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Study ID: D5170C00002

Title: Evaluation of Efficacy and Safety of MEDI2070 in Subjects With Active, Moderate to Severe Crohn's Disease

Protocol and Statistical Analysis Plan Date: 27-Mar-2018

A Phase 2b Double-blind, Multi-dose, Placebo-controlled Study to Evaluate the Efficacy and Safety of MEDI2070 in Subjects with Moderate to Severe Crohn's Disease Who Have Failed or Are Intolerant to Anti-tumor Necrosis Factor-alpha Therapy

Sponsor Protocol Number: D5170C00002

Application Number: IND number: 111773
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Investigational Product: MEDI2070

Sponsor: MedImmune Limited, a wholly owned subsidiary of AstraZeneca, Milstein Building, Granta Park, Cambridge, CB21 6GH, UK

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PROTOCOL SYNOPSIS

TITLE

A Phase 2b Double-blind, Multi-dose, Placebo-controlled Study to Evaluate the Efficacy and Safety of MEDI2070 in Subjects with Moderate to Severe Crohn's Disease Who Have Failed or Are Intolerant to Anti-tumor Necrosis Factor-alpha Therapy

HYPOTHESES

Primary Hypothesis: Administration of MEDI2070 will result in reduced intestinal inflammation, which will translate into an improved clinical remission rate (as measured by the Crohn's Disease Activity Index [CDAI]) compared with placebo in subjects with moderate to severe Crohn's disease (CD) who have failed or are intolerant to anti-tumor necrosis factor-alpha (TNFα) therapy.

OBJECTIVES

Primary Objective

To evaluate the efficacy of MEDI2070 versus placebo to induce clinical remission based on the CDAI score at Week 8 in subjects with moderate to severe CD who have failed or are intolerant to anti-TNFα therapy.

Induction Period Secondary Objectives:

1. To evaluate the efficacy of MEDI2070 versus placebo to induce remission at Week 16 based on the Simple Endoscopic Score for Crohn's Disease (SES-CD)
2. To evaluate the efficacy of MEDI2070 versus placebo to induce response at Week 16 based on the SES-CD
3. To evaluate the efficacy of MEDI2070 versus placebo to induce remission at Week 8 based on the Patient-reported Outcomes 2 score (PRO2)
4. To evaluate the efficacy of MEDI2070 versus placebo to induce response at Week 8 based on the PRO2
5. To evaluate the efficacy of MEDI2070 versus placebo to induce clinical response at Week 8 based on the CDAI
6. To evaluate the efficacy of MEDI2070 versus placebo to induce remission at Week 16 based on the PRO2
7. To evaluate the efficacy of MEDI2070 versus placebo to induce response at Week 16 based on the PRO2
8. To evaluate the efficacy of MEDI2070 versus placebo to induce clinical remission at Week 16 based on the CDAI
9. To evaluate the efficacy of MEDI2070 versus placebo to induce clinical response at Week 16 based on the CDAI
10. To demonstrate safety and tolerability of MEDI2070 therapy
11. To characterize the pharmacokinetics (PK) and immunogenicity of MEDI2070
12. To characterize the dose-response and exposure-response relationships

[redacted]

Maintenance Period Secondary Objectives:

1. To evaluate the efficacy of MEDI2070 versus placebo to induce clinical remission based on CDAI score at Week 28
2. To evaluate the efficacy of MEDI2070 versus placebo on remission at Week 28 based on the SES-CD
3. To evaluate the efficacy of MEDI2070 versus placebo on remission at Week 28 based on the PRO2
4. To evaluate the efficacy of MEDI2070 versus placebo on modified sustained remission, defined as remission at both Week 16 and at Week 28 based on the SES-CD
5. To evaluate the efficacy of MEDI2070 versus placebo on modified sustained remission, defined as remission at both Week 8 and at Week 28 based on the PRO2
6. To evaluate the efficacy of MEDI2070 versus placebo on modified sustained clinical remission, defined as clinical remission at both Week 8 and at Week 28 based on the CDAI

7. To evaluate the efficacy of MEDI2070 versus placebo on response at Week 28 based on the SES-CD
8. To evaluate the efficacy of MEDI2070 versus placebo on response at Week 28 based on the PRO2
9. To evaluate the efficacy of MEDI2070 versus placebo on clinical response at Week 28 based on the CDAI
10. To demonstrate safety and tolerability of MEDI2070 therapy
11. To characterize the PK and immunogenicity of MEDI2070

[redacted]

STUDY ENDPOINTS]

Primary Endpoint

CDAI clinical remission (CDAI score < 150) at Week 8

Induction Period Secondary Endpoints:

- SES-CD remission at Week 16
- SES-CD response at Week 16
- PRO2 remission at Week 8
- PRO2 response at Week 8
- CDAI clinical response at Week 8
- Abdominal pain remission at Week 8
- Abdominal pain response at Week 8
- Loose/liquid stool frequency remission at Week 8
- Loose/liquid stool frequency response at Week 8
- PRO2 remission at Week 16
- PRO2 response at Week 16
- CDAI clinical remission at Week 16
- CDAI clinical response at Week 16
- Abdominal pain remission at Week 16
- Abdominal pain response at Week 16
- Loose/liquid stool frequency remission at Week 16
- Loose/liquid stool frequency response at Week 16
- [redacted]
- Serum MEDI2070 concentration levels collected during the induction period
- Incidence of anti-drug antibodies (ADA) against MEDI2070

Maintenance Period Secondary Endpoints:

- CDAI clinical remission at Week 28
- SES-CD Remission at Week 28
- PRO2 Remission at Week 28
- CDAI Modified sustained clinical remission at Weeks 8 and 28
- [redacted]
- CDAI clinical response at Week 28
- SES-CD Response at Week 28
- PRO2 Response at Week 28
- Abdominal pain remission at Week 28
- Abdominal pain response at Week 28
- Loose/liquid stool frequency remission at Week 28
- Loose/liquid stool frequency response at Week 28
- Serum MEDI2070 concentration levels collected during the maintenance period
- Incidence of ADA against MEDI2070
- [redacted]

Induction and Maintenance Periods Safety Endpoints:

- Incidence and severity of treatment-emergent adverse events (TEAEs)
- Incidence of treatment-emergent serious AEs (TESAEs)
- Incidence and severity of treatment-emergent adverse events of special interest (AESIs), including:
  - Incidence and severity of infusion/injection-site reactions
  - Incidence and severity of hypersensitivity reactions
  - Incidence of malignancies
  - Major cardiac events, defined as myocardial infarction, stroke, or cardiovascular death
  - Incidence and severity of ocular adverse events (AEs), including cataracts
- Incidence of AEs leading to investigational product discontinuation
- Incidence of specific laboratory abnormalities

STUDY DESIGN

This is a 3-part Phase 2b study comprising a 16-week, double-blind, placebo-controlled, induction period; a 12-week, double-blind, placebo-controlled, maintenance period; and a 24-week, open-label period designed to evaluate the short-term efficacy and the short- and long-term safety of MEDI2070 in subjects with moderate to severe, active CD who have failed or are intolerant to anti-TNFα therapy as determined by the investigator. Subjects will be stratified based on the number of prior anti-TNFα agents that they have failed or not tolerated (1 vs > 1).

Approximately 342 subjects at approximately 300 centers worldwide will be randomly assigned to 1 of 5 treatment groups to receive intravenous (IV) and subcutaneous (SC) investigational product (MEDI2070 or placebo) once every 4 weeks (Q4W) during the double-blind, placebo-controlled, induction and maintenance periods. Subjects who complete the double-blind, placebo-controlled, maintenance period (Week 28) will have the option to enter a 24-week, open-label period in which they will receive open-label MEDI2070 (210 mg SC) Q4W (Weeks 28 through 48). All subjects will be followed for safety at 3 visits over 28 weeks (Weeks 60, 70, and 80 for subjects completing the open-label period) after their last dose of investigational product.

TARGET SUBJECT POPULATION

The subjects in this study will be 18 to 80 years of age, inclusive, with moderate to severe, active CD who, as determined by the investigator, have failed or are intolerant to anti-TNFα therapy. This includes subjects who have received an anti-TNFα agent at a dose approved for the treatment of CD and did not respond initially (ie, primary non-response), or responded initially but then lost response with continued therapy (ie, secondary non-response), or were intolerant to the medication.

INVESTIGATIONAL PRODUCT, DOSAGE, AND MODE OF ADMINISTRATION

Subjects will receive investigational product (MEDI2070 or placebo) by IV infusion and/or SC injection at Week 0 (Day 1) then once Q4W during the 16-week, double-blind, placebo-controlled, induction period (ie, Weeks 4, 8, and 12) and the 12-week, double-blind, placebo-controlled, maintenance period (ie, Weeks 16, 20, and 24). All subjects who complete the double-blind, maintenance period will have the option to enter the 24-week, open-label period. All subjects entering the open-label period will receive open-label MEDI2070 (210 mg SC) once Q4W (ie, Weeks 28, 32, 36, 40, 44, and 48).

A total of approximately 342 subjects will be randomly assigned to 1 of 5 treatment groups:

Treatment Group	Double-blind Period				Open-label Period
	Induction			Maintenance	
	Week 0	Week 4	Weeks 8 and 12	Weeks 16, 20, and 24	Weeks 28, 32, 36, 40, 44, and 48
1 - High (n = 76)	700 mg MEDI2070 IV + placebo SC	700 mg MEDI2070 IV + placebo SC	210 mg MEDI2070 SC	210 mg MEDI2070 SC	210 mg MEDI2070 SC
2 - High-medium (n = 76)	280 mg MEDI2070 IV + placebo SC	210 mg MEDI2070 SC + placebo IV	210 mg MEDI2070 SC	210 mg MEDI2070 SC	210 mg MEDI2070 SC
3 - Low-medium (n = 76)	210 mg MEDI2070 SC + placebo IV	105 mg MEDI2070 SC + placebo IV	105 mg MEDI2070 SC	105 mg MEDI2070 SC	210 mg MEDI2070 SC
4 - Low (n = 38)	70 mg MEDI2070 SC + placebo IV	35 mg MEDI2070 SC + placebo IV	35 mg MEDI2070 SC	35 mg MEDI2070 SC	210 mg MEDI2070 SC
5 - Placebo (n = 76)	Placebo SC and IV	Placebo SC and IV	Placebo SC	Placebo SC	210 mg MEDI2070 SC

STATISTICAL ANALYSIS PLAN

Sample size:

With a total sample size of approximately 342 and a randomization ratio of 2:1:2:2:2, the sample sizes are 76, 38, 76, 76, and 76 for placebo and MEDI2070 low, low-medium, high-medium, and high dose groups, respectively. A 10% dropout rate is assumed for each treatment group during the induction period.

Assuming a placebo CDAI remission rate of 12% and MEDI2070 high dose CDAI clinical remission rate of 31% at Week 8 of the induction period, approximately 76 subjects per treatment group will provide at least 85% power to detect a 19% difference in CDAI clinical remission rates at Week 8 between MEDI2070 high dose versus placebo, using a two-sided test at a significance level of $\alpha = 0.10$. The minimum detectable difference in CDAI clinical remission rates at Week 8 will be 11%.

Assuming a 5% placebo SES-CD remission rate and 20% MEDI2070 high dose SES-CD remission rate at Week 16 of the induction period, the given sample size will provide at least 81% power to detect a 15% difference in SES-CD remission rates at Week 16 between MEDI2070 high dose versus placebo using a two-sided test at a significance level of $\alpha = 0.10$. The minimum detectable difference in SES-CD remission rates at Week 16 will be 10%.

In addition, recent data suggest that subjects with elevated baseline levels of serum IL-22 may have enhanced treatment response to MEDI2070 therapy. The power is also estimated for CDAI clinical remission at Week 8 in the high-IL-22 subpopulation. Assuming approximately 50% of subjects have elevated baseline levels of serum IL-22, and assuming these subjects are approximately equally distributed between treatment groups, there will be 38 high-IL-22 subjects in the MEDI2070 high dose and placebo groups, respectively. Assuming a placebo CDAI clinical remission rate of 15% and MEDI2070 high dose CDAI clinical remission rate of 42% at Week 8 of the induction period, 38 subjects per treatment group will provide at least 80% power to detect a difference of 27% between the MEDI2070 high dose group and placebo within the high-IL-22 subpopulation, using a two-sided test at a significance level of $\alpha = 0.10$. The minimum detectable difference in CDAI clinical remission rates at Week 8 within high-IL-22 subpopulation will be 17%.

Statistical analyses:

The primary analysis will be conducted in ITT population. The primary efficacy endpoint is CDAI clinical remission at Week 8 of the induction period. The primary comparison of interest will be MEDI2070 high dose group versus placebo. The comparisons between MEDI2070 high-medium dose versus placebo, low-medium dose versus placebo, and MEDI2070 low dose versus placebo will also be conducted.

For the primary efficacy endpoint and other dichotomous endpoints, difference in response rates between MEDI2070 dose groups and placebo group and associated 90% confidence interval will be provided. P-values for comparisons between any MEDI2070 dose groups and placebo will be obtained from a logistic regression model adjusting for prior anti-TNFα use (1 vs > 1). In the event the number of responses is too small (ie, < 5), exact logistic regression will be performed instead. The statistically significant treatment effect will be tested against two-sided alpha level of 0.10. A sensitivity analysis will be performed by extending the logistic regression model planned above via adjusting for baseline CDAI score and/or other baseline covariates for subjects in the ITT population. In addition, a stratified Cochran Mantel Haenszel test or a stratified exact test may be performed in the event of small number of responses. Further, the subgroup analysis will be conducted for primary and key secondary endpoints to verify the treatment effect in pre-specified individual strata. Missing data for dichotomous endpoints will be handled using the non-responder imputation method through the end of the placebo-controlled, double-blind period.

For continuous endpoints, comparisons between any MEDI2070 dose groups and placebo will be performed using a mixed-effects repeated-measures model adjusting for prior anti-TNFα use (1 vs > 1) assuming missing at random mechanism. Other methods to handle the missing data may be explored. The details will be described in the Statistical Analysis Plan (SAP).

The dose-response trend for the induction period will be tested. The details will be described in the SAP.

Interim analysis:

An interim analysis may be conducted when at least 75% of the total planned number of subjects has completed the Week 16 visit or withdrawn prior to the Week 16 visit. This analysis would evaluate primary and secondary endpoints through Week 16. Since this is a Phase 2b study, the interim analysis is intended to assist internal decision making and does not include a possibility to stop for efficacy or futility. Thus, there is no alpha level adjustment for the final analysis. To ensure the blinding of each subject's treatment assignment throughout the

placebo-controlled, double-blind, maintenance period, the interim analysis will be performed by a limited number of sponsor personnel who are not involved in the conduct of the study. Study site personnel and sponsor personnel who are associated directly with the conduct of this study and study subjects will remain blinded to the subject-specific treatment assignment as well as the outcomes of the interim analysis until the completion of the double-blind, maintenance period.

The primary analysis will be performed when all subjects complete the initial 16-week, induction period. A further analysis is planned when all subjects complete the 28-week, randomized, placebo-controlled, double-blind period. All data available by the time of the primary analysis database snapshot will be included in the analysis, including available data through Week 28 and the open-label period for a certain proportion of subjects. The final analysis for the study, including all study periods and all data, will be performed at the end of the study.

A Data Monitoring Committee will review safety data on a regular basis until the last subject completes Week 28.

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ADA	anti-drug antibody(ies)
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
[redacted]	[redacted]
C_{max}	maximum concentration
CRP	C-reactive protein
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	Electronic Data Capture
e-diary	electronic diary
EU	European Union
GCP	Good Clinical Practice
GI	gastrointestinal
GMP	Good Manufacturing Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IBD	inflammatory bowel disease
[redacted]	[redacted]
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFNγ	interferon-gamma
IgG2	immunoglobulin G2
IL	interleukin
IL-23R	interleukin-23 receptor
IRB	Institutional Review Board
ITT	Intent to Treat
IV	intravenous(ly)
IVRS/IWRS	interactive voice/web response system
[redacted]	[redacted]

Abbreviation or Specialized Term	Definition
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MS	multiple sclerosis
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events V4.03
NK	natural killer
PE	polyethylene
PGIC-IBD	Patient Global Impression of Change-Inflammatory Bowel Disease
PK	pharmacokinetic(s)
PPD	purified protein derivative
PRO	patient-reported outcome
PRO2	Patient-Reported Outcomes-2 score
PVC	polyvinyl chloride
Q4W	every 4 weeks
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SES-CD	Simple Endoscopic Score for Crohn's Disease
SID	subject identification
SRT	Safety Review Team
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TNFα	tumor necrosis factor-alpha
ULN	upper limit of normal
USA	United States of America
w/v	weight per volume

1 INTRODUCTION

1.1 Disease Background

Crohn's disease (CD) is a chronic transmural inflammatory disease of unknown etiology that most commonly affects the distal ileum and colon, and may occur in any part of the gastrointestinal (GI) tract. CD occurs most commonly between the ages of 15 and 35 years, although patients of any age may be affected. Patients with CD have uncontrolled inflammation that causes direct or collateral damage to the intestinal mucosa. The leading current hypothesis is that, in genetically predisposed individuals, this inflammation can result either from persistence of inflammatory stimulus, due to impaired gut barrier function, or from a dysregulated inflammatory response (Sandborn et al, 2008; Rutgeerts et al, 2003). Clinical signs and symptoms include chronic diarrhea, abdominal pain, cachexia, abdominal mass, or tenderness, as well as the overt signs of fistulae. The disease course is variable; patients can experience a severe initial flare followed by few symptoms over the next 10 years (43%) or symptoms that are chronic and persistent (19%) or relapsing remitting (32%; Baumgart and Sandborn, 2012).

Commonly used medical therapies include aminosalicylates (including sulfasalazine and mesalamine), systemic corticosteroids, immunosuppressive agents (eg, azathioprine and methotrexate), antibacterial agents, and biologic agents (eg, adalimumab, infliximab, certolizumab, and vedolizumab). Despite the availability of these medical therapies, the remaining morbidity and the complications of CD (eg, intestinal obstruction and or perforation, fistula formation, malnutrition) continue to warrant new therapies.

Interleukin (IL)-23, a member of the IL-12 family of cytokines, is a heterodimeric cytokine consisting of 2 subunits: p40 and p19. The p40 subunit is shared by IL-12 and IL-23 as a common subunit, and is targeted by inhibitors of IL-12/23 (eg, ustekinumab and briakinumab). The main known effects of IL-23 are to drive the differentiation of T-helper 17 cells, as well as macrophages, natural killer (NK) cells, dendritic cells, and innate lymphoid cells leading to up-regulation of IL-17, IL-22, tumor necrosis factor-alpha (TNFα), granulocyte-macrophage colony-stimulating factor, and interferon-gamma (IFNγ), and down-regulation of IL-10 (Eken et al, 2014).

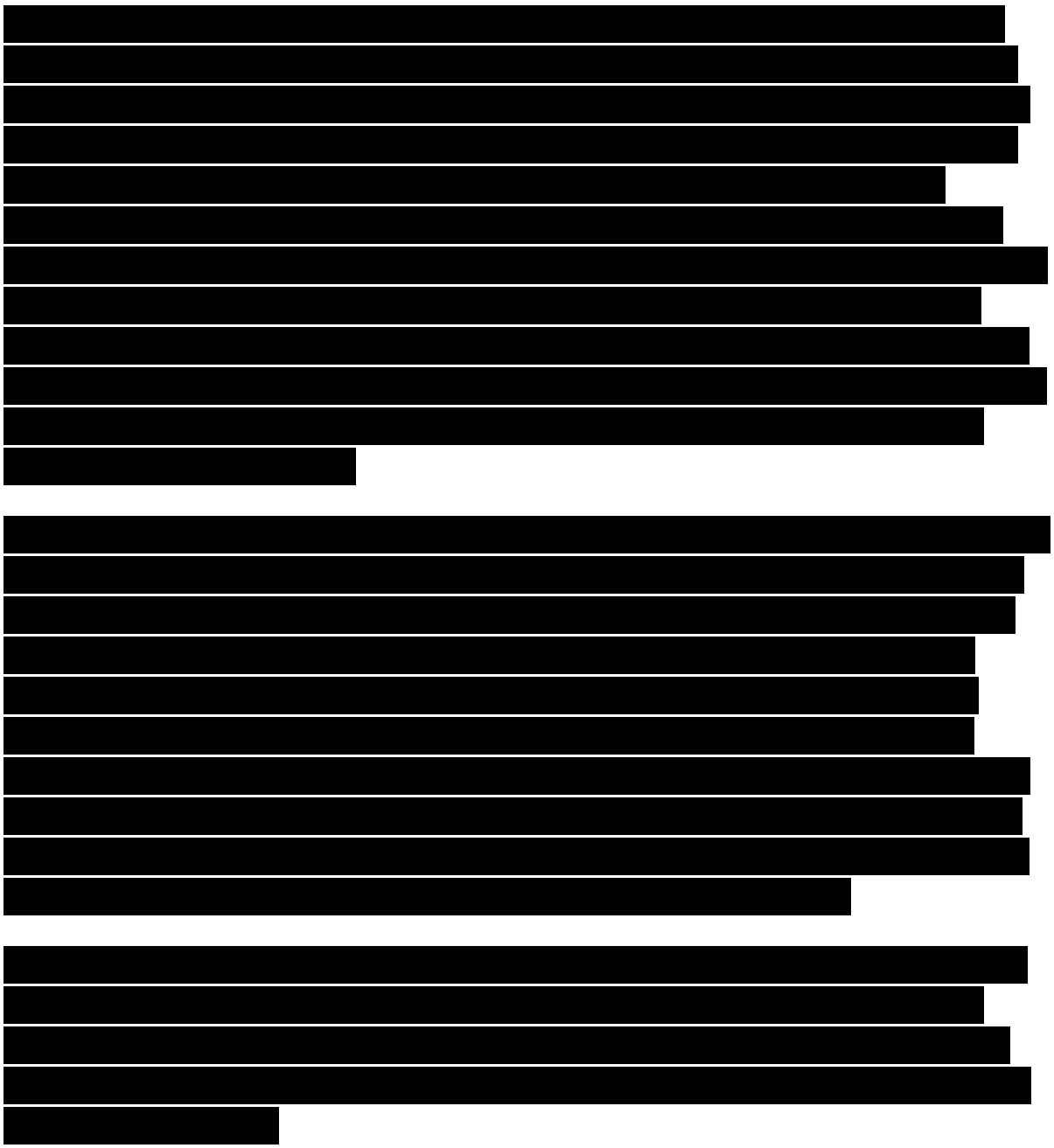
Studies in patients have demonstrated that IL-23 is upregulated in cells and target tissues of CD and ulcerative colitis, while IL-12 is not (Schmidt et al, 2005). Similar observations have been reported in psoriatic lesion skin (Lee et al, 2004), dendritic cells from patients with multiple sclerosis (MS; Vaknin-Dembinsky et al, 2006), and active lesions from patients with MS (Li et al, 2007). Genome-wide association studies in CD and psoriasis patients showed

significant association between polymorphisms in the unique IL-23 receptor (IL-23R) component and disease (Cargill et al, 2007; Duerr et al, 2006). Furthermore, allelic variants of IL-23R have shown significant correlation with the frequency of ulcerative colitis (Cargill et al, 2007), rheumatoid arthritis (Farago et al, 2008), ankylosing spondylitis (Burton et al, 2007), and MS (Illes et al, 2008).

