 3 treatment arms: TAK-018 low dose (0.30 g BID), TAK-018 high dose (1.5 g BID), or placebo (approximately 32 subjects per arm) and will be treated for a 26-week treatment period to begin on D1. Study drug is taken immediately after a meal (ie, breakfast and dinner) with water BID, approximately 8 to 12 hours apart. While on

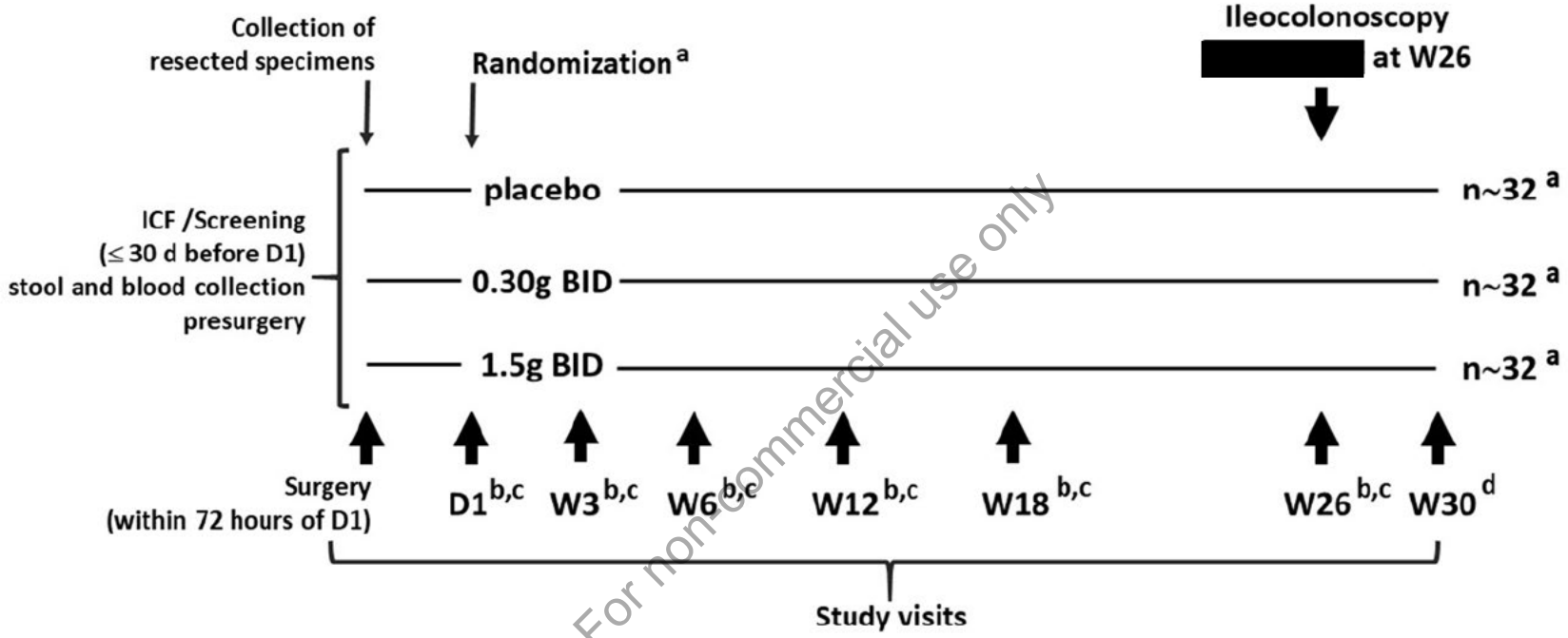
treatment, subjects will have study visits at W3, W6, W12, W18, and W26, with a final study visit at W30, 30 days after the W26 endoscopy. Study visits at D1 and W26 are clinic visits; study visits at screening, W3, W6, W12, W18, and W30 may be conducted as clinic or HHC visits to provide flexibility for subjects.

Blood samples will be collected presurgery and at all study visits after dosing starts to characterize disease progression, response to study drug, safety parameters, and the PK of TAK-018 (see Appendix B). Blood samples will be collected at all study visits not to exceed 425 mLs per subject over the study period. Subjects will also provide stool samples before surgery during the screening period and at W3, W6, W12, W18, W26, and W30. Fecal calprotectin will be measured before surgery during the screening period and in every stool collection. Endoscopic assessment will be performed at the end of the 26-week treatment period (W26) and will be assessed by central readers.

The study consists of a screening period (up to 30 days before randomization), a 26-week treatment period that begins within 72 hours after surgery (starting when the subject arrives at the postsurgery recovery ward or unit), and a final study visit at W30, 30 days after the W26 endoscopy. The end of study visit will be the final study visit at W30 or, for subjects who discontinue early, will occur 30 days after their last dose of study drug. The study overview is depicted in Figure 6.a.

Subjects who discontinue study drug treatment (refer to Section 9.6) will complete an early termination (ET) visit upon discontinuation and a final visit 30 days after their last dose of study drug.

Figure 6.a Schematic of TAK-018-2001 Study Design



BID: twice daily; D1: Day 1; HHC: home health care; ICF: informed consent form; PK: pharmacokinetic; W3: Week 3; W6: Week 6; W12: Week 12; W18:Week 18; W26: Week 26; W30: Week 30.

6.2 Justification for Study Design Components

6.2.1 Subject Population

Up to 60% of patients with CD will require a major abdominal resection within 10 years of their diagnosis, and a majority of them will develop postoperative recurrence within 1 year after surgery [2-6]. The high prevalence of AIEC reported in patients with CD is likely associated with the high recurrence rate after bowel resection [16,33,35,36] (MOBIDIC study; clinicaltrials.gov/ct/show/NCT02882841; accessed 07 January 2019). Since TAK-018 is designed to prevent AIEC adhesion and subsequent invasion of the gut epithelium, we expect it to inhibit or reduce AIEC gut recolonization in the postoperative CD population after surgery. Given the unique MOA of TAK-018, subjects should be administered study drug as soon as possible after surgery. The majority of ileocecal resections for CD are laparoscopic, which has resulted in reduced postoperative complications, earlier oral tolerance for diet, and earlier hospital discharge [37]. Therefore, subjects eligible for this study will have undergone a planned laparoscopic ileocecal resection and are able to take study drug within 72 hours after surgery. The proof of concept data derived from the postoperative CD subject population will inform the further development of TAK-018.

6.2.2 Sample Size

This study is planned to randomize approximately 96 subjects stratified by smoking status (active smoker vs nonsmoker/previous smoker) in a 1:1:1 ratio to each of 3 treatment arms (Figure 6.a). Sample size justification is described in Section 13.3.

6.2.3 Study Drug Dose

TAK-018 will be investigated at a low dose and high dose to characterize the benefit-risk profile and exposure-response relationship. The available safety data from healthy volunteers and subjects with active CD have demonstrated that TAK-018 is tolerated up to 1.5 g BID for 2 weeks. Safety margin calculations (Section 4.3) based on plasma exposure data from both healthy volunteers and subjects with active CD support further investigation. The higher dose (1.5 g) is selected to further evaluate the safety profile when dosed for a longer duration and also to better explore the therapeutic benefit for subjects with postoperative CD. Based on 99% inhibitory concentration (IC_{99}) values estimated from in vitro potency tests, a lower dose (0.3 g), projected to provide benefit, is selected to explore the efficacious dose/exposure range of TAK-018 and to inform dose selection in future studies.

6.2.4 Duration of Study

The pivotal 39- and 26-week toxicity studies in dogs and rats, respectively, administered oral and SC TAK-018 support the 26-week treatment period with TAK-018 in the current study. An individual subject's participation in this study is up to 34 weeks (4-week screening period, 26-week treatment period, 4-week safety follow-up) with the global study duration of approximately 2 to 3 years.

6.2.5 Endpoints

The primary endpoint is the percentage of subjects with endoscopic recurrence at W26. Endoscopic recurrence is defined as Rutgeerts score ≥i2 (i2, i3, i4; Appendix C). The safety endpoints are the percentage of subjects who experience TEAEs, SAEs, and/or clinically significant changes in vital signs, standard laboratory tests and procedures (eg, clinical chemistry, hematology, urinalysis). Secondary endpoints are measured changes in the FCP levels and determination of PK. [redacted]

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or ET of the study.

- If ≥2 subjects experience a Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 Grade ≥3 event, or 1 or more subjects experience a Grade 4 event that are considered related to study drug treatment by the investigator or sponsor, enrollment in the study will be interrupted for a review of all the available safety data. Study enrollment will resume if the event is considered unlikely to be related to treatment with study drug. If there is no reasonable explanation regarding the event causality other than a relationship to study drug, the sponsor will terminate the study.
- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known benefit/risk profile for the TAK-018, such that the benefit/risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises patient safety.
- The sponsor elects to terminate or suspend the study due to plans to modify, suspend, or discontinue development of the study drug.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of the Study Sites

In the event that the sponsor, an institutional review board (IRB)/independent ethics committee (IEC) or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for ET or suspension will be provided by the sponsor. The procedure will be followed by applicable study sites during termination or study suspension.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

Each subject must meet all of the following inclusion criteria to be randomized into the study. A subject is considered enrolled in the study after randomization and upon receiving the first dose of study drug on D1.

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. Subject signs and dates a written informed consent form (ICF), and any required privacy authorization before performance of any study-related procedures not part of standard medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.
3. Male or female subject aged ≥18 years or local legal age at signing of ICF.
4. Subject must have a documented diagnosis of CD confirmed by endoscopic biopsy before resection or by tissue obtained at resection.
5. Subject is planned to undergo a laparoscopic ileocecal resection with primary anastomosis within 72 hours before randomization (D1). Confirmation that no active disease has been left behind after resection will be based on surgeon's documentation in the operative report.
6. Subject with postoperative discontinuation of all concomitant medications specifically related to the treatment of CD. This includes anti-TNF-α and anti-integrin therapy, anti-IL 12/23, thiopurines and other immunomodulators, steroids, 5-aminosalicylates, and prophylactic use of antibiotics for the prevention of postoperative recurrence such as metronidazole.
7. Subject has resumed oral intake and is capable of swallowing tablets within 72 hours after surgery.
8. Female subject who is:
   - Postmenopausal for at least 1 year before signing of the informed consent, OR
   - Surgically sterile, OR
   - If she is of childbearing potential, agrees to practice 1 highly effective method of contraception (specified in Section 9.3.17) and 1 additional effective (barrier) method at

the same time, from the time of signing the informed consent through 40 days after the last dose of study drug, OR

- Agrees to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Male subject, even if surgically sterilized (ie, status postvasectomy), who:

- Agrees to practice effective barrier contraception (specified in Section 9.3.17) during the entire study treatment period and through 100 days after the last dose of study drug, OR
- Agrees to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

9. Subject with suitable venous access for the study-required blood sampling, including PK sampling.

7.2 Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not to be randomized into the study.

