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Protocol for Study M20-371

Moderate to Severe Crohn's Disease: A Phase 2 Safety and Efficacy Study of ABBV-154

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FULL TITLE: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of ABBV-154 in Subjects with Moderately to Severely Active Crohn's Disease (CD): AIM-CD

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1 SYNOPSIS

Title: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of ABBV-154 in Subjects with Moderately to Severely Active Crohn's Disease (CD): AIM-CD	
Background and Rationale:	ABBV-154 is an antibody-drug conjugate (ADC) composed of adalimumab (the active component of Humira®) conjugated to phosphorylated A-1677770, a proprietary glucocorticoid receptor modulator (GRM, also referred to as the GRM payload), which is being developed for the treatment of immune-mediated inflammatory diseases. ABBV-154 has the potential to deliver an anti-inflammatory payload to activated immune cells that express transmembrane tumor necrosis factor and minimize systemic exposure to the free GRM payload. Therefore, ABBV-154 is a promising novel therapeutic agent which may achieve transformational efficacy while reducing side effects caused by systemic glucocorticoid exposure.
Objective(s) and Endpoint(s):	Primary Objective: To assess the efficacy, safety, and tolerability of ABBV-154 in comparison with placebo in subjects with moderately to severely active CD who had inadequate response to or were intolerant of prior biologics. Secondary Objectives: To assess the pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of ABBV-154. Primary Endpoint: Achievement of endoscopic response at Week 12 in the Induction Period defined as a decrease in Simple Endoscopic Score for Crohn's Disease (SES-CD) > 50% from Baseline (or for subjects with isolated ileal disease and a Baseline SES-CD of 4, at least a 2-point reduction from Baseline). Secondary Endpoints: Achievement of the following: • Clinical remission per Crohn's Disease Activity Index (CDAI) at Week 12 in the Induction Period defined as a CDAI < 150. • Clinical remission per average daily liquid or very soft stool frequency (SF) and average daily abdominal pain (AP) score (SF/AP) at Week 12 in the Induction Period defined as average daily liquid or very soft SF ≤ 2.8 and not worse than Baseline AND average daily AP score ≤ 1 and not worse than Baseline. • Endoscopic response per SES-CD at Week 40 in the Maintenance Period. • Clinical remission per CDAI at Week 40 in the Maintenance Period. • Clinical remission per SF/AP at Week 40 in the Maintenance Period. All endoscopic endpoints will be scored by a central reviewer.
Investigator(s):	Multicenter
Study Site(s):	Approximately 200 sites, globally.

Study Population and Number of Subjects to be Enrolled:	265 adults with moderately to severely active CD who had inadequate response to or were intolerant of prior biologics
Investigational Plan:	This is a randomized, double-blind, placebo-controlled Phase 2b study to assess the safety, tolerability, PK, PD, immunogenicity, and efficacy of ABBV-154 in subjects with moderately to severely active CD who had inadequate response to or were intolerant of prior biologics. The enrollment for subjects with prior adalimumab use is capped at approximately 30% of the total enrolled subjects. The study comprises 3 periods: a 12-Week Double-Blind Placebo-Controlled Induction Period, a 12-Week Double-Blind Re-Induction Period (for subjects who are considered as clinical non-responders and endoscopic non-responders), and a 40-Week Double-Blind Placebo-Controlled Maintenance Period. At the Baseline Visit of the Induction Period, approximately 265 subjects will be randomized in a 1:1:1:1:1 ratio into 4 ABBV-154 treatment groups or placebo: 1. Induction Group 1: Loading dose of 150 mg intravenously (IV) at Week 0, followed by 80 mg subcutaneous (SC) at Week 2 and every other week (EOW); 2. Induction Group 2: Loading dose of 300 mg IV at Week 0, followed by 230 mg SC at Week 2 and EOW; 3. Induction Group 3: Loading dose of 600 mg IV at Week 0, followed by 530 mg SC at Week 2 and EOW; 4. Induction Group 4: Loading dose of 600 mg IV at Week 0, followed by 530 mg SC at Week 4 and 8 and placebo at Weeks 2, 6, and 10; and 5. Induction Group 5: Matching placebo (IV and SC). At Week 12 of the Induction Period, subjects achieving clinical response, defined as a decrease in CDAI ≥ 100 points from Baseline (CR100) of the Induction Period AND/OR endoscopic response (per local read) will receive treatment in the 40-Week Maintenance Period as follows: 1. Induction Group 1: Re-randomized in a 1:1 ratio to receive ABBV-154 80 mg SC EOW or matching placebo; 2. Induction Groups 2 to 4: Re-randomized in a 1:1:1 ratio to receive ABBV-154 80 mg SC EOW, ABBV-154 230 mg SC EOW, or matching placebo; 3. Induction Group 5: ABBV-154 80 mg SC EOW At Week 12 of the Induction Period, subjects who are categorized as clinical non-responders and endoscopic non-responders (per local read) will be re-randomized into the Re-Induction Period. Subjects who demonstrate inadequate response at or after Week 8 in the Induction Period may receive Rescue Therapy with oral glucocorticoids (per protocol). Subjects who receive Rescue Therapy, fail to complete glucocorticoid tapering by Week 6, or increase doses of or initiate treatment with aminosalicylates or immunomodulators in the Induction Period will be

	considered non-responders, regardless of clinical response or endoscopic response (per local read) at Week 12 and will be re-randomized in a 1:1 ratio into 2 ABBV-154 treatment groups in the 12-Week Re-Induction Period as follows: 1. Re-Induction Group 1: Loading dose of 300 mg IV at Week 0, followed by 230 mg SC at Week 2 and EOW; 2. Re-Induction Group 2: Loading dose of 600 mg IV at Week 0, followed by 530 mg SC at Week 2 and EOW. Subjects who achieve clinical response AND/OR endoscopic response (per local read) at Week 12 of the Re-Induction Period will be re-randomized into the Maintenance Period as described above for subjects achieving clinical response AND/OR endoscopic response (per local read) at Week 12 of the Induction Period. Subjects who do not achieve either clinical response or endoscopic response (per local read) after the Re-Induction Period will be discontinued and will have a follow-up visit scheduled 70 days after last study drug administration. To determine endoscopic response status for re-randomization into the Maintenance Period, the SES-CD score per local read at Week 12 of the Induction/Re-Induction Period and the SES-CD score per central read at Baseline will be used. In the case of missing data where either clinical response or endoscopic response cannot be determined, subjects will be considered non-responders for the re-randomization criteria evaluation. Subjects who have an inadequate response at or after Week 4 in the Maintenance Period will be eligible to receive Rescue Therapy with a single dose of ABBV-154 600 mg IV followed by ABBV-154 230 mg SC EOW. Subjects who have received rescue therapy with ABBV-154 for at least 4 weeks and who continue to demonstrate inadequate response may receive additional Rescue Therapy with oral glucocorticoids, aminosalicylates, or immunomodulators. The primary analysis for the Induction Period and Re-Induction Period will be performed after all subjects have either completed Week 12 of the Induction Period and Re-Induction Period, respectively, or prematurely discontinued study participation. The final analysis will be conducted after all subjects have either completed Week 40 of the Maintenance Period plus the follow-up visit or prematurely discontinued study participation. To ensure the integrity of the trial, the study sites and subjects will remain blinded until the final database lock is completed. The Wearable Device Substudy will enroll up to approximately 75 subjects in countries and sites where the digital health technology device is deployed and available. For subjects participating in the substudy, data for sleep parameters, daily physical activity, and SF data will be collected continuously throughout the 12-Week Induction Period.

Key Eligibility Criteria:	Male or female between 18 and 75 years of age inclusive at the time of Screening. Confirmed diagnosis of CD for at least 3 months prior to Baseline of the Induction Period. CDAI score 220 to 450 at Baseline of the Induction Period. Endoscopic evidence of mucosal inflammation as documented by an SES-CD of ≥ 6 for ileocolonic or colonic disease or SES-CD of ≥ 4 for isolated ileal disease as scored by a central reader. All eligible scores must exclude the presence of narrowing component. Demonstrated intolerance or inadequate response to one or more of the following biologic agents: infliximab, adalimumab, certolizumab pegol, vedolizumab, natalizumab, ustekinumab, or risankizumab. Subjects with prior intolerance to adalimumab are not eligible to enroll.
Study Drug and Duration of Treatment:	Screening up to 35 days (minimum of 8 days). Overall maximum individual treatment duration is planned for up to 448 days (~64 weeks) with the following: • Double-Blind Induction Period for 12 weeks with placebo or ABBV-154: Induction Group 1) loading dose of 150 mg IV at Week 0, followed by 80 mg SC at Week 2 and EOW; Induction Group 2) loading dose of 300 mg IV at Week 0, followed by 230 mg SC at Week 2 and EOW; Induction Group 3) loading dose of 600 mg IV at Week 0, followed by 530 mg SC at Week 2 and EOW; Induction Group 4) loading dose of 600 mg IV at Week 0, followed by 530 mg SC at Weeks 4 and 8, and placebo at Weeks 2, 6, and 10; and Induction Group 5) matching placebo. • Double-Blind Re-Induction Period for 12 weeks in subjects who are considered as clinical non-responders and endoscopic non-responders at Week 12 of the Induction Period: Re-Induction Group 1) ABBV-154 300 mg IV at Week 0 of the Re-Induction Period, followed by 230 mg SC at Week 2 and EOW or Re-Induction Group 2) ABBV-154 600 mg IV at Week 0 of the Re-Induction Period, followed by 530 mg SC at Week 2 and EOW; • Double-Blind Maintenance Period for 40 weeks with placebo or ABBV-154 80 mg SC EOW or 230 mg SC EOW; Follow-up Period of 70 days after last study drug administration.
Date of Protocol Synopsis:	20 December 2022

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted?

There are a number of anti-inflammatory biologic therapies available to treat patients with Crohn's disease (CD), including infliximab, adalimumab, certolizumab pegol, vedolizumab, natalizumab, and ustekinumab. In particular, the efficacy and safety of anti-tumor necrosis factor (anti-TNF) monoclonal antibodies, including adalimumab, in CD is well established.[1,2,3] Adalimumab demonstrated superior efficacy for inducing and maintaining clinical remission compared to placebo in moderate to severe CD patients who failed conventional therapies and infliximab.[4,5] However, while the available biologic treatments have provided therapeutic options for CD patients, there remain high treatment failure rates associated with existing agents.[6] Patients with CD treated with anti-TNF agents do not respond at rates of 10% to 40% to initial treatment (primary nonresponse) and additional subjects are observed to lose response over time (secondary loss of response).[7] Similar patterns of primary nonresponse and secondary loss of response have been observed with other classes of anti-inflammatory biologics used to treat CD.[8,9] Despite the availability of multiple advanced therapies for the treatment of CD patients, the overall burden of surgery remains high in this population at 3.8 intestinal resections per 100 person-years. Therefore, a large unmet need remains for the treatment of CD.[10]

Glucocorticoids have been shown to be efficacious for inducing clinical remission in CD. While nontargeted glucocorticoids with systemic exposure and limited systemic exposure have not been shown to be effective for maintenance treatment,[11] approximately 25% of CD patients are glucocorticoid-dependent receiving chronic or recurrent systemic glucocorticoids.[12,13,14,15] However, the administration of glucocorticoids is limited due to their long-term side effect profile including (but not limited to) hypothalamic-pituitary-adrenal axis (HPA) suppression, osteoporosis, hyperglycemia, glaucoma, and skin atrophy.[16] Thus, the full efficacy of glucocorticoid therapy is often limited with existing agents due to systemic side effects.

ABBV-154 is an anti-TNF antibody-drug conjugate (ADC) composed of adalimumab (the active component of Humira®) conjugated to phosphorylated A-1677770, a proprietary glucocorticoid receptor modulator (GRM, also referred to as the GRM payload) via an [redacted] linker. Binding of the adalimumab portion of the ABBV-154 ADC to activated immune cells that express transmembrane TNF is intended to deliver the anti-inflammatory payload intracellularly. The monoclonal antibody portion of the ADC provides targeted delivery of the GRM payload to minimize systemic exposure to the free GRM payload. Therefore, ABBV-154 is a promising novel therapeutic agent which may achieve transformational efficacy while reducing side effects caused by systemic glucocorticoid exposure.

This is a dose-ranging study to explore the efficacy and safety of ABBV-154 in subjects with moderately to severely active CD who continue to have unmet medical need, and to inform subsequent clinical studies in the indication.

2.2 Benefits and Risks to Subjects

The clinical efficacy of TNF inhibitors and glucocorticoids in the treatment of CD is well established. By utilizing expression of transmembrane TNF on activated immune cells, ABBV-154 has the potential to deliver an anti-inflammatory payload intracellularly, while minimizing systemic exposure to the free GRM payload. Based on the data discussed in the ABBV-154 Investigator's Brochure, ABBV-154 is expected to demonstrate a positive benefit-risk profile for the treatment of CD.

Medical review of the safety data from the Phase 1, single ascending dose study did not identify any unexpected risk or trend in the healthy volunteer population (including Japanese and Chinese subjects). For further details, please see the ABBV-154 Investigator's Brochure.

In clinical settings, TNF antagonists and glucocorticoids have been associated with increased risk for serious infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens. Subjects with a recent history of these events will be excluded from the study. Other known adverse events (AE) for glucocorticoids include hypertension, hypothalamic pituitary-adrenal axis (HPA) suppression, decreased bone-formation, diabetes, glaucoma, and cataracts. Signs of infection, blood pressure changes, blood glucose levels, HPA axis suppression, and bone mineral density will be closely monitored during the study.

TNF antagonists have also been associated with an increased risk for serious allergic reactions, including anaphylaxis; infusion reactions; malignancy (including nonmelanoma skin cancer [NMSC], lymphoma, and leukemia); worsening or new onset heart failure; and rarely hepatitis B virus (HBV) reactivation, central nervous system events, demyelinating disease, pancytopenia (including aplastic anemia), and lupus-like syndrome. Subjects with a history of these events, other than successfully treated NMSC or localized carcinoma in situ of the cervix, will be excluded from the study. Signs and symptoms of these events will be closely monitored.

The safety profile specific to the adalimumab component of ABBV-154 is well-established for marketed doses. In addition, adalimumab has been studied at doses up to 10 mg/kg intravenously (IV), which is higher than the doses planned in this study, with a safety profile consistent to Humira® product labeling. Potential risks will be minimized through the selection of appropriate study subjects defined by the eligibility criteria and subject safety will be monitored by an unblinded independent data monitoring committee (DMC) and regular blinded review of safety data by the study team (see Section 5.10). In addition, guidance for toxicity management and stopping rules are provided to ensure subject safety (see Section 6.2).

Based on the totality of the data, ABBV-154 is expected to demonstrate therapeutic benefit in the treatment of CD with a positive benefit-risk profile for development in the treatment of this disease.

In view of the coronavirus pandemic 2019 (COVID-19), the benefit-risk profile of various immunomodulatory therapies on COVID-19 are being evaluated. Currently, the effects of ABBV-154 on the course of COVID-19 are not well defined. Guidance regarding severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination is provided for investigators in Section 5.4.

The safety and effectiveness of the device component (non-investigational device) for use as described in labeling has been demonstrated through literature review, pre-clinical, and clinical data as

appropriate, and the device is certified, cleared, approved, or registered for marketing. The benefits of the device in use, as labeled and as planned for this clinical study, have been demonstrated to outweigh the residual risks.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

Primary

The primary objective of the study is to assess the efficacy, safety, and tolerability of ABBV-154 in comparison with placebo in subjects with moderately to severely active CD who had inadequate response to or were intolerant of prior biologics.