In the clinic, anti-IL-12/23p40 antibodies (eg, ustekinumab and briakinumab) have been shown to induce clinical responses in CD (Phase 2 studies; Toedter et al, 2009; Sandborn et al, 2008; Mannon et al, 2004) and psoriasis (Phase 2 and Phase 3 studies; Gordon et al, 2012; Kimball et al, 2012; Langley et al, 2012; Gottlieb et al, 2011; Reich et al, 2011; Strober et al, 2011; Leonardi et al, 2008; Papp et al, 2008). Phase 1 and Phase 2 clinical studies with anti-IL-23 antibodies MEDI2070 (Amgen Study 20080767) and CNTO 1959 (Sofen et al, 2011) in subjects with psoriasis have demonstrated clinical efficacy comparable with antibodies targeting both IL-12 and IL-23, indicating that therapeutic effects of the anti-IL-12/23p40 antibodies may be due to neutralization of IL-23 alone.

[redacted]

[redacted]



Refer to the current version of the Investigator's Brochure for details.

1.5 Rationale for Conducting the Study

CD is a chronic, relapsing-remitting, inflammatory disease of the GI tract. Some patients may have persistent clinically active disease. The current treatment options for patients with moderate to severe CD, refractory to standard therapies that include 5-aminosalicylates, glucocorticosteroids, 6-mercaptopurine, azathioprine, methotrexate, anti-TNFα mAbs, and vedolizumab are limited. MEDI2070 is being developed as a treatment for CD to reduce

intestinal inflammation and improve signs and symptoms. Study CD-IA-MEDI2070-1147 demonstrated improved clinical responses and remission rates as measured by CDAI. This study, D5170C00002, seeks to confirm those observations, and to extend them to include assessments of clinical responses as demonstrated by improvement of symptoms and of colonic mucosal appearance as observed on endoscopy.

1.5.1 Benefit-risk Assessment

Results from previous clinical studies have provided safety and tolerability data for MEDI2070 and shown significantly greater efficacy for MEDI2070 compared with placebo for achieving CDAI response, CDAI 100-point improvement, and decreases in C-reactive protein (CRP) and fecal calprotectin (Study CD-IA-MEDI2070-1147). No safety risk of MEDI2070 was identified. In Study CD-IA-MEDI2070-1147, TEAEs, TEAEs of ≥ Grade 3 severity, TESAEs and TEAEs leading to discontinuation of investigational product occurred in equivalent numbers of subjects in the placebo and MEDI2070 groups. TEAEs related to investigational product and adverse events of special interest (AESIs), including infections, were more common in the placebo group. The combination of observed efficacy and apparent safety in the Phase 2a study (CD-IA-MEDI2070-1147) suggests an acceptable benefit-risk balance to justify exposing approximately 5-fold more subjects with moderate to severe CD to the range of doses planned in this study.

Although no safety risks for MEDI2070 have been identified, the immunoregulatory role of IL-23 in humans is not completely understood. Potential risks include infections, malignancies, complications associated with vaccination, infusion reactions, injection-site reactions, hypersensitivity, immune complex disease, and neurological and visual toxicities. Subjects will be closely monitored during the study with regular full blood analysis including differential white cell count and serum chemistry to monitor the risk of infection. Visual acuity tests, ophthalmoscopy, and complete physical and neurologic examinations will be performed at screening and during the study. In addition, live/attenuated vaccinations will not be permitted during the study. Exclusion criteria have been formulated to ensure that subjects at increased potential risk due to the mechanism of action of MEDI2070 are not enrolled in the study.

In addition, an independent Data Monitoring Committee (DMC) will monitor and protect the safety of the subjects through review of safety data on a regular basis throughout the double-blind period of the study; ie, until the last subject completes Week 28 (see Section 4.8.9.

1.6 Research Hypotheses

1.6.1 Primary Hypothesis

Administration of MEDI2070 will result in reduced intestinal inflammation, which will translate into an improved clinical remission rate (as measured by the CDAI) compared with placebo in subjects with moderate to severe CD who have failed or are intolerant to anti-TNFα therapy.

1.6.2 Secondary Hypotheses

1. Administration of MEDI2070 will result in reduced intestinal inflammation, which will translate into an improved appearance of the colonic and ileal mucosa (as measured by the Simple Endoscopic Score for Crohn's Disease [SES-CD]) compared with placebo in subjects with moderate to severe CD who have failed or are intolerant to anti-TNFα therapy.
2. Administration of MEDI2070 will result in reduced intestinal inflammation, which will translate into an improved clinical remission rate (as measured by the Patient-Reported Outcomes-2 score [PRO2] and its individual components) compared with placebo in subjects with moderate to severe CD who have failed or are intolerant to anti-TNFα therapy.
3. [redacted]

2 OBJECTIVES

2.1 Objectives

2.1.1 Primary Objective

The primary objective of the study is to evaluate the efficacy of MEDI2070 versus placebo to induce clinical remission based on the CDAI score at Week 8 in subjects with moderate to severe CD who have failed or are intolerant to anti-TNFα therapy.

2.1.2 Secondary Objectives

2.1.2.1 Induction Period

1. To evaluate the efficacy of MEDI2070 versus placebo to induce remission at Week 16 based on the SES-CD
2. To evaluate the efficacy of MEDI2070 versus placebo to induce response at Week 16 based on the SES-CD
3. To evaluate the efficacy of MEDI2070 versus placebo to induce remission at Week 8 based on the PRO2

4. To evaluate the efficacy of MEDI2070 versus placebo to induce response at Week 8 based on the PRO2
5. To evaluate the efficacy of MEDI2070 versus placebo to induce clinical response at Week 8 based on the CDAI
6. To evaluate the efficacy of MEDI2070 versus placebo to induce remission at Week 16 based on the PRO2
7. To evaluate the efficacy of MEDI2070 versus placebo to induce response at Week 16 based on the PRO2
8. To evaluate the efficacy of MEDI2070 versus placebo to induce clinical remission at Week 16 based on the CDAI
9. To evaluate the efficacy of MEDI2070 versus placebo to induce clinical response at Week 16 based on the CDAI
10. To demonstrate safety and tolerability of MEDI2070 therapy
11. To characterize the PK and immunogenicity of MEDI2070
12. To characterize the dose-response and exposure-response relationships

[redacted]

2.1.2.2 Maintenance Period

1. To evaluate the efficacy of MEDI2070 versus placebo to induce clinical remission based on CDAI score at Week 28
2. To evaluate the efficacy of MEDI2070 versus placebo on remission at Week 28 based on the SES-CD
3. To evaluate the efficacy of MEDI2070 versus placebo on remission at Week 28 based on the PRO2
4. To evaluate the efficacy of MEDI2070 versus placebo on modified sustained remission, defined as remission at both Week 16 and at Week 28 based on the SES-CD
5. To evaluate the efficacy of MEDI2070 versus placebo on modified sustained remission, defined as remission at both Week 8 and at Week 28 based on the PRO2
6. To evaluate the efficacy of MEDI2070 versus placebo on modified sustained clinical remission, defined as clinical remission at both Weeks 8 and 28 based on the CDAI
7. To evaluate the efficacy of MEDI2070 versus placebo on response at Week 28 based on the SES-CD
8. To evaluate the efficacy of MEDI2070 versus placebo on response at Week 28 based on the PRO2
9. To evaluate the efficacy of MEDI2070 versus placebo on clinical response at Week 28 based on the CDAI
10. To demonstrate safety and tolerability of MEDI2070 therapy
11. To characterize the PK and immunogenicity of MEDI2070
12. [redacted]

[redacted]

2.2 Study Endpoints

Remission and response will be assessed by both clinical and PRO measures. The following definitions will be used:

- CDAI clinical remission: CDAI score of < 150
- CDAI clinical response: Decrease from baseline in the CDAI of ≥ 100 points
- SES-CD remission: Total SES-CD score ≤ 4, with:
  - No subscore > 2, and
  - Segments scored at baseline that cannot be observed on a subsequent examination will be scored with an imputed value unchanged from baseline
- SES-CD response: Decrease from baseline in SES-CD ≥ 50%; segments scored at baseline that cannot be observed on a subsequent examination will be scored with an imputed value unchanged from baseline.
- PRO2 remission (loose/liquid stool frequency/abdominal pain): Remission achieved for both abdominal pain and loose/liquid stool frequency
- PRO2 response: (loose/liquid stool frequency/abdominal pain): Remission or response in one symptom (either abdominal pain or stool frequency) plus response in the other
  - Abdominal pain remission: On an 11-point (0 to 10) pain scale: During 1 week, no daily score > 2
  - Abdominal pain response: On an 11-point (0 to 10) pain scale: ≥ 30% reduction in weekly pain score from baseline

- Loose/liquid stool frequency remission: Counting stools identified as Type 6 or 7 on Bristol Stool Scale, during 1 week, each daily loose loose/liquid stool count ≤ 3
- Loose/liquid stool frequency response: Counting stools identified as Type 6 or 7 on Bristol Stool Scale, ≥ 30% reduction in weekly loose/liquid stool count compared to baseline

2.2.1 Primary Endpoint

The primary endpoint is CDAI clinical remission (CDAI score < 150) at Week 8.

2.2.2 Secondary Endpoint(s)

2.2.2.1 Induction Period

1. SES-CD remission at Week 16
2. SES-CD response at Week 16
3. PRO2 remission at Week 8
4. PRO2 response at Week 8
5. CDAI clinical response at Week 8
6. Abdominal pain remission at Week 8
7. Abdominal pain response at Week 8
8. Loose/liquid stool frequency remission at Week 8
9. Loose/liquid stool frequency response at Week 8
10. PRO2 remission at Week 16
11. PRO2 response at Week 16
12. CDAI clinical remission at Week 16
13. CDAI clinical response at Week 16
14. Abdominal pain remission at Week 16
15. Abdominal pain response at Week 16
16. Loose/liquid stool frequency remission at Week 16
17. Loose/liquid stool frequency response at Week 16

[redacted]

20. Serum MEDI2070 concentration levels collected during the induction period
21. Incidence of ADA against MEDI2070

2.2.2.2 Maintenance Period

1. CDAI clinical remission at Week 28
2. SES-CD remission at Week 28

3. PRO2 remission at Week 28
4. CDAI Modified sustained clinical remission at Week 8 and Week 28

[redacted]

7. CDAI clinical response at Week 28
8. SES-CD response at Week 28
9. PRO2 response at Week 28
10. Abdominal pain remission at Week 28
11. Abdominal pain response at Week 28
12. Loose/liquid stool frequency remission at Week 28
13. Loose/liquid stool frequency response at Week 28
14. Serum MEDI2070 concentration levels collected during the maintenance period
15. Incidence of ADA against MEDI2070

[redacted]

[redacted]

2.2.4 Safety Endpoints

1. Incidence and severity of TEAEs
2. Incidence of TESAEs
3. Incidence and severity of treatment-emergent AESIs, including:
   a. Incidence and severity of infusion/injection-site reactions
   b. Incidence and severity of hypersensitivity reactions
   c. Incidence of malignancies
   d. Major cardiac events, defined as myocardial infarction, stroke, or cardiovascular death
   e. Incidence and severity of ocular AEs, including cataracts
4. Incidence of AEs leading to investigational product discontinuation
5. Incidence of specific laboratory abnormalities

3 STUDY DESIGN

3.1 Description of the Study

3.1.1 Overview

This is a 3-part Phase 2b study (Figure 3.1.1-1) comprising a 16-week, double-blind, placebo-controlled, induction period; a 12-week, double-blind, placebo-controlled, maintenance period; and a 24-week, open-label period designed to evaluate the short-term efficacy and the short- and long-term safety of MEDI2070 in subjects with moderate to severe, active CD who have failed or are intolerant to anti-TNFα therapy as determined by the investigator. Subjects will be stratified based on the number of prior anti-TNFα agents that failed or were not tolerated (1 vs > 1).

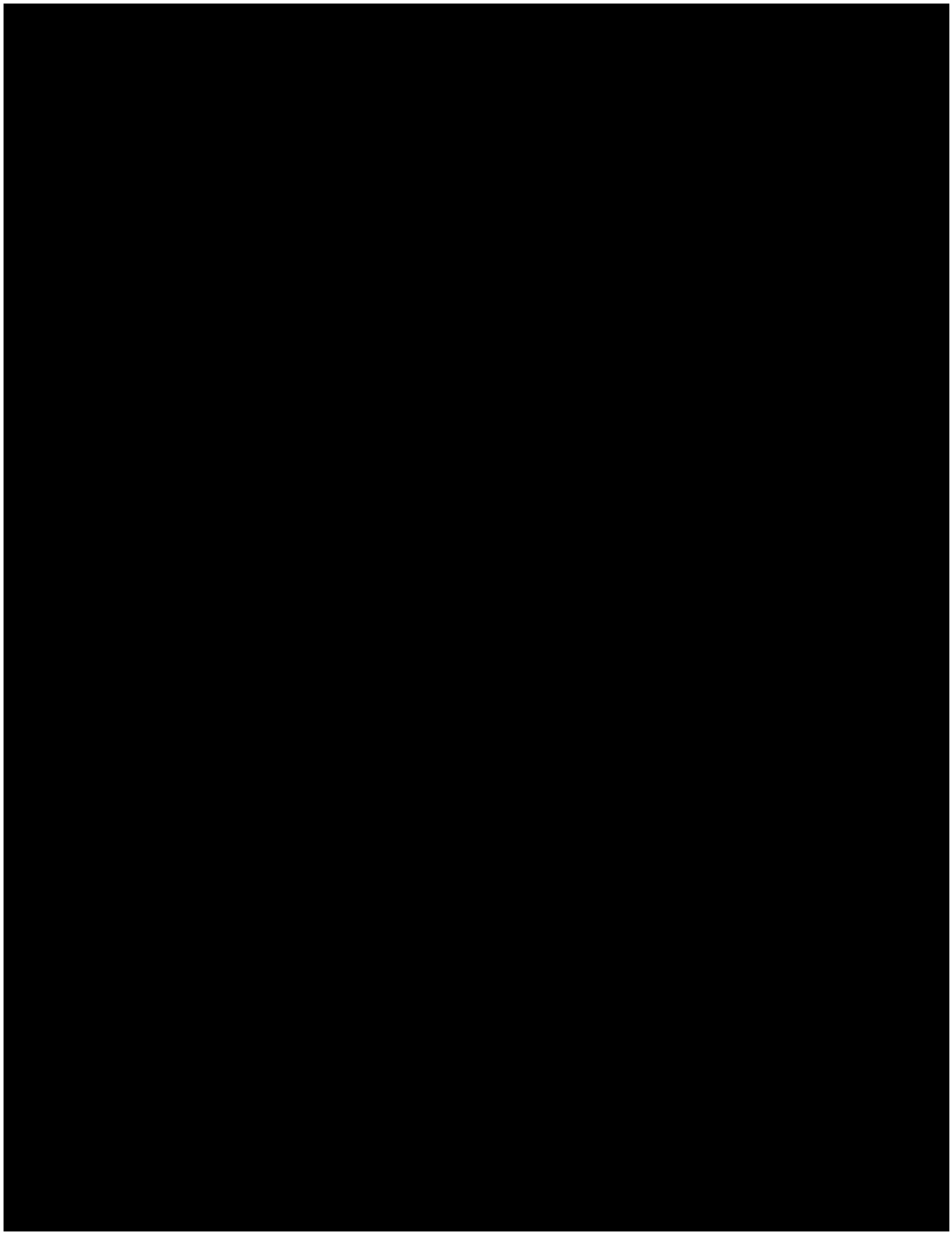
Approximately 342 subjects at approximately 300 centers worldwide will be randomly assigned to 1 of 5 treatment groups to receive IV and SC investigational product (MEDI2070 or placebo) once Q4W during the double-blind, placebo-controlled, induction and maintenance periods. Subjects who complete the double-blind, placebo-controlled, maintenance period (Week 28) will have the option to enter a 24-week, open-label period in which they will receive open-label MEDI2070 (210 mg SC) Q4W (Weeks 28 through 48).

All subjects will be followed for safety at 3 visits over 28 weeks (Weeks 60, 70, and 80 for subjects completing the open-label period) after their last dose of investigational product.

An interim analysis may be conducted when at least 75% of the total planned number of subjects has completed the Week 16 Visit or withdrawn prior to the Week 16 Visit. The study site personnel and sponsor personnel who are directly associated with the conduct of

this study and the study subjects would remain blinded to the subject-specific treatment assignment as well as the results of this analysis until the completion of the double-blind, maintenance period. No changes to the conduct of this study or data analysis are planned based on the interim analysis.

The primary analysis will be performed when all subjects complete the initial 16-week, induction period. A further analysis is planned when all subjects complete the 28-week, randomized, placebo-controlled, double-blind period. The final analysis, including all study periods and all data, will be performed at the end of the study.



[redacted]

[redacted]

Subjects will be randomized to 1 of 5 treatment groups using a [redacted] formulation of MEDI2070 (Table 3.1.2-1).

Table 3.1.2-1 Treatment Regimen

Treatment Group	Double-blind Period				Open-label Period
	Induction			Maintenance	
	Week 0	Week 4	Weeks 8 and 12	Weeks 16, 20, and 24	Weeks 28, 32, 36, 40, 44, and 48
1 - High (n = 76)	700 mg MEDI2070 IV + placebo SC	700 mg MEDI2070 IV + placebo SC	210 mg MEDI2070 SC	210 mg MEDI2070 SC	210 mg MEDI2070 SC
2 - High-medium (n = 76)	280 mg MEDI2070 IV + placebo SC	210 mg MEDI2070 SC + placebo IV	210 mg MEDI2070 SC	210 mg MEDI2070 SC	210 mg MEDI2070 SC
3 - Low-medium (n = 76)	210 mg MEDI2070 SC + placebo IV	105 mg MEDI2070 SC + placebo IV	105 mg MEDI2070 SC	105 mg MEDI2070 SC	210 mg MEDI2070 SC
4 - Low (n = 38)	70 mg MEDI2070 SC + placebo IV	35 mg MEDI2070 SC + placebo IV	35 mg MEDI2070 SC	35 mg MEDI2070 SC	210 mg MEDI2070 SC
5 - Placebo (n = 76)	Placebo SC and IV	Placebo SC and IV	Placebo SC	Placebo SC	210 mg MEDI2070 SC

IV = intravenous; SC = subcutaneous

3.1.3 Management of Investigational Product Related Toxicities

MEDI2070 has no identified toxicities. There is no provision for dose reduction or increase. No antidotes or other treatments to directly reverse the effect of MEDI2070 are available. In the event of suspected toxicity, supportive medical care should be provided, in close consultation with the sponsor's medical monitor/study physician.

3.2 Study Design and Dose Rationale

[redacted]

[redacted]

3.2.2 Rationale for Study Population

Subjects in this study will be 18 to 80 years of age, inclusive, with moderate to severe, active CD who, as determined by the investigator, have failed or are intolerant to anti-TNFα agents. This includes subjects who have received an anti-TNFα agent at a dose approved for the treatment of CD and did not respond initially (ie, primary non-response), or responded initially but then lost response with continued therapy (ie, secondary non-response), or were intolerant to the medication. This subject population was selected as it is anticipated that this will be the target population for treatment with an anti-IL-23 antibody. In the Phase 2a study (CD-IA-MEDI2070-1147), MEDI2070 demonstrated efficacy, without an identified safety risk, in a population of 18 to 65 years of age with moderate to severe, active CD. This study seeks to confirm and expand upon those observations, and to extend them into an older population 66 to 80 years of age. Most currently available treatments for moderate to severe CD, including glucocorticosteroids, immunomodulators, and anti-TNFα agents are associated with significant adverse effects. The mechanism of action of MEDI2070, and the results of the Phase 2a study in subjects with CD, suggests that MEDI2070 has the potential to offer effective treatment in the elderly with a reduced risk of adverse effects.

3.2.3 Rationale for Endpoints

The primary and some of the secondary endpoints chosen have been extensively used in previous CD development programs and are considered suitable to demonstrate the beneficial effects of MEDI2070 in the subject population. The CDAI measures the severity of active disease using symptom scores that are monitored over the prior week and defines response or remission of CD, and has been the acceptable regulatory endpoint for evaluating treatment efficacy in CD.

Other secondary endpoints include measures of efficacy in CD, which together with the safety and tolerability of MEDI2070 will be critical in establishing its potential clinical utility as a CD treatment, and may have relevance as acceptable regulatory endpoints in the near future.

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

Approximately 342 subjects at approximately 300 centers worldwide will be randomized for this study.

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1. Age 18 to 80 years, inclusive, at the time of screening
[redacted]
5. Moderate to severely active CD, as defined by:
   a. CDAI score [redacted] AND
   b. Evidence of active intestinal mucosal inflammation, [redacted]

[redacted]

7. Prior treatment with at least one anti-TNFα agent at a dose approved for the treatment of CD with failure to respond initially (ie, primary non-response), or initial response followed by loss of response with continued therapy (ie, secondary non-response [redacted]

8. Females of childbearing potential who are sexually active with a nonsterilized male partner must use at least one highly effective method of contraception from screening, and must agree to continue using such precautions [redacted]

9. Nonsterilized males who are sexually active with a female partner of childbearing potential must use condom and spermicide

10. Subjects have no known history of active tuberculosis (TB)

ii. Documented history of a completed course of adequate prophylaxis for latent TB (per local standard of care)

[redacted]

4.1.3 Exclusion Criteria

Any of the following would exclude the subject from participation in the study:

[redacted]

3. A clinical manifestation of short bowel syndrome (defined as requiring oral or parenteral supplemental or total nutrition in order to maintain stable body weight)

[redacted]

6. A stricture with obstructive symptoms within 3 months prior to Day 1
7. Bowel surgery within 12 weeks prior to Day 1, or has planned bowel surgery within 24 weeks from Day 1
8. Subject has ileostomy and/or colostomy
9. Subject has clinical evidence of an infected abscess during screening
10. Bowel perforation or evidence of non-inflammatory obstruction during the 6 months prior to Day 1
11. Stool positive for *Clostridium difficile* toxin at screening

[redacted]

[redacted]

22. Subject has evidence of a recent (within 6 months of Day 1) infection, requiring inpatient hospitalization
23. Subject received treatment for infection with IV or oral (within 14 days of Day 1) antibiotics or antivirals
24. Subject received any type of live attenuated vaccine < 4 weeks prior to Day 1 or is planning to receive any such vaccine over the course of the study
25. Subject tested positive for hepatitis B virus surface antigen, hepatitis C virus antibody, and/or human immunodeficiency virus (HIV) at screening
26. Subject has any underlying condition that predisposes subject to infections (eg, history of splenectomy)
27. Subject has known history of drug or alcohol abuse within 1 year of Day 1. [redacted]
28. History of cancer, except for basal cell carcinoma or in situ carcinoma of the cervix treated with apparent success with curative therapy ≥ 12 months prior to screening

[redacted]

31. Subject is currently enrolled in another investigational device or drug study, or less than 30 days or 5 half-lives, whichever is longer, since ending another investigational device or drug study(s), or receiving other investigational agent(s)

[redacted]

33. Subject is pregnant, breastfeeding, or plans to become pregnant during the study

[redacted]

4.1.4 Subject Enrollment and Randomization

Study participation begins (ie, a subject is "enrolled") once written informed consent is obtained (see Section 7.4 for details). Once informed consent is obtained, a subject identification (SID) number will be assigned by a central interactive voice/web response system (IVRS/IWRS), and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The SID number will be used to identify the subject during the screening process and throughout study participation, if applicable.