1. Subject has active perianal CD.
2. Subject has had >3 previous surgical procedures for CD.
3. Subject has macroscopically active CD that was not resected at the time of surgery as documented in the surgeon's operative report.
4. Subject with small bowel resection that exceeds 100 cm or a subject who is considered at risk of short bowel syndrome by the surgeon or investigator.
5. Subject has any significant intraoperative or postoperative complications such as anastomotic leak, surgical site infection, or inability to tolerate oral intake.
6. Subject is unable or unwilling to undergo or has contraindications to ileocolonoscopic procedures as assessed by the investigator.
7. Subject has inadequate renal or hepatic function postsurgery and before randomization based on the following laboratory parameters:
   - Total bilirubin >1.5× the institutional upper limit of normal (ULN) unless subject has known Gilbert's syndrome that can explain the elevation of bilirubin, or
   - Serum alanine aminotransferase (ALT) >3× the institutional ULN, or
   - Creatinine >1.5× the institutional or central laboratory ULN or estimated creatinine clearance <50 mL/minute/1.73 m^2 for subjects with serum creatinine concentrations above the institutional or central laboratory limits.

8. Subject has any unstable or uncontrolled cardiovascular, pulmonary, hepatic, renal, genitourinary, coagulation, immunological, endocrine/metabolic, neurologic, active substance abuse, psychiatric or other medical disorder not related to the subject's primary disease that, in the opinion of the investigator, would confound the study results, compromise subject safety, or interfere with completion of the study.
9. Subject has active or latent tuberculosis, regardless of treatment history, as evidenced by any of the following: history of tuberculosis, OR positive QuantiFERON test or 2 successive indeterminate QuantiFERON tests, OR a tuberculin skin test reaction ≥10 mm (≥5 mm in subjects receiving the equivalent of >15 mg/day prednisone).*
10. Subject has chronic hepatitis B (hepatitis B surface antigen positive, or positive for both hepatitis B surface antibody and hepatitis B core antibody but negative for hepatitis B surface antigen) or hepatitis C infection (evident by viral replication by polymerase chain reaction) within 30 days of randomization.*
11. Subject has a history of HIV or tests positive for HIV at screening.*
12. If female, the subject is pregnant, lactating or breastfeeding, or intending to become pregnant before, during, or within 40 days after last dose of the study drug; or intending to donate ova during such time period.
13. If male, the subject intends to donate sperm during this study or for 100 days thereafter.
14. Subject has a current diagnosis of biliary obstruction.
15. Subject demonstrates significant undernutrition at the time of screening (body mass index <18.5 kg/m^2, and weight loss >15% within 6 months, and serum albumin <3 g/dL) [39].
16. A subject who, in the opinion of the investigator, is unwilling or unlikely to comply with the requirements of the study.
17. Subject has participated in another clinical study within the past 30 days before completing informed consent or has received any investigational compound within 30 days before screening.
18. Subject has received TAK-018 (previously known as EB8018) in a previous clinical study.
19. Subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
20. Subject has a history of hypersensitivity or allergies to TAK-018, including any excipients contained in the study drug formulation.
21. Subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within the past 12 months.

22. Subject takes or is required to take excluded medications listed in Section 8.3.

* Exclusion Criteria 9 through 11 are included as a precaution because rescue therapy with immunomodulating or immunosuppressing agents is allowed for subjects with recurrent CD after which these subjects will discontinue from the study. There are no concerns specific to study drug regarding these criteria.

8.0 STUDY DRUG/CLINICAL STUDY MATERIAL MANAGEMENT

This section contains information regarding all medications and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol.

8.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented before administration. Subjects in the PK subgroup (Appendix B) will take their first dose of study drug at the clinic on D1 (if previously discharged) after predose blood collection. For the study visit at W3, study drug should be taken after the predose blood collection completes.

8.1.1 TAK-018 or Matching Placebo

The sponsor will supply study sites with study drug (ie, TAK-018 and placebo tablets with identical appearance) to be taken PO immediately after a meal (ie, breakfast and dinner) with water BID approximately 8 to 12 hours apart. If a subject forgets to take the study drug at the scheduled time, regularly scheduled dosing should be resumed without re-adjusting the schedule of administration. Subjects should take their study drug tablets with approximately 8 ounces (1 cup, 240 mL) of water at each administration. If emesis occurs after taking study drug, symptoms should be managed with standard antiemetic therapy; a repeat (replacement) dose of study drug should not be taken. Subjects should adhere to the dosing schedule and resume dosing at the next scheduled time with the prescribed dosage.

Subjects should swallow the study medication whole and not chew it, grind it, or manipulate it in any way before swallowing.

8.1.1.1 TAK-018 Investigational Drug Product

The sponsor will supply study sites with TAK-018 tablets containing TAK-018 active substance and other commonly used compendial excipients including mannitol, microcrystalline cellulose, crospovidone Type A, povidone, colloidal anhydrous silica, and magnesium stearate with Opadry QX pink as the film coating. The tablets are supplied as 100 mg and 500 mg immediate-release, film-coated tablets, identical in appearance. Tablets are packed in bottles.

8.1.1.2 Matching Placebo

The sponsor will supply study sites with placebo tablets containing commonly used compendial excipients including mannitol, microcrystalline cellulose, povidone, colloidal anhydrous silica, and magnesium stearate with Opadry QX pink as the film coating, formulated to be identical in appearance to the active TAK-018 tablets.

8.1.1.3 Storage of Study Drug

Study drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Study drug tablets are to be stored in the original container at controlled room temperature as defined in the Pharmacy Manual. Study drug must be transported and stored under the conditions specified on the label, and remain in the original container until dispensed.

8.1.2 Dose and Regimen

Table 8.a describes the dose and tablet count that will be provided to each arm.

Table 8.a TAK-018 Dose and Regimen

Treatment Arm	Dose	Treatment Description Dose	Number of Tablets per Dose
A	Placebo BID		Three placebo tablets
B	TAK-018 BID	Low dose (0.30 g)	Three 0.10 g tablets
C	TAK-018 BID	High dose (1.5 g)	Three 0.50 g tablets

BID: twice daily.

8.2 Treatment Assignment and Dispensing Procedures

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria at screening are eligible for randomization on D1.

The investigator or investigator's designee will access the interactive response technology system (IRT) at screening to obtain the subject screen number. The investigator or the investigator's designee will use the IRT to randomize the subject into the study. The medication identification (ID) number of the study drug to be dispensed will then be provided by the IRT. The investigational drug blind will be maintained using the IRT. If sponsor-supplied drug is lost or damaged, site staff can request a replacement from IRT.

At subsequent drug-dispensing visits, the investigator or designee will again contact the IRT to request additional IMP for a subject. The medication ID number of the study drug to be dispensed will be provided by the IRT.

The IRT will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

Additional information is provided in the pharmacy/IRT manuals.

8.3 Excluded Concomitant Medications and Procedures While On-study

- Any medications intended specifically for the treatment of CD after surgery, including anti-TNF or anti-integrin therapy, anti-IL 12/23, thiopurines and other immunomodulators, steroids, 5-aminosalicylates, and prophylactic use of antibiotics for the prevention of

postoperative recurrence such as metronidazole. Systemic steroids for indications other than CD are not permitted.

- Any investigational agent other than the study drug administered as part of this study.
- Either approved or investigational biological agents for the treatment of other conditions (eg, rheumatoid arthritis), other than topicals or localized injections (eg, intraocular injections for wet macular degeneration).

8.4 Permitted Concomitant Medications and Procedures

Other medications considered necessary for the safety and well-being of the subject may be administered at the discretion of the investigator. These include prescription antibiotics for infections such as urinary tract infection and bronchitis. Use of anti-inflammatory agents is generally discouraged but short term use defined as ≤72 hours at any given time during the study period is permitted. Aspirin use for cardiovascular disease prophylaxis is permitted. Stress dose systemic steroids for surgery are permitted, and patients need to be tapered off all systemic steroids within 15 days after surgery. Topical steroids, inhaled steroids and intra-articular injections of steroids are permitted.

Any concomitant medications or supplements added or discontinued during the study and any dose or dose regimen changes should be recorded on the electronic case report form (eCRF).

8.5 Precautions and Restrictions

8.5.1 Reproductive Effects

It is not known what effects the study drug has on human pregnancy or development of the embryo or fetus. Therefore, female subjects participating in this study should avoid becoming pregnant, and male subjects should avoid impregnating a female partner. Nonsterilized female subjects of reproductive age group and male subjects should use effective methods of contraception (specified in Section 9.3.17) through defined periods during and after study treatment as specified in the following.

Female subjects must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to practice 2 effective methods of contraception (specified in Section 9.3.17) from the time of signing of the ICF through a minimum of 40 days after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

Male subjects, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:

- Practice effective barrier contraception (specified in Section 9.3.17) during the entire study treatment period and through a minimum of 100 days after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

8.6 Management of Clinical Events

8.6.1 Liver Test Abnormalities

For subjects with treatment-emergent ALT elevations ≥3× ULN, see Appendix D for additional monitoring, evaluation, and follow-up recommendations.

For any subject with ALT ≥3× ULN ***AND*** total bilirubin >2× ULN ***OR*** international normalized ratio (INR) >1.5× ULN for which an alternative etiology has not been found, report the event as an SAE, contact the sponsor's medical monitor within 24 hours, and follow the additional monitoring, evaluation, and follow-up recommendations in Appendix D. Potential events will be reported as SAEs (Section 10.2.3.4).

All subjects with liver abnormalities will be closely followed and follow-up laboratory tests as described in Appendix D must also be performed. Subjects will be followed until abnormalities return to normal or baseline or until all attempts to determine resolution of the event are exhausted.

8.6.2 Vomiting

For subjects who vomit after taking study drug, symptoms should be managed with standard antiemetic therapy. Subjects should not take a replacement dose but should adhere to the dosing schedule and resume dosing at the next scheduled time. In cases of recurrent vomiting, subjects should contact the site investigator.

8.6.3 Recurrence of CD

Based on clinical assessment, if the investigator feels that appropriate treatment is warranted for recurrence, the subject will discontinue study drug, begin institutional standard of care, will attend an early termination visit 30 days after last dose of study drug, and will be withdrawn from the study. The methodology used by the investigator to define recurrence (eg, endoscopic result, clinical instrument score, or other) should be documented in the eCRF.

8.7 Unblinding Procedure

The study drug blind shall not be broken by the investigator unless information concerning the study drug is necessary for the medical treatment of the subject. All study assessments and causality assessments should be performed before unblinding, if possible. In the event of a medical emergency, the study drug blind can be broken without permission from the sponsor, although the

medical monitor should be contacted immediately. In non-urgent cases (ie, a nonmedical emergency), the medical monitor must be contacted before the subject is unblinded.

For unblinding a subject, the study drug blind can be obtained by the investigator, by accessing the IRT.

Subjects discontinuing study participation for any other reason will be kept blind.

The sponsor must be notified as soon as possible if the study drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the eCRF.