- Primary Efficacy Objective: The primary efficacy objective of the study is to demonstrate a higher rate of endoscopic response after 12 weeks of treatment with ABBV-154 when compared to placebo in subjects with moderately to severely active CD who had inadequate response to or were intolerant of prior biologics.

The hypothesis corresponding to the primary efficacy objective is the proportion of subjects achieving endoscopic response with ABBV-154 is greater than that with placebo at Week 12. The estimand for the primary endpoint is defined as the difference in the proportion of subjects that achieve endoscopic response at Week 12 without use of concomitant medication that could confound the efficacy (see Section 7.3) and regardless of premature discontinuation of study drug, in each of the ABBV-154 dose groups compared with the placebo group in subjects with moderately to severely active CD who had inadequate response to or were intolerant of prior biologics.

- Secondary Efficacy Objectives: The secondary efficacy objectives of the study are to demonstrate greater efficacy with ABBV-154 treatment when compared with placebo treatment with respect to the secondary endpoints specified in Section 3.3, in subjects with moderately to severely active CD who had inadequate response to or were intolerant of prior biologics.
- The estimands corresponding to the secondary efficacy endpoints are as follows:
  - For endpoints in the Induction Period: The difference in the proportion of subjects that achieve a response without use of concomitant medication that could confound the efficacy (see Section 7.3) and regardless of premature discontinuation of study drug, in each of the ABBV-154 dose groups compared with the placebo group in subjects with moderately to severely active CD who had inadequate response to or were intolerant of prior biologics.
  - For endpoints in the Maintenance Period: The difference in the proportion of subjects that achieve a response without use of concomitant medication that could confound the efficacy (see Section 7.3) and regardless of premature discontinuation of study drug, in each of the ABBV-154 dose groups compared with the placebo group in subjects with moderately to severely active CD who had inadequate response to or were intolerant of prior biologics and achieved response after the 12-week induction treatment with ABBV-154.

Secondary Objectives

The secondary objectives are to assess the pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of ABBV-154.

3.2 Primary Endpoint

The primary endpoint is the achievement of endoscopic response at Week 12 in the Induction Period defined as a decrease in Simple Endoscopic Score for Crohn's Disease (SES-CD[17]) > 50% from Baseline (or for subjects with isolated ileal disease and a Baseline SES-CD of 4, at least a 2-point reduction from Baseline).

3.3 Secondary Endpoint(s)

Secondary Endpoint(s)

- Achievement of clinical remission per Crohn's Disease Activity Index (CDAI) at Week 12 in the Induction Period defined as CDAI < 150.
- Achievement of clinical remission per average daily liquid or very soft stool frequency (SF) and average daily abdominal pain (AP) score (SF/AP) at Week 12 in the Induction Period defined as average daily liquid or very soft SF ≤ 2.8 and not worse than Baseline AND average daily AP score ≤ 1 and not worse than Baseline.
- Achievement of endoscopic response per SES-CD at Week 40 in the Maintenance Period.
- Achievement of clinical remission per CDAI at Week 40 in the Maintenance Period.
- Achievement of clinical remission per SF/AP at Week 40 in the Maintenance Period.

3.4 Additional Efficacy Endpoints

In the Induction/Re-Induction/Maintenance Periods, the additional endpoints below will be analyzed at timepoints specified in the schedule of events table of the protocol (in this section, "Baseline" refers to the Baseline [Week 0, Day 1] of the Induction Period):

- Achievement of clinical remission per CDAI.
- Achievement of clinical remission per SF/AP.
- Achievement of clinical response defined as a decrease of CDAI ≥ 100 points from Baseline (CR100).
- Achievement of clinical response per SF/AP defined as ≥ 30% decrease in average daily liquid or very soft SF and/or ≥ 30% decrease in average daily AP score and both not worse than Baseline.
- Achievement of enhanced clinical response per SF/AP defined as ≥ 60% decrease in average daily liquid or very soft SF and/or ≥ 35% decrease in average daily AP score and both not worse than Baseline, and/or clinical remission per SF/AP.

- Achievement of endoscopic remission defined as SES-CD ≤ 4 and at least a 2-point reduction versus Baseline and no subscore > 1 in any individual variable.
- Change from Baseline in Inflammatory Bowel Disease Questionnaire (IBDQ[18,19]) total score.
- Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F[20]).
- Change from Baseline in the Bowel Incontinence Scale.
- Change from Baseline in CDAI.
- Change from Baseline in individual IBDQ domain scores (bowel, emotional, social, systemic).
- Change from Baseline in individual IBDQ items under Bowel Symptom domain (for Q1, Q5, Q9, Q13, Q17, Q20, Q22, Q24, Q26, and Q29).
- Achievement of IBDQ remission defined as IBDQ ≥ 170 points.
- Achievement of IBDQ response defined as increase in IBDQ ≥ 16 points from Baseline.
- Change from Baseline in 36-Item Short Form Health Survey (SF-36[21,22]).
- Change from Baseline in fecal calprotectin (FCP).
- Change from Baseline in high-sensitivity C-Reactive Protein (hs-CRP).
- Change from Baseline in average daily AP score.
- Change from Baseline in average daily liquid or very soft SF.
- Change from Baseline in SES-CD.
- Achievement of SES-CD ulcerated surface subscore ≤ 1 in each segment in subjects with a SES-CD ulcerated surface subscore ≥ 2 at Baseline.
- Achievement of ulcer-free endoscopy: SES-CD ulcerated surface subscore of 0 in subjects with SES-CD ulcerated surface subscore ≥ 1 at Baseline.
- Change from Baseline in daily physical activity for subjects participating in the Wearable Device Substudy.
- Change from Baseline in sleep parameters for subjects participating in the Wearable Device Substudy.
- Change from Baseline in stool frequency, as captured from the wearable device, for subjects participating in the Wearable Device Substudy.
- Patient Global Impression of Change – Crohn's Disease+ (PGIC-CD+).
- Change from Baseline in Patient Global Impression of Severity – Crohn's Disease+ (PGIS-CD+).
- Achievement of absence of bowel urgency.
- Change from Baseline in average daily bowel urgency frequency.
- Achievement of absence of rectal bleeding.

All endoscopic endpoints will be scored by a central reviewer.

SF/AP-based efficacy endpoints will be analyzed in the subset of subjects with an average daily liquid or very soft SF score ≥ 4 and/or average daily AP score ≥ 2 at Baseline.

3.5 Safety Measures

- Treatment emergent adverse events (TEAEs), serious adverse events (SAEs), AEs leading to discontinuation of the study drug;
- Occurrence of possible glucocorticoid-related AEs;
- Potentially clinically significant laboratory, vital signs, and electrocardiogram (ECG) variables.

3.6 Pharmacokinetic Endpoints

Serum or plasma concentrations of the conjugated ADC, total antibody, free payload A-1677770 will be determined at Baseline (pre-dose) of the Induction Period and at timepoints during the treatment period as specified in the Activity Schedule (Appendix D).

Development of anti-drug antibody (ADA) to ABBV-154 will be evaluated and if confirmed positive, titers will be measured. Samples that are confirmed positive may be further characterized in a validated neutralizing antibody (nAb) assay. Immunogenicity samples will be collected at Baseline (pre-dose) of the Induction Period and at timepoints as specified in the Activity Schedule (Appendix D).

3.7 Exploratory Biomarker Research

The effect of the ADC compound on glucocorticoid-related endpoints will be assessed by blood samples and intestinal tissue biopsies collected throughout the study at timepoints as specified in the Activity Schedule (Appendix D). The biomarkers to be analyzed include, but are not limited to the following:

- Neuroendocrine biomarkers (total and free cortisol and adrenocorticotropic hormone [ACTH])
- Bone formation (osteocalcin, procollagen type 1 N-propeptide [P1NP]), and bone resorption (C-terminal telopeptide of type I [CTX-I]) biomarkers
- Biopsy tissue only - Histological, proteomic, or genomic biomarkers (may include but not limited to glucocorticoid-related genes and proteins).

Provision of these biospecimens for biomarker research is mandatory, but they will not be collected from sites where local regulations do not allow for the collection, use, and storage of samples described in the protocol.

Additional optional biospecimens (whole blood for serum, plasma, peripheral blood mononuclear cells [PBMC], RNA, and DNA) will be collected throughout the study at timepoints as specified in the Activity Schedule (Appendix D) to evaluate known and/or novel disease-related or drug-related biomarkers in circulation. Types of biomarkers may include nucleic acids, proteins, cell populations, lipids, and/or metabolites, either free or in association with particular cell types. The analyses may include but are not limited to soluble proteins, genomic transcripts, blood leukocyte populations, and genetic analysis to

evaluate biomarker endpoints related to safety, disease state, and target pathway. Results from this optional biomarker research results may not be included in the clinical study report. Further details regarding the biomarker research rationale and collection time points are provided in the Operations Manual, Appendix F, Section 3.21.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a randomized, double-blind, placebo-controlled Phase 2b study to assess the safety, tolerability, PK, PD, immunogenicity, and efficacy of ABBV-154 in subjects with moderately to severely active CD who had inadequate response to or were intolerant of prior biologics. The enrollment for subjects with prior adalimumab use is capped at approximately 30% of the total enrolled subjects. The study comprises 3 periods: a 12-Week Double-Blind Placebo-Controlled Induction Period, a 12-Week Double-Blind Re-Induction Period (for subjects considered to be clinical non-responders and endoscopic non-responders), and a 40-Week Double-Blind Placebo-Controlled Maintenance Period.

At the Baseline Visit of the Induction Period, approximately 265 subjects will be randomized in a 1:1:1:1:1 ratio into 4 ABBV-154 treatment groups or placebo:

1. Induction Group 1: Loading dose of 150 mg IV at Week 0, followed by 80 mg subcutaneous (SC) at Week 2 and every other week (EOW);
2. Induction Group 2: Loading dose of 300 mg IV at Week 0, followed by 230 mg SC at Week 2 and EOW;
3. Induction Group 3: Loading dose of 600 mg IV at Week 0, followed by 530 mg SC at Week 2 and EOW;
4. Induction Group 4: Loading dose of 600 mg IV at Week 0, followed by 530 mg SC at Weeks 4 and 8, and placebo at Weeks 2, 6, and 10; and
5. Induction Group 5: Matching placebo (IV and SC).

At Week 12 of the Induction Period, subjects achieving clinical response, defined as a decrease in CDAI ≥ 100 points from Baseline (CR100) AND/OR endoscopic response (per local read) will receive treatment in the 40-Week Maintenance Period as follows:

1. Induction Group 1: Re-randomized in a 1:1 ratio to receive ABBV-154 80 mg SC EOW or matching placebo;
2. Induction Groups 2 to 4: Re-randomized in a 1:1:1 ratio to receive ABBV-154 80 mg SC EOW, ABBV-154 230 mg SC EOW, or matching placebo;
3. Induction Group 5: ABBV-154 80 mg SC EOW.

At Week 12 of the Induction Period, subjects who are categorized as clinical non-responders and endoscopic non-responders (per local read) will be re-randomized into the Re-Induction Period.

Subjects who demonstrate inadequate response at or after Week 8 in the Induction Period may receive Rescue Therapy with oral glucocorticoids as defined in Section 5.4.

Subjects who receive Rescue Therapy, fail to complete glucocorticoid tapering by Week 6, or increase doses of or initiate treatment with aminosalicylates or immunomodulators in the Induction Period will be considered non-responders, regardless of clinical response or endoscopic response (per local read) per the definitions above at Week 12 and will be re-randomized in a 1:1 ratio into 2 ABBV-154 treatment groups in the 12-Week Re-Induction Period as follows:

1. Re-Induction Group 1: Loading dose of 300 mg IV at Week 0, followed by 230 mg SC at Week 2 and EOW;
2. Re-Induction Group 2: Loading dose of 600 mg IV at Week 0, followed by 530 mg SC at Week 2 and EOW.

Subjects who achieve clinical response AND/OR endoscopic response (per local read) at Week 12 of the Re-Induction Period will be re-randomized into the Maintenance Period as described above for subjects achieving clinical response AND/OR endoscopic response (per local read) after Week 12 of the Induction Period. Subjects who do not achieve either clinical response or endoscopic response (per local read) after the Re-Induction Period will be discontinued and will have a follow-up visit scheduled 70 days after last study drug administration.

To determine endoscopic response status for re-randomization into the Maintenance Period, the SES-CD score per local read at Week 12 of the Induction/Re-Induction Period and the SES-CD score per central read at Baseline will be used. In the case of missing data where either clinical response or endoscopic response cannot be determined, subjects will be considered non-responders for the re-randomization criteria evaluation.

Subjects who have an inadequate response at or after Week 4 in the Maintenance Period will be eligible to receive Rescue Therapy with a single dose of ABBV-154 600 mg IV followed by ABBV-154 230 mg SC EOW. Subjects who have received rescue therapy with ABBV-154 for at least 4 weeks and who continue to demonstrate inadequate response may receive additional Rescue Therapy with oral glucocorticoids, aminosalicylates, or immunomodulators. Rescue Therapy options for the Maintenance Period are further described in Section 5.4.

The last dose of study drug will be given at Week 38 of the Maintenance Period. A follow-up visit will be scheduled 70 days after the last study drug administration.