A master log of all consented subjects will be maintained at the site and will document all screening failures (ie, subjects who are consented but do not meet study eligibility criteria and/or are not randomized), including the reason(s) for screening failure.

For the 28-week, double-blind period of the study, the IVRS/IWRS will be used for randomization of subjects to a treatment arm and assignment of blinded investigational product kit numbers. Subjects will be stratified based on the number of prior anti-TNFα agents that failed or were not tolerated (1 vs > 1). The randomization will be based on permutation block algorithm. The maximum number of subjects within each stratum will not be set a priori. During the 24-week, open-label period of the study, all subjects will receive 210 mg SC MEDI2070.

Subjects who fail to meet eligibility criteria may be rescreened once, if in the opinion of the investigator the assessments undertaken were not considered representative of the usual status of a subject's CD or general health.

4.1.5 Withdrawal from the Study

Subjects are at any time free to withdraw from the study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such subjects will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator and every attempt will be made to complete the early termination visit assessments (see Early Termination Visit and Safety Follow-up Period, Section 4.2.3). AEs will be followed up. If a subject withdraws from further participation in the study, then no further study visits or data collection should take place.

4.1.6 Discontinuation of Investigational Product

An individual subject will not receive any further investigational product if any of the following occur in the subject in question:

1. Withdrawal of consent from further treatment with investigational product or lost to follow-up
2. An AE that, in the opinion of the investigator or the sponsor, contraindicates further dosing
3. Subject has had, or requires intra-abdominal surgery
4. Pregnancy (see Section 5.6.4) or intention to become pregnant
5. Subject receives any live vaccine
6. Severe noncompliance to this study protocol, as determined by the investigator or medical monitor
7. Recurrence of significant CD symptoms, that warrants escalation in therapy, according to investigator judgment, at any time during the study
8. Subject develops a malignant neoplasm
9. Mycobacterial infections, systemic fungal infections, or viral infections requiring hospitalization or parenteral antiviral therapy
10. Failure to receive a scheduled dose of investigational product within the dosing window during the double-blind periods of the study (Section 3.1.2)
11. Failure to receive 2 consecutive scheduled doses of investigational product within the dosing window during the open-label period of the study (Section 3.1.2)

Subjects who are permanently discontinued from further receipt of investigational product, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as

having permanently discontinued treatment. Subjects who permanently discontinue treatment may either be considered to have completed the study or not to have completed the study.

Subjects who are permanently discontinued from receiving investigational product will be followed for safety for 28 weeks after the last dose of investigational product, including the collection of any protocol specified blood, urine, or fecal specimens, unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study. In addition, subjects who are permanently discontinued from further receipt of investigational product will be referred for appropriate medical care by the investigator, as required. Such referral will be taken in coordination with the subjects' personal physician.

Subjects will be considered lost to follow-up only if no contact has been established by the time the study is completed (as defined in Section 6.3.3) such that there is insufficient information to determine the subject's status at that time.

Note: Subjects refusing to return to the site or to continue participation in the study should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing subjects throughout the study period. If contact with a missing subject is re-established, the subject should not be considered lost to follow-up and any evaluations should resume according to this protocol.

4.1.7 Replacement of Subjects

Subjects who withdraw from the study after having been randomized will not be replaced.

4.1.8 Withdrawal of Informed Consent for Data and Biological Samples

Biological Samples Obtained for the Main Study

Study data are protected by the use of an SID number, which is a number specific to the subject. The investigator is in control of the information that is needed to connect a study sample to a subject. A subject's consent to the use of data does not have a specific expiration date, but the subject may withdraw consent at any time by notifying the investigator. If consent is withdrawn, any samples collected prior to that time may still be given to and used by the sponsor but no new data or samples will be collected unless specifically required to monitor safety of the subject.

Samples Obtained for Genetic Research or Future Research

Samples obtained for genetic research or future research will be labeled with a sample identification number. If the subject withdraws consent for participating in the genetic research or future research, the sponsor will locate the subject's sample and destroy it.

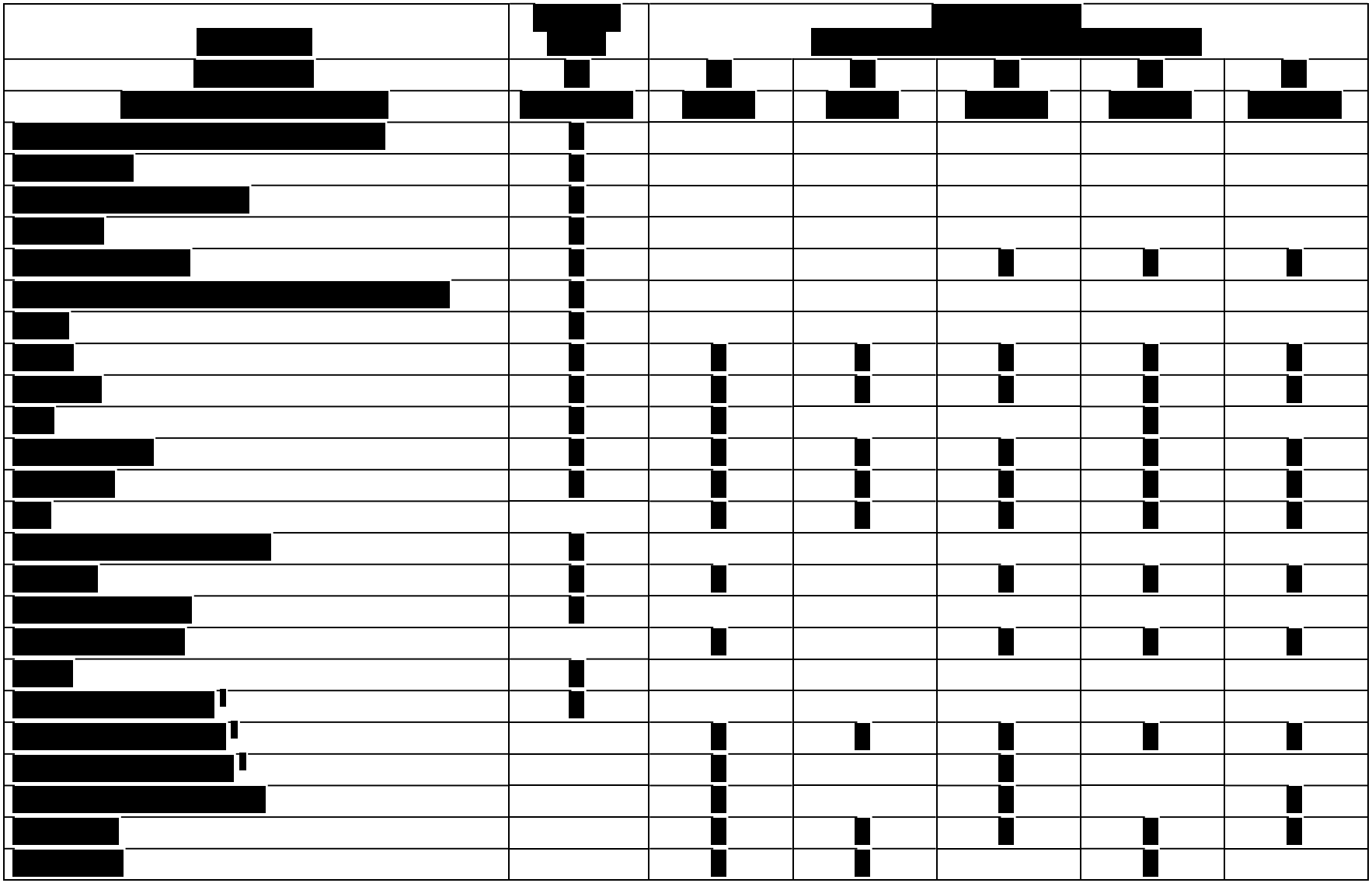
If the subject consents to have his/her samples used for genetic research or future research, this additional research may not start immediately and may start at any time during the storage period. The subject's sample(s) including any specimens of extracted deoxyribonucleic acid (DNA) will be stored by the sponsor with similar samples from other subjects at a secure central laboratory. The subject's samples will not be kept for more than 25 years after the end of the study in which they were collected. If the subject chooses not to allow his/her study samples to be used for genetic research or future research, the samples will be destroyed by the sponsor once they are no longer required for the main study.

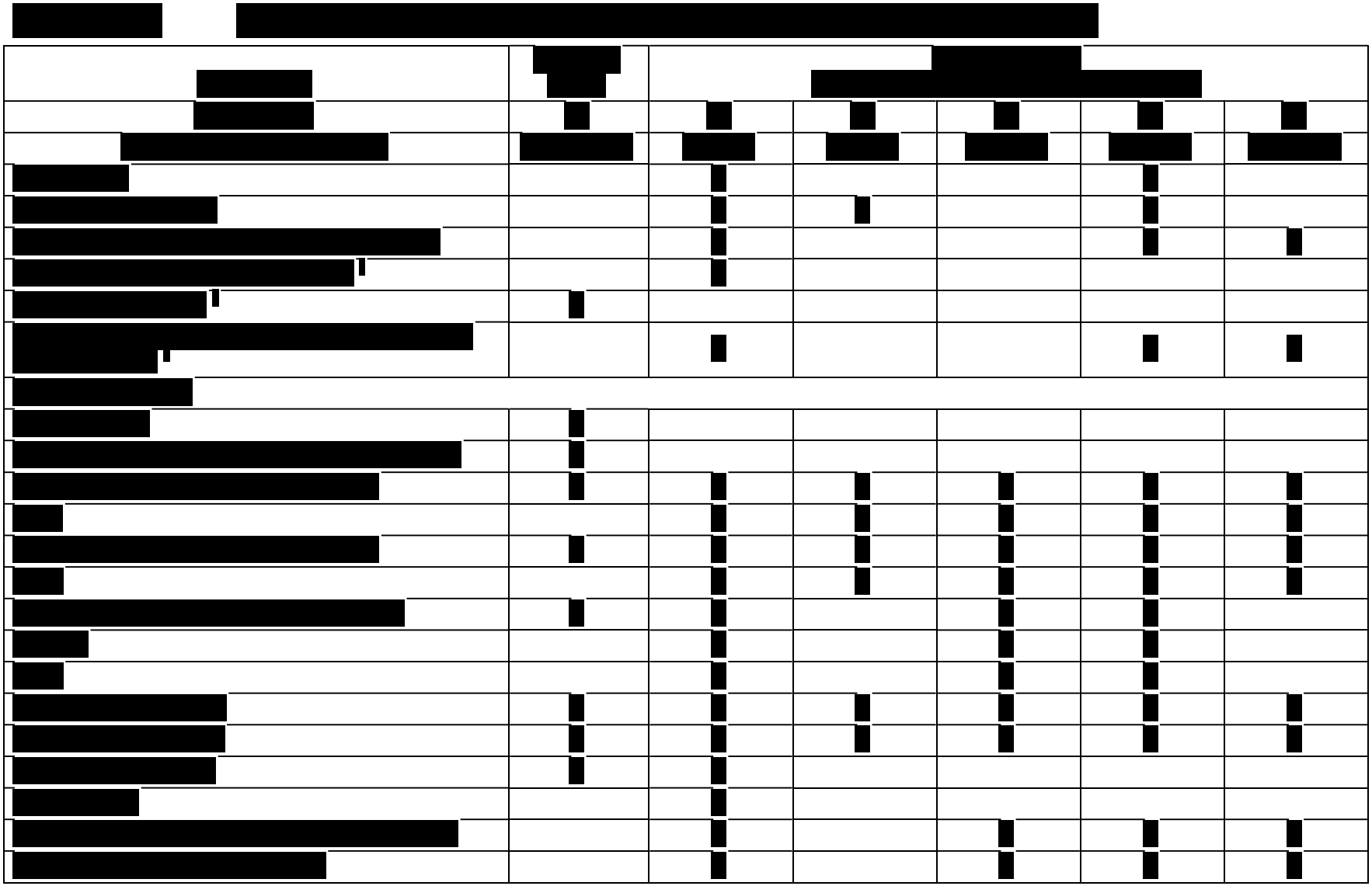
If consent is withdrawn after a sample has been taken but before the subject's sample is sent to the sponsor for genetic research or future research, the investigator will arrange to have it destroyed. If consent is withdrawn after the subject's sample(s) have been sent to the sponsor for genetic research or future research, the sponsor and the investigator will ensure that these sample(s) are destroyed unless the sample identification number has been removed and the subject can no longer be linked to any sample(s). However, if the subject's samples have already been used for research, the sponsor is not required to destroy results of this research. In this case only the remaining sample(s) will be destroyed.

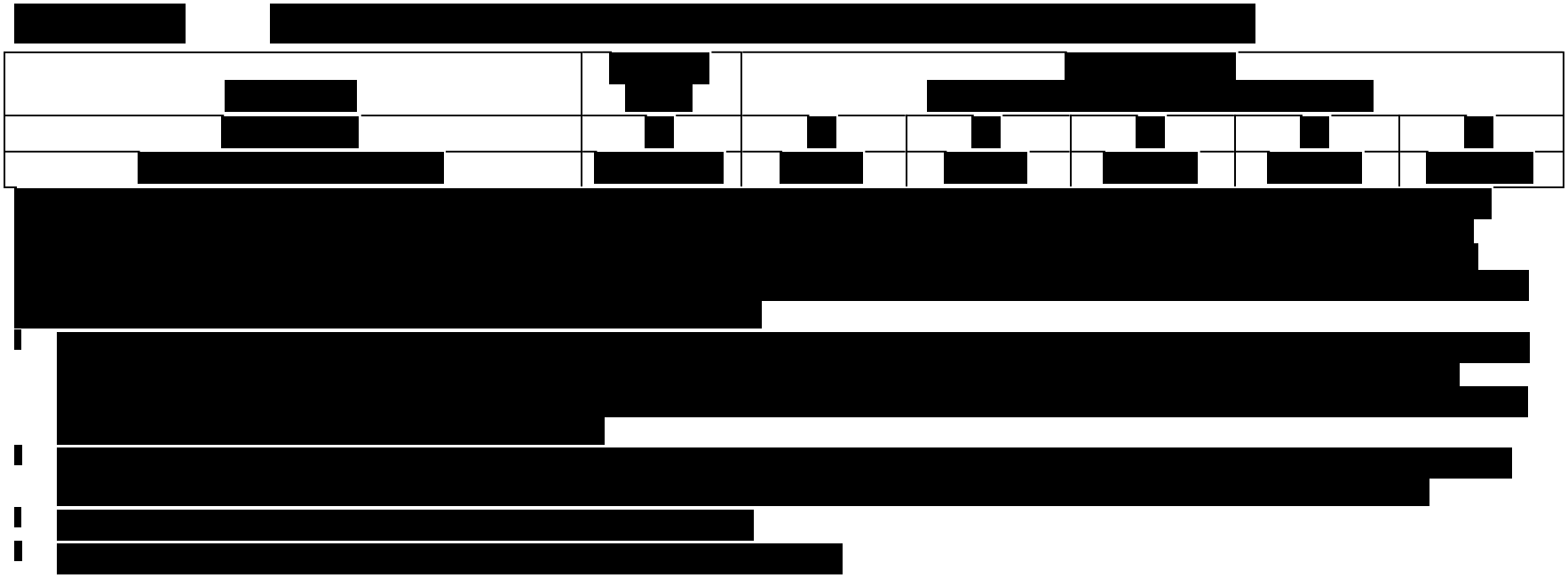
[redacted]

[redacted]

[redacted]







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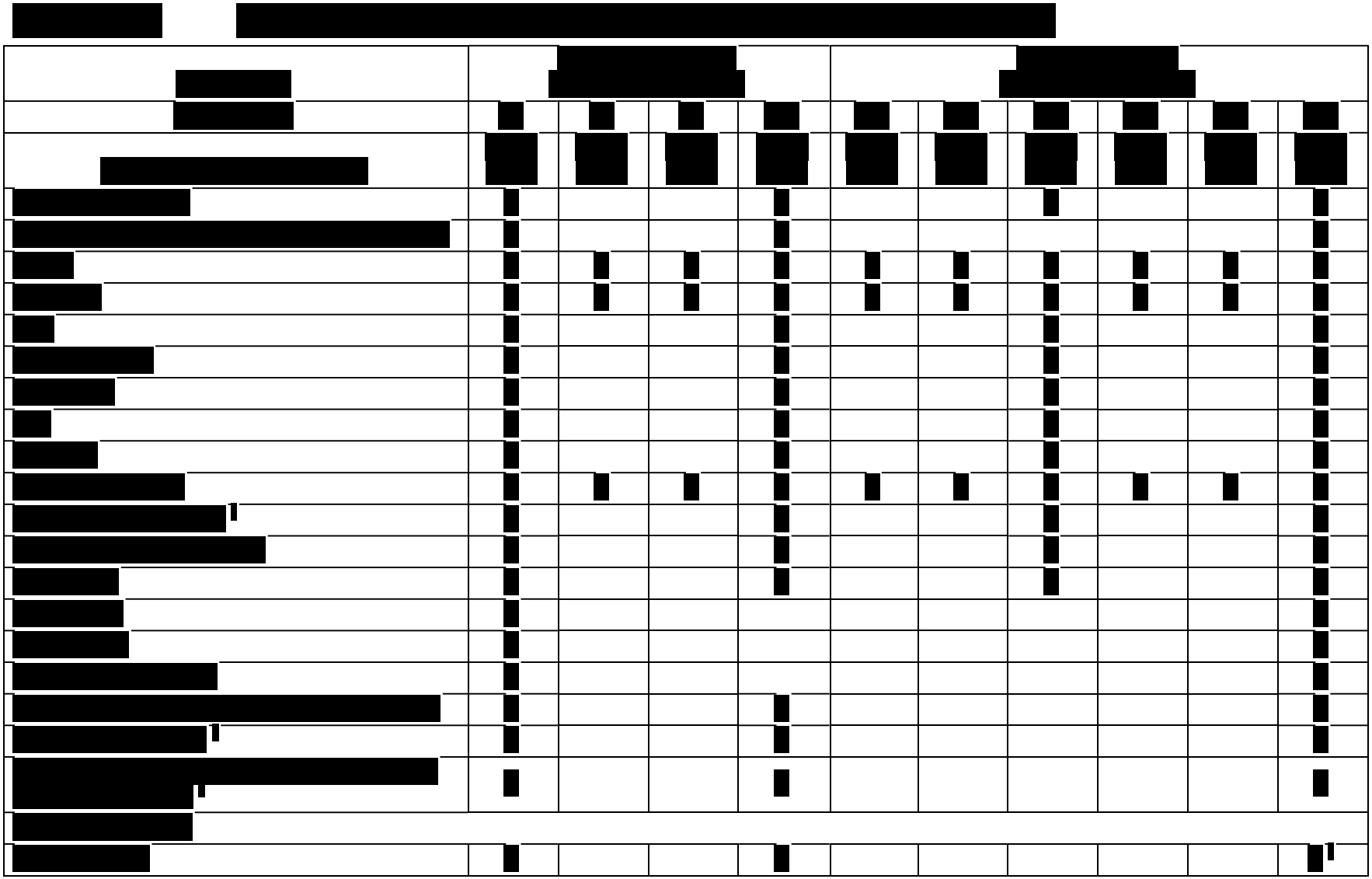

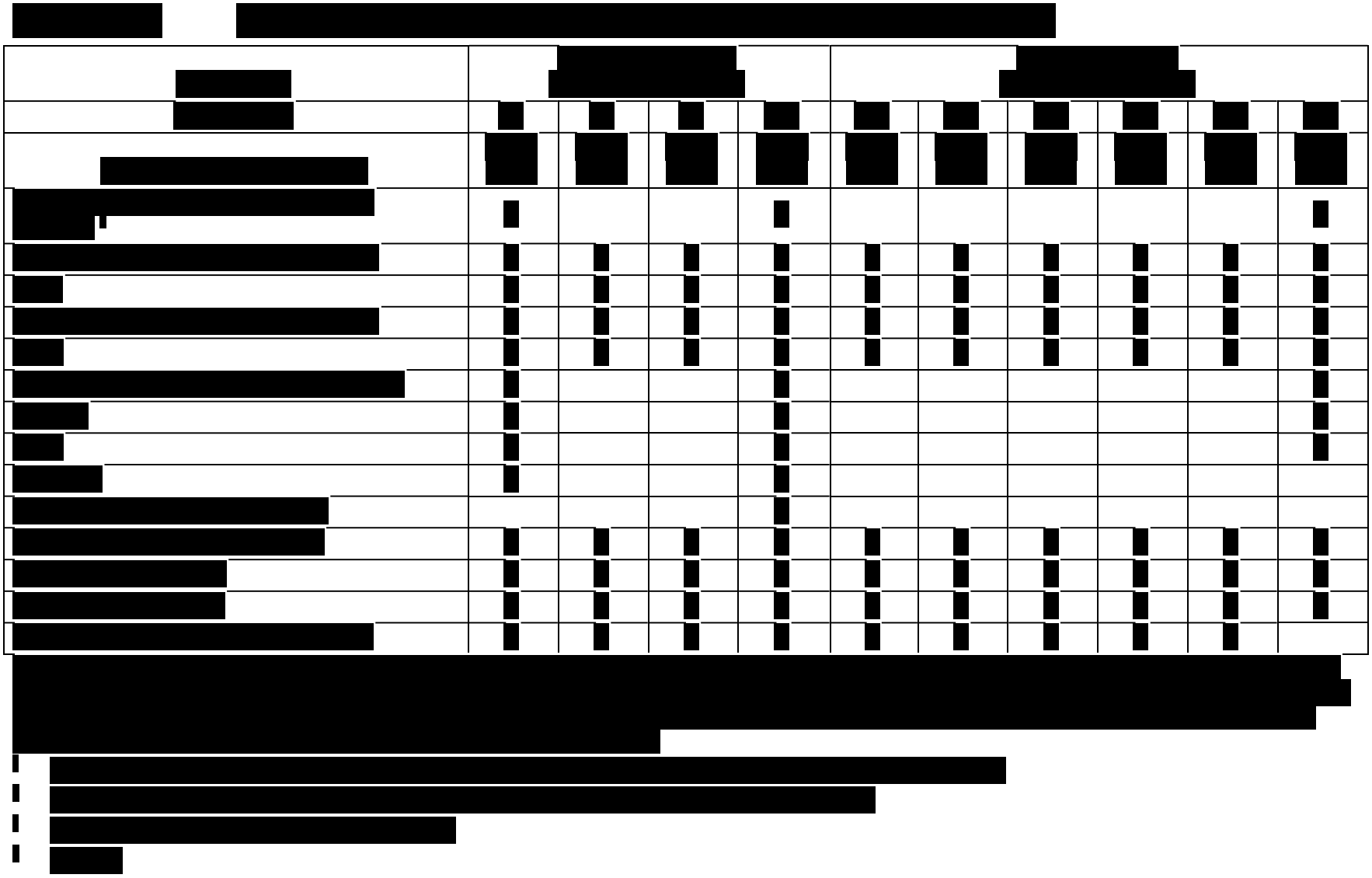

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[redacted]	[redacted]	[redacted]		[redacted]

4.3 Description of Study Procedures

4.3.1 Efficacy

4.3.1.1 Crohn's Disease Activity Index

The CDAI is a composite index with weighted domains that quantifies the global disease severity in a single numerical score. It is the oldest and most widely used of several multi-item instruments that have been developed and is validated for use in clinical studies to measure disease activity in CD (Best et al, 1976; Sands and Ooi, 2005). The CDAI measures the severity of active disease using symptom scores that are monitored over the previous week and includes subject-reported symptoms, physician-assessed signs, and laboratory markers. The CDAI score is calculated by summing weighted scores for subjective items (number of liquid or very soft stools, abdominal pain and general well-being) recorded by a diary during a 1-week period, and objective items (associated symptoms, taking antidiarrheal agents such as loperamide/opiates, abdominal mass, hematocrit, daily morning temperature,

and body weight). The CDAI scores range from 0 to 600, with higher scores indicating greater disease activity. Subjects with scores of < 150, 150 to 219, and 220 to 450 represent remission, mild disease, and moderate to severe disease, respectively; whereas subjects with scores of > 450 have very severe disease (Buxton et al, 2007). The CDAI will be calculated at the site in order to determine the eligibility for the study.