8.8 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee. The site will maintain source documents in addition to entering data into the IRT.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug, the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, the investigator or designee should acknowledge the receipt of the shipment in the IRT. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must ensure that 100% accountability is maintained for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes but is not limited to:

- Frequently verifying that actual inventory matches documented inventory.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.
- Continuously monitoring expiration dates, if expiry date is provided.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The IRT will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

All study drug not returned to the site by a subject must be investigated by the site and appropriately documented on the drug accountability log.

Before site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction. Accountability for clinical study material being destroyed at the site must be documented using a study accountability tracking document or equivalent document. In addition, a certificate of destruction document must be provided by the sites that can identify or allow traceability to the batches, and/or medication ID numbers involved, and actual quantities destroyed. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

9.0 STUDY CONDUCT

9.1 Study Personnel and Organizations

The contact information for the Takeda project clinician for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator for each member state/country (where applicable), and the contract research organization (CRO) team may be found in the study manual. A full list of investigators is available in the sponsor's investigator database.

9.2 Informed Consent and Screening

9.2.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained to begin screening and before any protocol-directed procedures are performed.

9.2.2 Screening

Investigators must account for all subjects who sign informed consent. If a subject is found to be not eligible, the investigator should complete the appropriate eCRF, noting the primary reason for screen failure. The IRT should be contacted as a notification of screen failure. Subject numbers assigned to subjects who fail screening should not be reused.

Rescreening of subjects is permitted in this study based on investigator discretion and approval by the sponsor or the sponsor's designee for the following reasons:

- If laboratory test results are outside protocol-defined limits (Section 7.2), the test can be repeated once during screening at the principal investigator's (PI's) discretion. If the repeat value is again outside protocol limits, then the subject is a screen failure.
- A subject's scheduled surgical procedure is delayed, resulting in randomization on Day 1 to fall outside the 30-day period after their initial screening.

Before a subject may be rescreened, a new ICF must be completed. Rescreened subjects must be assigned a new screen number using IRT and all Part 1 screening procedures must be repeated for each subject who is rescreened.

9.3 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. Refer to the schedule of events (SOE), in Appendix A, for timing of assessments. Additional details are provided as necessary in the sections that follow. Of note, the ileocecal resection is an entry criterion and *not* considered a study-related procedure and should be completed as per institution's standard of care. D1 of the clinical study begins within 72 hours *after* surgery when the patient has been randomized to 1 of the 3 study arms.

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood collected over the course of the study from an individual subject is not to exceed 425 mL.

9.3.1 Inclusion/Exclusion Criteria

The inclusion and exclusion criteria will be assessed during screening and before randomization.

9.3.2 Randomization and Enrollment

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization. All eligible subjects will be randomized on D1 (using the IRT as described in Section 8.2) 1:1:1 to either TAK-018 low dose (0.30 g BID), TAK-018 high dose (1.5 g BID), or placebo (BID) for a 26-week treatment period. Randomization will be stratified by smoking status collected as active smokers versus nonsmokers and previous smokers (defined as subjects who stopped smoking at least 3 months before ileocecal resection) [40]. Subjects will receive the treatment for the assigned study arm and according to the study schedule. Study procedures for D1 are shown in Appendix A and Appendix B.D1 procedures will occur either in the hospital before discharge or during an office visit if the subject has already been discharged.

A subject is considered enrolled in the study upon completion of the ICF.

9.3.3 Demographics and Medical History

Demographic information to be obtained during screening will include but is not limited to the date of birth or age depending on local regulations, race, ethnicity, and sex of the subject.

During the screening period, a complete medical and surgical history will be compiled for each subject, including whether the subject has or had any significant conditions or diseases relevant to the disease under study. All CD-related medications taken previously and CD-related procedures should be recorded in the medical history. In addition, concomitant medications will be recorded as specified in Section 9.3.9.

9.3.4 Physical Examination

A physical examination (complete or targeted) will be completed at the times specified in the SOE (Appendix A). Any clinically relevant findings at baseline will be documented. The physical

examination may be conducted as nurse assessments during HHC visits, if applicable and according to local regulations/requirements.

A complete physical examination will include examination of general appearance, skin, head, eyes, ears, nose, throat, neck, lungs, abdomen (including liver and spleen), lymph nodes, extremities, cardiovascular system, genitourinary system, musculoskeletal system, and neurological system.

A targeted physical examination will include examination of lungs, abdomen, skin, and cardiovascular system.

Any physical examination finding that is assessed by the investigator as a clinically significant change (worsening) compared to a baseline value will be considered an AE and will be recorded and monitored as described in Section 10.2.

9.3.5 Subject Height and Weight

Height will be measured only during screening. Weight will be measured as part of all physical examinations (Appendix A).

9.3.6 Vital Signs

Vital sign measurements include blood pressure, heart rate, respiration rate, and body temperature to be determined at the times specified in the SOE (Appendix A). On study visit days, vital sign measurements should be performed before administration of study drug.

9.3.7 Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be performed at the time points specified in the SOE (Appendix A).

9.3.8 [redacted]

[redacted].

9.3.8.1 [redacted]

[redacted].

9.3.8.2 [redacted]

[redacted]

9.3.9 Concomitant Medications and Procedures

Medications or supplements used by the subject and therapeutic procedures completed by the subject will be recorded in the eCRF from signing the ICF through 30 days after their last dose of study drug. See Section 8.3 and Section 8.4 for a list of medications and therapies that are prohibited and/or allowed during the study.

Concomitant medications may be prescribed by a physician or obtained by the subject over the counter and are not provided by the sponsor.

9.3.10 AEs

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the SOE (Appendix A). Refer to Section 10.0 for details regarding definitions, documentation, and reporting of AEs, SAEs, and overdose.

9.3.11 Clinical Laboratory Evaluations

Clinical laboratory evaluations as specified in the SOE (Appendix A) will be performed by a central laboratory. Local laboratories may be used to conduct assessments needed more rapidly and for urgent medical management throughout the study per investigator's discretion. For example, to qualify a subject for randomization and to ensure timely study drug initiation on D1, subject eligibility may be based on local laboratory results. If central laboratory results are available, they should be used to determine eligibility for randomization on D1. Clinical laboratory evaluations performed by the central laboratory will be captured in the clinical database; any local laboratory results should be maintained in a subject's source documents and entered in electronic data capture (EDC) as applicable.

Clinical laboratory evaluations to be conducted during this study are summarized in Table 9.a.

9.3.11.1 Pregnancy Test

For women of childbearing potential, a serum pregnancy (choriogonadotropin beta) test will be completed at screening and a urine pregnancy test predose at D1, W3, W6, W12, W18, W26, and

W30. The results from these tests must be available and negative before subsequent doses of study drug are taken. Additional pregnancy testing may be performed during the study at the discretion of the investigator, upon request of an IEC/IRB, or if required by local regulations.

9.3.11.2 Clinical Hematology, Chemistry, and Liver Tests

The clinical laboratory tests (clinical hematology, blood chemistry, and liver tests) to be conducted during the study are summarized in Table 9.a. The central laboratory will perform these tests and return the results to the investigator, who is responsible for reviewing and filing them. Blood samples for these analyses will be obtained at the time points specified in the SOE (Appendix A).

For subjects with treatment-emergent ALT elevations ≥3× ULN, see Appendix D for additional monitoring, evaluation, and follow-up recommendations. Graded laboratory abnormalities will be defined using CTCAE Version 5.

Table 9.a Clinical Hematology, Chemistry, and Liver Tests

Hematology	**Serum Chemistry**	
Hematocrit	Albumin	Glucose
Hemoglobin	Bicarbonate (HCO_3)	Phosphate
Red blood cells (RBC)	Blood urea nitrogen (BUN)	Potassium
Leukocytes with differential including neutrophils, monocytes, and lymphocytes	Calcium	Sodium
	Creatinine	Urate
Platelets	Chloride	
Liver Tests		
Alkaline phosphatase	Bilirubin (total, direct, and indirect)	
ALT	GGT	
AST	Lactate dehydrogenase	
Other:		
HIV	Urine pregnancy hCG (predose on dosing days) and beta hCG to confirm positive urine result for female subjects of childbearing potential	
Hepatitis panel, including HBsAg, anti-HCV, and HCV PCR		
C-reactive protein	FSH, if menopause is suspected	
INR		

ALT: alanine aminotransferase; AST: aspartate aminotransferase; FSH: follicle-stimulating hormone; GGT: gamma glutamyl transferase; HBsAg: hepatitis B surface antigen; hCG: human chorionic gonadotropin; HCV, hepatitis C virus; INR: international normalized ratio; PCR: polymerase chain reaction.

9.3.11.3 Urinalysis

Urine samples will be analyzed centrally. Urinalysis will include the parameters shown in Table 9.b and urine samples will be obtained at the time points specified in the SOE (Appendix A).

Table 9.b Clinical Urinalysis Tests

Urinalysis	
Bilirubin	pH
Glucose	Protein
Ketones	Specific gravity
Leukocytes	Turbidity and color
Nitrite	Urobilinogen
Occult blood	

9.3.12 Stool Sample for Fecal Calprotectin

Stool samples will be collected at the time points specified in the SOE (Appendix A) for analysis of fecal calprotectin. [redacted] Refer to the laboratory manual for details on collecting, processing, storage, and shipment of stool samples.

9.3.13 Ileocolonoscopy [redacted]

Ileocolonoscopies will be conducted at the end of study drug treatment at W26. Bowel prep requirements will follow the institutional standard of care. [redacted]

9.3.14 PK Sample Collection

Blood samples (1 sample per collection) for PK analysis will be collected at the time points specified in the PK SOE (Appendix B). Approximately one-third of subjects may participate in the PK subgroup for relatively more intensive collections at D1 and W3. All other subjects will be required to provide sparse PK samples as outlined in the SOE (Appendix A) and PK SOE (Appendix B).

In addition to the scheduled PK sample collections, blood samples to measure TAK-018 plasma concentrations may be obtained during the on-treatment period and within 30 days after the last dose of study treatment, if clinically feasible, at the time of an AE that is judged by the investigator to be treatment-related. The unscheduled PK collections will be left to the discretion of the investigator.

The actual date and time of the sample collection and the date and time for the last dose on the day before the collection day and for the first dose on the collection day should be accurately recorded in the EDC. When predose samples are scheduled, subjects should be instructed to bring their study drug to the clinic with them so the predose sample can be collected before study drug is taken. Predose samples should be collected within 30 minutes before dosing and postdose samples should be collected within 10% of the nominal time from dosing. While all efforts should be made to obtain the PK samples at the scheduled nominal time (or within the designated time frame specified in the PK SOE [Appendix B]), collections outside of the allowed time window may not

be considered a protocol deviation if the actual collection time as well as date and time of dosing are accurately captured.

Samples will be collected and stored for batch analysis of TAK-018 using a validated analytical method. Detailed instructions for handling, processing, storing, and shipping of plasma samples are provided in the laboratory manual.