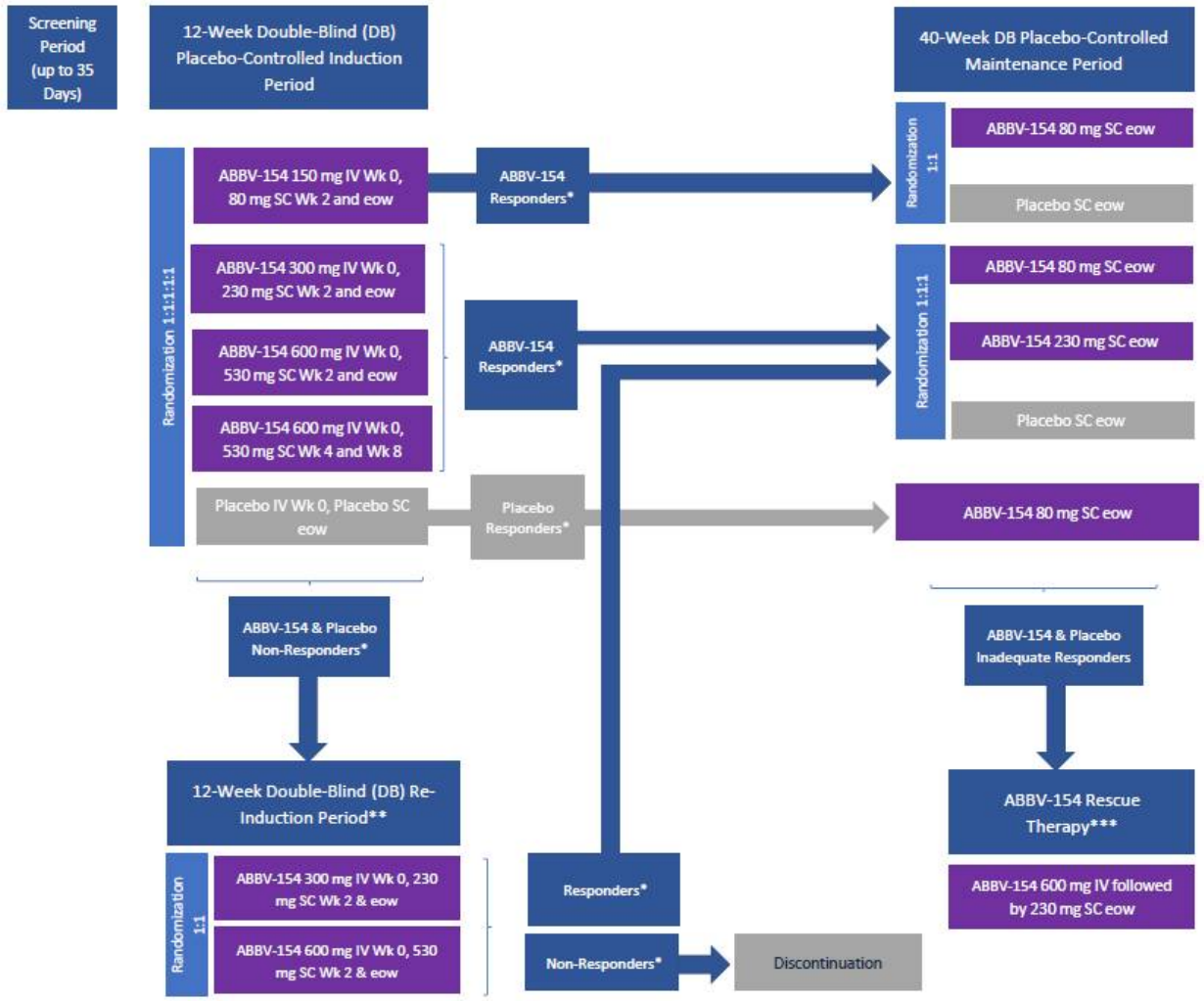
The Primary Analysis for the Induction Period and Re-Induction Period will be performed after all subjects have either completed Week 12 of the Induction Period and Re-Induction Period, respectively, or prematurely discontinued study participation. The final analysis will be conducted after all subjects have completed Week 40 of the Maintenance Period plus the 70-day Follow-up Visit or prematurely discontinued study participation. To ensure the integrity of the trial, the study sites and subjects will remain blinded until the final database lock is completed (see Section 7.1).

Interim analyses may be performed as outlined in Section 7.8.

The Wearable Device Substudy will enroll up to approximately 75 subjects in countries and sites where the digital health technology device is deployed and available. For subjects participating in the substudy, data for sleep parameters, daily physical activity, and stool frequency will be collected continuously throughout the Induction Period.

The schematic of the study is shown in Figure 1. Further details regarding study procedures are located in the Operations Manual. See Section 5.1 for information regarding eligibility criteria.

Figure 1. Study Schematic



DB = double-blind; EOW = every other week; IV = intravenous; SC = subcutaneous; Wk = week

* Responders are defined as clinical responders AND/OR endoscopic responders (per local read), and non-responders are defined as clinical non-responders AND endoscopic non-responders (per local read). Clinical responder is defined at Week 12 of the Induction Period or Re-Induction Period as a decrease in CDAI ≥ 100 points from Baseline (CR100). Endoscopic responder is defined at Week 12 of the Induction Period or Re-Induction Period as a decrease in SES-CD > 50% from Baseline (or for subjects with isolated ileal disease and a Baseline SES-CD of 4, at least a 2-point reduction from Baseline) (per local read). In the case of missing data where clinical response and endoscopic response cannot be calculated, subjects will be considered as non-responders for the re-randomization criteria evaluation.

** Only subjects who are considered to be clinical non-responders and endoscopic non-responders (per local read) at Week 12 of the Induction Period will be re-randomized into the Re-Induction Period.

*** Subjects with inadequate response at/after Week 4 of the Maintenance Period will be eligible to receive Rescue Therapy consisting of ABBV-154 600 mg IV followed by ABBV-154 230 mg SC EOW.

4.2 Discussion of Study Design

Choice of Control Group

Placebo has been selected as the appropriate control group to evaluate the primary and secondary efficacy endpoints as double-blind, placebo-controlled study designs are generally acknowledged as standard for unbiased estimates of treatment differences. There is no anticipated medical risk for subjects randomized to placebo given that subjects have already demonstrated inadequate response or intolerance to at least one of the available biologic treatment options and may receive Rescue Therapy during the Induction and Maintenance Periods if they demonstrate inadequate response as per protocol-specified criteria.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. Most efficacy and safety-related measurements in this study are standard for assessing disease activity in subjects with CD. In addition, a new wearable device for data collection and exploratory patient-reported outcome (PRO) measures will be evaluated to inform use in future clinical studies. Furthermore, possible glucocorticoid-reported related AEs will be adjudicated as specified in Section 5.11. All clinical and laboratory procedures in this study are standard and generally accepted.

Suitability of Subject Population

The mechanism of action of ABBV-154 has the potential to improve disease activity in CD subjects. While this is the first study to test ABBV-154 in CD subjects, safety results of ABBV-154 in healthy volunteers indicate no safety issues of concern and no dose limiting toxicity.

Selection of Doses in the Study

As shown in Figure 1, four 12-week ABBV-154 induction regimens, two 12-week ABBV-154 re-induction regimens, two 40-week ABBV-154 maintenance regimens, and one ABBV-154 rescue therapy regimen have been selected for evaluation in this Phase 2b dose-ranging study in subjects with CD who have had prior inadequate response to or intolerance of biologics.

All induction regimens in the study have an IV loading dose at Week 0 to enable faster achievement of steady-state levels, followed by SC doses administered EOW from Week 2 or every 4 weeks (E4W) at Week 4 and Week 8. The low induction regimen is expected to result in total antibody exposures that are comparable to the approved adalimumab CD dosing regimen, and additional efficacy is expected from the delivery of the GRM payload into activated immune cells. All selected induction regimens are adequately separated from each other with minimal overlapping exposures and cover a wide dose range to enable robust characterization of the dose/exposure-response relationship and selection of Phase 3 induction doses. The E4W regimen provides the optionality of exploring an alternate dosing frequency. The selected induction regimens are predicted to result in exposures that are similar to or lower than the maximum exposures safely tested in the ABBV-154 first-in-human study and are projected to be covered by adequate safety margins relative to no-observed-adverse-effect level exposures observed at a dose of 80 mg/kg/week SC in the 26-week Good Laboratory Practice -compliant toxicology study in cynomolgus monkeys. Projected ABBV-154 and payload safety margins for the highest induction dosing

regimen are at least 6×, based on predicted ABBV-154 human exposures and the observed toxicokinetic data in the 26-week cynomolgus monkey study.

For the Re-Induction Period, subjects will be re-randomized to the mid and high EOW induction dosing regimens to increase the chances of initial non-responders achieving clinical response AND/OR endoscopic response.

During the Maintenance Period, 2 dosing regimens of ABBV-154, 80 and 230 mg SC EOW will be evaluated which are equivalent to the EOW dose level of the low and mid doses during the Induction Period. The selected doses are expected to be sufficient to maintain response and to enable selection of Phase 3 maintenance doses.

Subjects who have an inadequate response at or after Week 4 in the Maintenance Period will be eligible to receive Rescue Therapy with a single dose of ABBV-154 600 mg IV followed by ABBV-154 230 mg SC EOW, to assess whether their response status can be recaptured.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation. (In this section, "Baseline" refers to the Baseline [Week 0, Day 1] of the Induction Period.)

Consent

- 1. Subject must be able to understand and willing to adhere to all protocol requirements and voluntarily sign and date an informed consent, approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.

Demographic and Laboratory Assessments

- 2. Adult **male or female**, at least 18 years old and not more than 75 years of age at the time of Screening.
- 3. Body Mass Index (BMI) ≥ 18.0 to ≤ 39.9 kg/m^2 after rounding to the nearest tenth at the time of Screening. BMI is calculated as weight in kg divided by the square of height measured in meters.
- 4. **Laboratory values** must meet the following criteria within the Screening Period:
  - Serum aspartate aminotransferase (AST) ≤ 2.5 × upper limit of normal (ULN);
  - Serum alanine transaminase (ALT) ≤ 2.5 × ULN;
  - Total bilirubin ≤ 1.5 × ULN;
  - Estimated glomerular filtration rate (eGFR) by simplified 4-variable Modification of Diet in Renal Disease formula ≥ 60 mL/min/1.73 m^2;

- Absolute neutrophil count (ANC) ≥ 1,500/µL;
- Absolute lymphocyte count (ALC) ≥ 800/µL;
- Platelet count ≥ 75,000/µL;
- Glycated hemoglobin (hemoglobin A1c [HbA1c] ≤ 8.5%);
- Serum potassium >3.0 mmol/L and < 5.5 mmol/L; and
- Thyroid-stimulating hormone <10.0 mIU/L.

Disease/Condition Activity

- 5. Subject must have a confirmed diagnosis of CD for at least 3 months prior to Baseline. Appropriate documentation of biopsy results consistent with the diagnosis of CD, in the assessment of the Investigator, must be available.
- 6. Subject must have a CDAI score of 220 to 450 at Baseline.
- 7. Subject must have endoscopic evidence of mucosal inflammation as documented by an SES-CD of ≥ 6 for ileocolonic or colonic disease or SES-CD of ≥ 4 for isolated ileal disease as scored by a central reader. All eligible scores must exclude the presence of narrowing component.
- 8. Subject must not have evidence of current fistulizing disease, abscess (abdominal or perianal), symptomatic bowel strictures, fulminant colitis, toxic megacolon, or any other manifestation of CD that might require surgery while enrolled in the study.
- 9. Subject must not have ostomy or ileoanal pouch.
- 10. Subject must not have a diagnosis of short gut or short bowel syndrome.
- 11. Subject must not have a history of surgical bowel resection within the past 3 months prior to Baseline, history of > 3 bowel resections due to progression of CD (note: ostomy reversal and hernia repair are not considered related to progression of CD), or > 2 missing segments of the following 5 segments: terminal ileum, right colon, transverse colon, sigmoid and left colon, and rectum.

Subject History

- 12. Subject must have demonstrated intolerance or inadequate response to one or more of the following biologic agents as defined below. Subjects who discontinued biologic agents only for reasons other than inadequate response or intolerance (e.g., change of insurance) are not eligible to enroll. Subjects with prior intolerance to adalimumab are not eligible to enroll. Where mandated by local requirements: subjects with prior exposure to adalimumab must not have evidence of anti-adalimumab antibodies prior to Baseline.
  - Demonstration of intolerance requires no minimum dose or duration of use.
  - Inadequate response defined as signs and symptoms of persistently active disease (in the opinion of the Investigator) despite a history of one or more of the following:
    - At least one 6-week induction regimen of infliximab (≥ 5 mg/kg IV at Weeks 0, 2, and 6);

- At least one 4-week induction regimen of adalimumab (one 160 mg SC dose at Week 0, followed by one 80 mg SC dose at Week 2 [or one 80 mg SC dose at Week 0, followed by one 40 mg SC dose at Week 2, in countries where this dosing regimen is approved]);
- At least one 4-week induction regimen of certolizumab pegol (400 mg SC at Weeks 0, 2, and 4);
- At least one 6-week induction regimen of vedolizumab (300 mg IV at Weeks 0, 2, and 6);
- At least one 12-week induction regimen of natalizumab (300 mg IV every 4 weeks);
- At least one 8-week induction regimen of ustekinumab (260 mg [≤ 55 kg] or 390 mg [> 55 to ≤ 85 kg] or 520 mg [> 85 kg] IV, followed by 90 mg SC at Week 8);
- At least one 8-week induction regimen of risankizumab (600 mg IV at Weeks 0, 4, and 8);
- Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit of the above biologic agents.

13. Subject must not have a current or history of infection including:
    - Chronic recurring infections(s) and/or active viral infection that, based on the investigator's clinical assessment, makes the subject an unsuitable candidate for the study;
    - Active infection(s) requiring hospitalization or treatment with parenteral anti-infectives within 30 days, or oral anti-infectives within 14 days prior to the first dose of study drug administration;
    - Active tuberculosis (TB) or meets TB exclusionary parameters (See specific requirements for TB testing and prophylaxis in the Operations Manual);
    - Positive Clostridium difficile stool assay during the Screening Period;
    - Subjects in Japan only: positive result of beta-D-glucan (screening for Pneumocystis jirovecii infection) or two consecutive indeterminate results of beta-D-glucan during the Screening period;
    - Confirmed COVID-19 infection: the Baseline visit must be at least 10 days from onset of signs/symptoms or positive SARS-CoV-2 test; symptomatic subjects must have recovered, defined as resolution of fever without use of antipyretics and improvement of symptoms;
    - Suspected COVID-19 infection: subjects with signs/symptoms suggestive of COVID-19 infection, should undergo molecular testing (e.g., polymerase chain reaction [PCR]) or have 2 negative antigen test results at least 24 hours apart to rule out SARS-CoV-2 infection or must be asymptomatic for at least 10 days without use of antipyretics.
    - Subject must not have evidence of the following:
        - Hepatitis B virus (HBV): A positive test result for hepatis B surface antigen (HBs Ag) or detectable HBV DNA PCR qualitative test for subjects who are hepatitis B core antibody (HBc Ab) positive (and for hepatitis B surface antibody [HBs Ab] positive subjects where mandated by local requirements);
        - Hepatitis C virus (HCV): A detectable HCV RNA in any subject with anti-HCV antibody (HCV Ab);

- Human Immunodeficiency virus (HIV) infection defined as confirmed positive anti-HIV antibody (HIV Ab) test.

14. Subject must not have a history of the following medical diseases or disorders:
    - Suspected or confirmed adrenal insufficiency;
    - Hypothyroidism for which the subject is not receiving physiological replacement therapy.
    - Moderate to severe congestive heart failure (New York Heart Association Class III or IV).
    - Uncontrolled hypertension defined as confirmed systolic blood pressure > 160 mm Hg or diastolic blood pressure > 100 mm Hg at rest despite regular treatment under standard of care.
    - Glaucoma, osteonecrosis, or osteoporosis with high risk of fracture (e.g., T score ≤ -2.5 with history of fragility fracture).
    - Organ transplant which requires continued immunosuppression.
    - Demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
    - Active or suspected malignancy or history of any malignancy within the last 5 years, except for successfully treated nonmelanoma skin cancer (NMSC) or localized carcinoma in situ of the cervix. Regardless of the time since remission, subjects with any history of lymphoma, leukemia, melanoma, Merkel cell carcinoma, colon carcinoma, or small bowel carcinoma.
    - History of any medical condition other than CD that is likely to require systemic glucocorticoid treatment during the study (e.g., asthma and chronic obstructive pulmonary disease [COPD]) per investigator judgement.
    - Allergic reaction or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class. This includes anaphylactic reaction to any agent (e.g., food products or bee sting), hereditary fructose intolerance, or a reaction to any immunoglobulin G (IgG) containing product.
    - Dysplasia of the gastrointestinal tract or found to have dysplasia, other than completely removed low-grade dysplastic lesions, in any biopsy performed during the Screening endoscopy.
    - Hepatic cirrhosis.
15. For subjects in the Wearable Device Substudy, subjects with history of pre-existing sleep disorders, including insomnia requiring regular sleep medication, obstructive sleep apnea, restless leg syndrome, or currently on prescription sleep medications should not participate in the Wearable Device Substudy but may participate in the study as a whole if meeting all other eligibility criteria.
16. Subject must not have a history of clinically significant (per investigator's judgment) drug or alcohol abuse within the last 12 months prior to Baseline.