The CDAI assessments will be performed at each study visit starting with Visit 2.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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4.3.3 Medical History, Physical Examination, Vital Signs, and Electrocardiogram

4.3.3.1 Medical, Surgical, and Crohn's Disease History

A complete medical and surgical history will be performed at screening and will include CD history, and current medical conditions, past or present cardiovascular disorders, respiratory, GI, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, dermatological, psychiatric, genitourinary, and drug history or any other diseases or disorders. Smoking history and alcohol consumption will also be collected.

4.3.3.2 Chest X-ray

Subjects with a positive PPD test, or an indeterminate QuantiFERON-TB test, or subjects with a history of using anti-TNFα agents for a treatment course of 1 year or longer, who have discontinued an anti-TNFα agent within 6 months prior to screening, must obtain a subsequent chest x-ray that shows no evidence of active TB. If required, a chest x-ray will be completed during the screening period. The chest x-ray may be substituted with documentation of a previous chest x-ray performed within 1 month prior to the first dose of investigational product according to the inclusion criteria.

4.3.3.3 Physical and Neurological Examinations

Physical examinations will be performed by a physician, physicians' assistant, or certified nurse practitioner, and will include examination of the following: general appearance, head, ears, eyes, nose, throat, neck, skin, cardiovascular system, respiratory system, abdominal system, and basic neurological examination. The subject's weight (each study visit) will be recorded in kg with one decimal place, and height (Screening visit only) will be recorded in cm. If converting from inches, height will be recorded to one decimal place. Measurements should be done with light clothing and no shoes. Complete physical examinations will be

performed according to the Schedule of Study Procedures in [redacted]

Demographic characteristics such as sex, race, and ethnicity will also be collected.

4.3.3.4 Visual Acuity Tests and Ophthalmoscopy Examination

The visual acuity test and ophthalmoscopic examination should be performed according to the Schedule of Study Procedures in [redacted]. The visual acuity test will be used to determine the smallest letters a person can read on a standardized chart (eg, Snellen chart or other suitable chart) or a card held 4 to 6 meters (14 to 20 feet) away. The test should be done in a health care provider's office or other suitable environment. The subject will be asked to stand or sit approximately 6 meters (20 feet) from the eye chart with both eyes open. One eye should be gently covered while the subject reads out loud the smallest line of letters they can see on the chart. Best corrected visual acuity (use of corrective refractive lenses is permitted) should be recorded.

The ophthalmoscopic examination should include visually magnified inspection of the internal eye structures and also assessment of the quality of the eye's red reflex after the pupil has been dilated. The appearance of the optic disc and retinal vasculature should be examined and any anomalies in the appearance of the internal ocular structures should be recorded. The presence or absence of cataracts should be noted.

4.3.3.5 Vital Signs

Vital signs (blood pressure, temperature, pulse rate, and respiration rate) will be obtained at all study visits after the subject has been resting for at least 5 minutes. Subjects are instructed to avoid any hot or cold drinks for 30 minutes if an oral temperature assessment is performed.

[redacted]

[redacted]

[redacted]

Injection-Site Reactions

The site of injection will be assessed at every visit at which there is an SC injection through the end of the open-label period. Injection-site reactions will be recorded as AEs according to the criteria described in Section 5.4.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Pregnancy Test (females of childbearing potential only)

- Urine human chorionic gonadotropin (hCG)
- Serum beta-hCG (at screening only)

[redacted]

[redacted]

[redacted]

Specific procedures for sample collection, processing, storage, and shipment can be found in a separate Laboratory Manual provided to the sites.

4.3.6 Immunogenicity Evaluation

Serum samples to measure the presence of ADAs against MEDI2070 will be collected prior to administration of investigational product [redacted]

Instructions for sample collection, processing, storage, and shipment can be found in a separate Laboratory Manual provided to the sites.

4.3.7 Biomarker Evaluation and Methods

Blood and stool samples will be collected and analyzed to evaluate protein, nucleic acid, and cellular biomarkers that relate to MEDI2070 treatment. All biomarker analyses will be conducted to generate hypotheses associated with the mechanisms of action of MEDI2070, identify subsets of subjects responsive to MEDI2070, and to characterize a gene signature.

Specific procedures for sample collection, processing, storage, and shipment can be found in a separate Laboratory Manual provided to the sites.

4.3.7.1 Blood Biomarker Evaluation

Whole blood samples will be collected in [redacted] for total ribonucleic acid (RNA) sample preparation. RNA may be used in the analyses of transcript expression using both [redacted] and stored for future analyses.

A second whole blood sample will be collected to evaluate, but will not be limited to the following cell populations: [redacted]. Blood serum and plasma samples will be collected for analysis of circulating soluble factors in relation to inflammatory cell activities. Factors to be analyzed may include, but are not limited to: [redacted]. Additional assays to evaluate levels of [redacted] may be conducted.

[redacted]

4.3.7.2 Stool Analysis of Fecal Calprotectin and Microbiome

Stool specimens from whole stools already being collected for quantitative determination of fecal calprotectin levels will be collected to support assessment of changes over time in the composition of the [redacted]. The clinical sites will collect the specimens from stool delivered to the sites by subjects, for processing, shipping, and subsequent testing. Detailed sample collection instructions and kits for the subjects, and specimen processing and shipping instructions and kits for the sites, will be provided through the central laboratory to support centralized testing for each exploratory objective. Stool specimens associated with any study visit at which an ileocolonoscopy is scheduled should be collected prior to the start of the bowel preparation for the ileocolonoscopy.

[redacted].

4.3.8 Pharmacogenomics

An additional optional blood sample collection is scheduled to support exploratory study of the relationships between pharmacodynamics and clinical responses in participants, and [redacted] and other pathways implicated in IBD pathogenesis using pharmacogenetic methods including but not limited to [redacted]

[redacted] Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

[redacted]

[redacted]

4.4 Study Suspension or Termination

The sponsor reserves the right to temporarily suspend or terminate this study at any time. The reasons for temporarily suspending or terminating the study may include but are not limited to the following:

1. The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects
2. Subject enrollment is unsatisfactory
3. Non-compliance that might significantly jeopardize the validity or integrity of the study
4. Sponsor decision to terminate development

If MedImmune determines that temporary suspension or termination of the study is required, MedImmune will discuss the reasons for taking such action with all participating investigators (or head of the medical institution, where applicable). When feasible, MedImmune will provide advance notice to all participating investigators (or head of the medical institution, where applicable) of the impending action.

If the study is suspended or terminated for safety reasons, MedImmune will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. MedImmune will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) promptly and provide the reason(s) for the suspension/termination. If the study is suspended for safety reasons and it is deemed appropriate by the sponsor to resume the study, approval from the relevant regulatory authorities (and IRBs/IECs when applicable) will be obtained prior to resuming the study.

4.5 Investigational Products

[redacted]

[redacted]

4.5.1.1 Investigational Product Dose Preparation

The investigational product manager will select the kit assigned by the IVRS/IWRS to prepare the subject's dose.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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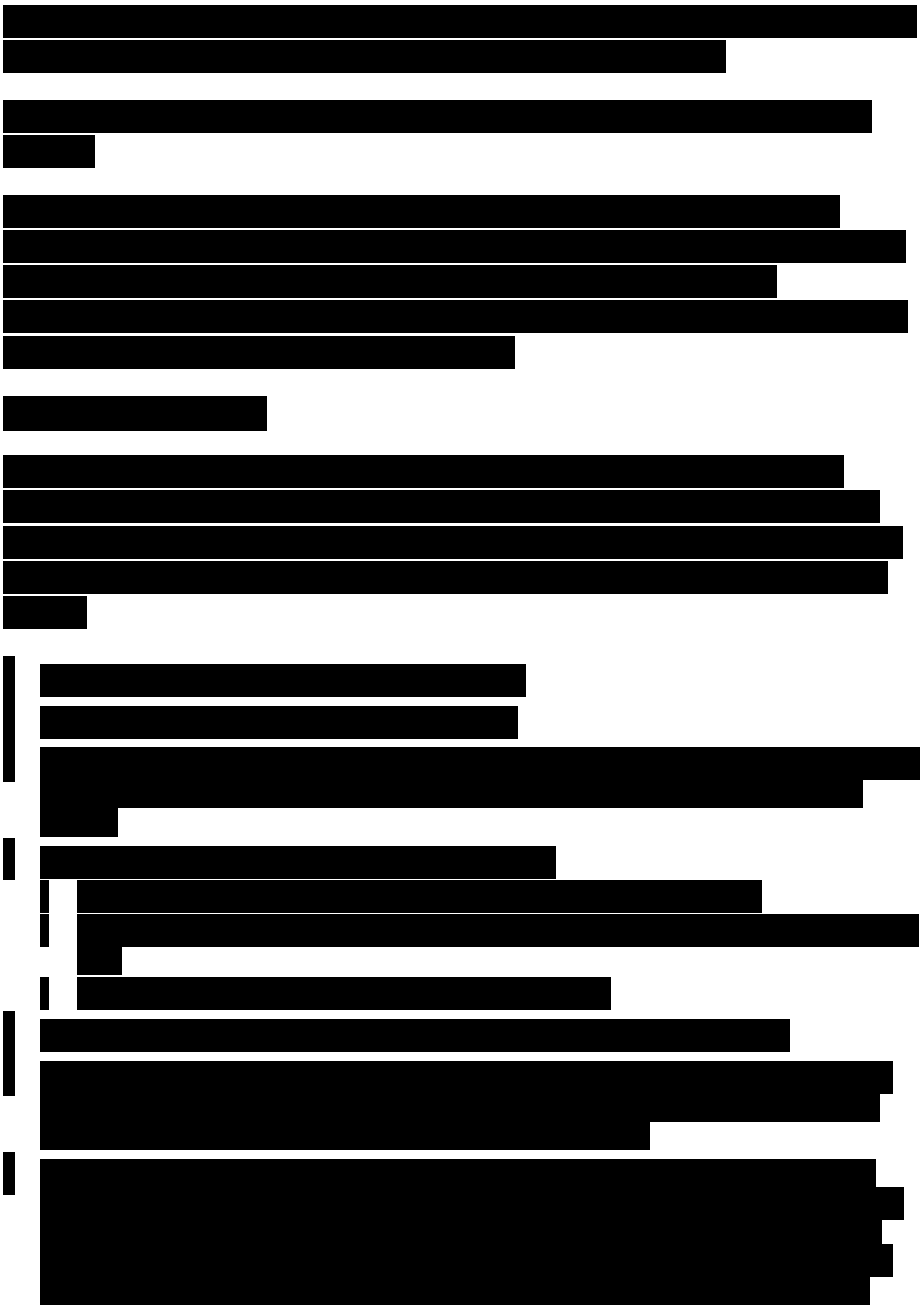

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[redacted]

IV = intravenous; OL = open-label; SC = subcutaneous

[redacted]

[redacted]

[redacted]

Infections

If according to the investigator a subject shows signs of a clinically significant infection during the double-blind, placebo-controlled period, the subject will be withdrawn from the study. A clinically significant infection will be defined as:

- An infection that meets criteria for a TESAE
- An infection that is Grade 3 or higher severity
- A mycobacterial infection
- A systemic fungal infection
- A viral infection requiring parenteral antiviral therapy

- A bacterial infection requiring IV antibiotics

During the open-label period, MEDI2070 should not be administered to a subject with a clinically significant active infection treated with oral or IV antimicrobials, antivirals, or antifungals until it is confirmed by the investigator that the infection has resolved.

Abnormal Liver Function Test

Investigational product will not be administered to any subject with an ALT and/or AST of > 3.0 × ULN and concurrent elevated bilirubin > 2.0 × ULN.

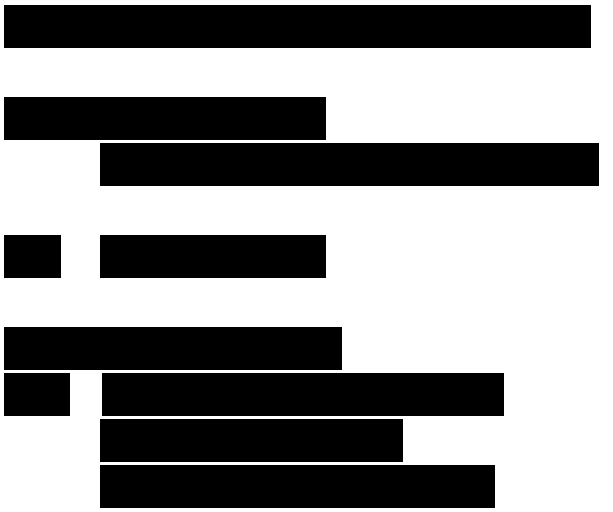
Other Events

Investigational product will not be administered to a subject subsequent to an event that in the opinion of the investigator or the sponsor contraindicates further dosing or could result in complications.

4.5.1.7 Reporting Product Complaints

Any defects with the investigational product must be reported *immediately* to the MedImmune Product Complaint Department by the site with further notification to the site monitor. All defects will be communicated to MedImmune and investigated further with the Product Complaint Department. During the investigation of the product complaint, all investigational product must be stored at labeled conditions unless otherwise instructed.

MedImmune contact information for reporting product complaints:



4.5.2 Additional Study Medications

No other study medications are required for use in this clinical study protocol.

4.5.3 Labeling

Labels for the investigational product will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The label will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local languages, as required.

4.5.4 Storage

[redacted]

4.5.5 Treatment Compliance

Investigational product is administered by study site personnel, who will monitor compliance. The administration of all investigational product should be recorded in the appropriate sections of the eCRF.

4.5.6 Accountability

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to MedImmune. All unused investigational product will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune.

It is the investigator/institution's responsibility to establish a system for handling investigational product to ensure that:

- Deliveries of investigational product from the sponsor are correctly received by a responsible person (eg, a pharmacist)
- Such deliveries are recorded
- Investigational product supplies are handled and stored safely and properly
- Investigational product is only dispensed to subjects in accordance with this protocol

- Any unused investigational product is accounted for and returned to designated facility or the sponsor for destruction upon authorization by the sponsor. Certificates of destruction should be signed and filed.

At the end of the study, it must be possible to reconcile delivery records with records of usage and returned stocks. Any discrepancies must be accounted for. Certificates of delivery and return must be signed, preferably by the investigator or a pharmacist.

4.6 Treatment Assignment and Blinding

4.6.1 Methods for Assigning Treatment Groups

For the double-blind induction and maintenance periods of the study, an IVRS/IWRS will be used to randomize subjects to a treatment arm, assign a unique randomization code, and assign investigational product kit numbers. A total of approximately 342 subjects will be randomized into 1 of 5 treatment groups:

- Treatment Group 1: MEDI2070 – high (76 subjects)
- Treatment Group 2: MEDI2070 – high-medium (76 subjects)
- Treatment Group 3: MEDI2070 – low-medium (76 subjects)
- Treatment Group 4: MEDI2070 – low (38 subjects)
- Treatment Group 5: Placebo (76 subjects)

Subjects will be stratified based on the number of prior anti-TNFα agents that failed or were not tolerated (1 vs > 1). The randomization will be based on permutation block algorithm. The maximum number of subjects within each stratum will not be set a priori.

During the 24-week, open-label period of the study, all subjects will receive 210 mg SC MEDI2070.

A subject is considered randomized into the study when the investigator notifies the IVRS/IWRS that the subject meets eligibility criteria and the IVRS/IWRS provides the assignment of blinded investigational product kit numbers to the subject.

Investigational product (MEDI2070 or placebo) must be administered the same day the investigational product is assigned. If there is a delay in the administration of investigational product such that it will not be administered within the specified timeframe, the study monitor must be notified immediately.

4.6.2 Methods for Ensuring Blinding

This study includes double-blind induction and maintenance periods. Neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received (International Conference on Harmonisation [ICH] E9; see Section 4.6.3.2 for unblinding related to planned analysis). Since MEDI2070 and placebo can be distinguished, investigational product will be handled by an unblinded investigational product manager and handed over to qualified site staff who will administer the investigational product to subjects. An independent investigational product monitor will also be unblinded to perform investigational product accountability. In the event that the treatment allocation for a subject becomes known to the investigator or other study staff involved in the management of study subjects, the sponsor must be notified immediately. If the treatment allocation for a subject needs to be known to treat an individual subject for an AE, the investigator must notify the sponsor immediately and, if possible, before unblinding the treatment allocation.

4.6.3 Methods for Unblinding

4.6.3.1 Unblinding in the Event of a Medical Emergency

In the event of a medical emergency, the investigator may unblind an individual subject's investigational product allocation. Instructions for unblinding an individual subject's investigational product allocation are contained in the IVRS/IWRS manual. In general, unblinding should only occur if management of the medical emergency would be different based on the subject having received investigational product. In the majority of cases, the management of a medical emergency would be the same whether or not investigational product was received by the subject. If this was the case, the investigational product allocation should not be unblinded.

MedImmune retains the right to unblind the treatment allocation for TESAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

If a subject's investigational product allocation is unblinded prior to that subject having completed the Week 28 visit and all its associated assessments, the subject should be discontinued from investigational product.

4.6.3.2 Unblinding for Planned Analysis Purposes

An interim analysis may be performed, as described in in Section 4.8.10. The analysis would be conducted by a limited number of sponsor personnel who are not involved in the conduct

of the study. The study site personnel and sponsor personnel directly associated with the conduct of this study and the study subjects will remain blinded to the subject-specific treatment assignment and to the outcome of interim analysis until the completion of the 28-week placebo-controlled, double-blind period. No changes to the conduct of this study or data analysis are planned based on the interim analysis.

The primary analysis will be performed when all subjects complete the initial 16-week, induction period. A further analysis is planned when all subjects complete the 28-week, maintenance period. At the time of the primary analysis, selected personnel from the sponsor will be unblinded to individual treatment assignments as will be outlined in an unblinding plan. The MedImmune clinical team, study subjects, site monitors, and investigators will remain blinded to subject-specific treatment assignments. The study will be formally unblinded when the last subject reaches the end of the maintenance period.

4.7 Restrictions During the Study and Concomitant Treatment(s)

The investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF.

4.7.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as “excluded” as listed in Section 4.7.2. Specifically, subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, antidiarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.

In addition, the following concomitant medications for CD are permitted during the study:

- 5-aminosalicylates, only if being taken at baseline
- Prednisone up to 20 mg/day or equivalent, only if being taken at baseline
- Budesonide up to 9 mg/day, only if being taken at baseline
- Azathioprine, only if being taken at baseline
- 6-mercaptopurine, only if being taken at baseline
- Methotrexate, only if being taken at baseline

- Oral antibiotics for CD (except for the treatment of acute illness), only if being taken at baseline
- Probiotics (eg, Culturelle and *Saccharomyces boulardii*), only if being taken at baseline
- Antidiarrheals (eg, loperamide and diphenoxylate with atropine) for control of chronic diarrhea, only if being taken at baseline

The investigator may not increase the subject's dose of the permitted concomitant medications listed above, and may not initiate treatment with any of these medications after the deadlines specified in the inclusion criteria, Section 4.1.2, criterion #6.

The dose of the medications listed above may not be reduced during the subject's study participation before the Week 16 assessments, including ileocolonoscopy, have been completed, with the exception that antidiarrheal agents may be stopped if the subject has had no stools in 3 consecutive days. After any such stopping of antidiarrheal agents during the double-blind period, if any recurrence of loose stools occurs prior to Week 8, antidiarrheal use should be immediately resumed.

Subjects receiving oral corticosteroids should initiate oral corticosteroid tapering as per local standard of care if, after Week 16, they have achieved both:

- SES-CD response (see Section 2.2), AND
- PRO2 response (see Section 2.2)

For assessment of the SES-CD score for the purpose of tapering oral corticosteroid therapy, the investigators' own scoring of these results may be used in place of central scoring.

In the event that the dose of any of the medications listed above must be reduced for the subject's safety, investigational product must be withdrawn and an early termination visit must be completed.

Background CD medication is not regarded as investigational product, and will not be provided by the sponsor.

4.7.2 Prohibited Concomitant Medications

Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

The following medications or interventions are considered exclusionary and are not permitted as specified below through Week 52 of the study. The sponsor must be notified if a subject receives any of these during the study:

- Natalizumab (Tysabri®)
- Anti-TNFα agents
- Vedolizumab
- Any commercially available or experimental biologic agent, eg, ustekinumab
- Calcineurin inhibitors eg, cyclosporine (Neoral®) and tacrolimus (FK 506/Prograf®)
- Mycophenolate mofetil (CellCept®)
- Sirolimus (rapamycin)
- IV or intramuscular steroids
- Topical (rectal) aminosalicylic acid (eg, mesalamine) or topical (rectal) steroids
- Thalidomide
- Live attenuated vaccine
- Intra-abdominal surgery
- Elemental diet
- Any experimental product or device as specified in Section 4.1.3 (exclusion criterion #31)

In the event that a subject receives a treatment/intervention listed above, investigational product must be withdrawn and an Early Termination Visit must be completed (see Early Termination visit, Section 4.2.3).

4.8 Statistical Evaluation

4.8.1 General Considerations

Full details of statistical analyses will be described in the Statistical Analysis Plan (SAP), which will be finalized prior to unblinding.

All data will be provided in data listings sorted by treatment group and subject number. Tabular summaries will be presented by treatment group and by visit for all efficacy endpoints. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics, including number of observations, mean, standard deviation, median, minimum, and maximum. Day 1 will be defined as the day of first investigational product administration.

For the purpose of statistical analyses, the data from the placebo-controlled, double-blind period and open-label period will be analyzed separately. Unless otherwise stated, all efficacy analyses will be conducted with a two-sided test at a significance level of $\alpha = 0.10$. Nominal p-values will be provided without multiplicity adjustment.

Through the end of the double-blind period, missing data for dichotomous endpoints will be handled using the non-responder imputation method, and missing data for continuous endpoints will be handled using mixed effects repeated measures analysis assuming missing at random mechanism.

4.8.2 Sample Size and Power Calculation

With a total sample size of approximately 342 and a randomization ratio of 2:1:2:2:2, the sample sizes are 76, 38, 76, 76, and 76 for placebo and MEDI2070 low, low-medium, high-medium, and high dose groups, respectively. A 10% dropout rate is assumed for each treatment group in the induction period.