9.3.15 [redacted]

9.3.16 Changes to Study Procedures Due to a Pandemic

The following information provides guidance regarding changes to the study procedures that could be implemented for study participants or study sites that are impacted by a pandemic (eg, coronavirus disease [COVID-19] or other future similar unexpected public health concerns) that require physical distancing that may result in subjects missing their visits. This guidance takes references from the Food and Drug Administration (FDA) Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency Guidance for Industry, Investigators, and Institutional Review Boards, March 2020 and updated on 02 July 2020, the European Medicines Agency (EMA) Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic, Version 3 (28 April 2020), and the EMA Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials, dated 26 June 2020.

Because a pandemic (eg, COVID-19) may peak in different regions at different times and restrictions implemented by local laws and recommendations may vary, any decision on procedural changes should be made on a case-by-case basis by the PI, in consultation with the study team (and the medical team as needed), while maintaining patient safety and confidentiality as the priority.

Procedural changes due to COVID-19 (or other similar pandemic) may include the following:

- ICF Procedure: If necessary, informed consent from a potential or current study participant may be obtained via electronic informed consent capabilities, or an electronic face-to-face consent interview when these individuals are unable to travel to the site, based on local regulations or requirements.
- Subject visits at screening, W3, W6, W12, W18, and W30 may be conducted as clinic or HHC visits to extend flexibility to patients during a pandemic (eg, COVID-19 or other similar pandemic). HHC visits will be documented in the study records. The data collected from HHC visits may be handled differently in the final data analysis, with this documented in the statistical analysis plan (SAP).
- Study visit windows are extended to ±7 days to provide more flexible scheduling for HHC or telehealth visits (Appendix A).
- For HHC visits, collection of clinical laboratory samples (blood draws or other diagnostic tests) will be performed by the investigator or the study coordinator or by a qualified health care professional who are allowed to enter the study participant's home.
- ECG procedures: For HHC visits, ECGs may be performed by a qualified health care professional who is authorized/certified to perform such tests routinely.
- Allow 'remote visits' via virtual communications (eg, TeleHealth application) in conjunction with HHC visits and/or as an unscheduled safety assessment on subject well-being.
- Allow the use of a web-based back-up system on electronic devices.

- Allow transfer of study participants to investigational sites away from risk zones or closer to their home.
- Deviations from protocol-specified procedures (eg, not collecting a study sample such as postdose bloodwork) will be recorded as related to a pandemic (eg, COVID-19 or other similar pandemic).
- Secure direct-to-patient delivery of the study drug from the investigational site to subjects electing to engage in HHC visits.

9.3.17 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for a minimum of 40 days after the last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception (Section 8.5.1). In addition, they must be advised not to donate ova during this period.

From signing of informed consent, throughout the duration of the study, and for a minimum of 100 days after the last dose of study drug, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with spermicidal cream or jelly) (Section 8.5.1). In addition, they must be advised not to donate sperm during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (eg, defined as at least 1 year since last regular menses with a follicle-stimulating hormone [FSH] >40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented) (Section 8.5.1).

**Sterilized males should be at least 1 year post-vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate (Section 8.5.1).

A highly effective method of contraception is defined as one that has no higher than a 1% failure rate. In this study, the only highly effective methods of contraception are:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, including oral, intravaginal, and transdermal formulations.
- Progestogen-only hormonal contraception associated with inhibition of ovulation, including oral, injectable, and implantable formulations.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion.
- Vasectomized partner.

- Sexual abstinence.

Barrier methods (eg, male condom PLUS spermicide, cap [plus spermicidal cream or jelly] PLUS male condom and spermicide, diaphragm [plus spermicidal cream or jelly] PLUS male condom and spermicide) can be used each time the subject has intercourse in addition to methods listed in the table above to ensure acceptable protection level.

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the study.

During the course of the study, urine human chorionic gonadotropin (hCG) pregnancy tests will be performed (Section 8.5.1) only for women of childbearing potential and female subjects will receive continued guidance with respect to the avoidance of pregnancy and ova donation as part of the study procedures (Appendix A). In addition to a negative serum hCG pregnancy test at screening, women of childbearing potential must have urine hCG pregnancy test administered at clinic visits on D1 and W26, and on study visits at W3, W6, W12, W18, and W30. Negative results are required before receiving or taking subsequent doses of study drug.

Male subjects must be advised not to donate sperm from signing of informed consent to a minimum of 100 days after the last dose of study drug.

9.4 Completion of Study Treatment

Subjects will be considered to have completed study drug treatment if they discontinue study drug for any of the reasons outlined in Section 9.6. For subjects who discontinue due to AEs, all AEs must be collected and reported as indicated in sections 10.2 and 10.3. For all other subjects, treatment will be considered completed after the final dose of study drug at W26.

9.5 Completion of Study

Study completion will occur once all randomized subjects have completed all study procedures (including the final study visit 30 days after the W26 endoscopy) as specified in the SOE (Appendix A). The primary reason for completion of study will be recorded in the eCRF.

9.6 Discontinuation of Treatment with Study Drug

Study drug must be permanently discontinued for subjects meeting any of the criteria presented below. The primary reason for discontinuation from treatment with study drug or withdrawal of the subject from the study should be recorded in the eCRF using the following categories. For screen failure subjects, refer to Section 9.2.2.

1. Recurrence of CD that requires immunosuppressive or immunomodulating therapy per assessment by investigator.
2. The subject has experienced a pretreatment event or AE that requires ET because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the pretreatment event or AE. In addition, dosing for any individual

subject will be discontinued if the subject experiences an AE Grade ≥3 (based on CTCAE criteria Version 5.0) that is considered related to study drug treatment by the investigator or sponsor. Dosing for any individual subject will also be discontinued if the subject experiences an AE that warrants discontinuation from further dosing, as determined by the investigator, for that subject's well being. Subjects who prematurely discontinue study drug will complete all study procedures for ET as specified in the SOE (Appendix A).

3. Subjects with treatment-emergent ALT elevations should be evaluated to determine whether study drug should be continued, interrupted, or discontinued. See Appendix D.
4. Significant protocol deviation. The discovery post-randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
5. Pregnancy. The subject is found to be pregnant and must be withdrawn immediately. The procedure is described in Section 10.2.3.5.
6. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
7. Voluntary withdrawal by subject. The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).
8. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.

Once study drug has been prematurely discontinued, all study procedures outlined for the ET visit will be completed as specified in the SOE (Appendix A).

Those subjects who discontinue study drug before completing the full treatment course are allowed to remain in the study for posttreatment assessments and procedures as outlined in the SOE (Appendix A) if no alternate therapy is started. If alternate therapy is started for recurrence of CD, subjects will complete an ET visit 30 days after the last dose of study drug and no further study procedures will be completed.

9.7 Withdrawal of Subjects from Study

The investigator may discontinue a subject's study participation at any time during the study. A subject may be withdrawn from the study for any of the following reasons:

- Lost to follow-up.
- Study (or study arm) terminated by sponsor.
- Voluntary withdrawal by subject.

The consequence of study withdrawal is that no new information will be collected from the withdrawn subject and added to the existing data or any database after the end of treatment/ET visit 30 days after last dose is completed.

Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator.

9.8 Study Compliance

Study drug will be administered or dispensed only to eligible subjects under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

Subjects will receive a sufficient quantity of study drug for each treatment period and a diary in which to record their dosing. The study staff will check the subject's diary versus the subject's supply of remaining study drug at each study visit to ensure proper compliance with dosing. The site's pill count will be used to determine compliance and this data entered in the EDC. Subjects who are not compliant with the dosing schedule may be withdrawn from the study, following assessment of the noncompliance by the PI and/or the sponsor. The PI should review cases with <80% dosing compliance at any given visit to assess for significance as well as if, in the PI's opinion, there is a high likelihood that the subject will remain noncompliant.

9.9 Posttreatment Follow-up Assessments

Follow-up will begin the first day after the last dose of study drug and after completion of the W26 endoscopy and will continue through 30 days after the W26 endoscopy, concluding at the final study visit at W30. Subjects who discontinue before their W26 endoscopy will be followed for 30 days after their last dose of study drug.

9.10 Final Visit or ET

The last study visit occurs 30 days after the last dose of study drug for all subjects. For subjects who complete study treatment, the final visit occurs at W30, 30 days after the W26 endoscopy. The investigator must complete the end of study eCRF.

9.11 Post Study Care

Study drug is administered for a defined period during the study and will not be supplied by the sponsor after the subject has completed the study. The subject should return to the care of a physician and standard therapies as required.

9.12 Biological Sample Retention and Destruction

In this study, [redacted] may be preserved and retained for long-term storage for up to but not longer than 15 years or as required by local applicable law. The sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

All samples collected during the study will be stored securely with limited access and the sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

When subjects request disposal of a stored sample during the retention period, the site will notify the storage facility to destroy the sample according to the procedure specified in the laboratory manual. The facility will destroy the sample in accordance with the procedure and notify the site and sponsor.

Subjects who consented and provided such samples can withdraw their consent and request disposal of stored samples at any time. The sponsor should be notified of consent withdrawal.

10.0 ADVERSE EVENTS

10.1 Definitions

An AE (nonserious and serious) is any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study. The event does not necessarily have to have a causal relationship with the drug. An AE can be any unfavorable and unintended sign or symptom, or disease temporally associated with the use of the drug, whether or not it is considered related to the investigational product.

AE (Nonserious and Serious) Guidelines

AEs include	AEs do not include
• Worsening of a pre-existing illness or condition. • An increase in frequency or intensity of a pre-existing episodic event or condition. • Continuous persistent disease or symptoms present at baseline that worsen following the administration of study drug. • Complications from elective surgery or procedures. • Signs or symptoms associated with an overdose.	• Pre-existing disease or conditions present before treatment that do not worsen. • The disease being treated or associated symptoms or signs unless more severe than the subject's baseline condition. • Preplanned or elective surgery or procedures. • Medical or surgical procedures - the condition that leads to the procedure is the AE.

AE: adverse event.

10.1.1 SAEs

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

1. Results in death.
2. Is life threatening. The term “life threatening” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
4. Results in persistent or significant disability/incapacity.
5. Is a congenital anomaly/birth defect.

6. Is an important medical event.

Medical and scientific judgement should be exercised in deciding whether an event is an important medical event. An important medical event may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These events should be considered serious.

The events in Takeda Medically Significant AE List (Table 10.a) are considered important medical events that should be handled as serious.