- 17. There must be no reason the investigator believes that the subject is an unsuitable candidate to participate in the study, receive study drug, or would be placed at risk by participating in the study (e.g., because of a medical condition or illness other than CD that is not well controlled regardless of treatment).

Contraception

- 18. Females of childbearing potential must not have a positive serum pregnancy test at the Screening Visit and must have a negative urine pregnancy test at Baseline, prior to the first dose of study drug. Local practices may require a serum pregnancy test at Baseline. Subjects with a borderline serum pregnancy test at Screening must not have a clinical suspicion of pregnancy or other pathological cause of a borderline result and a serum pregnancy test ≥ 3 days later to document continued lack of a positive result (unless prohibited by local requirements).
- 19. Female subjects of childbearing potential must practice at least 1 protocol-specified **method of birth control**, that is highly effective from Baseline through at least 70 days after the last dose of study drug. Local practices may require 2 methods of birth control. Female subjects of non-childbearing potential do not need to use birth control. Where mandated by local requirements: Female subjects of childbearing potential must practice at least 1 protocol-specified method of birth control, that is highly effective from Study Day 1 through at least 150 days after the last dose of study drug.
- 20. Females must not be **pregnant, breastfeeding, or considering becoming pregnant** and may not donate eggs during the study or for approximately 70 days (150 days where mandated by local requirements) after the last dose of study drug.
- 21. If male, and subject is **sexually active with female partner(s) of childbearing potential**, he must agree, from Baseline through at least 70 days (150 days where mandated by local requirements) after the last dose of study drug, to practice the protocol-specified contraception.
- 22. If male, must not be considering **fathering a child or donating sperm** during the study or for approximately 70 days (150 days where mandated by local requirements) after the last dose of study drug.

Concomitant Medications

- 23. Subject must have discontinued CD-related antibiotics or be on a stable dose of CD-related antibiotics for at least 14 days prior to Baseline.
- 24. Subject must have discontinued oral aminosalicylates (e.g., balsalazide, mesalamine, olsalazine, sulfasalazine, aminosalicylate) or be on a stable dose of oral aminosalicylates for at least 14 days prior to Baseline.
- 25. Subject must have discontinued oral glucocorticoids for at least 14 days prior to Baseline OR must have been on ≤ 1 of the following oral glucocorticoids for at least 14 days prior to Baseline and on a stable dose as specified below for at least 7 days prior to Baseline:
  - Budesonide ≤ 9 mg/day;
  - Beclomethasone ≤ 5 mg/day;

- Prednisone or equivalent ≤ 20 mg/day.

If enrolling on oral glucocorticoids subject must be willing and able to follow the protocol defined prespecified glucocorticoid-tapering regimen.

26. Subject must not have been treated with any of the following:
    - Intra-articular, intramuscular, IV, trigger point or tender point, intra-bursa, or intra-tendon sheath glucocorticoid in the preceding 8 weeks prior to the first dose of the study drug; or
    - Super high potency and/or high potency topical glucocorticoids in the preceding 1 week prior to the first dose of study drug.
27. If subject is using inhaled glucocorticoids for a stable medical condition, must be at stable dose ≥ 4 weeks prior to the Baseline visit.
28. Subject on azathioprine (AZA), 6-mercaptopurine (6-MP), or methotrexate (MTX) must:
    - Be on the current course for ≥ 42 days prior to Baseline, and on a stable dose for ≥ 30 days prior to Baseline, OR
    - Have discontinued these therapies ≥ 30 days prior to Baseline.
29. Subject must not have received cyclosporine, tacrolimus, or mycophenolate mofetil within 30 days prior to Baseline.
30. Subject must have discontinued all biologic therapies used for the treatment of CD or with potential for additive immunosuppressive effect prior to the first dose of study drug. Subjects may not have prior exposure to ABBV-154. Use of biologic therapies for indications other than CD may be approved by the AbbVie TA MD on a case-by-case basis. If there is documentation of an undetectable drug level measured by a commercially available assay for any of the biologics given in eligibility criterion #12, there is a no minimum washout period prior to Baseline. The washout periods required prior to the Baseline Visit are specified below or at least 5 times the mean terminal elimination half-life for other biologic therapies:
    - ≥ 8 weeks for infliximab, adalimumab, certolizumab, vedolizumab, and natalizumab;
    - ≥ 12 weeks for ustekinumab and risankizumab.
31. Subject must not have been treated with any investigational drug within 30 days or 5 half-lives of the drug (whichever is longer) prior to Baseline and must not be currently enrolled in another interventional clinical study. The eligibility criterion applies to any drug that was investigational at the time of protocol approval regardless of regulatory approval status of the drug for the treatment of CD.
32. Subject must not have received any live vaccine with replicating potential within 28 days prior to Baseline (or longer if required locally) or be expected to need a live vaccination with any live vaccine with replicating potential during study participation including at least 70 days after the last dose of the study drug. Live vaccines that are incapable of replicating (e.g., JYNNEOS monkeypox vaccine) are permitted.

- 33. Subject must have discontinued nonsteroidal anti-inflammatory drugs (NSAIDs) with the exception of low-dose aspirin daily and selective COX-2 inhibitors at least 14 days prior to the Screening endoscopy and may not use NSAIDS other than low-dose aspirin and selective COX-2 inhibitors during the remainder of the Screening Period. Subjects entering on low-dose aspirin or selective COX-2 inhibitors must be on stable dose ≥ 1 week prior to the first dose of study drug.
- 34. Subject must not have received exclusive enteral nutrition or any parenteral nutrition within 14 days prior to Baseline.
- 35. Subject must not have received fecal microbial transplantation within 30 days prior to Baseline.
- 36. Subject must not have received therapeutic enema or suppository, other than required for endoscopy, within 14 days prior to endoscopy used for Screening or during the Screening Period.
- 37. Subject must not have received apheresis (e.g., Adacolumn apheresis) within 60 days prior to Screening or during the Screening Period.
- 38. Subject must not have been treated with oral traditional Chinese medicine within 4 weeks prior to Baseline.
- 39. Subject must have no systemic use of known strong cytochrome P450 3A (CYP3A) inhibitors from Screening through the end of study drug administration (refer to Table 1 in Section 5.3 for examples of commonly used strong CYP3A inhibitors). Subjects may not use herbal therapies or other traditional medicines with unknown effects on CYP3A from Screening through the end of study drug administration.

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified (in this section, "Baseline" refers to the Baseline [Week 0, Day 1] of the Induction Period):

- Females, Non-Childbearing Potential

  Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:

  1. Premenopausal female with permanent sterility or permanent infertility due to one of the following:
     - Permanent sterility due to a hysterectomy, bilateral salpingectomy, bilateral oophorectomy;
     - Non-surgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals.

2. Postmenopausal female
    - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
    - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level ≥ 30 IU/L.

- Females, Childbearing Potential
    - Females of childbearing potential must avoid pregnancy while taking study drug(s) and for at least 70 days (150 days where mandated by local requirements) after the last dose of study drug.
    - Females must commit to one of the following methods of birth control:
        - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation-initiated at least 30 days prior to Baseline.
        - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to Baseline.
        - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
        - Intrauterine device.
        - Intrauterine hormone-releasing system.
        - Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
        - Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

If required per local practices, male or female condom with or without spermicide OR cap, diaphragm or sponge with spermicide should be used in addition to one of the birth control methods listed above (excluding true abstinence).

Contraception recommendations related to use of concomitant therapies prescribed (e.g., MTX) should be based on the local label.

During the course of the study, female subjects may change from "of Childbearing Potential" to "of Non-Childbearing Potential" if meeting criteria outlined above under "Females, Non-Childbearing Potential." If needed to confirm post-menopausal status after the screening visit, follicle-stimulating hormone level may be obtained at any time during the study.

Contraception Requirements for Males

Male subjects who are sexually active with a female partner of childbearing potential, must agree to use male condoms, even if the male subject has undergone a successful vasectomy, from Baseline through at least 70 days (150 days where mandated by local requirements) after the last dose of study drug.

5.3 Prohibited Medications and Therapy

Subjects must be able to safely discontinue any prohibited medications as specified in Section 5.1 and Section 5.4. Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

The following medications are prohibited through the end of study drug administration:

- All biologic therapies used for the treatment of CD or with potential for additive immunosuppressive effect including but not limited to the following (including biosimilars): abatacept (Orencia®), adalimumab (Humira®), anakinra (Kineret®), belimumab (Benlysta®), certolizumab pegol (Cimzia®), etanercept (Enbrel®), golimumab (Simponi®), infliximab (Remicade®), natalizumab (Tysabri®), rituximab (Rituxan®), tocilizumab (Actemra®), ustekinumab (Stelara®), vedolizumab (Entyvio®), and risankizumab (Skyrizi®).
- Investigational agents
- All other therapies with a potential therapeutic impact on CD (except for those allowed per protocol) including but not limited to the following: Janus kinase (JAK) inhibitors such as tofacitinib, cyclosporine, tacrolimus, or mycophenolate mofetil.
- Live vaccination (see Section 5.4).
- Rectal therapy, with the exception of those required for endoscopy.
- IV, intramuscular, intra-articular, epidural, intra-bursal, intra-tendon sheath, trigger or tender point, or rectal administration of glucocorticoids;
- Super high potency and/or high potency topical glucocorticoids (see Operations Manual [Appendix F], Section 3.5). From Weeks 0 to 28 of the Maintenance Period super high potency and/or high potency topical glucocorticoids are permitted for non-CD-related adverse events.
- Corticotropin gel injection (e.g., Acthar®)
- Apheresis (e.g., adacolumn apheresis).
- Exclusive enteral nutrition or any parenteral nutrition.
- NSAIDs with the exception of low dose aspirin daily and selective COX-2 inhibitors.
- Traditional oral Chinese medicine (e.g., tripterygium glycosides, sinomenine, total glucosides of white paeony).

Strong CYP3A Inhibitors

Systemic use of known strong cytochrome P450 3A (CYP3A) inhibitors (includes over-the-counter or prescription medicines, vitamins and/or herbal supplements) is not permitted from Screening through

the end of study drug administration. Table 1 includes examples of commonly used strong CYP3A inhibitors. In addition, herbal therapies and other traditional medicines with unknown effects on CYP3A are not permitted from Screening through the end of study drug administration.

Table 1. Examples of Commonly Used Strong CYP3A Inhibitors

Strong CYP3A Inhibitors
Boceprevir
Cobicistat
Clarithromycin
Conivaptan
Grapefruit (fruit or juice)
Indinavir
Itraconazole
Ketoconazole
Lopinavir/Ritonavir
Mibefradi
Nefazodone
Nelfinavir
Posaconazole
Ritonavir
Saquinavir
Telaprevir
Telithromycin
Troleandomycin
Voriconazole

CYP3A = cytochrome P450 3A

5.4 Prior and Concomitant Therapy

Aminosalicylates, immunomodulators, CD-related antibiotics: Dose adjustment is prohibited during the Induction Period, the Re-Induction Period, and after Week 28 of the Maintenance Period except in the event of moderate-to-severe treatment-related toxicities and after discussion with the AbbVie Therapeutic Area Medical Director (TA MD) or if subject meets protocol defined rescue criteria. All subjects receiving CD-related antibiotics may discontinue treatment after the Induction Period or Re-Induction Period at the discretion of the investigator. Subjects who continue CD-related antibiotics at Week 0 of the Re-Induction Period will maintain their CD-related antibiotics and respective doses through the Re-Induction Period. CD-related antibiotics may be initiated at any time for the treatment of an AE.

Inhaled glucocorticoids: Subjects may take inhaled glucocorticoids if used for a stable medical condition and at stable dose ≥ 4 weeks prior to the Baseline Visit (Week 0, Day 1 of the Induction Period). Short-term use (≤ 14 days) of an inhaled glucocorticoid at an increased dose/frequency for treatment of an AE unrelated to CD is permissible.

Use of concomitant biologic therapies for indications other than CD (e.g., denosumab or intravitreal administration of VEGF inhibitors such as brolucizumab) may be approved by the AbbVie TA MD on a case-by-case basis.

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded from 30 days prior to study drug administration through the post-treatment visit (70-day follow-up visit).

Any questions regarding concomitant or prior therapy should be raised to the AbbVie TA MD. Information regarding potential drug interactions with ABBV-154 can be located in the ABBV-154 Investigator's Brochure.

Subjects must be able to safely discontinue any prohibited medications as specified in eligibility criteria in Section 5.1 or 5 half-lives or 4 weeks, whichever is longer, prior to initial study drug administration. Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

Vaccines

If the subject and investigator choose to receive/administer live vaccines with replicating potential, these vaccinations must be completed (per local label) at least 28 days (or longer if required locally) before first dose of study drug. Live vaccines (except non-replicating live vaccines – e.g., JYNNEOS monkeypox vaccine) are prohibited during the study and for at least 70 days after the last dose of study drug. Examples of live vaccines with replicating potential include, but are not limited to, the following:

- Monovalent live influenza A (H1N1) (intranasal);
- Seasonal trivalent live influenza (intranasal);
- Zostavax (herpes zoster, live attenuated);
- Rotavirus;
- Varicella (chicken pox);
- Measles-mumps-rubella or measles-mumps-rubella-varicella;
- Oral polio vaccine;
- Smallpox/monkeypox vaccine capable of replicating (ACAM2000®);
- Yellow fever;
- Bacille Calmette-Guérin (BCG);
- Typhoid (oral).

Administration of inactivated (non-live) vaccines is permitted prior to or during the study according to local practice guidelines. Examples of common vaccines that are inactivated, toxoid, or biosynthetic include, but are not limited to the following: injectable influenza vaccine, pneumococcal, Shingrix (zoster vaccine, recombinant, adjuvanted), and pertussis (Tdap) vaccines.

COVID-19 Pandemic-Related Vaccination Guidance

Given the ongoing COVID-19 pandemic, selected non-live vaccines (e.g., mRNA, non-replicating viral vector, protein subunit, etc.) to prevent SARS-CoV-2 infection may be administered during screening or the treatment period, as long as components of the vaccine are not contraindicated.

The decision to receive a locally available vaccine should be based on local guidance and an individual discussion between the treating physician and the subject.

The potential impact of ABBV-154 on SARS-CoV-2 vaccination is unknown. Therefore, study drug should be administered as follows:

- The first dose of study drug, when possible, is preferred to be given at least ± 7 days from the SARS-CoV-2 vaccine administration.

Note: The above guidance applies to all SARS-CoV-2 vaccine doses given as part of the complete treatment course.

These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines and as more data are collected in real-world scenarios and clinical trials.

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine electronic case report form (eCRF). Refer to the Operations Manual for instructions on reporting any AEs associated with the COVID-19 vaccine.

Rescue Concomitant Medications/Therapy

Unless qualifying for Rescue Therapy or undergoing mandatory tapering for glucocorticoids as described below, no changes may be made to oral glucocorticoids, aminosalicylates, or immunomodulators during the Induction and Re-Induction Periods, or after Week 28 of the Maintenance Period.