Assuming a placebo CDAI clinical remission rate of 12% and MEDI2070 high dose CDAI clinical remission rate of 31% at Week 8 of the induction period, approximately 76 subjects per treatment group will provide at least 85% power to detect a 19% difference in CDAI clinical remission rates at Week 8 between MEDI2070 high dose versus placebo, using a two-sided test at a significance level of $\alpha = 0.10$. The minimum detectable difference in CDAI clinical remission rates at Week 8 will be 11%.

Assuming a 5% placebo SES-CD remission rate and 20% MEDI2070 high dose SES-CD remission rate at Week 16 of the induction period, the given sample size will provide at least 81% power to detect a 15% difference in SES-CD remission rates at Week 16 between MEDI2070 high dose versus placebo using a two-sided test at a significance level of $\alpha = 0.10$. The minimum detectable difference in SES-CD remission rates at Week 16 will be 10%.

[redacted]

4.8.3 Analysis Populations

Details of each population below and any additional population, if needed, will be described in the SAP.

4.8.3.1 Intent to Treat Population

The ITT population includes all subjects who are randomized into the study and receive any dose of investigational product for the 28-week, placebo-controlled, double-blind period. Subjects will be analyzed according to their randomized treatment group, regardless of whether subjects receive an investigational product different from that they were randomized to. The ITT population will be used as the primary population for all efficacy analyses. Disposition summary, demographics, baseline characteristics, protocol deviation, and efficacy endpoints will utilize this analysis population.

4.8.3.2 As-treated Population

The as-treated population includes all subjects who receive any amount of investigational product. Subjects will be analyzed according to the actual treatment received during the placebo-controlled, double-blind period even if it is different from that the subject was randomized to. Analysis of safety endpoints and summary of investigational product administration from the placebo-controlled, double-blind period will utilize this analysis population.

4.8.3.3 Pharmacokinetics Population

The PK population includes all subjects who receive at least one dose of investigational product and have at least one PK sample containing detectable MEDI2070. The PK population will be used for the PK analysis of the serum PK samples and the evaluation of immunogenicity.

4.8.3.4 Open-label Population

The open-label population includes all subjects who are enrolled in the open-label period and receive at least one dose of open-label MEDI2070 210 mg SC. Both efficacy and safety

information from the open-label period will be reported based on this population. Data from the open-label period will be reported by double-blind treatment group and both combined.

4.8.4 Efficacy

Efficacy data from the placebo-controlled, double-blind period and open-label period will be analyzed separately.

4.8.4.1 Primary Efficacy Analysis

The primary analysis will be conducted in the ITT population. The primary efficacy endpoint is CDAI remission at Week 8 of the induction period. The primary comparison of interest will be MEDI2070 high dose group versus placebo. The comparisons between MEDI2070 high-medium dose group versus placebo, low-medium dose group versus placebo, and MEDI2070 low dose group versus placebo will also be conducted.

Missing data will be handled using the non-responder imputation method through the end of the placebo-controlled, double-blind period; ie, any subject with missing information on the primary endpoint will be assumed as a non-responder. In addition, subjects with a clinically meaningful increase in steroid use will also be assumed to be non-responders for the primary analysis perspective. Clinical meaningful increase in steroid dose is defined as an increase of at least 5 mg/day for at least 3 days of prednisone, or equivalent, or an increase of at least 3 mg/day for at least 3 days of budesonide.

The difference in CDAI clinical remission rates at Week 8 between MEDI2070 dose groups and placebo group and associated 90% confidence interval will be provided. P-values for comparisons between any MEDI2070 dose group and placebo will be obtained from a logistic regression model adjusting for the number of prior anti-TNFα agents that failed or were not tolerated (1 vs > 1). In the event the number of remissions is too small (ie, < 5), the exact logistic regression will be performed instead. The statistically significant treatment effect will be tested against two-sided alpha level of 0.10.

4.8.4.2 Additional Analyses of the Primary Endpoint

A sensitivity analysis for the primary efficacy endpoint will be performed by extending the logistic regression model planned above via adjusting for baseline CDAI score and/or other baseline covariates for subjects in the ITT population. The following baseline covariates may be assessed and the final model will only include the significant baseline covariates.

- Age

- Sex
- Race
- Region (USA, non-USA)
- Baseline body mass index
- Disease duration
- Baseline CDAI score
- [redacted]
- Baseline CRP
- Baseline fecal calprotectin
- Smoking status at baseline

A stratified Cochran Mantel Haenszel test adjusting for the number of prior anti-TNFα agents that failed or were not tolerated (1 vs > 1), or stratified exact test in the event of a small number of remissions, may also be performed. Missing data will be handled using the non-responder imputation method through the end of the double-blind induction and maintenance periods.

The dose-response trend for the double-blind induction period will be tested using a Cochran-Armitage trend test. Other dose-response models may be explored; ie, multiple comparison procedure modelling method. The details of the dose-response analysis will be described in the SAP.

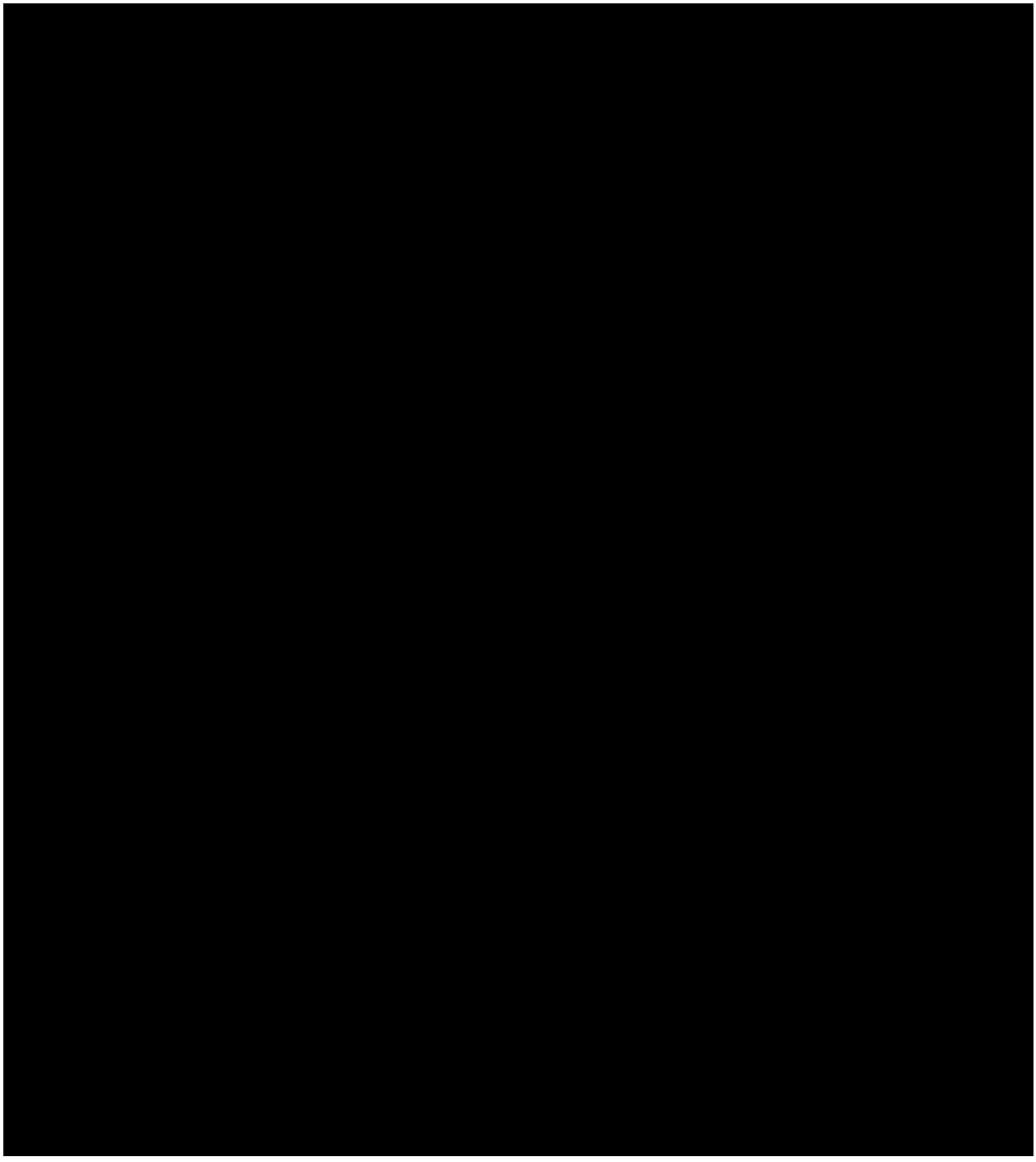
The exposure-response trend for the placebo-controlled, double-blind, induction period will be tested. The details of the exposure-response analysis will be described in a separate document.

4.8.4.3 Secondary Efficacy Analyses

Double-blind Induction and Maintenance Periods

The efficacy endpoints from the placebo-controlled, double-blind, induction and maintenance periods will be summarized descriptively and displayed graphically by visit and by treatment using the ITT population. The secondary efficacy endpoints with dichotomous outcomes from double-blind, induction and maintenance periods will be analyzed in a similar way to the primary efficacy endpoint.

The dose-response analysis may be repeated for secondary endpoints in the double-blind, induction period, including but not limited to SES-CD remission and response at Week 16, PRO2 remission and response at Week 8 and Week 16, CDAI response at Week 8 and Week 16, and CDAI clinical remission at Week 16.



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[redacted]

4.8.5 Safety

The analysis of safety endpoints will include TEAEs including TESAEs, AESIs, TEAEs resulting in permanent discontinuation of investigational product, laboratory values, vital signs, and ECGs. Safety data from the placebo-controlled, double-blind period will be analyzed using the as-treated population. Safety data from the open-label period will be analyzed using open-label population.

4.8.5.1 Analysis of Adverse Events

AEs will be monitored during the study and the data analyzed with respect to incidence within each treatment group as well as severity and potential relationship of the TEAEs to investigational product. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs. AEs with onset on or after the first dose of investigational product or with onset prior to the first dose of investigational product that increase in severity on, or after the first dose of investigational product will be considered treatment-emergent. TEAEs will be summarized by system organ class and preferred term. Tabular summaries of TEAEs will be provided as follows but not limited to:

- Incidence rate of TEAEs by treatment arm, system organ class, and preferred term

- Incidence rate of fatal TEAEs, TESAEs, TEAEs leading to permanent discontinuation of investigational product, treatment-related TESAEs, and AESIs will be provided
- Incidence rate of treatment-emergent and infectious AEs occurring in at least 5% of the subjects in any treatment arm by preferred term in descending order of frequency
- Incidence rate of TESAEs occurring in at least 1% of the subjects in any treatment arm

Analyses will also be performed for:

- Systemic hypersensitivity events; specific analyses will be performed for anaphylactic reactions
- Clinically significant infections; the frequency of serious infections, in particular GI infections, will be summarized for each treatment arm. For infections, whenever possible, the pathogen should be identified and recorded.
- Malignancies: events of malignancy will also be summarized for each treatment arm
- Infusion/injection-site reactions; the frequency of infusion/injection-site reactions will be summarized for each treatment arm
- Major cardiac events, defined as myocardial infarction, stroke, or cardiovascular death
- Ocular AEs, including cataracts; events of ocular AE, including cataracts, will be summarized for each treatment arm
- Surgery for CD: the time to onset of surgery for CD complications will be summarized for each treatment arm

4.8.5.2 Analysis of Clinical Laboratory, Vital Sign, and ECG Parameters

Associated laboratory parameters such as hepatic profile, renal function, and hematology values will be grouped and presented together. For each laboratory test, individual subject values outside the standard reference range will be flagged and listed. Shift tables will be produced showing the frequency of shifts from baseline to the worst on-study value in and out of the normal range, as well as by visit. Changes from baseline to each visit for each laboratory parameter will also be summarized.

The change from baseline to each visit for each of the vital sign variables will be summarized. Abnormal vital sign values will be flagged and listed.

The overall interpretation of the ECG results (Normal; Abnormal, not Clinically Significant; and Abnormal, Clinically Significant) will be summarized by treatment groups and by visit.

4.8.6 Patient-reported Outcomes

The study will utilize several PRO instruments. Data from the PROs will be analyzed to achieve 2 key purposes: (1) identification of the best symptom definitions to meet the emerging requirement for a symptom-based endpoint in future pivotal studies involving patients with CD, and (2) development of data to assist in providing content validation for the symptom collection and reporting methods. The sequence in which scoring instruments that contain PRO components (CDAI) or PROs will be collected at a given study visit will be in this order:

1. CDAI
[redacted]
4. PGIC-IBD (Visits 7 and 10 only)
5. Cognitive Patient Interview (selected subjects, Visit 10 or Early Termination Visit only)

The PRO endpoints will be summarized descriptively by treatment group and by visit. Data from the Cognitive patient interview will be analyzed and reported separately (ie, not in the Clinical Study Report).

4.8.7 Analysis of Immunogenicity/Pharmacokinetics

Descriptive statistics of serum MEDI2070 concentration data will be provided by visit. Individual and mean serum concentration-time profiles of MEDI2070 will be generated and included in the report. Pharmacokinetic data obtained in this study will be combined with all available PK data for MEDI2070 and analyzed using population PK methodology. For PK data analysis, time zero is defined as the beginning of infusion.

The presence of ADAs to MEDI2070 in serum will be assessed. Immunogenicity results (binding and, if positive, neutralizing) will be summarized by the number and percentage of subjects who develop detectable ADAs. If possible, the relationship between PK and ADA status will be summarized.

4.8.8 Additional Analyses

Data from [redacted] and mucosal biopsy analysis will be descriptive in nature and will be presented in a separate report (ie, not in the clinical study report).

4.8.9 Data Monitoring Committee

An external DMC will monitor and protect the safety of the subjects through review of safety data on a regular basis throughout the double-blind treatment period of the study, ie, until the last subject completes Week 28. The DMC members will be selected for their expertise. The voting members of the DMC will be comprised of external individuals including the DMC chair. Summaries of unblinded data will be prepared and provided to the DMC. To minimize the potential introduction of bias, DMC members will not have direct contact with the study site personnel or subjects. The data for review will be outlined in the DMC charter and will be agreed to in advance by the DMC members.

The DMC will review safety data on a regular basis as set out in the DMC charter. Subject enrollment will continue during DMC review of safety data. The available unblinded safety data for the randomized subjects will be evaluated by the DMC. Safety and efficacy summaries will be prepared prior to each meeting.

The DMC will recommend modifications of the protocol to enhance subject safety and to recommend early termination of the study if there is strong evidence that MEDI2070 poses a safety concern to subjects with CD. In addition, the sponsor's Safety Review Team (SRT) will review data on a regular basis throughout the course of the study. During the double-blind period, the SRT will remain blinded to the treatment assignments of the subjects. After the last subject has entered the open-label period of the study, the SRT will have access to unblinded data.

[redacted]

[redacted]

5 ASSESSMENT OF SAFETY

5.1 Definition of Adverse Events

The ICH Guideline for Good Clinical Practice E6(R1) defines an AE as:

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

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires medical intervention by the investigator, or a finding judged by the investigator as medically significant should be reported as an AE. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine red blood cell

increased). Abnormal laboratory values that are not, in the investigator's opinion, medically significant and do not require intervention should not be reported as AEs.

AEs may be treatment emergent (ie, occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or serious adverse event (SAE).

5.2 Definition of Serious Adverse Events

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in offspring of the subject
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

5.3 Definition of Adverse Events of Special Interest

An AESI is one of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or nonserious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

5.3.1 Hepatic Function Abnormality (Hy's Law)

Hepatic function abnormality meeting the definition of Hy's law is considered an AESI. See Section 5.6.2 for the definition and reporting of AESIs of hepatic function abnormality.

5.3.2 Infusion Reactions

Infusion of biological products is commonly associated with infusion-related reactions. Anaphylaxis and infusion-related reactions have some common manifestations and may be difficult to distinguish from each other. Infusion related reactions are commonly observed during or shortly after the first time exposure to therapeutic mAbs delivered through IV infusion. These reactions are less common following subsequent exposures. Unlike infusion related reactions, anaphylaxis is a rare event, usually occurring after subsequent exposure to an antigen, and it is most commonly accompanied by severe systemic skin and or mucosal reactions. The investigator is advised to carefully examine symptoms of adverse reactions observed during or shortly after exposure to MEDI2070, and consider the above mentioned facts prior to making a final diagnosis. Reactions occurring at the time of or shortly after subsequent infusions of investigational product are to be judged by the investigator at his/her own discretion. For the Investigator's convenience and to facilitate consistency in judgments a copy of the National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network guidance for anaphylaxis diagnosis is provided in Appendix 3.

AEs of infusion reactions (also termed infusion-related reactions) are of special interest to the sponsor. Instructions to the site on how to record in the eCRF and report these events to the sponsor are provided in Section 5.4.3.1 and Section 5.6.3.

5.3.3 Other Adverse Events of Special Interest

Other AESIs include malignancies, hypersensitivity reactions (eg, anaphylaxis), ocular AEs, including cataracts, and major cardiac events, defined as myocardial infarction, stroke, or cardiovascular death. Instructions to the site on how to record in the eCRF and report these events to the sponsor are provided in Section 5.4.3.2 and Section 5.6.

5.4 Recording of Adverse Events

AEs will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. AEs will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to the sponsor (see

Section 5.2 for the definition of SAEs and Appendix 2 for guidelines for assessment of severity and relationship. If an AE evolves into a condition that meets the regulatory definition of "serious," it will be reported as an SAE.

5.4.1 Time Period for Collection of Adverse Events

AEs will be collected from time that written informed consent is obtained until the end of subject participation in the study. New (nonserious) AEs that start after the reporting period has ended will not be collected. All AEs that start during the reporting period will be followed to resolution until the end of subject participation in the study.

All SAEs will be recorded from the time of informed consent.

5.4.2 Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the subject's last AE assessment or other assessment/visit as appropriate in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. MedImmune retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

5.4.3 Recording of Adverse Events of Special Interest

5.4.3.1 Infusion-related Reactions

Events of infusion-related reaction (as defined in Section 5.3.2) should be recorded according to the definitions of AE and SAE (Section 5.1 and Section 5.2, respectively). If reporting AE/SAE as a term "infusion reaction" or "infusion-related reaction" the site should also provide symptoms of the reaction. Whenever possible, time of the reaction should be provided.

5.4.3.2 Other Adverse Events of Special Interest

AESIs (as defined in Section 5.3.3) should be recorded according to the definitions of AE and SAE (Section 5.1 and Section 5.2, respectively).

5.5 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other site personnel will inform the appropriate sponsor representative(s) within 1 day, ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated sponsor representative works with the investigator to ensure that all the necessary information is provided to the sponsor patient safety data entry site within 1 calendar day of initial receipt for fatal and life-threatening events and within 5 calendar days of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform sponsor representatives of any follow-up information on a previously reported SAE within 1 calendar day; ie, immediately but no later than 24 hours of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the Electronic Data Capture (EDC) system, an automated email alert is sent to inform the designated sponsor representative(s).

If the EDC system is not available, then the investigator or other study site personnel reports a SAE to the appropriate sponsor representative by telephone. The sponsor representative will advise the investigator/study site personnel how to proceed.

5.6 Other Events Requiring Immediate Reporting

5.6.1 Overdose

An overdose is defined as a subject receiving a dose of investigational product in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on a MedImmune investigational product occurs in the course of the study, then the investigator or other site personnel inform appropriate sponsor representatives immediately, or no later than 24 hours of when he or she becomes aware of it.

The designated sponsor representative works with the investigator to ensure that all relevant information is provided to the sponsor's patient safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply; see Section 5.5. For other overdoses, reporting must occur within 30 days.

5.6.2 Hepatic Function Abnormality

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN may need to be reported as SAEs. Please refer to Appendix 4 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

5.6.3 Other Adverse Events of Special Interest

AESI (as defined in Section 5.3 and subsections) are required to be reported ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety, even if the event is considered to be nonserious.

5.6.4 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the sponsor.

5.6.4.1 Maternal exposure

If a subject becomes pregnant during the course of the study she must not receive additional doses of investigational product but will not be withdrawn from the study.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs during the study, then the investigator or other site personnel will inform the appropriate sponsor representatives within 1 day; ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated sponsor representative works with the investigator to ensure that all relevant information is provided to the sponsor's patient safety data entry site within 1 or 5 calendar days for SAEs (see Section 5.5) and within 30 days for all other pregnancies. The same timelines apply when the outcome information is available.

The pregnancy reporting module in the eCRF is used to report the pregnancy and the pregnancy outcome module is used to report the outcome of the pregnancy.

5.6.4.2 Paternal exposure

No data exist about the possible effects on pregnancy or the child resulting from a pregnancy induced by the sexual activity of a man exposed to MEDI2070. Male subjects should refrain from fathering a child or donating sperm during the study and for 26 weeks following the last dose.

Pregnancy of the subject's partner(s) is not considered to be an AE; however, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality), occurring from the date of the first dose until 26 weeks after the last dose should, if possible, be followed up and documented. Informed consent for gathering of information about the course and outcome of the pregnancy will be sought from the female partners of male subjects who become pregnant during the course of the study. Should the investigator become aware of a pregnancy in the partner of a male study subject who has received investigational product, then the investigator or other site personnel will inform the appropriate sponsor representatives within 1 day; ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated sponsor representative works with the investigator to ensure that all relevant information is provided to the sponsor's patient safety data entry site within 1 or 5 calendar days for SAEs (see Section 5.5) and within 30 days for all other pregnancies. The same timelines apply when the outcome information is available.

The pregnancy reporting module in the eCRF is used to report the pregnancy and the pregnancy outcome module is used to report the outcome of the pregnancy.

6 STUDY AND DATA MANAGEMENT

6.1 Training of Study Site Personnel

Before the first subject is entered into the study, a MedImmune representative will review and discuss the requirements of the clinical study protocol and related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilized.

The principal investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

6.2 Monitoring of the Study

During the study, a MedImmune representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that investigational product accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The MedImmune representative will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

6.2.1 Source Data

Refer to the Clinical Study Agreement for location of source data.

6.2.2 Study Agreements

The Principal Investigator at each/the center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between MedImmune and the Principal Investigator must be in place before any study-related procedures can take place, or subjects are enrolled.

6.2.3 Archiving of Study Documents

The Investigator follows the principles outlined in the Clinical Study Agreement.

6.3 Study Timetable and End of Study

6.3.1 Subject Completion

An individual subject who does not enter the 24-week, open-label period will be considered to have completed the double-blind period of the study if the subject was followed up through to the end of Week 28 of the study regardless of the number of doses of investigational product that was received. An individual subject who enters the open-label period will be considered to have completed the study if the subject was followed up through the end of Week 52 regardless of the number of doses of investigational product received.

Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow-up, or the subject refuses to return for all follow-up visits (see Section 4.1.5 and Section 4.1.6).

Subject completion date will be recorded in the eCRF.

6.3.2 Site Completion

Site completion is defined as the date of the last protocol-specified visit/assessment for the last subject in the study at the given study site. All materials or supplies provided by the sponsor will be returned to the sponsor or designee upon site completion of the study, as directed by the site monitor. The investigator will notify the IRB/IEC when the study has been completed at his/her site.

6.3.3 End of Study

The end of the study (“study completion”) is defined as the date of the last protocol-specified visit/assessment for the last subject in the study.