Table 10.a Takeda Medically Significant AE List by System Organ Class

Blood and lymphatic system disorders	**Pregnancy, puerperium, and perinatal conditions**
Agranulocytosis	Spontaneous abortion
Aplastic anaemia	Stillbirth and fetal death
Cardiac disorders	**Renal and urinary disorders**
Torsade de pointes	Acute renal failure
Ventricular fibrillation	**Respiratory, thoracic, and mediastinal disorders**
Ventricular tachycardia	Acute respiratory distress syndrome
Hepatobiliary disorders	Acute respiratory failure
Acute liver failure	Pulmonary fibrosis
Hepatic necrosis	Pulmonary hypertension
Immune system disorders	**Skin and subcutaneous tissue disorders**
Anaphylactic shock	Stevens-Johnson syndrome
Infections and infestations	Toxic epidermal necrolysis
Confirmed or suspected endotoxin shock	**Vascular disorders**
Confirmed or suspected transmission of infectious agent by a medicinal product	Malignant hypertension
COVID-19 pneumonia	
COVID-19–related disease	
Nervous system disorders	
Convulsive seizure	
Malignant hyperthermia	
Neuroleptic malignant syndrome	

AE: adverse event; COVID-19: coronavirus disease 2019.
Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

10.1.2 Overdose

An overdose is a known deliberate or accidental administration of study drug, either to or by a study subject, at a dose above that assigned to that individual subject.

10.2 AE Procedures

10.2.1 Assigning Severity of AEs

All AEs, including clinically significant treatment-emergent laboratory abnormalities, will be graded according to National Cancer Institute CTCAE, Version 5.0. Grade descriptions are:

Grade 1 Mild: asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Fatal AE: an event that results in the death of the subject.

Refer to the full version of the CTCAE V 5.0 grading when evaluating the severity of AEs.

10.2.2 Assigning Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which a causal relationship is at least a reasonable possibility (ie, the relationship between drug administration cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible).
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

10.2.3 Collection and Reporting of AEs, SAEs, Overdose, and Abnormal Liver Test Results

10.2.3.1 Collection Period

Collection of AEs (ie, AEs and SAEs) will commence at the time the subject signs the informed consent and will continue until 30 weeks after the first dose of study drug or until screen failure. A final study visit will be conducted at W30, 30 days after the W26 endoscopy, for final study

assessments. For subjects who discontinue before administration of study medication, AEs will be followed until the subject discontinues study participation. For subjects who discontinue study drug treatment or ET, collection of AEs/SAEs will continue for 30 days after their last dose of study drug or last study visit, including defined follow-up visits.

10.2.3.2 Reporting SAEs

Regardless of causality, SAEs must be reported by the investigator to the Takeda medical monitor and the Global Patient Safety Evaluation department or designee within 24 hours of becoming aware of the event. Reporting to the Global Patient Safety Evaluation department or designee will be done by transmitting an EDC SAE report. If transmission of an EDC SAE report is not feasible within 24 hours of receiving the event, then a facsimile (fax) of the completed Takeda paper-based SAE form should be submitted to the fax number provided below. A sample of the paper-based SAE form and processing directions are in the study manual.

SAE Reporting Contact Information		
Fax numbers:	**United States and Canada** +1-224-554-1052	**Rest of World** +1-224-554-1052
Email address:	PVSafetyAmericas@tpna.com	eupv@tgrd.com

In case of fax, site personnel need to confirm successful transmission of all pages and include an email address on the cover sheet so that an acknowledgment of receipt can be returned via email within 1 business day.

Email submission of SAE forms with a PDF attachment should only be used in the case where fax is not possible and EDC is not feasible within 24 hours of receiving the event. In case of email, site personnel need to confirm successful transmission by awaiting an acknowledgment of the receipt via email within 1 business day.

If SAEs are reported via fax or by email, EDC must be updated as soon as possible with the appropriate information. Information in the SAE report or form must be consistent with the data provided on the eCRF.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

SAE Follow-up

If information not available at the time of the first report becomes available at a later date, then the investigator will transmit a follow-up EDC SAE report (or a paper-based SAE form if an EDC SAE report is not feasible) or provide other documentation immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.2.3.3 Reporting Overdose

Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on eCRF(s). SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.3.2.

10.2.3.4 Reporting of Abnormal Liver Test Results and Other Laboratory Test Abnormalities

For any subject with ALT ≥3× ULN ***AND*** total bilirubin >2× ULN ***OR*** INR >1.5× ULN for which an alternative etiology has not been found, report the event as an SAE, contact the sponsor's medical monitor within 24 hours, and follow the additional monitoring, evaluation, and follow-up recommendations in Appendix D.

Other Grade 3 or 4 laboratory abnormalities (per CTCAE Version 5) should be assessed for clinical significance by the investigator or qualified subinvestigator. Clinically significant laboratory abnormalities should be confirmed by repeat testing and the medical monitor should be contacted.

10.2.3.5 Reporting Pregnancy

If any subject is found to be pregnant within 40 days of the last dose of study drug, she should be withdrawn from the study. In addition, any pregnancies in the partner of a male subject during the study or within 100 days after the last dose (whichever comes later) should also be recorded following authorization from the subject's partner.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to placebo need not be followed.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the female subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received (blinded or unblinded, as applicable).

All pregnancies, including female partners of male subjects, in subjects on active study drug will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

10.3 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions and any other applicable SAEs to regulatory authorities, including the EMA, investigators and

IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, suspected unexpected serious adverse reactions will be submitted to the regulatory authorities as expedited reports within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor supplied drug administration or in the overall conduct of the study. The study site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with local regulations.

11.0 STUDY-SPECIFIC COMMITTEES

An external data and safety monitoring committee is not being considered for this study as the MOA of the investigational TAK-018 is locally acting on gut microbiota and does not suppress or interact with a subject's immune response. Safety data will be monitored continuously throughout the study. Study level stopping criteria are outlined in Section 6.3.1.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. If selected for coding, AEs, medical history, and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject who signs an ICF.

The sponsor or its designee will supply study investigative sites with access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, CRO partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Any change, modification, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, contact information of the person making the correction, the date the correction was made, and the reason for change.

The PI must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the PI must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by sponsor monitors. The sponsor (or designee) will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the ID log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copies of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and the sponsor (or designees). Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the study site agreement between the investigator and sponsor.

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A SAP will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

13.1.1 Analysis Sets

The following analysis sets will be used:

- Full analysis set (FAS) will include all subjects who are randomized and received at least 1 dose of study drug. Subjects in this set will be analyzed by the treatment arm to which the subjects were randomized.

- Safety analysis set will include all randomized subjects who receive at least 1 dose of study drug. Subjects in this set will be analyzed according to the treatment received.
- Response-evaluable set will include all randomized subjects who received at least 1 dose of study drug and who underwent endoscopy at W26.
- PK analysis set: Subjects from the safety analysis set with at least 1 reported PK concentration.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Baseline and demographic information will be listed and summarized by treatment arm and overall using the full analysis set. For continuous variables, the summary will consist of descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum). For categorical variables, the summary will consist of percentage of subjects in each category.

Medical history and concurrent medical conditions will be summarized by system organ class and preferred term. Medication history and concomitant medications will be summarized by preferred term and therapeutic class.

13.1.3 Efficacy Analysis

All efficacy endpoints will be analyzed using the FAS.

Primary efficacy analysis: The primary endpoint of proportion of subjects with endoscopic recurrence of CD at W26 in each of the two TAK-018 dose arms will be compared to the corresponding proportion in the placebo arm using the Cochran-Mantel-Haenszel (CMH) test using the randomization stratification factor (smoking status). In the case of small cell sizes (<5), the Fisher's exact test will be used instead of the CMH test. The point estimates for the treatment difference (TAK-018 – placebo) for each dose, along with the associated 80% and 95% CIs will be presented. When data necessary in the determination of the primary endpoint is missing, it will be handled using nonresponder imputation, eg, a subject will be classified as a nonresponder at W26 if no endoscopy was performed. In addition, sensitivity analysis will be performed for the primary efficacy analysis using the response-evaluable set.

The secondary efficacy endpoint of percentage of subjects with FCP >135µg/g will be summarized descriptively by treatment arm for each time point.

Continuous longitudinal efficacy endpoints will be analyzed using a mixed-effect model repeated measures (MMRM) model to compare each dose of the TAK-018 arms to the placebo arm. Continuous endpoints measured at a single time-point will be analyzed using an ANCOVA model. Binary endpoints will be analyzed using the methodology used for the primary efficacy endpoint.

Further details will be provided in the SAP.

13.1.4 PK Analysis

Measured plasma concentrations of TAK-018 by time will be summarized descriptively using the PK set. Individual plasma concentration data versus time will be presented in a data listing. Further

analysis may be performed as deemed necessary for the interpretation of the data and will not be reported in the clinical study report. These analyses will be part of a separate report.

13.1.5 [redacted]

[redacted]

13.1.6 [redacted]

[redacted]

13.1.7 Safety Analysis

Safety analysis will be performed using the safety analysis set. No statistical inference will be made for safety analyses.

The percentage of subjects with TEAEs and/or SAEs that occur on or after the first dose date and during the follow-up period 30 days after the last dose date of the study drug will be summarized by MedDRA System Organ Class and Preferred Term, by severity, and by relationship to study drug for each treatment arm.

Change from baseline in clinical laboratory tests and vital signs will be summarized descriptively by treatment arm. Subjects with markedly abnormal values for laboratory tests and vital signs will be summarized and listed.

13.2 Interim Analysis

No interim analysis is planned.

13.3 Determination of Sample Size

This study is planned to randomize approximately 96 subjects stratified by smoking status (active smoker vs nonsmoker/previous smoker) in a 1:1:1 ratio to each of 3 treatment arms (approximately 32 subjects per arm).

Assuming the true recurrence rate in the placebo arm to be 50% [40,46], a total of 81 subjects will provide at least 75% power to detect a 25% or larger difference in recurrence rates between treatment and placebo arms for a 2-sided chi-squared test at a 0.2 level of significance. To account for an assumed dropout rate of 15%, approximately 96 subjects will be randomized in this study.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or sponsor's designee (as long as blinding is not jeopardized), including but not limited to the investigator's binder, study drug, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated, it will be reported to regulatory authorities as a serious breach of GCP and the protocol.

The investigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the United States [US] FDA and the United Kingdom [UK] Medicines and Healthcare products Regulatory Agency [MHRA]). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the responsibilities of the investigator that are listed in Appendix G. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state, federal, and/ local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the investigator's brochure (IB), a copy of the ICF, and, if applicable, subject recruitment materials and advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study, ie, before shipment of the sponsor-supplied drug or study-specific activity. The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. If required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. The sponsor will ship drug/notify site once the sponsor has confirmed the

adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the study. Until the site receives drug/notification, no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor (or designee).

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, and the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and, if applicable, the subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC.

The subject must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether to participate in the study. If the subject determines he or she will participate in the study, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject at the time of consent and before the subject enters into the study. The subject should be instructed to sign using their legal names, not nicknames, using a ballpoint pen with either blue or black ink. The investigator must also sign and date the ICF and subject authorization (if applicable)

at the time of consent and before the subject enters into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICFs must be reviewed and signed by relevant subjects in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

Subjects who consented and provided a pharmacogenomic sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Investigators will notify sponsor of consent withdrawal.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will be linked to the sponsor's clinical study database or documentation only via an unique ID number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique ID number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, US FDA, UK MHRA), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain identifying personal information removed, eg, subject name, address, and other identifier fields not collected on the subject's eCRF.