In the Induction Period, starting at or after the completion of the Week 8 Visit and thereafter (Week 8 through Week 12), subjects who demonstrate inadequate response as defined below may receive Rescue Therapy with oral glucocorticoids (≤ 20 mg/day prednisone or equivalent, ≤ 9 mg/day budesonide, or ≤ 5 mg/day beclomethasone). Changes in aminosalicylates, or immunomodulators are not permitted during the Induction Period.

In the Maintenance Period, starting at or after the completion of the Week 4 Visit and thereafter (Week 4 through Week 40), subjects who demonstrate inadequate response as defined below will be eligible to receive rescue therapy with a single dose of ABBV-154 600 mg IV at the respective visit, followed by ABBV-154 230 mg SC after 2 weeks and EOW thereafter.

In the Maintenance Period, subjects who have received rescue therapy with ABBV-154 for at least 4 weeks and who continue to demonstrate inadequate response, as defined below, may receive

additional rescue therapy with oral glucocorticoids (≤ 20 mg/day prednisone or equivalent, ≤ 9 mg/day budesonide, or ≤ 5 mg/day beclomethasone), aminosalicylates, or immunomodulators.

In the Induction Period after the Week 8 Visit and in the Maintenance Period after the Week 4 Visit, inadequate response may also be confirmed at unscheduled visits and visits where collection of CDAI components was not planned.

Rescue Therapy is not permitted in the Re-Induction Period.

Subjects who receive protocol-defined glucocorticoid Rescue Therapy, initiate glucocorticoids (other than inhaled) after Baseline without qualifying for Rescue Therapy, fail to complete glucocorticoid tapering by Week 6, or who increase doses of or initiate treatment with aminosalicylates or immunomodulators during the Induction Period will be considered non-responders and will be re-randomized into the Re-Induction Period. All subjects who fulfill the clinical response AND/OR endoscopic response (per local read) definition at Week 12 of the Re-Induction Period will be re-randomized into the Maintenance Period.

The criteria for inadequate response are the following:

- Induction Period: Presence of clinical symptoms defined as CDAI ≥ 220 and not achieving a decrease in CDAI ≥ 35 points from Baseline of the Induction Period.
- Maintenance Period: Presence of clinical symptoms defined as CDAI ≥ 220 and an increase in CDAI ≥ 70 points from Baseline of the Maintenance Period.
- And, for both the Induction Period and Maintenance Period, presence of at least 1 of the following objective markers of inflammation:
  - hs-CRP ≥ ULN, and worse than the lowest value assessed during the study, or
  - FCP ≥ 250 µg/g, and worse than the lowest value assessed during the study, or
  - SES-CD, excluding the narrowing component, ≥ 6 (≥ 4 for isolated ileal disease), as scored by the site investigator at an endoscopy.

The last available values for hs-CRP and FCP will be used for assessment of inadequate response.

Use of Rescue Therapy in subjects who qualify is at the investigator's discretion and not mandatory.

5.5 Withdrawal of Subjects and Discontinuation of Study

AbbVie may terminate this study prematurely at any time, either in its entirety or partially (discontinue one or more treatment groups) or at any site. The study may be discontinued or terminated in case of an unacceptable risk, any relevant toxicity, or a negative change in the risk/benefit assessment. This might include the occurrence of AEs with a character, severity or frequency that is new in comparison to the existing risk profile. In addition, data derived from other clinical trials or toxicological studies which negatively influence the benefit-risk assessment might cause discontinuation or termination of the study. The investigator may also stop the study at his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator. Advance notice is not required by either party if the study is stopped due to safety concerns.

A subject may voluntarily withdraw from the study at any time for any reason. An investigator may discontinue a subject's participation at any time for any reason. The AbbVie TA MD may mandate individual subject discontinuation from study drug in case of a safety concern.

Subjects must have study drug discontinued immediately if any of the following occur:

- Abnormal laboratory result or AE that meets the criteria for discontinuation of study drug as stated in Section 6.2, or rule out safe continuation of the study drug, as determined by the investigator or the AbbVie TA MD.
- Serious infection (e.g., sepsis) that cannot be adequately controlled within 2 weeks by anti-infective treatment or would put the subject at risk with continuation of study drug.
- Subject is noncompliant with TB prophylaxis (if applicable) or develops active TB at any time during the study.
- Malignancy or high-grade dysplasia of the gastrointestinal tract, except for localized NMSC or carcinoma in-situ of the cervix.
- The subject develops an anaphylactic reaction or anaphylactic shock.
- The investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from study drug or the study.
- Eligibility criteria violation was noted after the subject started study drug and continuation of the study drug would place the subject at risk.
- Introduction of prohibited medications or dosages and continuation of the study drug would place the subject at risk.
- The subject becomes pregnant while on study drug.
- Subject is significantly noncompliant with study procedures, which would put the subject at risk for continued participation in the trial as determined by the investigator or AbbVie TA MD.
- Subject is prematurely unblinded to study drug assignment by the investigator or AbbVie TA MD.

State of Emergency or Pandemic-Related Acceptable Protocol Modification

During states of emergency or pandemic situations, it might be necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. Acceptable mitigation strategies are identified and included in the Operations Manual in Appendix F.

The investigator should contact the AbbVie TA MD before discontinuing a subject from the study for a reason other than described in the protocol to ensure all acceptable mitigation steps have been explored.

5.6 Follow-Up After Subject Discontinuation of Study Drug or from Study

Discontinuation of Study Drug and Continuation of Study Participation

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should be encouraged to continue to be followed for all regularly scheduled visits as outlined in the Protocol Activities tables in the Operations Manual (Appendix F, Section 2) and adhere to all study procedures except for administration of study drug, endoscopy, annual TB testing, PK, and plasma/serum or other biomarker or exploratory research sample collection unless a subject decides to discontinue study participation entirely (withdrawal of informed consent). Subjects should continue to be advised on the scientific importance of their data even if they discontinue treatment with study drug early. Following the discontinuation of study drug, the subject should be treated in accordance with the investigator's best clinical judgment irrespective of whether the subject decides to continue participation in the study.

In addition, a 70-Day Follow-up Visit after the last dose of study drug is required to ensure all treatment-emergent AEs/SAE have been resolved. All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug or study participation. This information will be recorded on the appropriate eCRF page. For subjects who discontinue study drug but continue study participation, the 70-Day Follow-up Visit is not required if at least one visit has occurred at least 70 days since the last dose of study drug.

Premature Discontinuation of Study (Withdrawal of Informed Consent)

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation visit should be completed as soon as possible, preferably within 2 weeks, and preferably prior to initiation of another therapy.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made, and 1 certified letter must be sent and documented in the subject's source documentation.

If a subject withdraws from study follow up or withdraws permission for the collection of their personal data, the study staff may still use available public records to obtain information about survival status only, as appropriate per local regulations.

In the event a subject withdraws consent from the clinical study, biomarker research will continue unless the subject explicitly requests analysis to be stopped. When AbbVie is informed the subject has withdrawn and no longer wishes biomarker samples research to continue, samples will not be analyzed, and no new biomarker analysis data will be collected for the withdrawn subject or added to the existing data or database(s). A subject may withdraw consent for biomarker research at any time and remain in the clinical study. Data generated from clinical study and/or biomarker research, before subject withdrawal of consent, will remain part of the study results.

5.7 Study Drug

ABBV-154 and matching placebo will be manufactured and provided by AbbVie (Table 2). Each dose will be administered by a healthcare professional either intravenously or as a subcutaneous injection in the abdomen or thigh. Blinded study drug will be administered at approximately the same time of day, preferably between 7 am and 11 am, beginning at the Baseline Visit (Week 0, Day 1) of each period. The study drug can be taken with or without food. Refer to Section 6.2 for required observation periods after each IV and SC doses. The last dose of study drug will be given at Week 38 of the Maintenance Period.

ABBV-154 and matching placebo syringes and vials will be packaged in cartons with quantities sufficient to accommodate the study design. Each pre-filled syringe (PFS), vial, and carton will be labeled per local requirements and these labels must remain affixed to the syringe, vial, and carton. Each kit will contain a unique kit number. This kit number is assigned to a subject via Interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Study drug must not be dispensed without contacting the IRT system. Site staff will complete all blank spaces on the label before dispensing study drug for the subject. Study drug is for investigational use only and will only be used for the conduct of this study.

Upon completion of or discontinuation from study treatment, all original study drug units (containing unused study drugs) will be returned to the sponsor (or designee) or destroyed on site. All return or destruction procedures will be according to instructions from the sponsor and according to local regulations following completion of drug/device accountability procedures.

Table 2. Investigational Product

Study Drug	Dosage Form	Strength	Route of Administration	Manufacturer
ABBV-154	Lyophilized powder for solution for infusion in vials	50 mg (50 mg/mL when reconstituted with 1.2 mL of sterile water for injection)	Intravenous	AbbVie
Matching Placebo	Lyophilized powder for solution for infusion in vials	N/A	Intravenous	AbbVie
ABBV-154	0.8 mL, 1.5 mL solution for injection in PFS	100mg/ml	SC Injection in abdomen or thigh	AbbVie
Matching Placebo	Placebo solution for injection in PFS	N/A	SC Injection in abdomen or thigh	AbbVie

N/A = not applicable; PFS = prefilled syringe; SC = subcutaneous

5.8 Randomization/Drug Assignment

All subjects will be assigned a unique identification number by the IRT at the screening visit. For subjects who rescreen, the screening number assigned by the IRT at the initial screening visit should be used. The IRT will assign a randomization number that will encode the subject's treatment group

assignment according to the randomization schedule. Randomization into the 12-Week Double-Blind Induction Period, the 12-Week Double-Blind Re-Induction Period, and the 40-Week Double-Blind Maintenance Period is outlined in Section 4.1.

Randomization at Baseline (Week 0, Day 1) of the Induction Period will be stratified as follows:

- Baseline glucocorticoid use (yes/no);
- Endoscopic disease severity (SES-CD < 15; SES-CD ≥ 15); and
- Inadequate response to adalimumab (yes/no).

Re-randomization at Baseline (Week 0, Day 1) of the Re-Induction Period will be stratified as follows:

- Treatment group in the Induction Period

Re-randomization at Baseline (Week 0, Day 1) of the Maintenance Period will be stratified as follows:

- Achievement of CR100 at entry of the Maintenance Period (Week 12 of the Induction/Re-Induction Period)
- For subjects who enter from the Induction Period: ABBV-154 dose groups in the Induction Period
- For subjects who enter from Re-Induction Period:
  - ABBV-154 dose groups in the Re-Induction Period
  - Induction Period treatment: ABBV-154 (any dose group) versus placebo

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team) will remain blinded to each subject's treatment-assignment in each study period until the Primary Analysis of the respective period. The investigator, study site personnel, and the subject will remain blinded to each subject's assignment throughout the study. Selected AbbVie personnel may be unblinded to treatment assignment after an interim analysis to support regulatory interactions; details will be included in the interim unblinding plan (IUP). To maintain the blind, the ABBV-154 and placebo PFS and vials provided for the study will be identical in appearance. The IRT will provide access to unblinded subject treatment information in the case of a medical emergency.

In the event of a medical emergency that requires unblinding of the study drug assignment, the investigator is requested to contact the AbbVie TA MD prior to breaking the blind. However, if an urgent therapeutic intervention is necessary which warrants breaking the blind prior to contacting the AbbVie TA MD, the investigator can directly access the IRT system to break the blind without AbbVie notification or agreement. Unblinding is available in the IRT system via the Subject Unblinding by Site transaction, which is available only to the investigator. If the IRT system is unavailable, unblinding may occur by contacting the technical support of the IRT vendor via either phone (preferred) or email (support@endpointclinical.com). For country-specific phone numbers, please see the following website: http://www.endpointclinical.com/help-desk. In the event the blind is broken before notification to the AbbVie TA MD, the AbbVie TA MD should be notified within 24 hours of the blind being broken. The

date and reason that the blind was broken must be conveyed to AbbVie and recorded on appropriate eCRF.

5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified including those that may be due to the COVID-19 pandemic), the investigator is responsible for notifying independent ethics committee (IEC)/independent review board (IRB), regulatory authorities (as applicable), and AbbVie.

5.10 Data Monitoring Committee

An external DMC will be established to safeguard the interest of trial subjects by assessing the safety of the interventions during the trial as well as for monitoring of the integrity and interpretability of the trial. A separate DMC charter will be prepared outside of the protocol and will further describe the roles and responsibilities of the DMC members, frequency, and scope of the data reviews, and expectations for blinded communications. The first DMC review of unblinded safety data will occur after approximately 30 subjects (6 subjects/treatment group) have reached Week 8. The DMC will be requested to review the unblinded safety data at an earlier timepoint if the sponsor notes on blinded data review any of the following:

- Fatal or life-threatening event considered to have a reasonable possibility of being related to study drug by the investigator or sponsor;
- Serious hypersensitivity reaction considered to have a reasonable possibility of being related to study drug by the investigator or sponsor;
- Higher than anticipated rate of serious infection as compared to the rate for serious infection in subjects with CD receiving adalimumab in the Humira clinical trials.

5.11 Glucocorticoid Adjudication Committee

An independent adjudication committee will be established to adjudicate systemic glucocorticoid AEs. A separate charter will be prepared outside of the protocol and will describe the roles and responsibilities of the adjudication committee members, frequency of data reviews, and expectations for blinded communications.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device damage or not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event.

Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/ Adverse Events and Serious Adverse Events

An adverse event is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations" such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an adverse event or not. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meets protocol-specific criteria (see Section 6.2 regarding toxicity management), and/or if the investigator considers them to be adverse events.

The investigators will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. All adverse events will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and/or the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

Expected manifestations of CD that do not constitute worsening of the underlying condition are not to be recorded as AEs unless the event results in a serious outcome.

If any of the following events are reported, then the following supplemental report must be completed.

Event	Supplemental Report
Cardiac events **Myocardial infarction or unstable angina** **Heart failure** **Cerebral vascular accident and transient ischemic attack** **Cardiovascular procedures (SAE Supplemental Procedure eCRF)**	MACE eCRF
Discontinuation or interruption of study drug due to a hepatic-related AE **A hepatic-related SAE** **Confirmed ALT/AST > 3 × ULN**	Hepatic eCRF
Renal impairment **Renal dysfunction** **Renal failure** **Confirmed serum creatinine >1.5 × the baseline value (of the Induction Period) and > ULN**	Renal eCRF
Adrenal insufficiency	Adrenal insufficiency eCRF
COVID-19 infection	COVID-19 eCRF
Hypersensitivity Reaction	Hypersensitivity reaction eCRF

ALT = alanine aminotransferase; AST = aspartate transaminase; eCRF = electronic case report form; COVID-19 = coronavirus pandemic 2019; MACE = major adverse cardiac event; SAE = serious adverse event; ULN = upper limit of normal

If an adverse event, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance or contract research organization (as appropriate) as a serious adverse event within 24 hours of the site being made aware of the serious adverse event (refer to Section 4.2 of the Operations Manual for reporting details and contact information):

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All adverse events reported from the time of study drug administration until 70 days after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, study procedure-related serious and nonserious adverse events will be collected from the time the subject signs the study-specific informed consent.

The following definitions will be used for Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reaction (SUSAR):

SAR	Defined as all noxious and unintended responses to an Investigational Medicinal Product (IMP) related to any dose administered that result in an SAE as defined above.
SUSAR	Refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the sponsor or the investigator, is unexpected (not listed in the applicable Reference Safety Information), and meets one of the above serious criteria.