6.4 Data Management

Data management will be performed according to the Data Management Plan. An EDC system will be used for data collection and query handling. The investigator will ensure that

data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

6.5 Medical Monitor Coverage

Each subject will be provided with contact information for the principal investigator. In addition, each subject will receive a toll-free number intended to provide the subject's physician access to a medical monitor 24 hours a day, 7 days a week in the event of an emergent situation where the subject's health is deemed to be at risk. In this situation, when a subject presents to a medical facility where the treating physician or health care provider requires access to a physician who has knowledge of the investigational product and the clinical study protocol and the principal investigator is not available, the treating physician or health care provider can contact a medical monitor through this system, which is managed by a third party vendor.

7 ETHICAL AND REGULATORY REQUIREMENTS

7.1 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice (GCP), and applicable regulatory requirements.

7.2 Subject Data Protection

This study will have 3 separate ICFs, a main protocol ICF, a pharmacogenomics blood sample donation ICF, and a Cognitive Patient Interview (for subset of study subjects participating in these interviews). The main ICF will include a specific separate section with subject signature for consent to perform the optional intestinal mucosal biopsies. The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

MedImmune will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, a MedImmune medical monitor or an investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory Authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

7.3 Ethics and Regulatory Review

An IRB/IEC should approve the final study protocol, including the final version of the main ICF, the pharmacogenomics blood sample ICF, the Cognitive Patient Interview ICF, and any other written information and/or materials to be provided to the subjects. The investigator will ensure the distribution of these documents to the applicable IRB/IEC, and to the study site staff.

The opinion of the IRB/IEC should be given in writing. The investigator should submit the written approval to MedImmune before enrollment of any subject into the study.

The IRB/IEC should approve all advertising used to recruit subjects for the study.

MedImmune should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IRB/IEC annually.

Before enrollment of any subject into the study, the final study protocol, including the final version of the ICFs, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

Safety updates/reports, including suspected unexpected serious adverse reactions (SUSARs), where relevant, will be provided to Regulatory Authorities, IRBs/IECs, and investigators according to local requirements.

Each principal investigator is responsible for providing the IRB/IEC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. MedImmune will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

7.4 Informed Consent

The principal investigator(s) at each center will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICFs is/are stored in the investigator's Study File
- Ensure a copy of the signed ICF is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the ICF that is approved by an IRB/IEC

7.5 Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and MedImmune.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol.

The amendment is to be approved by the relevant IRB/IEC and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

MedImmune will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to IRB/IEC see Section 7.3.

If a protocol amendment requires a change to a site's ICF, MedImmune and the site's IRB/IEC are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each IRB/IEC.

7.6 Audits and Inspections

Authorized representatives of MedImmune, a regulatory authority, or an IRB/IEC may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact MedImmune immediately if contacted by a regulatory agency about an inspection at the site.

[redacted]

[redacted]

[redacted]

[redacted]

9 CHANGES TO THE PROTOCOL

All changes described below have been incorporated into the current version of the protocol.

9.1 Protocol Amendment 1, 18Nov2015

This amendment has been implemented to meet the requirements of the regulatory agency. Text revisions have been incorporated into the body of Protocol Amendment 1 and changes are summarized below.

1. Section 4.1.2 (Inclusion Criteria): Inclusion criterion 9 was modified to state that the male condom plus spermicide method must be used in conjunction with another method specified in Table [redacted]
2. Section 4.1.6 (Discontinuation of Investigational Product): Criterion 7 was revised to make it applicable to the entire study (formerly only applied to the 24-week, open-label period). Text was modified to clarify that recurrence of significant CD symptoms, that warrants escalation in therapy, according to investigator judgment, will result in discontinuation of the investigational product.
3. Section 4.2.1 (Screening and Induction Periods): Text was modified to clarify that screening assessments may be carried out over more than one visit to the site.
4. Section 4.7.1 (Permitted Concomitant Medications): Text was modified to clarify that the investigators may use their own assessment of the SES-CD score to decide whether or not to begin oral glucocorticosteroid tapering after Week 16.

Appendix 1 Signatures

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Signature of Principal Investigator

A Phase 2b Double-blind, Multi-dose, Placebo-controlled Study to Evaluate the Efficacy and Safety of MEDI2070 in Subjects with Moderate to Severe Crohn's Disease Who Have Failed or Are Intolerant to Anti-tumor Necrosis Factor-alpha Therapy

I, the undersigned, have reviewed this protocol and amendments, and I agree to conduct this protocol in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), any applicable laws and requirements, and any conditions required by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

I understand that the protocol may not be modified without written approval of the sponsor. All changes to the protocol must be submitted to the applicable regulatory authority and IRB/IEC, and must be approved by the IRB/IEC prior to implementation except when necessary to eliminate immediate hazards to the subjects or when the change(s), as deemed by the sponsor, involves only logistical or administrative changes. Documentation of IRB/IEC approval must be sent to the sponsor immediately upon receipt.

Signature and date: _____

Name and title: _____

Address including postal code: _____

_____

Telephone number: _____

Site/Center Number (if available)_____

Appendix 2 Additional Safety Guidance

Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V4.03 as provided in below. The determination of severity for all other events not listed in the CTCAE should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

Grade 1 (mild)	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2 (moderate)	An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Grade 3 (severe)	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
Grade 4 (life threatening)	An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).
Grade 5 (fatal)	Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 5.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

Assessment of Relationship

Relationship to Investigational Product

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product.

An event will be considered "not related" to use of the investigational product if any of the following tests are met:

- An unreasonable temporal relationship between administration of the investigational product and the onset of the event (eg, the event occurred either before, or too long after, administration of the investigational product for it to be considered product-related)
- A causal relationship between the investigational product and the event is biologically implausible (eg, death as a passenger in an automobile accident)
- A clearly more likely alternative explanation for the event is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related event)

Individual AE/SAE reports will be considered "related" to use of the investigational product if the "not related" criteria are not met.

"Related" implies that the event is considered to be "associated with the use of the drug" meaning that there is "a reasonable possibility" that the event may have been caused by the product under investigation (ie, there are facts, evidence, or arguments to suggest possible causation).

Relationship to Protocol Procedures

The investigator is also required to provide an assessment of relationship of SAEs to protocol procedures on the SAE Report Form. This includes nontreatment-emergent SAEs (ie, SAEs that occur prior to the administration of investigational product) as well as treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection, washout of an existing medication). The following guidelines should be used by investigators to assess the relationship of SAEs to the protocol:

Protocol related: The event occurred due to a procedure/intervention that was described in the protocol for which there is no alternative etiology present in the subject's medical record.

Not protocol related: The event is related to an etiology other than the procedure/ intervention that was described in the protocol (the alternative etiology must be documented in the study subject's medical record).

Appendix 3 National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis

Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson FN Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report -- Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-7.

National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to > 95% of all cases of anaphylaxis (for all 3 categories).

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

Appendix 4 Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a subject meets potential Hy's Law (PHL) criteria at any point during the study.

The investigator participates, together with MedImmune clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the investigational product.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AE and SAE according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

AST or ALT ≥ 3 × ULN together with total bilirubin (TBL) ≥ 2 × ULN at any point during the study following the start of investigational product irrespective of an increase in ALP.

Hy's Law (HL)

AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN, where no other reason, other than the investigational product, can be found to explain the combination of increases; eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

The investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the sponsor study representative
- Determine whether the subject meets PHL criteria by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

Follow-up

Potential Hy's Law Criteria Are Not Met

If the subject does not meet PHL criteria the investigator will:

- Inform the sponsor representative that the subject has not met PHL criteria
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria Are Met

If the subject does meet PHL criteria the investigator will notify the sponsor study representative who will then inform the central study team. The medical monitor contacts the investigator, to provide guidance, discuss and agree an approach for the study subject's follow-up and the continuous review of data. Subsequent to this contact the investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.

- Complete the Liver eCRF Modules as information becomes available
- If at any time (in consultation with the medical monitor) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Medical Monitor will contact the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the investigational product. The medical monitor and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an AE/SAE, record the AE/SAE in the eCRF accordingly and follow the sponsor standard processes

If it is agreed that there is no explanation that would explain the ALT or AST and TBL elevations other than the investigational product:

- Report an SAE (report term 'Hy's Law') according to sponsor standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned

If there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term ‘Potential Hy’s Law’) applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

FDA Guidance for Industry (issued July 2009) ‘Drug-induced liver injury: premarketing clinical evaluation’:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Statistical Analysis Plan

A Phase 2b Double-blind, Multi-dose, Placebo-controlled Study to Evaluate the Efficacy and Safety of MEDI2070 in Subjects with Moderate to Severe Crohn's Disease Who Have Failed or Are Intolerant to Anti-Tumor Necrosis Factor-alpha Therapy

Protocol Number: D5170C00002

Final: 8 Dec 2015 by MedImmune

Amendment #1: 27 Mar 2018 by Allergan

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List of Abbreviations

Abbreviation or Specialized Term	Definition
AE	Adverse Event
AESI	Adverse Event Of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
[redacted]	[redacted]
CRP	C-reactive protein
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DB	Double-Blind
ECG	Electrocardiogram
eCRF	electronic Case Report Form
IBD	Inflammatory Bowel Disease
[redacted]	[redacted]
IL	interleukin
ITT	Intent To Treat
IV	Intravenous
IVRS/IXRS	Interactive Voice/Web Response System
[redacted]	[redacted]
MACE	Major Adverse Cardiac Events
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse events
OL	Open-Label
PGIC-IBD	Patient Global Impression of Change-Inflammatory Bowel Disease
PK	Pharmacokinetic (s)
PT	Preferred Terms
PROs	Patient Reported Outcomes
PRO2	Patient-Reported Outcomes-2 score
Q4W	Every 4 Weeks
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SPP	Statistical Programming Plan
SC	Subcutaneous
SD	Standard Deviation
SES-CD	Simple Endoscopic Score for Crohn's Disease
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TNFα	Tumor Necrosis Factor-alpha

Abbreviation or Specialized Term	Definition
ULN	Upper Limit of Normal
WBC	White Blood Cell

1 INTRODUCTION

This document describes the statistical analyses plan specified in the protocol D5170C00002. The scope of this plan addresses statistical analyses as they apply to safety and efficacy objectives, including the primary, intermediate and final analyses unless otherwise specified (e.g. analyses related to pharmacokinetic (PK) and translational science measurements will not be discussed in this document). A separate statistical programming plan (SPP), containing table templates and specifications, will be created to be used in conjunction with this document.

The study, however, was early terminated; 29 subjects were randomized to one of the five treatment groups by the time of the study termination.

2 STUDY OVERVIEW

The following study objectives were copied from the original protocol. However, the study was early terminated; 29 subjects were randomized to one of five treatment groups by the time of the study termination. Due to the small number of subjects in the study, only descriptive statistics for limited efficacy endpoints are provided. However, all data will be listed.

2.1 Study Objectives

2.1.1 Primary Study Objective

To evaluate the efficacy of MEDI2070 versus placebo to induce clinical remission based on the CDAI score at Week 8 in subjects with moderate to severe Crohn's Disease (CD) who have failed or are intolerant to anti-TNFα therapy.

2.1.2 Secondary Study Objectives

Induction Period Secondary Objectives:

1. To evaluate the efficacy of MEDI2070 versus placebo to induce remission at Week 16 based on the Simple Endoscopic Score for Crohn's Disease (SES-CD)
2. To evaluate the efficacy of MEDI2070 versus placebo to induce response at Week 16 based on the SES-CD
3. To evaluate the efficacy of MEDI2070 versus placebo to induce remission at Week 8 based on the Patient-reported Outcomes 2 score (PRO2)
4. To evaluate the efficacy of MEDI2070 versus placebo to induce response at Week 8 based on the PRO2
5. To evaluate the efficacy of MEDI2070 versus placebo to induce clinical response at Week 8 based on the CDAI

6. To evaluate the efficacy of MEDI2070 versus placebo to induce remission at Week 16 based on the PRO2
7. To evaluate the efficacy of MEDI2070 versus placebo to induce response at Week 16 based on the PRO2
8. To evaluate the efficacy of MEDI2070 versus placebo to induce clinical remission at Week 16 based on the CDAI
9. To evaluate the efficacy of MEDI2070 versus placebo to induce clinical response at Week 16 based on the CDAI
10. To demonstrate safety and tolerability of MEDI2070 therapy
11. To characterize the pharmacokinetics (PK) and immunogenicity of MEDI2070
12. To characterize the dose-response and exposure-response relationships

[redacted]

Maintenance Period Secondary Objectives:

1. To evaluate the efficacy of MEDI2070 versus placebo to induce clinical remission based on CDAI score at Week 28
2. To evaluate the efficacy of MEDI2070 versus placebo on remission at Week 28 based on the SES-CD
3. To evaluate the efficacy of MEDI2070 versus placebo on remission at Week 28 based on the PRO2
4. To evaluate the efficacy of MEDI2070 versus placebo on modified sustained remission, defined as remission at both Week 16 and at Week 28 based on the SES-CD
5. To evaluate the efficacy of MEDI2070 versus placebo on modified sustained remission, defined as remission at both Week 8 and at Week 28 based on the PRO2
6. To evaluate the efficacy of MEDI2070 versus placebo on modified sustained clinical remission, defined as clinical remission at both Week 8 and at Week 28 based on the CDAI
7. To evaluate the efficacy of MEDI2070 versus placebo on response at Week 28 based on the SES-CD

8. To evaluate the efficacy of MEDI2070 versus placebo on response at Week 28 based on the PRO2
9. To evaluate the efficacy of MEDI2070 versus placebo on clinical response at Week 28 based on the CDAI
10. To demonstrate safety and tolerability of MEDI2070 therapy
11. To characterize the PK and immunogenicity of MEDI2070

[redacted]

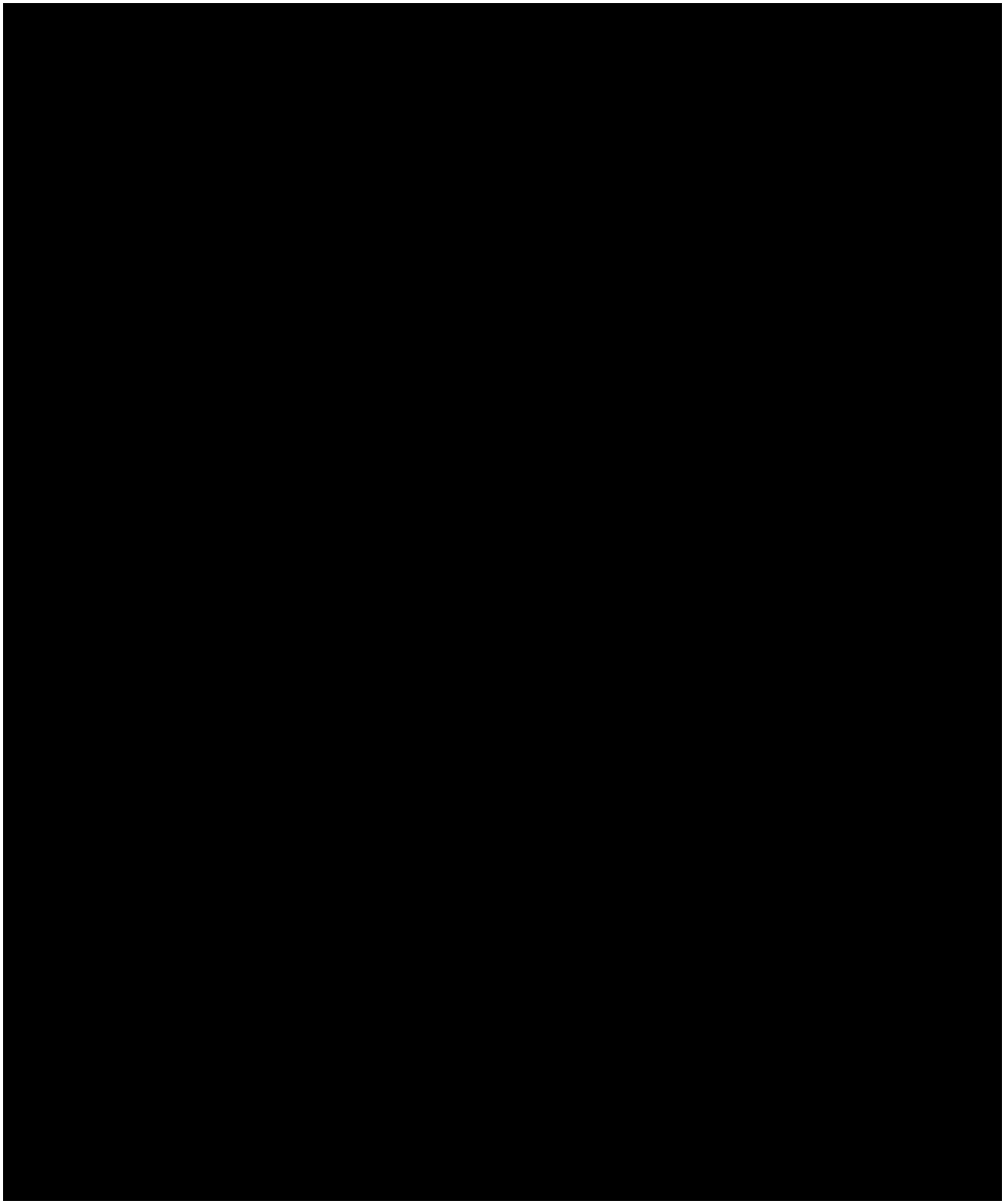
2.2 Study Design

This is a 3-part Phase 2b study comprising a 16-week, double-blind, placebo-controlled, induction period; a 12-week double-blind, placebo-controlled, maintenance period; and a 24-week, open-label period designed to evaluate the short-term efficacy and the short- and long- term safety of MEDI2070 in subjects with moderate to severe, active CD who have failed or are intolerant to anti-TNFα therapy as determined by the investigator. Subjects will be stratified based on the number of prior anti-TNFα agents that they have failed (1 versus > 1).

Approximately 342 subjects at approximately 300 centers worldwide will be randomly assigned to 1 of 5 treatment groups to receive intravenous (IV) and subcutaneous (SC) investigational product (MEDI2070 or placebo) once every 4 weeks (Q4W) during the double-blind, placebo-controlled induction and maintenance periods. Subjects who complete the double-blind, placebo controlled maintenance period (Week 28) will have the option to enter a 24-week, open-label period in which they will receive open-label MEDI2070 (210 mg SC) Q4W (Weeks 28 through 48). All subjects will be followed for safety at 3 visits over 28 weeks (Weeks 60, 70, and 80 for subjects completing the open-label period) after their last dose of investigational product.

The study, however, was early terminated; 29 patients were randomized to one of the five treatment groups by the time of the termination.

Figure 2-1 Study Flow Diagram



2.3 Treatment Assignment and Blinding

Subjects will receive investigational product (MEDI2070 or placebo) by IV infusion and/or SC injection at Week 0 (Day 1) then once Q4W during the 16-week, double-blind, placebo-controlled, induction period (i.e., Weeks 4, 8, and 12) and the 12-week double-blind, placebo-controlled, maintenance period (i.e., Weeks 16, 20, and 24). All subjects who complete the double-blind maintenance period will have the option to enter the 24-week open-label treatment period. All subjects entering the open-label period will receive open-label MEDI2070 (210 mg SC) once Q4W (i.e., Weeks 28, 32, 36, 40, 44, and 48).

A total of approximately 342 subjects will be randomly assigned to one of five treatment groups:

Treatment Group	**Double-blind Treatment Period**				**Open-label Period**
	Induction			**Maintenance**	
	Week 0	**Week 4**	**Weeks 8, and 12**	**Weeks 16, 20, and 24**	**Weeks 28, 32, 36, 40, 44, and 48**
Treatment Group 1 High (n = 76)	700 mg MEDI2070 IV + placebo SC	700 mg MEDI2070 IV + placebo SC	210 mg MEDI2070 SC	210 mg MEDI2070 SC	210 mg MEDI2070 SC
Treatment Group 2 High-medium (n = 76)	280 mg MEDI2070 IV + placebo SC	210 mg MEDI2070 SC + placebo IV	210 mg MEDI2070 SC	210 mg MEDI2070 SC	210 mg MEDI2070 SC
Treatment Group 3 Low-medium (n = 76)	210 mg MEDI2070 SC + placebo IV	105 mg MEDI2070 SC + placebo IV	105 mg MEDI2070 SC	105 mg MEDI2070 SC	210 mg MEDI2070 SC
Treatment Group 4 Low (n = 38)	70 mg MEDI2070 SC + placebo IV	35 mg MEDI2070 SC + placebo IV	35 mg MEDI2070 SC	35 mg MEDI2070 SC	210 mg MEDI2070 SC
Treatment Group 5 Placebo (n = 76)	Placebo SC and IV	Placebo SC and IV	Placebo SC	Placebo SC	210 mg MEDI2070 SC

IV = intravenous; SC = subcutaneous

The study, however, was early terminated; 29 subjects were randomized to one of the five treatment groups by the time of the study termination.

2.4 Sample Size

With a total sample size of approximately 342 and a randomization ratio of 2:1:2:2:2, the sample sizes are 76, 38, 76, 76, and 76 for placebo and MEDI2070 low, low-medium, high-medium, and high dose groups, respectively. A 10% dropout rate is assumed for each treatment group during the induction period.

Assuming a placebo CDAI remission rate of 12% and MEDI2070 high dose CDAI remission rate of 31% at Week 8 of the induction period, approximately 76 subjects per treatment group will provide at least 85% power to detect a 19% difference in CDAI remission rates at Week 8 between MEDI2070 high dose versus placebo, using a two-sided test at a significance level of $\alpha = 0.10$. The minimum detectable difference in CDAI remission rates at Week 8 will be 11%.

Assuming a 5% placebo SES-CD remission rate and 20% MEDI2070 high dose SES-CD remission rate at Week 16 of the induction period, the given sample size will provide at least 81% power to detect a 15% difference in SES-CD remission rates at Week 16 between MEDI2070 high dose versus placebo using a two-sided test at a significance level of $\alpha = 0.10$. The minimum detectable difference in SES-CD remission rates at Week 16 will be 10%.

The study, however, was early terminated; 29 subjects were randomized to one of the five treatment groups by the time of the study termination.

3 Statistical Methods

3.1 General Considerations

All data will be provided in data listings. Tabular summaries for limited efficacy and safety parameters in the double-blind treatment period will be presented by treatment group.

All efficacy data will be summarized using the analysis visits. The analysis visit windowing rules will be defined based on study days of post-baseline. The details of analysis visit windowing rules will be described in Section 3.4.

Day 1 will be defined as the day of first investigational product administration. For any variable, unless otherwise defined, the baseline value is the last non-missing assessment taken prior to the first

investigation product administration. The change from baseline will be calculated by subtracting the baseline values from the individual post-baseline values. If either the baseline or post-baseline value is missing, the change from baseline is set to missing.

The following conventions will be applied to all data presentations and summary.

- For continuous endpoints, arithmetic mean, and median will be formatted to one more decimal place than the measured value. SD will be formatted to two more decimal place than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value.
- For categorical variables, the count and percentage of responses will be presented in the form XX (XX.X%) where the percentage is in the parentheses.
- Data analyses will be conducted using SAS® version 9.4 (SAS Institute Inc., Cary, NC) or higher.