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public

disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the clinical study site agreement. In the event of any discrepancy between the protocol and the clinical study site agreement, the clinical study site agreement will prevail.

15.4.2 Clinical Trial Registration

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda policy/standards. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

As needed, Takeda and investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Takeda may assist participants or potential participants in finding a clinical trial by helping them locate trial sites closest to their homes by providing the investigator name, address, and phone number via email/phone or other methods preferred by callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to the sponsor providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov, clinicaltrialsregister.eu for studies conducted in the European Union, and other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda policy/standards, applicable laws, and/or regulations.

Data Sharing

The sponsor is committed to responsible sharing of clinical data with the goal of advancing medical science and improving subject care. Qualified independent researchers will be permitted to use data collected from subjects during the study to conduct additional scientific research, which may be unrelated to the study drug or the subject's disease. The data provided to external researchers will not include information that identifies subjects personally.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the clinical study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Events

Study Period	Screening [a]		Study Visits [b]							ET [h]
	Part 1 [c]	Part 2	W0 [d,e]	W3 [e,f]	W6 [e]	W12 [e]	W18 [e]	W26 [e,g]	W30 [e,g]	
			D1	D21 ±7d	D42 ±7d	D84 ±7d	D126 ±7d	D182 ±7d	D212 ±7d	
Informed consent	X									
Inclusion/Exclusion criteria	X		X							
Randomization [d]			X							
Demographics/Medical /Surgical history	X									
Complete PE [f]	X			X						
Targeted PE [i]			X		X	X	X	X	X	X
Vital signs [j]	X		X	X	X	X	X	X	X	X
ECG [k]	X			X		X		X	X	X
Concomitant medications and procedures	Recorded from the signing of the ICF through a maximum of 30 weeks after the first dose of study drug.									
AE reporting	AEs are recorded from signing of the ICF for a maximum of 30 weeks after the first dose of study drug. [g, h]									
Laboratory Assessments										
HIV, Hepatitis B/C [l]	X									
FSH / Pregnancy test [m]	X		X	X	X	X	X	X	X	X
Hematology/Chemistry [n]	X		X	X	X	X	X	X	X	X
Liver tests [n]	X		X	X	X	X	X	X	X	X
INR	X		X	X	X	X	X	X	X	X
Urinalysis [o]	X		X	X	X	X	X	X	X	X
Resected tissue [c]		X								
Other Samples/Assessments										

Study Period	Screening [a]		Study Visits [b]							ET [h]
	Part 1 [c]	Part 2	W0 [d,e]	W3 [e,f]	W6 [e]	W12 [e]	W18 [e]	W26 [e,g]	W30 [e,g]	
			D1	D21 ±7d	D42 ±7d	D84 ±7d	D126 ±7d	D182 ±7d	D212 ±7d	
Plasma PK collection: continuous PK [p]			X	X						
Plasma PK: sparse PK [p]			X	X	X	X	X	X		
Blood sample for RNA [q]	X			X				X		X
[redacted]										
Stool sample for fecal calprotectin [q]	X			X	X	X	X	X	X	X
[redacted]										
Ileocolonoscopy [redacted]								X		
[redacted]										
Study drug distribution and compliance check [u]			X	X	X	X	X	X		X

AE: adverse event; COVID-2019: coronavirus disease 2019; D: day; ECG: electrocardiogram; eCRF: electronic case report form; ET: early termination; FSH: follicle stimulating hormone; HHC: home health care; ICF: informed consent form; IEC: independent ethics committee; INR: international normalized ratio; IRB: institutional review board; PE: physical examination; PK: pharmacokinetics; [redacted]; W: week.

[a] Part 1 of screening visit must occur before the subject's planned laparoscopic ileocecal resection (Part 2). The ICF must be signed before protocol-specified procedures are conducted. Unless otherwise noted, the screening visit must occur within 30 days before randomization (W0/D1). The ICF may be signed >30 days before D1.

[b] Visits should be performed on the scheduled day (as shown) but are allowed ±7 days as indicated for each visit.

[c] All screening procedures for Part 1 screening must be completed before a subject's planned surgical procedure occurs. The surgical procedure includes a planned laparoscopic ileocecal resection with primary anastomosis. The ileocecal resection is an entry criterion that is not considered a study-related procedure and should be completed per an institution's standard of care. Refer to the study manual for details on collection, processing, storage, and shipment of the resected sample.

[d] Randomization will be stratified by smoking status (Section 9.3.2) and occurs on D1 within 72 hours after surgery. Other than PK sampling (refer to Appendix B), study procedures on D1 should be conducted predose.

Study Period	Screening [a]		Study Visits [b]							ET [h]
	Part 1 [c]	Part 2	W0 [d,e]	W3 [e,f]	W6 [e]	W12 [e]	W18 [e]	W26 [e,g]	W30 [e,g]	
			D1	D21 ±7d	D42 ±7d	D84 ±7d	D126 ±7d	D182 ±7d	D212 ±7d	

[e] Study visits on D1 and W26 are clinic visits; study visits at W3, W6, W12, W18, and W30 may be conducted as clinic or HHC visits.

[f] The W3 visit includes a complete PE. A complete PE will include examination of general appearance, skin, head, eyes, ears, nose, throat, neck, lungs, abdomen (including liver and spleen), lymph nodes, extremities, cardiovascular system, genitourinary system, musculoskeletal system, neurological system, and weight; height will be measured only during screening. HHC visits related to COVID-19 or other similar pandemic may be performed by qualified health care professionals.

[g] All subjects will have a final study follow-up visit 30 days after their last dose of study drug. For subjects who complete study treatment, the final study visit will occur at W30, 30 days after the W26 endoscopy for final study assessments.

[h] Subjects who terminate study early will have a final follow-up visit 30 days after their last dose of study drug. This will include a targeted PE (see footnote i), vital signs, and chemistry/hematology/liver tests.

[i] A targeted PE will include examination of lungs, abdomen, skin, and cardiovascular system. Body weight measurement should also be collected.

[j] Vital sign measurements include blood pressure, heart rate, oxygen saturation, respiration rate, and body temperature. On clinic visit days, vital sign measurements should be performed before study drug is taken.

[k] Standard 12-lead ECG.

[l] Immunodeficiency and hepatitis virus testing are required to be performed only at the screening visit, unless satisfactory documentation of negative results of all such tests within 30 days of randomization are available.

[m] Pregnancy testing will be performed as follows or as otherwise required by local regulations. A serum choriogonadotropin beta pregnancy test will be performed only for subjects of childbearing potential during screening. A urine choriogonadotropin beta pregnancy test will be performed only for subjects of childbearing potential predose on scheduled study visits at D1, W3, W6, W12, W18, W26, and W30. The results must be negative before subsequent study drug is distributed. Additional pregnancy testing may be performed during the study at the discretion of the investigator, upon request of an IEC/IRB, or if required by local regulations. For postmenopausal subjects, FSH screening will be performed and if below 40 IU/L, the need for adequate contraception (Section 9.3.17) should be confirmed before study drug is distributed.

[n] Blood samples should be collected on study visit days (D1 predose, and at W3, W6, W12, W18, and W26) and at W30 and at ET. Refer to the laboratory manual for details on collection, processing, storage, and shipment of these samples.

[o] Urine samples should be collected on study visit days (D1 predose, and at W3, W6, W12, W18, and W26) and at W30 and at ET. Urinalysis is performed centrally and includes dipstick for blood, protein, pH, specific gravity, ketones, bilirubin, nitrite, urobilinogen, leukocytes and glucose (microscopic examination, if abnormal).

[p] Blood samples for PK analysis will be collected as shown in Appendix B. Refer to the laboratory manual for details on collection, processing, storage, and shipment of plasma PK samples.

[q] Refer to the laboratory manual for details on collection, processing, storage, and shipment of these samples.

[redacted]

Study Period	Screening [a]		Study Visits [b]							ET [h]
	Part 1 [c]	Part 2	W0 [d,e]	W3 [e,f]	W6 [e]	W12 [e]	W18 [e]	W26 [e,g]	W30 [e,g]	
			D1	D21 ±7d	D42 ±7d	D84 ±7d	D126 ±7d	D182 ±7d	D212 ±7d	

[redacted]

[u] Study drug dosing compliance will be recorded in the subject eCRF. W26 consists of a compliance check only; study drug treatment ends at W26.

Appendix B Schedule of PK Samples

Study Time (Week/Day):	**Week 0 / Day 1**		**Week 3 / Day 21**		**Week 6 / Day 42**	**Week 12 / Day 84**	**Week 18**	**Week 26**
Sampling time (hr) [a]:	PK subgroup	Others	PK subgroup	Others	All	All	All	All
Predose	X [b]	X [c]	X [b]	X [d]	X [c]	X [c]	X [c]	X [e]
1	X		X					
2	X		X					
3	X		X					
4	X		X					
6	X		X					
8	X [f]		X [f]					
12	X [f]		X [f]					

PK: pharmacokinetics.

Approximately one-third of subjects will participate in the PK subgroup. The actual date and time of the sample collection and the date and time for the last dose on the day before the collection day and for the first dose on the collection day should be accurately recorded in the electronic data capture. In addition to the scheduled PK sample collections, blood samples to measure TAK-018 plasma concentrations may be obtained during the on-treatment period and within 30 days after the last dose of study treatment, if clinically feasible, at the time of an adverse event that is judged by the investigator to be treatment-related. The unscheduled PK collections will be left to the discretion of the investigator.

[a] PK sampling times are relative to the most recent dose (in hours).

[b] PK samples on Day 1 and Week 3 collected 30 minutes predose.

[c] One blood sample collected at beginning of study visit and another blood sample collected at the end of the study visit. These 2 collections should be made at least 30 minutes apart.

[d] One blood sample collected predose and another blood sample collected between 2 to 4 hours postdose.

[e] One blood sample collected before endoscopy on Week 26.

[f] Blood samples for PK should be collected at these times; however, these samples are optional.

Appendix C Rutgeerts Grading Scale for Endoscopic Recurrence at the Ileocolonic Anastomosis and Preanastomotic Ileum

Rutgeerts Score	Endoscopic Description of Lesions
i0	No lesions.
i1	≤5 aphthous ulcers.
i2	>5 aphthous ulcers with normal mucosa between lesions or lesions are confined to the anastomosis.
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa.
i4	Diffuse inflammation with larger ulcers, nodules, and/or narrowing.

Source: Adapted from Rutgeerts P, Geboes K, Vantrappen G, et al. Predictability of the postoperative course of Crohn's disease. Gastroenterology. 1990;99(4):956-63.