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local requirements.

Adverse events will be monitored throughout the study to identify any safety topics of interest that may indicate a trend or risk to subjects.

Safety Topics of Interest

The following Safety Topics of Interest will be monitored during the study:

- Serious infections;
- Opportunistic infections;
- Active TB;
- Hypersensitivity reactions;
- Serious allergic reactions;
- Malignancies;
- Systemic glucocorticoid side effects;
- Adrenal insufficiency;
- Iatrogenic Cushing's syndrome.

Adverse Event Severity and Relationship to Study Drug

The investigator will rate the severity of each adverse event according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 5.0), which can be accessed at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

Pregnancy

While not an adverse event, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.5). If a pregnancy occurs in a study subject or in the partner of a study subject, information regarding the pregnancy and the outcome will be collected.

In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained prior to collection of any such information. AbbVie will provide a separate consent form for this purpose. Pregnancy in a subject's partner will be collected from the date of the first dose through 70 days following the last dose of study drug.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

6.2 Toxicity Management

For subjects who discontinue study drug but continue study participation and are on standard of care therapies, these toxicity management requirements do not apply (including alerts from the central laboratory) and any intolerability to standard of care therapies should be managed by the prescribing physician.

Elective surgery is not allowed during the Induction and Re-Induction Periods of the study. If the subject undergoes elective surgery, study drug should be interrupted at least 2 weeks prior to the planned surgery. If the subject must undergo emergency surgery, the study drug should be interrupted at the time of the surgery. After surgery, allow reintroduction of study drug once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

Management of Hypersensitivity and Serious Allergic Reactions

Subjects should be closely monitored and assessed for the development of signs and symptoms of hypersensitivity reactions, including anaphylaxis. For any hypersensitivity reaction, appropriate therapy should be instituted per standard of care. Study drug should be discontinued if a subject develops anaphylaxis.

Emergency medical equipment and personnel trained to evaluate and manage infusion-related reactions and anaphylaxis should be immediately available during dosing and the post-treatment observational period.

In the event of a suspected systemic postdose hypersensitivity reaction, if the clinical situation allows, every effort should be made to obtain a serum sample within 2 hours but no later than 6 hours from symptom onset for additional blood tests specified in the Operations Manual, Section 3.19 Hypersensitivity Testing.

IV infusion of study drug for loading dose: The following infusion times should be applied dependent on the subject's individual body weight:

Subject's Body Weight	Infusion Time
≥ 54 kg	60 min
44 to 53 kg	75 min
36 to 43 kg	90 min
27 to 35 kg	120 min

Subjects should be closely monitored for signs and symptoms of hypersensitivity reactions, including anaphylaxis.

Study drug should be interrupted and appropriate therapy instituted if an infusion reaction occurs. If symptoms are mild (e.g., flushing without respiratory symptoms or vital sign changes) and quickly improve with cessation of the infusion, re-starting study drug at a lower infusion rate may be an option. Study drug should be discontinued if a subject develops a severe infusion reaction or anaphylaxis (refer to definitions of severity of Infusion Related Reaction given below and in CTCAE v5.0).

- Mild to Moderate: transient symptoms, responds to minimal intervention (e.g., antihistamines, IV fluids)
- Severe: prolonged symptoms, multiple organ systems affected, life-threatening

Subjects should be observed for at least 30 minutes after infusion. If new onset of symptoms occurs during or after completion of the infusion, subjects should receive standard of care or remain at the site for further observation until symptoms have resolved. Subjects with mild to moderate infusion reactions who are able to complete the IV infusion should be observed for at least 1 hour after infusion. These subjects may receive additional IV infusion loading doses during the Re-Induction Period and for ABBV-154 Rescue Therapy during the Maintenance Period (as applicable per the protocol) at the discretion of the investigator.

SC injection of study drug: After SC study drug injection, a 15- to 30-minute post-injection observational period is required.

Management of Serious Infections

Subjects should be closely monitored for the development of signs and symptoms of infection during and after treatment with study drug. Study drug should be interrupted if a subject develops a serious infection or a serious opportunistic infection. A subject who develops a new infection during treatment with study drug should undergo prompt diagnostic testing appropriate for an immunocompromised subject. As appropriate, antimicrobial therapy should be initiated, and the subject should be closely

monitored. Study drug may be restarted once the infection has been successfully treated. Subjects who develop active TB must be permanently discontinued from study drug.

Management of Malignancy

Subjects who develop high-grade dysplasia of the gastrointestinal tract or malignancy other than localized NMSC or carcinoma in-situ of the cervix must be discontinued from the study drug. Information including histopathological results should be queried for the confirmation of the diagnosis.

Management of Demyelinating Disease

Subjects must be discontinued from study drug with new onset of symptoms and/or radiographic evidence of central nervous system demyelinating disease (including multiple sclerosis), optic neuritis, or peripheral demyelinating disease (including Guillain Barré syndrome).

Management of Hypertension

Subjects should be closely monitored for the development of hypertension. Investigators should consider stopping the study drug if hypertension is not successfully controlled under standard of care.

Management of Hyperglycemia

Subjects should be closely monitored for the development of hyperglycemia. Investigators should manage the hyperglycemia with appropriate standard of care.

Management of Glucocorticoid Induced Adrenal Insufficiency

Subjects should be closely monitored for signs and symptoms of adrenal insufficiency (e.g., nausea, vomiting, lightheadedness, pale skin, unexplained weight loss, low blood pressure, electrolyte abnormalities [e.g., hyponatremia < 135 mmol/L, hyperkalemia > 5.5 mmol/L]) and if adrenal insufficiency is suspected, further assessment and management should follow local standard of care, which may include measuring cortisol levels and/or ACTH stimulation testing at a local laboratory. Glucocorticoid therapy with physiologic doses should be considered. After withdrawal of glucocorticoid therapy, adrenal insufficiency may persist for months; therefore, glucocorticoid therapy should be considered in any situation of stress (e.g., serious infection) occurring or in the months following withdrawal of study drug.

Management of COVID-19

Subjects should be closely monitored for COVID-19. Study drug should be interrupted if a subject has a confirmed diagnosis of COVID-19. Consider the interruption of study drug in subjects with signs and/or symptoms and suspicion of COVID-19.

Management of Select Laboratory Abnormalities

For any given laboratory abnormality, the investigator should assess the subject, apply the standard of care for medical evaluation and treatment following any local guidelines. Specific toxicity management guidelines for selected abnormal laboratory values are described in Table 3, and may require a supplemental eCRF to be completed. For subjects with ongoing laboratory abnormalities which require data entry into an eCRF, an additional eCRF related to subsequent laboratory abnormalities is only required if the subject has relevant changes in history (e.g., new onset signs or symptoms) or laboratory

values which have returned to normal reference range or its Baseline value followed by subsequent laboratory abnormalities meeting toxicity guidelines (considered a new event). All abnormal laboratory tests that are considered clinically significant by the investigator will be followed to a satisfactory resolution. If a repeat test is required, the repeat testing must occur as soon as possible.

Table 3. Specific Toxicity Management Guidelines for Abnormal Laboratory Values

Laboratory Parameter	Toxicity Management Guideline
ANC	If confirmed < 1000/µL by repeat testing with new sample, interrupt study drug dosing until ANC value returns to normal reference range or its BL value. Discontinue study drug if confirmed < 500/µL by repeat testing with new sample.
ALC	If confirmed < 500/µL by repeat testing with new sample, interrupt study drug dosing until ALC returns to normal reference range or its BL value.
Platelet count	If confirmed < 50,000/µL by repeat testing with new sample, interrupt study drug dosing until platelet count returns to normal reference range or its BL value.
AST or ALT	Interrupt study drug if confirmed ALT or AST > 3 × ULN by repeat testing with new sample and either a total bilirubin > 2 × ULN or an INR > 1.5. A separate blood sample for INR testing will be needed to measure INR at the time of repeat testing for ALT or AST. A repeat test of INR is not needed for determination if above toxicity management criteria are met. • Interrupt study drug if confirmed ALT or AST > 3 × ULN by repeat testing with new sample along with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5% increase from BL). • Interrupt study drug if confirmed ALT or AST > 5 × ULN by repeat testing with new sample for more than 2 weeks. • If ALT or AST > 8 × ULN, interrupt study drug immediately, confirm by repeat testing with a new sample, and contact the TA MD. Subjects with HBc Ab+ (irrespective of HBs Ab status) or HBs Ab+ (without a history of vaccination) and negative HBV DNA PCR testing at Screening who develop the following laboratory findings should have HBV DNA PCR testing performed within one week (based on initial elevated value): • ALT> 5 × ULN OR • ALT or AST > 3 × ULN if an alternative cause is not readily identified. • Note: A separate blood sample for HBV DNA PCR testing will be needed at the time of repeat testing for ALT or AST. A positive result for HBV DNA PCR testing will require immediate interruption of study drug (unless not acceptable by local practices) and a hepatologist consultation should occur within 1 week for recommendation regarding subsequent treatment. Subjects who meet any of the above criteria should be evaluated for an alternative etiology of the ALT or AST elevation and managed as medically appropriate. If applicable, the alternative etiology should be documented in the eCRF. If ALT or AST values return to the normal reference range or its BL value, study drug may be restarted. If restarting study drug, documentation should include reason that rechallenge is expected to be safe. If after clinically appropriate evaluation, no alternative etiology for ALT or AST elevation is found or the ALT or AST elevation has not resolved or is not trending down toward normal, the subject should be discontinued from study drug. For any confirmed ALT or AST elevations > 3 ULN, complete the appropriate supplemental hepatic eCRF(s).

Laboratory Parameter	Toxicity Management Guideline
Serum Creatinine	If serum creatinine is > 1.5 × the BL value and > ULN, repeat the test for serum creatinine (with subject in an euvolemic state) to confirm the results. If the results of the repeat testing still meet this criterion, then interrupt study drug and re-start study drug once serum creatinine returns to ≤ 1.5 × BL value and ≤ ULN. For the above serum creatinine elevation scenario, complete the appropriate supplemental renal eCRF(s).

ALC = Absolute lymphocyte counts; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BL = baseline; DNA = deoxyribonucleic acid; eCRF = electronic case report form; HBc Ab = Hepatitis B core antibody; HBs Ab = Hepatitis B surface antibody; HBV = hepatitis B virus; INR = international normalized ratio; PCR = polymerase chain reaction; TA MD = Therapeutic Area Medical Director; ULN = upper limit of normal
Note: Baseline value refers to the Baseline (Week 0, Day 1) visit of the Induction Period.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol are focused on primary and secondary analyses. Complete and specific details of the statistical analysis will be described in the Statistical Analysis Plan (SAP).

The Primary Analysis for the Induction Period and Re-Induction Period will be conducted after all subjects have completed Week 12 of the Induction Period and Re-Induction Period, respectively, or prematurely discontinued from the study.

A final analysis will be conducted after all subjects have completed Week 40 of the Maintenance Period plus the 70-day Follow-up Visit or prematurely discontinued from the study.

7.2 Definition for Analysis Populations

The following populations will be used for analyses:

- Intent-to-treat (ITT) Population: The ITT Population includes all subjects who were randomized and received at least 1 dose of study drug. The ITT Population will be analyzed as randomized (i.e., according to the randomized treatment assignment).
  - ITT1 Population: The subset of the ITT population who were randomized and received at least one dose of study drug in the Induction Period. The ITT1 Population is the primary analysis population for efficacy analyses of the Induction Period.
  - ITT2 Population: The subset of the ITT population who were randomized and received at least one dose of study drug in the Re-Induction Period. The ITT2 Population is the analysis population for efficacy analyses of the Re-Induction Period.
  - ITT3 Population: The subset of the ITT population who received ABBV-154 for 12 weeks before entering the Maintenance Period (including subjects were randomized to ABBV-154

dose groups in the Induction Period and entered the Maintenance Period from the Induction Period OR were randomized to the placebo group in the Induction Period and entered the Maintenance Period from the Re-Induction Period) AND were randomized and received at least one dose of study drug in the Maintenance Period. The ITT3 Population is the primary analysis population for efficacy analyses of the Maintenance Period.

- Safety Population: The Safety Population includes all subjects who received at least 1 dose of study drug. The Safety Population will be analyzed as treated (i.e., according to the actual treatment received).

7.3 Handling Potential Intercurrent Events for the Primary and Secondary Endpoints

Primary endpoint/Categorical secondary endpoints in the Induction Period:

- Subjects will be considered as not achieving response after receiving medications that could confound the assessment of efficacy, including protocol-defined Rescue Therapy for the Induction Period, initiating glucocorticoids after Baseline, failing to complete glucocorticoid taper by Week 6, and initiating/increasing doses of aminosalicylates or immunomodulators.
- Available data collected after study drug discontinuation will be used until the initiation of medications that could confound the assessment of efficacy.

Categorical secondary endpoints in the Maintenance Period:

- Subjects will be considered as not achieving response after receiving medications that could confound the assessment of efficacy, including protocol-defined Rescue Therapy for the Maintenance Period.
- Available data collected after study drug discontinuation will be used until the initiation of medications that could confound the assessment of efficacy.

7.4 Statistical Analyses for Efficacy

Efficacy analysis will be performed by the subject's randomized treatment group. All statistical tests will be performed at a 2-sided significance level of 0.1. A 95% confidence interval (CI) of the treatment difference between each ABBV-154 dose and placebo will be provided. The actual value of stratification factors will be used in the analysis.

For categorical variables, pairwise comparison will be made between each ABBV-154 dose and placebo using the Cochran-Mantel-Haenszel (CMH) test, adjusting for stratification factors (Section 5.8). Non-responder imputation incorporating multiple imputation (NRI-MI) to handle COVID-19 will be the primary approach to handle missing data for categorical endpoints.

For continuous variables, the comparison will be made between each ABBV-154 dose and placebo based on the mixed effect model repeated measures (MMRM) adjusting for visit, interaction between

treatment and visit, actual values of stratification factors as fixed factors, and baseline value (of the Induction Period) as a covariate. The MMRM will be the primary approach to handle missing values for continuous endpoints.

Summary and Analysis of the Primary Endpoint

The primary endpoint is the achievement of endoscopic response at Week 12 of the Induction Period. Comparison of the primary endpoint will be made between each ABBV-154 dose and placebo using CMH test adjusting for stratification factors. The points and CI estimate of the treatment difference for each ABBV-154 dose versus placebo will be presented.

One supplementary analysis for the primary endpoint is to test a prespecified set of dose-response models among ABBV-154 dose groups and the placebo group at Week 12 of the Induction Period using the Multiple Comparison Procedure – Modeling (MCP-Mod) method.

Summary and Analysis of Secondary Endpoints

Analysis of secondary efficacy endpoints is described above.

Summary and Analysis of Additional Efficacy Endpoints

Analysis of additional efficacy endpoints is described above.

Subgroup Analysis for Efficacy

To evaluate the consistency of efficacy across demographic and other baseline characteristics, the following subgroup analysis will be performed on the primary endpoint: Baseline glucocorticoid use (yes; no)

- Endoscopic disease severity (SES-CD < 15; SES-CD ≥ 15)
- Inadequate response to adalimumab (yes; no)
- Sex (female; male)
- Race (White; Non-white)
- Age (≥18 years to < 40 years, ≥40 years to < 65 years, ≥ 65 years)
- Inadequate response to prior anti-TNF biologics (yes; no)

If deemed necessary, additional subgroup analyses may be performed with details described in the SAP.