3.2 Analysis Populations

The analysis populations are defined in Table 3-1.

Table 3-1 Analysis Populations

Population	Description
Intent-to-treat (ITT) population	The Intent-to-Treat (ITT) Population includes all subjects who are randomized into the study and receive at least one whole dose of investigational product for the 28-week, double-blind, placebo-controlled treatment period. Subjects will be analysed according to their randomized treatment group, regardless of whether they receive an investigational product that is different from what they were randomized to.
Safety population	The Safety Population includes all subjects who receive at least one dose of investigational product. Subjects will be analyzed according to the actual treatment received during the placebo-controlled, double-blind treatment period even if it is different from what the subject is randomized to.
Open-label population	Open-label population includes all subjects who are enrolled in the open-label treatment period and have at least one dose of open-label MEDI2070 210 mg SC treatment.
PK population	The Pharmacokinetics (PK) Population includes all subjects who receive at least one dose of investigational product and have at least one PK sample containing detectable MEDI2070.

3.3 Handling of Dropouts and Missing Data

Subjects may be missing specific data points for a variety of causes. In general, data may be missing due to a subject's early withdrawal from study, a missed visit, or inability to evaluate an endpoint at a particular point in time. The general procedures outlined below describe what will be done when a data point is missing. Missing safety endpoints will not be imputed.

3.3.1 Missing and Incomplete Dates

For any listings, missing or incomplete dates will be listed as is.

In the case where the start or stop date of an event or medication is missing or incomplete, the following rules will be applied in the analysis:

Table 3-2 Missing Dates Imputation Rules

	Missing	Imputation	Exception
Start date (Adverse Events and concomitant medication)	Day	01	Default to Study Day 1 if an event starts the same year and month as Study Day 1 and Stop date is after Study Day 1
	Day/Month	01JAN	Default to Study Day 1 if an event started the same year as Day 1 and Stop date is after Study Day 1
	Day/Month/Year	No imputation	
Stop date (concomitant medication)	Day	Last day of the month	Default to the End of Study Date or the primary analysis cut-off date for ongoing subjects if the concomitant medication stopped the same year and month as the End of Study Date or primary analysis cut-off date
	Day/Month	31DEC	Default to the End of Study Date or the primary analysis cut-off date for ongoing subjects if the concomitant medication stopped the same year as the End of Study Date or primary analysis cut-off date
	Day/Month/Year	No imputation	

3.3.2 Missing Baseline Evaluation

For any endpoint, unless otherwise defined, the baseline value is the last non-missing assessment taken prior to the first investigational product administration. If the baseline is still missing following above definition, the baseline evaluation will not be imputed and will be considered as missing.

3.3.3 Missing Efficacy Evaluations

Through the end of the DB period (induction and maintenance periods), the missing efficacy data will be handled as described below:

- Missing data for dichotomous endpoints will be handled using the non-responder imputation method, i.e. any subject with missing information on the endpoint will be assumed as a non-responder.
- Missing data for continuous measures will not be imputed.
- Missing data for PRO components (e.g. IBDQ, CD-PRO) will be handled according to the scoring algorithm as described in corresponding sections. If the score is still missing, no further imputation will be done.

3.4 Analysis Visit Windowing Rules

The actual visit for a subject may not exactly coincide with their targeted visit date. The actual visit date will be mapped to the study visit following the analysis visit windowing rules below. Unless specified otherwise, all efficacy and safety analyses will be based on the analysis visits. If there are multiple records fall within the same defined analysis visit window, the non-missing record closest to the target day will be considered for the analysis.

If two non-missing assessment actual dates are equidistant from the target day, the later visit will be considered for analysis.

Composite endpoints (e.g. CDAI score) will be calculated for each date at which individual components are being measured before applying the analysis visit windows rather than to calculate visit window based individual component.

3.4.1 DB Treatment Period

DB Period Study Day 1 is defined as the first day of DB IP administration. For subjects who are randomized but not dosed after randomization, the Day 1 is defined as the date of randomization.

DB Period Study Day is defined as the number of days from the Double-blind Treatment Period Study Day 1.

- Before DB Period Study Day 1:

Double-blind Treatment Period Study Day = (Date of Interest – Date of DB Period Study Day 1)

- On or After DB Period Study Day 1:

DB Period Study Day = (Date of Interest – Date of DB Period Study Day 1) + 1

Unless otherwise specified, all efficacy analysis will apply the analysis visit window rules as defined in [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.4.2 OL Treatment Period

OL Period Study Day 1 is defined as the first day of OL IP administration. OL Period Study Day is defined as the number of days from OL Period Study Day 1.

- Before OL Period Study Day 1:

Open-Label Period Study Day = (Date of Interest – Date of OL Period Study Day 1)

- On or After OL Period Study Day 1:

OL Period Study Day = (Date of Interest – Date of OL Period Study Day 1) + 1.

[redacted]

3.5 Study Subjects

3.5.1 Subject Disposition and Completion Status

A summary of subject disposition throughout the study with respect to completion of double-blind induction and maintenance periods and open-label period will be provided. The number and percentage will be provided by treatment groups and overall using the randomized subjects as the denominator. The timing of and reasons for early withdrawal from treatment and from study will be tabulated and listed.

3.5.2 Demographics and Baseline Characteristics

Subject demographics and baseline characteristics will be listed for each subject. Following demographics and baseline characteristics will be summarized by treatment groups and overall using the ITT population. A summary of baseline disease characteristics may include, but not be limited to:

- Age
- Age (< 40 years, ≥ 40 years)
- Sex (Male, Female)
- Race (White, Black/African American, Asian, Other)
- Race (White, Non-white)
- Region (US, Non-US)
- Disease duration of CD (years)
- Disease duration (< 5 years, ≥ 5 years)
- Ethnic group (Hispanic or Latino, Other)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- Baseline disease location (ileum, not colon; colon, not ileum; or ileo-colonic, as observed at baseline ileocolonoscopy)
- Baseline CDAI score
- Baseline weekly abdominal pain score
- Baseline weekly loose/liquid stool count
- Baseline SES-CD score
- Baseline SES-CD score by baseline disease location subgroup (per subgroup of subjects with ileum, not colon; colon, not ileum; or ileo-colonic disease)
- Baseline CRP (mg/L)
- Baseline CRP (< 5 mg/L, ≥ 5 mg/L)
- Baseline fecal calprotectin (µg/g)
- Baseline fecal calprotectin (< 250 µg/g, ≥ 250 µg/g)
- Baseline fecal calprotectin (< 200 µg/g, ≥ 200 µg/g)
- [redacted]
- [redacted]

- Baseline IBDQ score
- Alcohol status (Never, Current and Former)
- Number of prior use of anti-TNF agents (1, > 1)
- Number of prior use of anti-TNFα agents (1, 2, ≥ 3)
- Prior use of vedolizumab (Yes, No)
- Use of 5-aminosalicylatesat baseline (Yes, No)
- Use of corticosteroids at baseline (Yes, No)
- Use of immunomodulators at baseline (Yes, No)
- Smoking status at baseline (Never, Current, Former)

3.5.3 Study Drug Exposure

Descriptive statistics for extent of exposure (in days) will be presented for the safety population and the OL population during the specified treatment period.

For DB period, the following summaries will be provided using for the safety population:

- Duration of exposure in the DB period

For OL period, the following summaries will be provided using the OL population:

- Duration of exposure in the OL period

Additionally, descriptive statistics for the cumulative exposure for overall MEDI2070 will be provided. If a subject entered both the DB period and OL period, the subject will be considered as the same subject and the exposure data will be combined from both periods.

3.5.4 Prior and Concomitant Medications

Prior medication refers to all medications that were started prior to the start of the first dose of investigational product.

Concomitant medication refers to all medications taken during the treatment period of the DB period and the OL period. Concomitant medications include medications continued from pre-treatment. Medications with missing start and stop dates will be counted as concomitant medications. Medications with partial start or stop dates will be handled as described in Section 3.3.1. Medications with start and stop dates which bracket the first dose date will be flagged as both prior and concomitant medications.

All prior and concomitant medications data will be coded by World Health Organization Drug Dictionary, version March 2017 or newer and listed for each subject by treatment groups.

3.5.5 CD History

The CD history will be listed using the safety population.

3.5.6 Medical and Surgical History

Abnormalities in subjects' medical and surgical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 20.1 or newer. Preferred Term (PT) in the medical history and surgical history will be listed using the safety population.

3.5.7 Physical, Neurological and Visual Examination

All data related to physical, neurological and visual examination will be listed for each subject.

3.5.8 Protocol Deviations

Protocol deviations will be recorded and are classified as critical, major, and minor deviation. Listing of critical and major protocol deviations will be provided by treatment group.

3.6 Efficacy Analyses

Efficacy data from the DB treatment period will be summarized descriptively by treatment group.

3.6.1 Primary Efficacy Endpoint(s) and Analyses

3.6.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is Crohn's Disease Activity Index (CDAI) remission at Week 8. CDAI remission is defined as a CDAI score of < 150. Refer to Appendix 6.1 for detail on CDAI score.

3.6.1.2 Primary Efficacy Analysis

The primary analysis will be conducted in the ITT population. The primary efficacy endpoint is CDAI remission at Week 8 of the induction period will be descriptively summarized.

3.6.1.3 Additional Analyses of the Primary Efficacy Endpoint

No sensitivity analyses of the primary efficacy endpoint will be performed.

3.6.2 Secondary Efficacy Endpoints and Analyses

3.6.2.1 Secondary Efficacy Endpoints

Remission and response will be assessed by both clinical and patient reported outcomes (PRO) measures. The following definitions will be used to define the secondary efficacy endpoints:

- CDAI clinical response: Decrease from baseline in the CDAI of ≥ 100 points
- SES-CD remission: Total SES-CD score ≤ 4, with:
  - No subscore > 2, and
  - Segments scored at baseline that cannot be observed on a subsequent examination will be scored with an imputed value unchanged from baseline
- SES-CD response: Decrease from baseline in SES-CD ≥ 50%; segments scored at baseline that cannot be observed on a subsequent examination will be scored with an imputed value unchanged from baseline.
- PRO2 remission (loose/liquid stool frequency/abdominal pain): Remission achieved for both abdominal pain and loose/liquid stool frequency
- PRO2 response: (loose/liquid stool frequency/abdominal pain): Remission or response in one symptom (either abdominal pain or stool frequency) plus response in the other
  - Abdominal pain remission: On an 11-point (0 to 10) pain scale: During 1 week, no daily score > 2
  - Abdominal pain response: On an 11-point (0 to 10) pain scale: ≥ 30% reduction in weekly pain score from baseline
  - Loose/liquid stool frequency remission: Counting stools identified as Type 6 or 7 on Bristol Stool Form Scale, during 1 week, each daily loose loose/liquid stool count ≤ 3
  - Loose/liquid stool frequency response: Counting stools identified as Type 6 or 7 on Bristol Stool Form Scale, ≥ 30% reduction in weekly loose/liquid stool count compared to baseline

Please note that hematocrit results from hematology central lab testing during the study were required to calculate the CDAI scores for a given visit. It was discovered post-sponsor-transition in August 2017 that central labs for hematology were not required to be taken per protocol during study visits V8 (W20/D141), V9 (W24/D169), V11 (W32/D225), V12 (W36/D253), V14 (W44/D309) and V15 (W48/D337); therefore, the hematocrit item scores and subsequent CDAI total scores could not be calculated for these study visits. It was therefore agreed that any CDAI scores obtained from the study database for the above 6 visits will not be included in any study analyses. Refer to Note to File in Appendix 6.3 for detail.

Refer to Appendix 6.1 and Appendix 6.2 for details on CDAI score and SES-CD score.

Table 3-7 List of Secondary Endpoints

	Secondary Efficacy Endpoints	
Induction Period		
Week 8	PRO2 Remission Abdominal pain remission Loose/liquid stool frequency remission	PRO2 Response Abdominal pain response Loose/liquid stool frequency response CDAI clinical Response
Week 16	SES-CD Remission PRO2 Remission CDAI clinical remission Abdominal pain remission Loose/liquid stool frequency remission	SES-CD Response PRO2 Response CDAI clinical response Abdominal pain response Loose/liquid stool frequency response
Maintenance Period		
Week 28	CDAI clinical remission SES-CD Remission PRO2 Remission Abdominal pain remission Loose/liquid stool frequency remission	CDAI clinical response SES-CD Response PRO2 Response Abdominal pain response Loose/liquid stool frequency response

3.6.2.2 Secondary Efficacy Analyses

The efficacy data from the DB induction and maintenance periods will be summarized descriptively by treatment group and by visit using the ITT Population.

The secondary efficacy endpoints with dichotomous outcomes will be summarized similarly as the primary analysis of the primary efficacy endpoint using the ITT population.

3.6.2.3 Predictive Biomarker Analyses

Due to a small number of subjects in the study, the predictive biomarker analyses will not be performed.

3.6.3 Exploratory Efficacy Endpoints and Analyses

3.6.3.1 Exploratory Efficacy Endpoints

Induction Period Exploratory endpoints:

3.6.3.2 Analyses of Exploratory Endpoints

Patient reported outcomes endpoints (e.g. change from baseline in IBDQ, change from baseline in newly developed PRO scores) will be described in Section 3.6.

The exploratory efficacy endpoints with continuous or ordinal outcomes (e.g. change from baseline in CRP and change from baseline in FCP) will be summarized descriptively.

3.6.4 Other Efficacy Analyses

3.6.4.1 Dose-Response Analysis

Due to a small number of subjects in the study, no dose-response analysis will be performed.

3.6.4.2 Efficacy Analysis for OL Treatment Period

Due to a small number of the subjects in the study, no efficacy analysis for OL Treatment Period will be performed.

3.6.5 Subgroup Analysis

Due to a small number of subjects in the study, no subgroup analysis will be performed.

3.7 Patient Reported Outcomes

The study will utilize several PRO instruments. The sequence in which scoring instruments that contain PRO components (CDAI) or PROs will be collected at a given study visit will be the following order:

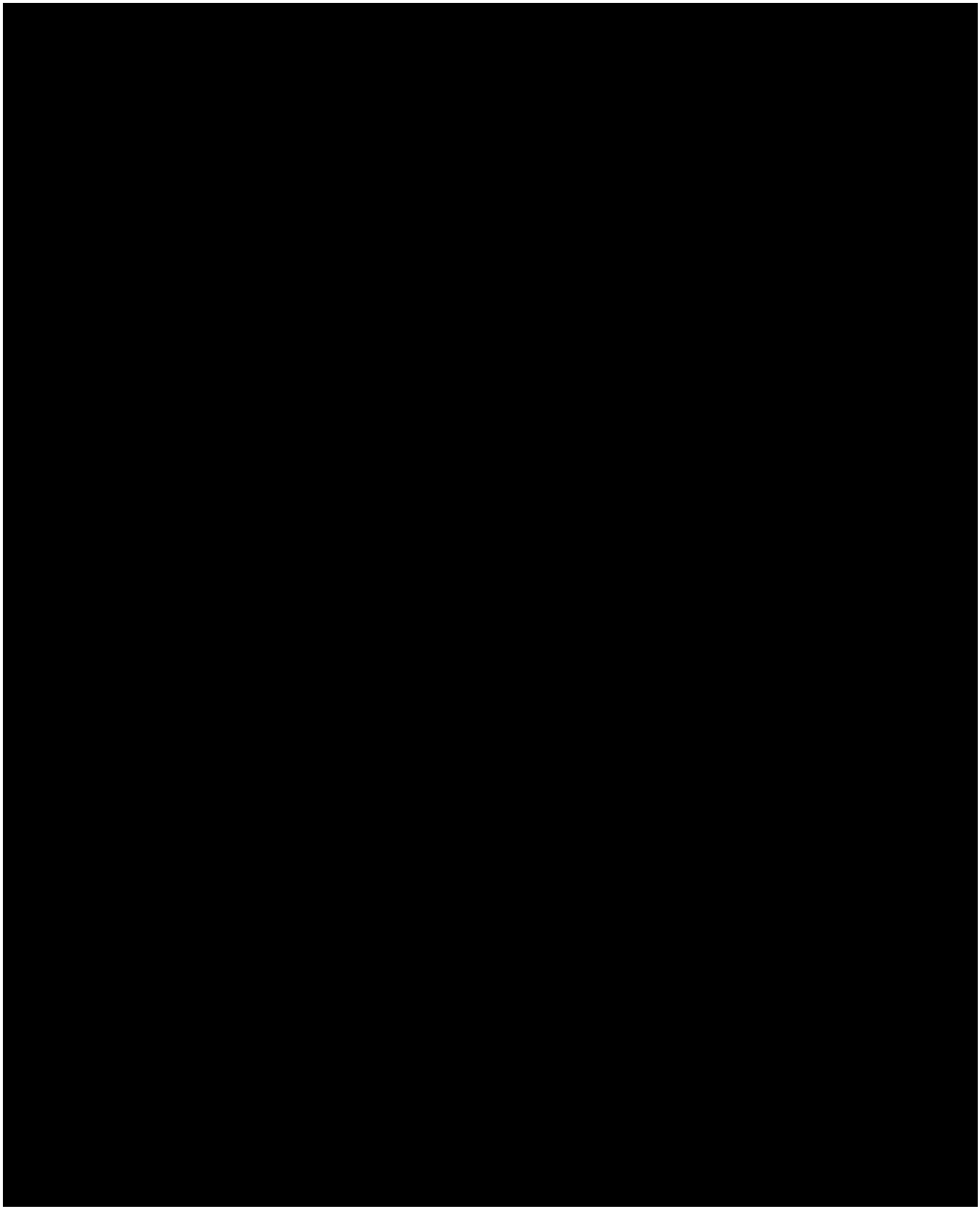
- CDAI
- Crohn's Disease Patient Reported Outcomes (CD-PRO)
- Inflammatory Bowel Disease Questionnaire (IBDQ)
- PGIC-IBD (Visits 7 and 10 only)
- Cognitive Patient Interview (selected subjects, Visit 10 or Early Termination Visit only)

Data from PGIC-IBD will be analyzed and reported separately (i.e. not in the clinical study report). Data from cognitive patient interviews was not available on account of early study termination.

The PRO data will be explored. A separate (supplementary) psychometric analysis plan (PAP) to explore the performance of the PRO instruments and to potentially develop new domain or total scores to inform endpoint development (including responder & remitter definitions) was developed by QuintilesIMS and the associated results will be reported separately in a psychometric analysis report (i.e. not in the clinical study report).

3.7.1 CDAI score

The two items from CDAI, "total number of liquid or very soft stools over past week" and "total abdominal pain score over past week", will be descriptively summarized over time.



3.8 Safety Analyses

The analysis of safety endpoints will include TEAEs, laboratory values, vital signs, and ECG. Only TEAEs and clinical laboratory evaluation from the 28-week placebo-controlled DB treatment period will be summarized using the safety population. All other safety endpoints will be listed. No statistical comparisons will be performed for the safety data.

3.8.1 Adverse Events and Serious Adverse Events

Adverse events (AE) will be coded by MedDRA and the type incidence, severity and relationship to study investigational product will be summarized. Specific adverse events will be counted once for each subject for calculating percentages. In addition, if the same adverse event occurs multiple times within a particular subject, the highest severity and level of relationship observed will be reported. All AEs and SAEs collected in the database (including those starting prior to first dose of study drug) will be listed. Any other information collected (e.g. relatedness to study drug, action taken etc.) will be listed as appropriate.

3.8.1.1 Pre-treatment AEs

The AEs with onset prior to the administration of the first dose of investigational product (MEDI2070 or placebo) will be considered as pre-treatment AEs for the DB treatment period. Pre-treatment AEs will be listed with a flag.

3.8.1.2 Treatment-Emergent AEs during DB Treatment Period

For subjects entering the OL treatment period, the TEAE will be defined as any AE with onset on or after the administration of the first dose of blinded investigational product up to the day prior to administration of the first OL SC dose. For subjects not entering the OL treatment period, the TEAE will be defined as any AE with onset on or after the administration of the first dose of blinded investigational product up to and including 28 weeks post last blinded dose.

All TEAEs including TESAEs, Adverse Event of Special Interest (AESIs), and TEAEs leading to permanent discontinuation of investigational product will be summarized overall. The TEAEs with severity grades will be summarized by grades assigned by National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE) V4.0. Tabular summaries of the TEAEs during the DB treatment period will be provided as follows:

- Incidence rate of TEAEs by SOC and PT
- Incidence rate of TEAEs by SOC, PT, and severity
- Incidence rate of related TEAE by SOC and PT
- Incidence rate of TESIs by SOC and PT

3.8.1.3 TEAEs during OL Treatment Period

TEAE for the OL treatment period will be defined as any AE with onset on or after the administration of the first open-label SC dose of MEDI2070 up to and including 28 weeks post-last dose. Incidence rate of TEAEs during OL treatment period will be summarized by SOC and PT using the OL population.

3.8.2 Deaths and Treatment Discontinuations due to Adverse Events

Deaths and treatment discontinuation due to AEs will be listed by treatment groups.

[redacted]

3.8.4 Vital Signs

Vital signs parameters, including blood pressure, temperature, pulse rate and respiration rate, will be obtained according to study schedule procedures. All vital signs parameters (blood pressure, temperature, pulse rate, and respiration rate) will be listed. Abnormal vital sign values will be flagged.

3.8.5 Electrocardiogram

12-lead Electrocardiogram (ECG) measurements will be performed according to the study schedule. The ECG data will be listed. The overall interpretation of the ECG results (Normal; Abnormal, not Clinically Significant; and Abnormal, Clinically Significant) will be listed.

3.9 Pharmacokinetics and Immunogenicity

The SAP for pharmacokinetics and immunogenicity will be presented separately.

4 Interim Analysis

Not applicable.

6 Appendix

6.1 CDAI Score

The CDAI is the oldest and most widely used of several multi-item instruments that have been developed and is validated for use in clinical studies to measure disease activity in CD (Best et al, 1976; Sands et al, 2005). The CDAI measures the severity of active disease using symptom scores that are monitored over the previous week and includes subject-reported symptoms, physician-assessed signs, and laboratory markers.

The CDAI score is calculated by summing weighted scores for subjective items (number of liquid or very soft stools, the degree of abdominal pain over a week (on a scale of 0-3, mild to severe) and general well-being (on scale of 1-4, "Generally well" to "Terrible") recorded by a diary during a 1-week period, and objective items (associated symptoms, taking antidiarrheal such as loperamide/opiates, abdominal mass, hematocrit, daily morning temperature, and body weight). The CDAI scores range approximately from 0 to 600, with higher scores indicating greater disease activity (See Table 6-1 for details).

The CDAI will be calculated at the site in order to determine the eligibility for the study. For statistical analysis, CDAI for all visits will be also calculated based on the data entered in the eCRF.