Appendix D Guidance on Liver Test Abnormality Monitoring, Evaluation, and Follow-up

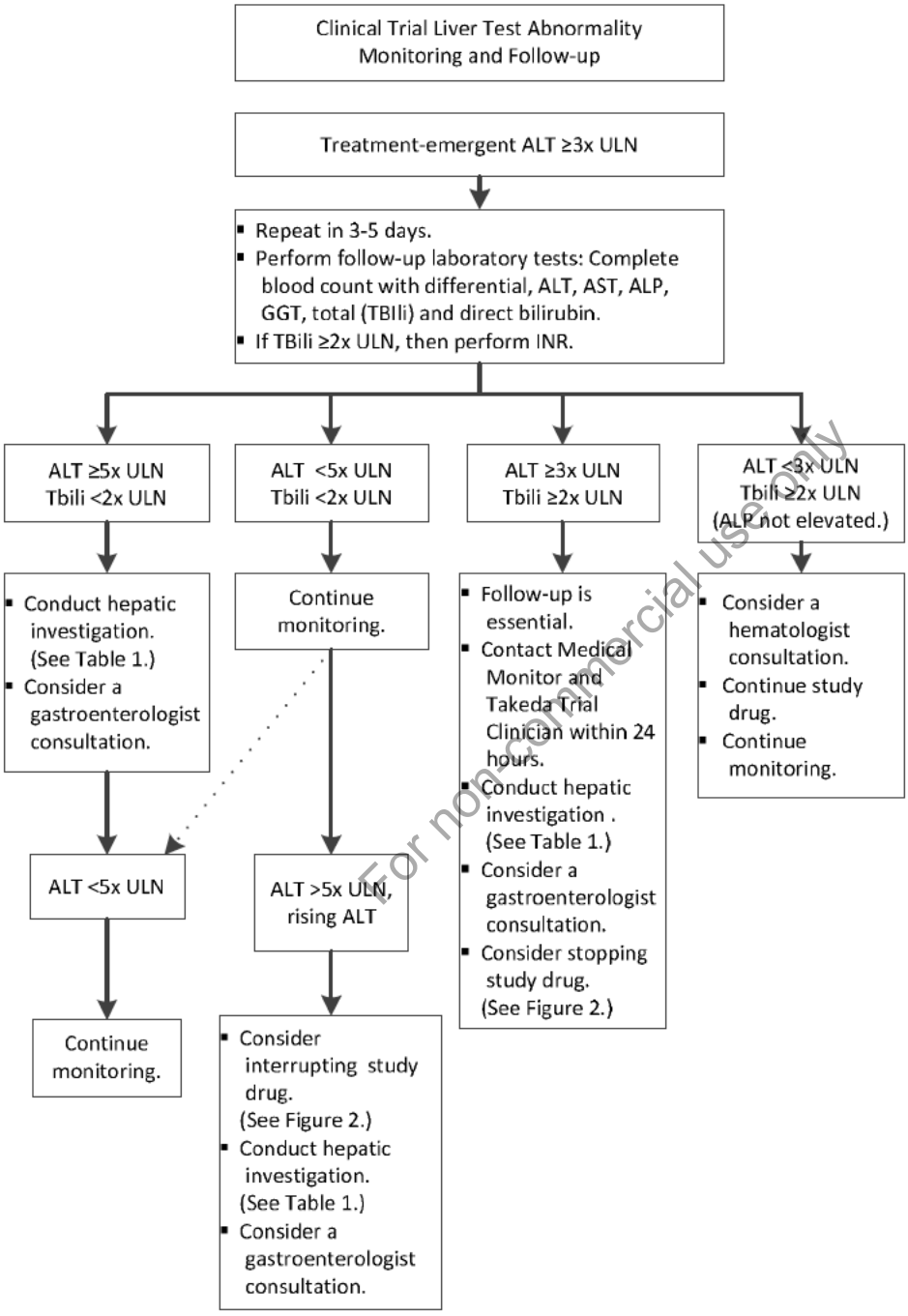
Investigators must be vigilant for abnormal liver test results in subjects during the clinical study. Transient fluctuations in serum aminotransferases occur commonly in clinical study subjects, but it is crucial that the investigator identifies and evaluates subjects with possible hepatic injury. This guidance is intended to aid investigations of abnormal liver tests in clinical study subjects who had no known liver disease and had either normal or near normal baseline liver tests (ie, ALT <2× ULN, total bilirubin <1.5× ULN, and ALP <1.5× ULN) at the time of enrollment.

In evaluating study subjects with abnormal liver test results, the investigator should perform follow-up laboratory tests to confirm the abnormal test results and monitor the subject. If the abnormal liver test results are confirmed, then the subject should be monitored and, if necessary, additional diagnostic tests should be performed as shown in Appendix D Figure 1. Suggested hepatic investigations are listed in Appendix D Table 1. Criteria for considering discontinuation of study drug are shown in Appendix D Figure 2.

Subjects with combined elevations in aminotransferase and bilirubin

If a subject has elevated ALT ≥3× ULN with concurrent elevated total bilirubin >2× ULN or elevated INR >1.5, the investigator must contact the sponsor's medical monitor within 24 hours. Hepatic investigations as suggested in Table 1 should be initiated. Any event of elevated ALT ≥3× ULN with concurrent elevated total bilirubin >2× ULN ***or*** elevated INR >1.5 for which an alternative etiology has not been identified must be reported as an SAE.

Appendix D Figure 1: Liver Test Abnormality Monitoring and Follow-up

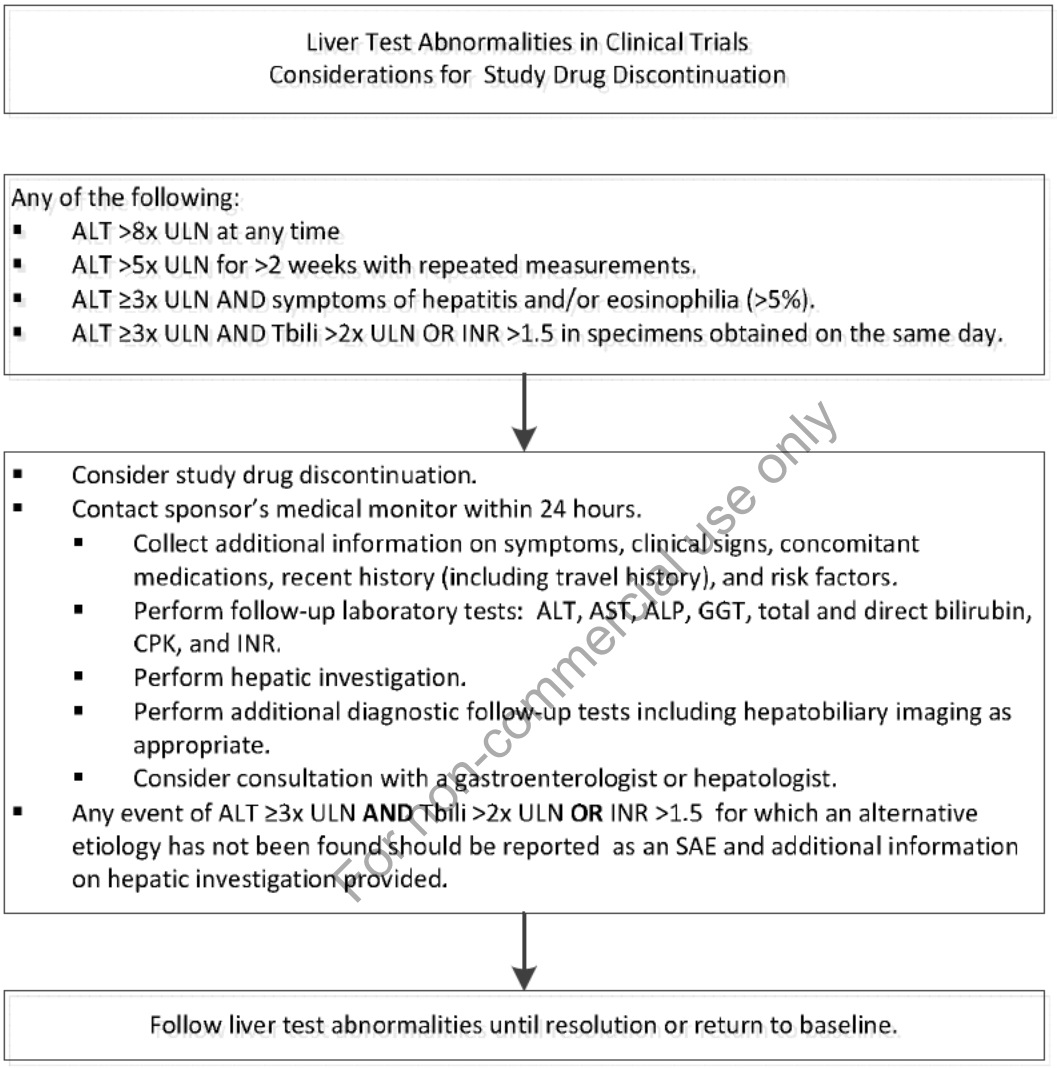


ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; INR, international normalized ratio; Tbili, total bilirubin; ULN, upper limit of normal.

Appendix D Table 1: Hepatic Investigation

Characteristic	Recommended Considerations
Medical history	• Concomitant medications (including over-the-counter medications such as acetaminophen, and herbal supplements) • Medical conditions (eg, ischemia, hypotension, severe hypoxemia, congestive heart failure, sepsis) • Alcohol intake • Hepatobiliary disorder • Previous liver disease or metabolic syndrome (eg, obesity, insulin resistance, diabetes, or dyslipidemia) • Travel history
Physical examination (symptoms, signs, and laboratory results)	• General malaise, fatigue, nausea, or vomiting • Right upper quadrant pain or tenderness, fever, jaundice, rash • Eosinophilia >5%
Hepatic/hepatobiliary imaging	Perform as appropriate (eg, abdominal ultrasound, computed tomography, magnetic resonance imaging, or other hepatobiliary imaging)
Viral hepatitis serology	• Hepatitis A antibody (total and IgM) • Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (anti-HBsAb)), Hepatitis B core antibody (IgM anti-HBc), Hepatitis C antibodies (anti-HCV) • Hepatitis E (IgG and IgM) • Consider PCR for Hepatitis B, C, and E • Consider Epstein-Barr virus serology (viral capsid antigen [VCA] nuclear antigen [EBNA], early antigen [EA]) • Consider cytomegalovirus serology (IgG and IgM)
Autoimmune hepatitis serology	• Anti-nuclear antibody (ANA) • Anti-smooth muscle antibody (ASMA) • Anti-liver-kidney-microsomal antibody (anti-LKM)

Appendix D Figure 2: Considerations for Study Drug Discontinuation for Liver Test Abnormalities



Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; GGT, gamma glutamyl transferase; INR, international normalized ratio; Tbili, total bilirubin.