7.5 Statistical Analysis for Pharmacokinetics and Immunogenicity

Concentrations of conjugated ADC, total antibody, and free payload (A-1677770) will be summarized at each time point using descriptive statistics.

Population PK analyses combining the data from this study and other studies may be performed and reported outside of the clinical study report.

Anti-drug antibody (ADA) and nAb incidence and ADA titer values will be summarized for each group using descriptive statistics.

7.6 Statistical Analysis of Biomarker Data

Analyses may be conducted on biomarker data for the purpose of identification of prognostic, predictive, surrogate, and pharmacodynamic biomarkers associated with efficacy or safety. The association of biomarkers to the efficacy or safety endpoints may be explored for each biomarker one at a time, and also for combinations of biomarkers via some multivariate predictive modeling approaches. Analyses may be reported outside of the clinical study report.

7.7 Statistical Analyses for Safety

All safety analyses will be performed using the Safety Population, as defined in Section 7.2. Data will be analyzed based on the actual treatment subjects received. TEAEs, laboratory assessments, and vital signs will be summarized. Details will be described in the SAP.

A TEAE for the Safety Population is defined as an AE newly occurred or worsened after the first dose of study drug and within 70 days after the last dose of study drug. The number and percentage of subjects experiencing TEAEs will be tabulated using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term, by severity, and by relationship to the study drug as assessed by the investigator. Summaries (including percentages and events per 100 patient years) of SAEs, deaths, and AEs leading to discontinuation will also be provided. Procedure related pretreatment AEs will be summarized separately.

For selected laboratory parameters, a listing of all subjects with any laboratory value that is Grade ≥ 3 of NCI CTCAE will be provided. Mean change in laboratory and vital signs variables will be summarized. Additional details for the safety analysis will be provided in the SAP.

7.8 Interim Analysis

An interim analysis will be performed when approximately 66% of the subjects (35 subjects per group) have reached Week 12 of the Induction Period or have prematurely discontinued the study to inform the development of future studies.

An additional interim analysis in the Maintenance Period might be performed to inform the development of future studies. The results from this analysis will not impact the conduct of the current study.

Selected AbbVie personnel may be unblinded to treatment assignment after an interim analysis to support regulatory interactions and future development decisions; details will be included in the IUP.

7.9 Overall Type I Error Control

Overall Type I error control is not planned in this Phase 2 study.

7.10 Sample Size Determination

Approximately 265 subjects will be randomized into 4 ABBV-154 treatment groups or placebo in a 1:1:1:1:1 ratio at Baseline of the Induction Period. There will be a cap of approximately 30% the total enrolled of subjects who had prior use of adalimumab treatment.

A total of 265 subjects (53 subjects per group) will provide more than 90% power to detect a 26% difference in endoscopic response rates at Week 12 of the Induction Period between an ABBV-154 group and the placebo group (assuming the response rate in the placebo group is 11%) using a Chi-square test at α level of 0.1 (two-sided).

Under the response rate assumptions for ABBV-154 and placebo in the Induction Period, it is expected that at least 40 subjects per group will be available for the analysis of endoscopic response at Week 40 in the Maintenance Period. This sample size (40 subjects per group) will provide more than 80% power to detect a 26% difference between ABBV-154 and placebo (assuming the response rate in the placebo group at Week 40 of the Maintenance Period is 11%) using a Chi-square test at α level of 0.1 (two-sided).

The total sample size (planned as 265 subjects) for the Induction Period may be adjusted to ensure at least 40 subjects per group for the analysis in the Maintenance Period.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

In the event a significant disaster/crisis (e.g., epidemic/pandemic, natural disaster, conflict/combat) occurs leading to difficulties in performing protocol-specified procedures, AbbVie may engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative

locations for data collection (e.g., use of a local lab instead of a central lab), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC.

8.3 Subject Confidentiality

For the protection of personal data, AbbVie has developed a robust security program focused on due diligence in design, managed change, and information security governance. Information Security policies govern the Information Security functions including identity and access management, operations, infrastructure, application, and third-party security requirements. The risk-based AbbVie Data Classification Tool dictates the level of scrutiny and control required for the relevant activities per AbbVie's Information Security policies taking into account the sensitivity of the data.

Before subject's data is shared with AbbVie, the study investigator and staff will replace any information that could directly identify a subject (such as name, address, and contact information) with an assigned numerical study identifier or "code" which AbbVie cannot link to that subject's identity in order to protect the confidentiality of the data.

AbbVie has a data protection impact assessment program to ensure and document the appropriate controls and safeguards stated above are in place for clinical trial data that it controls and maintains and these processing activities respect privacy of clinical trial subjects. AbbVie also maintains robust security incident response policies and procedures, including requirements for the containment of any data related incidents, the mitigation measures where needed, and notification to authorities or affected individuals where required.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s). During states of emergency or pandemic situations, remote data review/verification may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 START AND COMPLETION OF THE STUDY

The start-of-study is defined as the date of the first site activated.

The end-of-study is defined as the date of the last subject's last visit or the actual date of follow-up contact, whichever is later; and in the last country where the study was conducted.

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APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
6-MP	6-mercaptopurine
Ab	antibody
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibody
ADC	antibody-drug conjugate
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AP	abdominal pain
AST	aspartate aminotransferase
AZA	azathioprine
BCG	bacilli Calmette-Guérin
BL	Baseline
BMD	bone mineral density
BMI	body mass index
C diff	Clostridium difficile
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CO_2	carbon dioxide
COPD	chronic obstructive pulmonary disease
COVID-19	Coronavirus disease-2019
CR100	A decrease in CDAI ≥ 100 points from Baseline
CR70	A decrease in CDAI ≥ 70 points from Baseline
CTCAE	Common Terminology Criteria for Adverse Events
CTX	C-terminal telopeptide
CXR	chest x-ray
CYP3A	cytochrome P450 3A
DB	double-blind

Abbreviation	Definition
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DSUR	Development Safety Update Report
DXA	dual-energy x-ray absorptiometry
E4W	every 4 weeks
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	Estimate glomerular filtration rate
EIM	extra intestinal manifestation
EOW	every other week
ePRO	electronic patient-reported outcome
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FCP	fecal calprotectin
FSH	follicle stimulating hormone
GCP	good clinical practice
GRM	glucocorticoid receptor modulator
HbA1c	Hemoglobin A1c
HBc	Hepatitis B core
HBc Ab	Hepatitis B core antibody
HBs	Hepatitis B surface
HBs Ab	Hepatitis B surface antibody
HBs Ag	hepatis B surface antigen
HBV	hepatitis B virus
Hct	hematocrit
HCV	hepatitis C virus
HCV Ab	HCV antibody
HDL	high density lipoprotein
HIV	human immunodeficiency virus
HIV	human immunodeficiency virus
HPA	Hypothalamic-pituitary-adrenal axis
hs-CRP	high-sensitivity C-reactive protein

Abbreviation	Definition
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Council for Harmonisation
IEC	independent ethics committee
IgE	Immunoglobulin E
IgG	immunoglobulin G
IMP	Investigational Medicinal Product
IRB	institutional review board
IRT	Interactive response technology
ITT	Intent-to-treat
IU	International units
IUP	interim unblinding plan
IV	Intravenous (ly)
JAK	Janus kinase
LCMS	Liquid chromatography-mass spectrometry
LDL	low density lipoprotein
MACE	major adverse cardiac event
MCP-Mod	Multiple Comparison Procedure - Modeling
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Effect Model Repeated Measurements
mRNA	messenger RNA
MTX	methotrexate
N/A	not applicable
nAb	neutralizing antibody
NCI	National Cancer Institute
NMSC	nonmelanoma skin cancer
NRI-MI	Non-responder imputation incorporating multiple imputation
NSAID	nonsteroidal anti-inflammatory drug
OC	osteocalcin
P1NP	procollagen type 1 N-propeptide
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	pharmacodynamics

Abbreviation	Definition
PFS	pre-filled syringe
PGIC-CD+	Patient Global Impression of Change – Crohn's Disease+
PGIS-CD+	Patient Global Impression of Severity – Crohn's Disease+
PK	pharmacokinetic(s)
PPD	purified protein derivative
PPE	Personal Protective Equipment
PRO	Patient-reported outcome
PRO	patient-reported outcome
RNA	ribonucleic acid
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SES-CD	Simplified Endoscopic Score for CD
SF	stool frequency
SF-36	short form-36
SUSAR	suspected unexpected serious adverse reaction
TA MD	Therapeutic Area Medical Director
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
TSH	thyroid stimulating hormone
ULN	upper limit of normal
Wk	week

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M20-371: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of ABBV-154 in Subjects with Moderately to Severely Active Crohn's Disease (CD): AIM-CD

Protocol Date: 20 December 2022

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly (within 1 calendar day to AbbVie, the ethics committees/institutional review boards (as required) and other appropriate individuals (e.g., coordinating investigator, institution director):
    - Any departure from relevant clinical trial law or regulation, GCP, or the trial protocol that has the potential to affect the following:
    - Rights, safety, physical or mental integrity of the subjects in the clinical trial.
    - Scientific value of the clinical trial, reliability or robustness of data generated.
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date
Name of Principal Investigator (printed or typed)	

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	Study Project Manager	Clinical Study Leadership
[redacted]	Principal Medical Writer	Medical Writing
[redacted]	Global Development Lead	Therapeutic Area - Immunology
[redacted]	Medical Director	Therapeutic Area Medical Director
[redacted]	Statistics Director	Statistics
[redacted]	Director	Clinical Pharmacology & Pharmacometrics

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities across the 12-Week Induction Period, the 12-Week Re-Induction Period, and the 40-Week Maintenance Period subject encounters. The individual activities are described in detail in the **Operations Manual** (Appendix F). Allowed modifications due to state of emergency or pandemic situations are detailed in the Operations Manual.

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Study Activities Table

12-Week Double-Blind Induction Period

Activity	Screening	Visit Induction Period (Week)							Premature Discontinuation	Follow-up 70-Day Visit
		Baseline (Week 0, Day 1)	2	4	6	8	10	12		
INTERVIEWS AND QUESTIONNAIRES										
Subject information and informed consent	✓									
Confirm Eligibility	✓	✓								
Medical/Surgical History including disease specific history	✓	✓								
Alcohol use	✓									
Nicotine usage	✓									
Adverse Event Assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Record prior and concomitant medication/therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TB risk assessment questionnaire	✓									
SF-36		✓		✓		✓		✓	✓	
IBDQ		✓		✓		✓		✓	✓	
FACIT-Fatigue		✓		✓		✓		✓	✓	
PGIC-CD+				✓		✓		✓	✓	
PGIS-CD+		✓		✓		✓		✓	✓	
CDAI Components (may be performed at additional visits not marked if needed to confirm eligibility for Rescue Therapy)		✓	✓	✓		✓		✓	✓	
Automatic calculation of CDAI in EDC (may be performed at additional visits not marked if needed to confirm eligibility for Rescue Therapy)		✓				✓		✓		
Bowel Incontinence Scale		✓		✓		✓		✓	✓	
Dispense Subject Diary	✓									

Activity	Screening	Visit Induction Period (Week)							Premature Discontinuation	Follow-up 70-Day Visit
		Baseline (Week 0, Day 1)	2	4	6	8	10	12		
Subject Diary Review		✓	✓	✓	✓	✓	✓	✓	✓	
Dispense wearable device (substudy only)		✓	Subject wears device continuously and measures stool frequency.							
Collect wearable device (substudy only)								✓		
LOCAL LABS AND EXAMS										
Height	✓									
Body Weight	✓	✓	✓	✓		✓		✓	✓	✓
Vital Signs	✓	✓	✓	✓		✓		✓	✓	✓
Complete Physical Exam	✓	✓						✓	✓	
Symptom Directed Physical Exam			✓	✓		✓				
12-Lead ECG	✓							✓	✓	
Endoscopy (may be performed at additional visits not marked if needed to confirm eligibility for Rescue Therapy)	✓							✓	✓	
Automatic calculation of SES-CD score and endoscopic response status in EDC								✓		
Intestinal Biopsies	✓							✓		
DXA scan	✓									
Chest x-ray	✓									
Blood sample for anti-adalimumab antibody assay (where mandated by local requirements)	✓									
Urine pregnancy test (females of childbearing potential)		✓		✓		✓		✓	✓	✓
CENTRAL LABS										
Serum pregnancy test (females of childbearing potential); FSH, if applicable	✓									
hs-CRP		✓	✓	✓		✓		✓	✓	

Activity	Screening	Visit Induction Period (Week)							Premature Discontinuation	Follow-up 70-Day Visit
		Baseline (Week 0, Day 1)	2	4	6	8	10	12		
FCP		✓		✓				✓	✓	
Clostridium difficile test	✓									
Hematology	✓	✓	✓	✓		✓		✓	✓	✓
HbA1c	✓							✓		✓
Clinical Chemistry	✓	✓	✓	✓		✓		✓	✓	✓
Urinalysis	✓	✓		✓		✓		✓	✓	
Lipid Panel		✓						✓		
TSH	✓									
TB testing (QuantiFERON-TB Gold test and/or local PPD skin test)	✓									
HIV Test	✓									
HBV Test	✓							✓ if required by local regulations		
HCV Test	✓									
Beta-D-glucan (central or local lab; Japan only)	✓									
Blood samples for conjugated ADC (serum), total antibody (serum), free A-1677770 (plasma) assays		✓	✓	✓		✓		✓	✓	✓
Blood samples for ADA Assay including serum ADA titer and nAb assays		✓		✓		✓		✓	✓	✓
Blood sample for bone biomarkers P1NP, OC and CTX		✓	✓	✓		✓		✓		
Blood sample for free and total cortisol (serum)		✓	✓	✓		✓		✓	✓	✓
Blood sample for ACTH		✓	✓	✓		✓		✓	✓	✓
Optional Biomarker sample: Plasma/serum proteomic		✓	✓			✓		✓		
Optional biomarker sample: PBMC		✓	✓			✓		✓		
Optional biomarker sample: RNA		✓	✓			✓		✓		

Activity	Screening	Visit Induction Period (Week)							Premature Discontinuation	Follow-up 70-Day Visit
		Baseline (Week 0, Day 1)	2	4	6	8	10	12		
Optional biomarker sample: DNA		✓	✓			✓		✓		
℞ TREATMENT										
Assign Study Drug		✓								
Dispense Study Drug		✓	✓	✓	✓	✓	✓			
Administer Study Drug		✓	✓	✓	✓	✓	✓			
Inadequate response assessment to determine eligibility for rescue therapy (may be performed at additional visits not marked if needed to confirm eligibility for Rescue Therapy)						✓		✓		
Automatic determination of eligibility for the Maintenance Period in EDC								✓		

ACTH = adrenocorticotropic hormone; ADA = anti-drug antibody; ADC = antibody-drug conjugate; CDAI = Crohn's Disease Activity Index; CTX = C-terminal telopeptide of type 1 collagen; DNA = deoxyribonucleic acid; DXA = dual-energy X-ray absorptiometry; ECG = electrocardiogram; EDC = electronic data capture; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; FCP = Fecal calprotectin; FSH = follicle stimulating hormone; HbA1c = Hemoglobin A1c; HBV = hepatitis b virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hs-CRP = high sensitivity C-reactive protein; IBDQ = Inflammatory Bowel Disease Questionnaire; nAb = neutralizing antibody; OC = osteocalcin; P1NP = procollagen type I N-propeptide; PBMC = peripheral blood mononuclear cells; PGIC-CD+ = Patient Global Impression of Change – Crohn's Disease+; PGIS-CD+ = Patient Global Impression of Severity – Crohn's Disease+; PPD = purified protein derivative; RNA = ribonucleic acid; SF-36 = Short Form-36; TB = tuberculosis; TSH = thyroid stimulating hormone

12-Week Double-Blind Re-Induction Period

Activity	Visit Re-Induction (Week)							Premature Discontinuation	Follow-up 70-Day Visit
	Baseline (Week 0, Day 1)	2	4	6	8	10	12		
INTERVIEWS AND QUESTIONNAIRES									
Adverse Event Assessment		✓	✓	✓	✓	✓	✓	✓	✓
Record prior and concomitant medication/therapy		✓	✓	✓	✓	✓	✓	✓	✓
SF-36							✓	✓	
IBDQ							✓	✓	
FACIT-Fatigue							✓	✓	
PGIC-CD+							✓	✓	
PGIS-CD+							✓	✓	
CDAI Components		✓	✓		✓		✓	✓	
Automatic calculation of CDAI in EDC							✓		
Bowel Incontinence Scale							✓	✓	
Subject Diary Review		✓	✓	✓	✓	✓	✓	✓	
LOCAL LABS AND EXAMS									
Body Weight		✓	✓		✓		✓	✓	✓
Vital Signs		✓	✓		✓		✓	✓	✓
Complete Physical Exam							✓	✓	
Symptom Directed Physical Exam		✓	✓		✓				
12-Lead ECG							✓	✓	
Endoscopy							✓	✓	
Automatic calculation of SES-CD score and endoscopic response status in EDC							✓		
Intestinal biopsies							✓		

Activity	Visit Re-Induction (Week)							Premature Discontinuation	Follow-up 70-Day Visit
	Baseline (Week 0, Day 1)	2	4	6	8	10	12		
LOCAL LABS AND EXAMS									
Urine pregnancy test (females of childbearing potential)			✓		✓		✓	✓	✓
CENTRAL LABS									
hs-CRP		✓	✓		✓		✓	✓	
FCP							✓	✓	
Hematology		✓	✓		✓		✓	✓	✓
HbA1c							✓		✓
Clinical Chemistry		✓	✓		✓		✓	✓	✓
Urinalysis			✓		✓		✓	✓	
Lipid Panel							✓		
HBV test (if required by local regulations)							✓		
Blood samples for conjugated ADC (serum), total antibody (serum), free A-1677770 (plasma) assays							✓	✓	✓
Blood samples for ADA Assay (serum) including ADA titer and nAb assays (Central Lab shipping and lab handling)							✓	✓	✓
Blood sample for bone biomarkers P1NP, OC and CTX			✓				✓		
Blood sample for free and total cortisol (serum)			✓		✓		✓	✓	✓
Blood sample for ACTH			✓		✓		✓	✓	✓
Optional Biomarker sample: Whole Blood Plasma/serum proteomic			✓				✓		
Optional biomarker sample: Whole Blood Peripheral Blood Mononuclear Cells			✓				✓		

Activity	Visit Re-Induction (Week)							Premature Discontinuation	Follow-up 70-Day Visit
	Baseline (Week 0, Day 1)	2	4	6	8	10	12		
Optional biomarker sample: Whole Blood RNA			✓				✓		
Optional biomarker sample: Whole Blood DNA			✓				✓		
℞ TREATMENT									
Assign Study Drug	✓								
Administer Study Drug	✓	✓	✓	✓	✓	✓			
Dispense Study Drug	✓	✓	✓	✓	✓	✓			
Automatic determination of eligibility for the Maintenance Period in EDC							✓		

ACTH = adrenocorticotropic hormone; ADA = anti-drug antibody; ADC = antibody-drug conjugate; CDAI = Crohn's Disease Activity Index; CTX = C-terminal telopeptide of type 1 collagen; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EDC = electronic data capture; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; FCP = Fecal calprotectin; HbA1c = Hemoglobin A1c; HBV = hepatitis b virus; HCV = hepatitis C virus; hs-CRP = high sensitivity C-reactive protein; IBDQ = Inflammatory Bowel Disease Questionnaire; nAb = neutralizing antibody; OC = osteocalcin; P1NP = procollagen type I N-propeptide; PGIC-CD+ = Patient Global Impression of Change – Crohn's Disease+; PGIS-CD+ = Patient Global Impression of Severity – Crohn's Disease+; RNA = ribonucleic acid; SF-36 = Short Form-36

40-Week Maintenance Period

Activity	Baseline (Week 0, Day 1)	Maintenance Period (Week)																				Premature Discontinuation	Follow-up 70-Day Visit
		2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40		
INTERVIEWS AND QUESTIONNAIRES																							
Adverse Event Assessment		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Record concomitant medication/therapy		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TB risk assessment questionnaire																					✓		
SF-36					✓				✓				✓				✓				✓	✓	
IBDQ					✓				✓				✓				✓				✓	✓	
FACIT-Fatigue					✓				✓				✓				✓				✓	✓	
PGIC-CD+					✓				✓				✓				✓				✓	✓	
PGIS-CD+					✓				✓				✓				✓				✓	✓	
CDAI Components (may be performed at additional visits not marked if needed to confirm eligibility for Rescue Therapy)					✓				✓				✓				✓				✓	✓	
Automatic calculation of CDAI in EDC (may be performed at additional visits not marked if needed to confirm eligibility for Rescue Therapy)					✓				✓				✓				✓						
Bowel Incontinence Scale					✓				✓				✓				✓				✓	✓	
Subject Diary Review		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
LOCAL LABS AND EXAMS																							
Weight					✓				✓				✓				✓				✓	✓	✓
Vital Signs		✓			✓				✓				✓				✓				✓	✓	✓

Activity	Baseline (Week 0, Day 1)	Maintenance Period (Week)																				Premature Discontinuation	Follow-up 70-Day Visit
		2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40		
Complete Physical Exam													✓								✓	✓	
Symptom Directed Physical Exam					✓				✓								✓						
12-Lead ECG									✓												✓	✓	
Endoscopy (may be performed at additional visits not marked if needed to confirm eligibility for Rescue Therapy)																					✓	✓	
Intestinal Biopsies																					✓		
DXA scan																					✓		
Urine (U) pregnancy test (females of childbearing potential)			✓		✓		✓		✓		✓		✓		✓		✓		✓		✓	✓	✓
Chest x-ray (subjects with a newly positive PPD and/or QuantiFERON-TB Gold Plus test after Baseline or a positive response to TB risk questionnaire, Part I questions)																					✓		
CENTRAL LABS																							
hs-CRP					✓				✓				✓				✓				✓	✓	
FCP					✓				✓				✓				✓				✓	✓	
Hematology		✓			✓				✓				✓				✓				✓	✓	✓
HbA1c									✓								✓				✓	✓	✓
Clinical Chemistry		✓			✓				✓				✓				✓				✓	✓	✓
Urinalysis		✓			✓				✓				✓				✓				✓	✓	
Lipid Panel									✓				✓				✓				✓		
TB testing (QuantiFERON-TB Gold test and/or local PPD skin test)																					✓		

Activity	Baseline (Week 0, Day 1)	Maintenance Period (Week)																				Premature Discontinuation	Follow-up 70-Day Visit
		2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40		
HBV test (if required due to local regulations)							✓						✓						✓				
Blood samples for conjugated ADC (serum), total antibody (serum), free A-1677770 (plasma) assays					✓				✓				✓				✓				✓	✓	✓
Blood samples for ADA Assay (serum) including ADA titer and nAb assays (Central Lab shipping and lab handling)					✓				✓				✓				✓				✓	✓	✓
Blood sample for bone biomarkers P1NP, OC and CTX													✓								✓		
Blood sample for free and total cortisol (serum)		✓			✓				✓				✓				✓				✓	✓	✓
Blood sample for ACTH		✓			✓				✓				✓				✓				✓	✓	✓
Optional Biomarker sample: Whole Blood Plasma/serum proteomic													✓								✓		
Optional biomarker sample: Whole Blood PBMC													✓								✓		
Optional biomarker sample: Whole Blood RNA													✓								✓		
Optional biomarker sample: Whole Blood DNA													✓								✓		
℞ TREATMENT																							
Inadequate response assessment to determine eligibility for Rescue Therapy (may be performed at additional visits not marked if needed to confirm eligibility for Rescue Therapy)					✓				✓				✓				✓						

Activity	Baseline (Week 0, Day 1)	Maintenance Period (Week)																				Premature Discontinuation	Follow-up 70-Day Visit
		2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40		
Assign Study Drug	✓																						
Administer Study Drug	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Dispense Study Drug	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			

ACTH = adrenocorticotropic hormone; ADA = anti-drug antibody; ADC = antibody-drug conjugate; CDAI = Crohn's Disease Activity Index; CTX = C-terminal telopeptide of type 1 collagen; DNA = deoxyribonucleic acid; DXA = dual-energy X-ray absorptiometry; ECG = electrocardiogram; EDC = electronic data capture; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; FCP = Fecal calprotectin; HbA1c = Hemoglobin A1c; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hs-CRP = high sensitivity C-reactive protein; IBDQ = Inflammatory Bowel Disease Questionnaire; nAb = neutralizing antibody; OC = osteocalcin; P1NP = procollagen type I N-propeptide; PBMC = peripheral blood mononuclear cells; PGIC-CD+ = Patient Global Impression of Change – Crohn's Disease+; PGIS-CD+ = Patient Global Impression of Severity – Crohn's Disease+; PPD = purified protein derivative; RNA = ribonucleic acid; SF-36 = Short Form-36; TB = tuberculosis

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	29 August 2021
Version 2.0	11 October 2021
Version 1.1 (German Only)	28 January 2022
Version 2.1 (Belgium Only)	11 February 2022
Version 2.2 (German Only)	25 February 2022
Version 3.0	18 May 2022

The purpose of this version is to update the following sections:

Protocol

- Synopsis, Investigational Plan and Section 4.1, removed text that subjects who complete the study have an option to continue in a Long-Term Extension study.

  Rationale: The clinical development plan was updated to remove the Long-Term Extension study.

- Synopsis, Key Eligibility Criteria updated to include a subject history of inadequate response or intolerance to risankizumab.

  Rationale: Risankizumab has recently received regulatory approval for the treatment of CD. Updated language to include subjects with a history of inadequate response to or intolerance of treatment with risankizumab.

- Section 2.2, added a statement about the benefit-risk ratio of the device which is used in the study and clarified that the device is non-investigational.

  Rationale: To clarify the pre-filled syringe used in the study is a non-investigational device.

- Section 3.1, updated the wording for the population attribute of the estimand description.

  Rationale: To align with the evolving guidelines of the estimand framework, defining the population attribute as the target population instead of the analysis population. This update does not affect either the trial conduct or the statistical analysis.

- Section 5.1, updated eligibility criterion #11 to state that subjects must not have a disease history of > 3 bowel resections due to progression of CD.

  Rationale: To change the maximum number of prior bowel resections from ≥3 to >3 and specify the criterion applies only to prior bowel resections related to progression of CD in order to exclude subjects for whom limited benefit from study drug is anticipated. This change will allow the results of the study to be more generalizable to clinical practice, is aligned with another clinical development program, and does not affect the benefit-risk for subject participation.

- Section 5.1, updated eligibility criterion #12 to add subject history of at least one 8-week induction regimen of risankizumab (600 mg IV at Weeks 0, 4, and 8).

  Rationale: Risankizumab has recently received regulatory approval for the treatment of CD. Language updated to include subjects with a history of inadequate response to or intolerance of treatment with risankizumab and specify the minimum induction regimen required.

- Section 5.1, for eligibility criterion #28 added that subjects on azathioprine, 6-mercaptopurine, or methotrexate must have discontinued these therapies or be on a stable dose for ≥ 30 days prior to Baseline.

  Rationale: To clarify the washout period for the immunosuppressants azathioprine, 6-mercaptopurine, or methotrexate is ≥ 30 days prior to Baseline for a subject who has previously used and discontinued these therapies.

- Section 5.1, for eligibility criterion #30 added that the washout period required prior to the Baseline Visit is ≥ 12 weeks for risankizumab.

  Rationale: To specify a washout period for subjects treated with risankizumab.

- Section 5.1, for eligibility criterion #31 added that the eligibility criterion applies to any drug that was investigational at the time of protocol approval regardless of regulatory approval status of the drug for the treatment of CD.

  Rationale: To clarify this criterion applies to all drugs which were investigational for the treatment of CD at the time of protocol approval as additional drugs may receive regulatory approval for the treatment of CD during the conduct of this clinical trial.

- Section 5.1, for eligibility criterion #32 and Section 5.4, added language to specify that live vaccines with replicating potential are prohibited and that the JYNNEOS vaccine for prevention of monkeypox disease is permitted.

  Rationale: Monkeypox disease has emerged as a health issue during the conduct of the study. Administration of all live vaccines with replicating potential remains as prohibited during the study. However, administration of the JYNNEOS vaccine is allowed. The JYNNEOS vaccine, is used for the prevention of smallpox and monkeypox. It is a third-generation vaccine based on a live, attenuated non-replicating orthopoxvirus, Modified Vaccinia Ankara (MVA). MVA is a live virus that does not have the ability to replicate efficiently in humans and therefore can be given to immune compromised patients without the risk of developing a monkeypox infection.

- Section 5.3, added Risankizumab to the prohibited medications.

  Rationale: Risankizumab has recently received regulatory approval for the treatment of CD.

- Section 5.6, added "at least 70 days" to align with the 70-Day Follow-up Visit requirement as correctly described in Section 2.5 of the Operations Manual.

  Rationale: To add text which had been erroneously left out.

- Section 5.7, added language to detail study drug return or destruction procedures following subject completion or discontinuation from study treatment.

  Rationale: Language added per EU CT regulatory guidance.

- Section 7.3, updated the handling strategy for the intercurrent event of study drug discontinuation.

Rationale: To clarify the handling strategy after switching to other medications for CD following study drug discontinuation, since the use of other medications may confound assessments collected afterwards.

- Section 8.3, updated language to outline AbbVie information security policies and de-identification of subject health information.

  Rationale: To clarify details for subject confidentiality and protection of personal data to align with EU CT regulatory guidance.

- Appendix C, updated protocol signatories.

  Rationale: To update due to study personnel changes for this protocol amendment.

Operations Manual

- Section 1 and Section 4.2, removed the safety team contact number.

  Rationale: The phone number previously provided will no longer be supported.

- Section 2.3 and Section 3.14, for Maintenance Period Week 40, updated footnote "e" and respective section text to remove guidance for the assessment of endoscopy before the administration of the first dose of study drug in the Long-Term Extension study.

  Rationale: The Long-Term Extension study was removed from the investigational plan.

- Section 3.15, added for subject with an endoscopy that was performed before the Screening visit, no intestinal biopsy sample(s) are required to be collected at Screening.

  Rationale: To clarify that intestinal biopsies will not be collected at Screening if the endoscopy is not performed during the screening period.

- Section 4.2, updated language that the sponsor will be responsible for SUSAR reporting for the IMP in accordance with global and local requirements (not Directive 2001/20/EC).

  Rationale: To clarify SUSAR reporting per EU CT regulatory guidance.