Appendix E [redacted]

[redacted]

[redacted]

Appendix F [redacted]

[redacted]

Appendix G Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (non routine/non standard panel) screening assessments are NOT performed on potential subjects, before the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix H Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written ICF, the subject is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue

participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the ICF or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from screening throughout the duration of the study, and for a minimum of 40 days after last dose. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study, and for a minimum of 100 days after last dose. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical study information from this study will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix I Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the UK, US, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study drug.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix J Protocol History

Date	Amendment Number	Amendment Type	Region
08 October 2021	Amendment 05	Substantial	Global
30 July 2020	Amendment 04	Substantial	Global
14 January 2020	Amendment 03	Substantial	Global
05 December 2019	Amendment 02	Nonsubstantial	France
02 July 2019	Amendment 01	Substantial	Global
01 March 2019	Initial Protocol	Not applicable	Global

Rationale for Amendment 04

This document describes the changes in reference to the protocol incorporating Amendment 04. The primary reason for this amendment is to maintain subject safety, confidentiality, and study integrity in the context of health care delivery challenges presented by the coronavirus disease (COVID-19) pandemic. Amendment 04 provides flexibility to study participants to opt for home health care (HHC) solutions as permitted by local regulations. This "hybrid study design" will offer study participants the option of in clinic or HHC for study visits. Assessments after surgery and endoscopy at Week 26 are conducted at the clinic. All other study visits may be conducted by telehealth and HHC.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Changes in Amendment 04:

Protocol Amendment 04			
Summary of Changes Compared With TAK-018-2001 Amendment 03			
Description of Each Change and Rationale			***Section(s) Affected by Change***
Description		***Rationale***	
1	Specification that the surgical procedure is a prerequisite for enrollment to the study.	To clarify that surgery is not considered a study procedure.	Section 2.0 STUDY SUMMARY Section 6.1 Overview of Study Design
2	Reference to *study* visits to enable distinction between clinic (onsite) and home health care (HHC) visits.	To provide flexibility to subjects as related to a pandemic (eg, coronavirus disease [COVID-19]) or other future similar unexpected public health concerns requiring physical distancing resulting in subjects missing their visits.	Section 2.0 STUDY SUMMARY Section 4.3 Benefit/Risk Profile Section 6.1 Overview of Study Design Section 9.5 Completion of Study Section 9.10 Final Visit or ET Section 9.3.6 Vital Signs Section 9.3.8.1 [redacted] Section 9.3.8.2 [redacted] Section 10.2.3.1 Collection Period Appendix A Schedule of Events footnotes g, m, n, o, s

Protocol Amendment 04			
Summary of Changes Compared With TAK-018-2001 Amendment 03			
Description of Each Change and Rationale			
Description		***Rationale***	***Section(s) Affected by Change***
3	Specification of clinic visits on Day 1 (D1) and Week 26 (W26) and that study visits at screening and on W3, W6, W12, W18, and W30 may be conducted as clinic or HHC visits.	To provide flexibility to subjects as related to a pandemic (eg, COVID-19) or other future similar unexpected public health concerns requiring physical distancing resulting in subjects missing their visits.	Section 2.0 STUDY SUMMARY Section 6.1 Overview of Study Design and Figure 6.a Section 9.3.17 Contraception and Pregnancy Avoidance Procedure Appendix A Schedule of Events footnote e
4	Clarification regarding study drug administration related to changes in study procedures related to the pandemic.	To provide clarity when study drug should be taken relative to blood collections on given study visits and as related to a pandemic (eg, COVID-19) or other future similar unexpected public health concerns requiring physical distancing resulting in subjects missing their visits.	Section 8.1 Study Drug Administration
5	Clarification regarding physical examination (PE) during HHC visits.	To provide an alternative approach for PE at HHC visits related to a pandemic (eg, COVID-19) or other future similar unexpected public health concerns requiring physical distancing resulting in subjects missing their visits.	Section 9.3.4 Physical Examination Appendix A Schedule of Events footnote f
6	Clarification regarding where pharmacokinetic (PK) sample collection times are recorded.	To identify that PK sample collection times are recorded in the electronic data capture.	Section 9.3.14 PK Sample Collection Appendix B Schedule of PK Samples
7	Addition of information regarding changes to study procedures due to the pandemic.	To provide flexibility to subjects as related to a pandemic (eg, COVID-19) or other future similar unexpected public health concerns requiring physical distancing resulting in subjects missing their visits.	Section 9.3.16 Changes to Study Procedures Due to a Pandemic Appendix A Schedule of Events
8	Clarification regarding posttreatment follow-up assessments for subjects who complete the study and for those who discontinue early.	To provide clarity concerning the timing of the posttreatment follow-up assessment for all subjects.	Section 9.9 Posttreatment Follow-up Assessments
9	Addition of COVID-19–related terms to the Takeda Medically Significant Adverse Event list.	To be consistent with health authority guidance as related to the COVID-19 pandemic.	Section 10.1.1 SAEs Table 10.a
10	Correction that the safety	To correct a previous error	Section 13.1.7 Safety Analysis

Protocol Amendment 04			
Summary of Changes Compared With TAK-018-2001 Amendment 03			
Description of Each Change and Rationale			
Description		***Rationale***	***Section(s) Affected by Change***
	assessment does not include electrocardiogram changes from baseline.	regarding the planned statistical safety analyses.	
11	Changes in Appendix A	To provide clarity and flexibility regarding study procedures.	Appendix A Schedule of Events
12	Changes in Appendix D	To align with changes made by the internal Takeda liver subject matter expert guidance and to insert a clearer presentation of Figure 1.	Appendix D Guidance on Liver Test Abnormality Monitoring, Evaluation, and Follow-up

Rationale for Amendment 03

This document describes the changes in reference to the protocol incorporating Amendment 03.

The primary reason for this amendment is to change the protocol design from a safety/proof of mechanism study to an early proof of concept study. The original study design presented in Amendment 01 was limited by 3-month toxicology coverage, an inadequate dosing interval to assess the efficacy of TAK-018 in prevention of endoscopic recurrence. The recent availability of favorable long-term toxicology enables a 6-month dosing interval that also aligns with standard of care colonoscopy performed by treating physicians 6-months after surgery. Based on the longer treatment period, Protocol Amendment 03 contains additional changes to the study design that include a change in the primary endpoint to assess efficacy, identification of a safety objective distinct from efficacy objectives, clarifications to the secondary [redacted] endpoints, and changes in the statistical considerations that include an increase in the number of subjects and deletion of the interim analysis. Other changes in Protocol Amendment 03 are made to respond to US and European health authorities and ethics committees requests for information regarding Study TAK-018-2001, including the addition of the composition of study drug and placebo tablets. Updates have also been made to clarify logistical and operational aspects of the study.

In addition, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

For specific description of text changes and where the changes are located, see Appendix J.

Changes in Amendment 03:

1. Addition of results from the chronic toxicity studies in dogs and rats.
2. Updated information for the phase 1b Study EBFIM117.
3. Changes to the primary, safety, secondary, and exploratory objectives.

4. Change of the primary endpoint and clarification of the safety, secondary, [redacted] endpoints.
5. Updates and clarifications to the overall study design based on the longer duration of treatment that include the addition of a stratification factor at randomization, changes to sample size, and addition of a W30 clinic visit.
6. Updated the schematic of the TAK-018-2001 study design.
7. Extended the duration of study based on favorable long-term toxicology studies in dogs and rats.
8. Clarifications to the criteria for premature termination or suspension of the study.
9. Corrections to the inclusion criteria.
10. Clarifications of the exclusion criteria.
11. Clarification regarding study drug administration.
12. Addition of the composition of study treatment tablets and their storage.
13. Clarification regarding management of liver test abnormalities.
14. Clarifications to rescreening subjects.
15. Addition of stratification of subjects by smoking status during randomization.
16. [redacted]
17. Updated the time period for collection of concomitant medications and procedures.
18. Updated pregnancy testing requirements for longer treatment duration.
19. Clarifications to liver testing in Table 9.a.
20. Changed the timing of ileocoloscopy [redacted].
21. Clarification to the collection of unscheduled pharmacokinetic (PK) samples.
22. [redacted].
23. Clarification of completion of study.
24. Clarification regarding subject replacement.
25. Clarification of posttreatment follow-up assessments.
26. Clarification of the final visit.
27. Clarification of the grades of Common Terminology Criteria for Adverse Events, Version 5 (CTCAE V 5.0) used to assign severity of adverse events.
28. Addition of information regarding SAE reporting.
29. Clarification regarding study-specific committees.

30. Corrections to the statistical analyses sections.
31. Updates to Appendix A, Schedule of Events (and footnotes), to align with changes in the text.
32. Corrections and clarifications made to Appendix C.

Rationale for Amendment 02

This document describes the changes in reference to the protocol incorporating Amendment 02.

The primary reason for this amendment is to include revisions in response to feedback on the protocol from the French *Comité de Protection des Personnes (CPP)*, central ethics committee. A summary of the changes incorporated in this amendment is outlined below and detailed in Appendix J.

In addition, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

For specific description of text changes and where the changes are located, see Appendix J.

Changes in Amendment 02:

1. Clarification of the primary endpoint.
2. Clarification of the duration of the study.
3. Clarification of the exclusion criteria.

Rationale for Amendment 01

This document describes the changes in reference to the protocol incorporating Amendment 01.

The primary reason for this amendment is to include study stoppage criteria based on Common Terminology Criteria for Adverse Events (CTCAE) grading, inclusion of details relating to subject discontinuation, early termination, and to replace adverse event (AE) assessment terminology with the CTCAE, Version 5 scale. These revisions are being incorporated in response to feedback on the protocol from the United States (US) Food and Drug Administration (FDA). Updates have also been made to clarify logistical and operational aspects of the study.

In addition, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

For specific description of text changes and where the changes are located, see Appendix J.

Changes in Amendment 01:

1. Update to include descriptive information on nonclinical findings relating to rat specific renal tubular degeneration to align with the investigator brochure (IB).
2. Update to clarify when study drug should be taken in relation to meal consumption and clarification regarding when treatment will start.
3. Update that subjects who terminate early from the study will have a final visit 30 days after their last dose of study drug.

4. Inclusion of stopping criteria for the study and for individual subjects based on CTCAE grading.
5. Update to include surgeon's documentation that laparoscopic ileocecal resection removed active disease.
6. Clarification to the use of concomitant medications: those excluded postoperatively and prior to study treatment, and those permitted for subject safety and well-being.
7. Clarification that information regarding the interactive response technology system (IRT) is found in the pharmacy and IRT manuals.
8. Inclusion of rescreening criteria.
9. Clarification that height will be measured during screening.
[redacted].
11. Clarification that local laboratory results should be entered into the electronic data capture (EDC).
12. Inclusion of urinalysis assessment as part of study procedures.
13. Clarification to accurately record dosing before PK sample collections.
14. Clarification of the purpose of RNA samples.
15. Inclusion of details on compliance measurement in case of a discrepancy.
16. Replacement of AE intensity terminology with the CTCAE Version 5 scale.
17. Clarification regarding the internal monitoring committee.
18. Clarification to the statistical analyses conducted for efficacy, [redacted], interim analysis, and determination of sample size.
19. Updates to Appendix A, Schedule of Events, to align with clarifications within the text, [redacted].