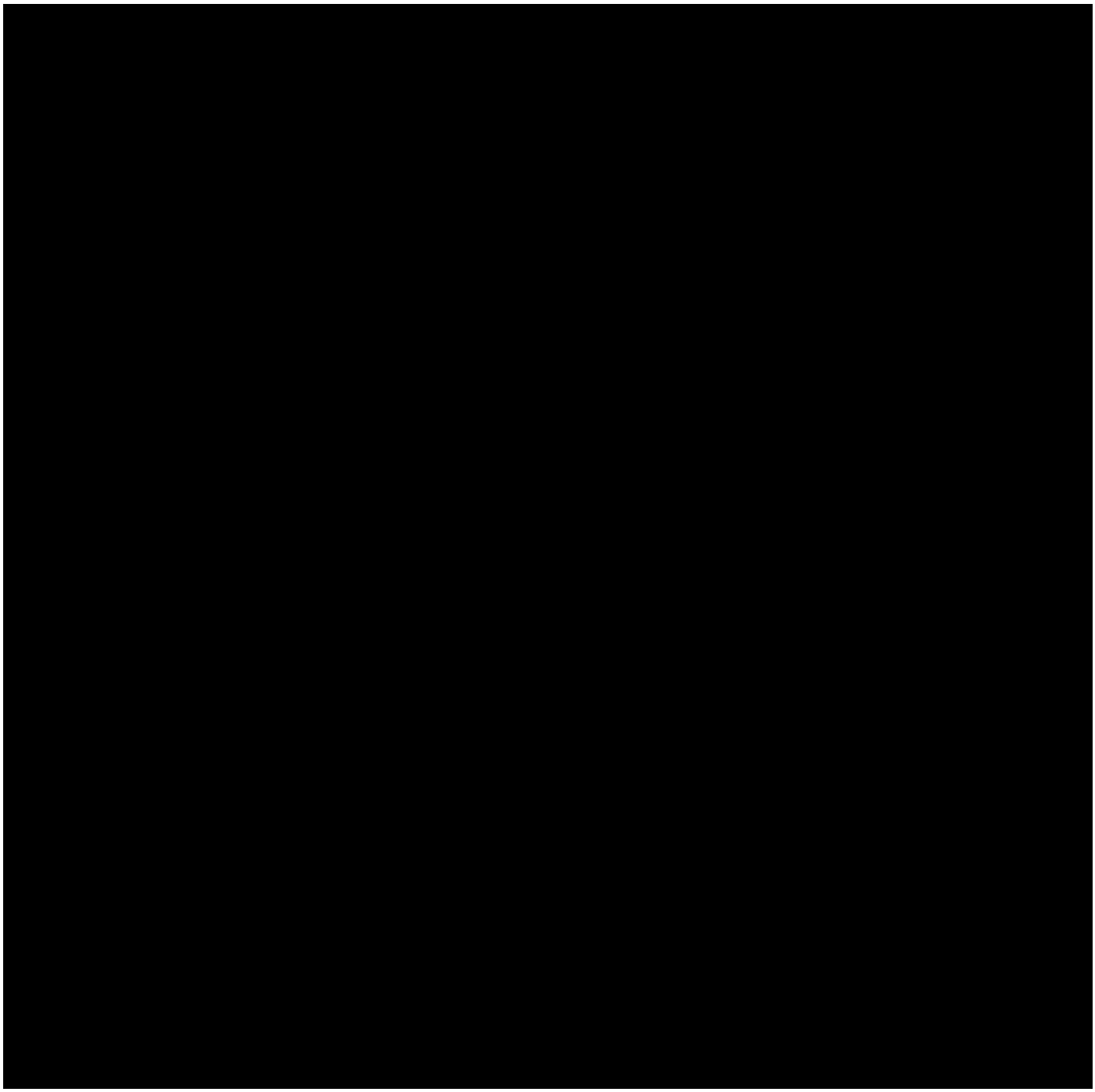
Table 6-1 Items Included in CDAI and Their Weights

Item	× Weight	Total
Total number of liquid or very soft stools over past week	×2	X_1
Total abdominal pain score (rating: 0-3) over past week (range: 0-21)	×5	X_2
Total general well-being score (rating: 1-4) over past week (range: 1-28)	×7	X_3
Sum of presence of following clinical signs over past week: 1. Arthritis/Arthralgia (1=yes, 0=no) 2. Iritis/ uveitis(1=yes, 0=no) 3. Erythema Nodosum/Pyoderma Gangrenosum/Aphthous Stomatitis (1=yes, 0=no) 4. Anal Fissure, Fistula or Abscess (1=yes, 0=no) 5. Other Fistula (1=yes, 0=no) 6. Fever >37.8 C During Past Week(1=yes, 0=no)	×20	X_4
Antidiarrheal use (Eg, Diphenoxylate hydrochloride) (0=none, 1=yes)	×30	X_5
Abdominal mass (none=0, equivocal=2, present=5)	×10	X_6
Deviation of Hematocrit levels (minimum value = 0) 47 - hematocrit (males) 42 - hematocrit (females)	×6	X_7 (if value<0, enter 0)
Weight ratio 100×(1-[Current body weight / standard weight]) Minimum = -10 for overweight subject Maximum = 10 for underweight subject	×1	X_8 (if value<-10, enter -10, if value >10, enter 10)
CDAI score		$\sum_{i=1}^{8} X_i$

In addition, following set of rules will be applied:

- For items 1, 2 and 3, if information is available only for ≤ 3 days, then CDAI score will be set to missing. Otherwise, the sub score for each of these three items will be calculated as mean value of item from available days × 7.
- For all items, if a subject doesn't have score for any of the sub categories, CDAI score will be set to missing.
- Any total CDAI score < 0 will be considered as 0 in the analysis.

Subjects with scores of < 150, 150 to 219, and 220 to 450 represent remission, mild disease, and moderate to severe disease, respectively; whereas subjects with scores of > 450 have very severe disease (Buxton et al, 2007).



6.3 Note to File

NOTE TO FILE

DATE: 19th Dec 2017
STUDY NUMBER: D5170C00002
RE: CDAI score at V8, V9, V11, V12, V14, V15 and Follow-up visits 1-3

Per the Schedules of Study Procedures (Tables 4.2.1-1 and 4.2.2-1) in the protocol, the CDAI (Crohn's Disease Activity Index) score was expected from Visit 2 (W0/D1) onwards.

Issue relating to visits V8, V9, V11, V12, V14, V15:
Hematocrit results from hematology central lab testing during the study were required to calculate the CDAI scores for a given visit. It was discovered post-sponsor-transition in Aug 2017 that central labs for hematology were not required to be taken per protocol during study visits V8 (W20/D141), V9 (W24/D169), V11 (W32/D225), V12 (W36/D253), V14 (W44/D309) and V15 (W48/D337); therefore the hematocrit item scores and subsequent CDAI total scores could not be calculated for these study visits. Per protocol, this did not impact inclusion/exclusion criteria and also did not impact study objectives or primary endpoints.

Some sites were using hematocrit values from previous visits in error, that were up to 4-8 weeks old, and therefore could have resulted in inaccurate total CDAI scores for the visits. Due to the Sponsor decision to close the study on 26th Sept 2017, this protocol omission of not including central lab testing for hematocrit values on those visits was not corrected via a protocol amendment.

It was therefore agreed that any CDAI scores obtained from the study database for the above 6 visits will not be included in any study analyses.

Issue relating to Follow up visits 1-3:
It was also discovered post-sponsor-transition in Nov 2017 that there was a programming issue where patients that were withdrawn or early terminated could not have follow-up visits recorded in the slate devices. This was due to programming of the slate not allowing for entry of data for any visits post Early Termination visits. The slate was programmed such that follow up visits would only trigger for patients that completed the study at V16 (W12/D85). Therefore, CDAI scores for withdrawn/early terminated patients could not be completed during their follow-up visits. CRF Health provided instructions on 21st Nov 2017 on how sites can record the Early Termination visit as V16, so that follow-up visits could be triggered and CDAI scores calculated. This will include data for any patients with follow up visits going forward from 4th Dec 2017 (date CRAs were provided with new instructions to discuss with sites). A blast email was also sent to all sites with instructions on 19th Dec 2017.

Due to the study closure and timing of LPLV due by 2nd Feb 2018, the CRF Health programming will not be updated. Per the vendor, the slate was programmed incorrectly due to a misunderstanding of the protocol.

[redacted]

Page 1 of 1

Statistical Analysis Plan

A Phase 2b Double-blind, Multi-dose, Placebo-controlled Study to Evaluate the Efficacy and Safety of MEDI2070 in Subjects with Moderate to Severe Crohn's Disease Who Have Failed or Are Intolerant to Anti-Tumor Necrosis Factor-alpha Therapy

Protocol Number: D5170C00002

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

List of Abbreviations

Abbreviation or Specialized Term	Definition
ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event Of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the serum concentration-time Cure
CI	Confidence Interval
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
[redacted]	[redacted]
CRP	C-reactive protein
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DB	Double-Blind
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
e-diary	Electronic diary
EOS	End of Study
IBD	Inflammatory Bowel Disease
[redacted]	[redacted]
IL	interleukin
IM	Immunogenicity
ITT	Intent To Treat
IV	Intravenous
IVRS/IXRS	Interactive Voice/Web Response System
[redacted]	[redacted]
LLOQ	Lower Limit of Quantification
MACE	Major Adverse Cardiac Events

Abbreviation or Specialized Term	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MCP-Mod	Multiple Comparison Procedure - Modelling
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse events
OL	Open-Label
PGIC-IBD	Patient Global Impression of Change-Inflammatory Bowel Disease
PK	Pharmacokinetic (s)
PT	Preferred Terms
PROs	Patient Reported Outcomes
PRO2	Patient-Reported Outcomes-2 score
Q4W	Every 4 Weeks
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SPP	Statistical Programming Plan
SC	Subcutaneous
SD	Standard Deviation
SES-CD	Simple Endoscopic Score for Crohn's Disease
SIDES	Subgroup Identification based on Differential Effect Search
SMQ	Standardised MedDRA Query
SOC	System Organ Class
STEPP	Subpopulation Treatment Effect Pattern Plot
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TNFα	Tumor Necrosis Factor-alpha
ULN	Upper Limit of Normal
WBC	White Blood Cell

1 INTRODUCTION

This document describes the statistical analyses plan specified in the protocol D5170C00002. The scope of this plan addresses statistical analyses as they apply to safety and efficacy objectives, including the primary, intermediate and final analyses unless otherwise specified (e.g. analyses related to pharmacokinetic (PK) and translational science measurements will not be discussed in this document). A separate statistical programming plan (SPP), containing table templates and specifications, will be created to be used in conjunction with this document.

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Study Objective(s)

To evaluate the efficacy of MEDI2070 versus placebo to induce clinical remission based on the CDAI score at Week 8 in subjects with moderate to severe Crohn's Disease (CD) who have failed or are intolerant to anti-TNFα therapy.

2.1.2 Secondary Study Objectives

Induction Period Secondary Objectives:

1. To evaluate the efficacy of MEDI2070 versus placebo to induce remission at Week 16 based on the Simple Endoscopic Score for Crohn's Disease (SES-CD)
2. To evaluate the efficacy of MEDI2070 versus placebo to induce response at Week 16 based on the SES-CD
3. To evaluate the efficacy of MEDI2070 versus placebo to induce remission at Week 8 based on the Patient-reported Outcomes 2 score (PRO2)
4. To evaluate the efficacy of MEDI2070 versus placebo to induce response at Week 8 based on the PRO2
5. To evaluate the efficacy of MEDI2070 versus placebo to induce clinical response at Week 8 based on the CDAI
6. To evaluate the efficacy of MEDI2070 versus placebo to induce remission at Week 16 based on the PRO2
7. To evaluate the efficacy of MEDI2070 versus placebo to induce response at Week 16 based on the PRO2
8. To evaluate the efficacy of MEDI2070 versus placebo to induce clinical remission at Week 16 based on the CDAI

9. To evaluate the efficacy of MEDI2070 versus placebo to induce clinical response at Week 16 based on the CDAI
10. To demonstrate safety and tolerability of MEDI2070 therapy
11. To characterize the pharmacokinetics (PK) and immunogenicity of MEDI2070
12. To characterize the dose-response and exposure-response relationships

[redacted]

Maintenance Period Secondary Objectives:

1. To evaluate the efficacy of MEDI2070 versus placebo to induce clinical remission based on CDAI score at Week 28
2. To evaluate the efficacy of MEDI2070 versus placebo on remission at Week 28 based on the SES-CD
3. To evaluate the efficacy of MEDI2070 versus placebo on remission at Week 28 based on the PRO2
4. To evaluate the efficacy of MEDI2070 versus placebo on modified sustained remission, defined as remission at both Week 16 and at Week 28 based on the SES-CD
5. To evaluate the efficacy of MEDI2070 versus placebo on modified sustained remission, defined as remission at both Week 8 and at Week 28 based on the PRO2
6. To evaluate the efficacy of MEDI2070 versus placebo on modified sustained clinical remission, defined as clinical remission at both Week 8 and at Week 28 based on the CDAI
7. To evaluate the efficacy of MEDI2070 versus placebo on response at Week 28 based on the SES-CD
8. To evaluate the efficacy of MEDI2070 versus placebo on response at Week 28 based on the PRO2
9. To evaluate the efficacy of MEDI2070 versus placebo on clinical response at Week 28 based on the CDAI
10. To demonstrate safety and tolerability of MEDI2070 therapy
11. To characterize the PK and immunogenicity of MEDI2070

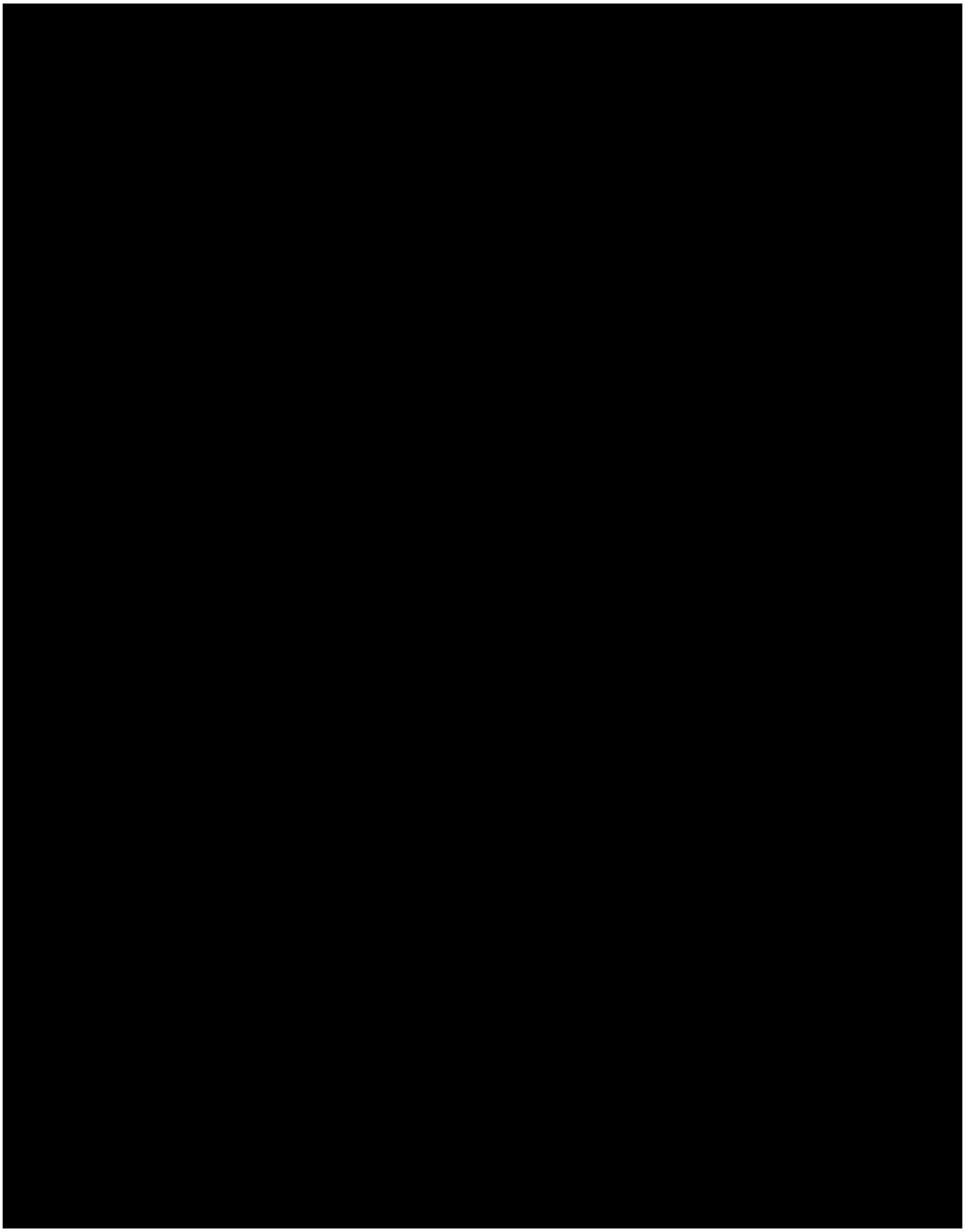
[redacted]

[redacted]

2.2 Study Design

This is a 3-part Phase 2b study comprising a 16-week, double-blind, placebo-controlled, induction period; a 12-week double-blind, placebo-controlled, maintenance period; and a 24-week, open-label period designed to evaluate the short-term efficacy and the short- and long-term safety of MEDI2070 in subjects with moderate to severe, active CD who have failed or are intolerant to anti-TNFα therapy as determined by the investigator. Subjects will be stratified based on the number of prior anti-TNFα agents that they have failed (1 versus > 1).

Approximately 342 subjects at approximately 300 centers worldwide will be randomly assigned to 1 of 5 treatment groups to receive intravenous (IV) and subcutaneous (SC) investigational product (MEDI2070 or placebo) once every 4 weeks (Q4W) during the double-blind, placebo-controlled induction and maintenance periods. Subjects who complete the double-blind, placebo controlled maintenance period (Week 28) will have the option to enter a 24-week, open-label period in which they will receive open-label MEDI2070 (210 mg SC) Q4W (Weeks 28 through 48). All subjects will be followed for safety at 3 visits over 28 weeks (Weeks 60, 70, and 80 for subjects completing the open-label period) after their last dose of investigational product.



2.3 Treatment Assignment and Blinding

Subjects will receive investigational product (MEDI2070 or placebo) by IV infusion and/or SC injection at Week 0 (Day 1) then once Q4W during the 16-week, double-blind, placebo-controlled, induction period (ie, Weeks 4, 8, and 12) and the 12-week double-blind, placebo-controlled, maintenance period (ie, Weeks 16, 20, and 24). All subjects who complete the double-blind maintenance period will have the option to enter the 24-week open-label treatment period. All subjects entering the open-label period will receive open-label MEDI2070 (210 mg SC) once Q4W (ie, Weeks 28, 32, 36, 40, 44, and 48).

A total of approximately 342 subjects will be randomly assigned to one of five treatment groups:

Treatment Group	Double-blind Period				Open-label Period
	Induction			Maintenance	
	Week 0	Week 4	Weeks 8, and 12	Weeks 16, 20, and 24	Weeks 28, 32, 36, 40, 44, and 48
Treatment Group 1 High (n = 76)	700 mg MEDI2070 IV + placebo SC	700 mg MEDI2070 IV + placebo SC	210 mg MEDI2070 SC	210 mg MEDI2070 SC	210 mg MEDI2070 SC
Treatment Group 2 High-medium (n = 76)	280 mg MEDI2070 IV + placebo SC	210 mg MEDI2070 SC + placebo IV	210 mg MEDI2070 SC	210 mg MEDI2070 SC	210 mg MEDI2070 SC
Treatment Group 3 Low-medium (n = 76)	210 mg MEDI2070 SC + placebo IV	105 mg MEDI2070 SC + placebo IV	105 mg MEDI2070 SC	105 mg MEDI2070 SC	210 mg MEDI2070 SC
Treatment Group 4 Low (n = 38)	70 mg MEDI2070 SC + placebo IV	35 mg MEDI2070 SC + placebo IV	35 mg MEDI2070 SC	35 mg MEDI2070 SC	210 mg MEDI2070 SC
Treatment Group 5 Placebo (n = 76)	Placebo SC and IV	Placebo SC and IV	Placebo SC	Placebo SC	210 mg MEDI2070 SC
IV = intravenous; SC = subcutaneous					

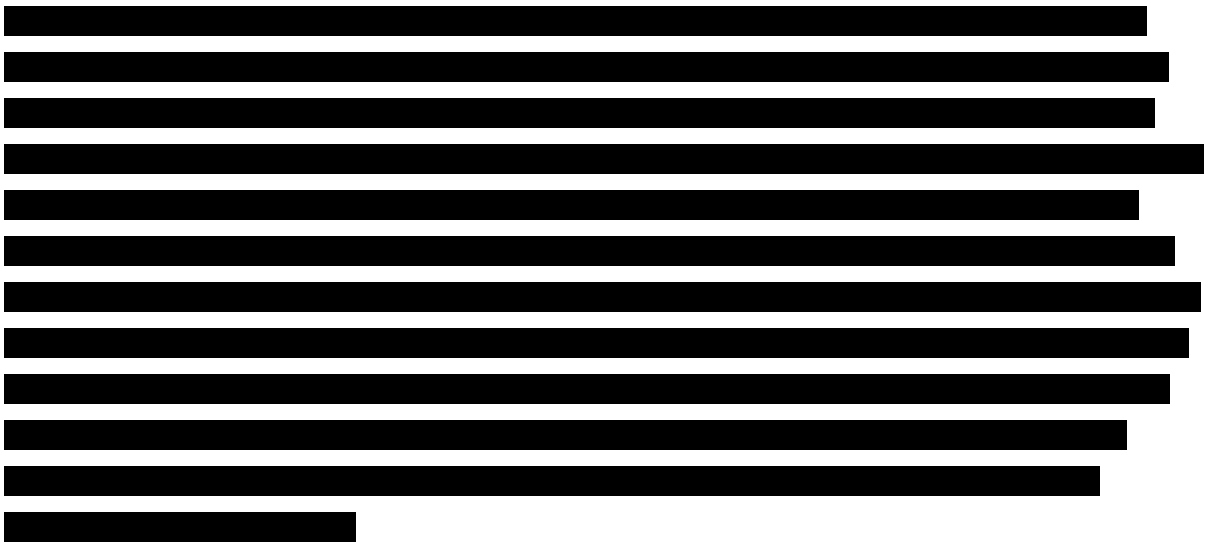
2.4 Sample Size

With a total sample size of approximately 342 and a randomization ratio of 2:1:2:2:2, the sample sizes are 76, 38, 76, 76, and 76 for placebo and MEDI2070 low, low-medium, high-medium, and high dose groups, respectively. A 10% dropout rate is assumed for each treatment group during the induction period.

Assuming a placebo CDAI remission rate of 12% and MEDI2070 high dose CDAI remission rate of 31% at Week 8 of the induction period, approximately 76 subjects per treatment group will provide at least 85% power to detect a 19% difference in CDAI remission rates at Week

8 between MEDI2070 high dose versus placebo, using a two-sided test at a significance level of $\alpha = 0.10$. The minimum detectable difference in CDAI remission rates at Week 8 will be 11%.

Assuming a 5% placebo SES-CD remission rate and 20% MEDI2070 high dose SES-CD remission rate at Week 16 of the induction period, the given sample size will provide at least 81% power to detect a 15% difference in SES-CD remission rates at Week 16 between MEDI2070 high dose versus placebo using a two-sided test at a significance level of $\alpha = 0.10$. The minimum detectable difference in SES-CD remission rates at Week 16 will be 10%.



3 STATISTICAL METHODS

3.1 General Considerations

All data will be provided in data listings sorted by treatment group and subject number. Tabular summaries will be presented by treatment group. Data from OL period will be summarized by DB treatment group in additional to overall column.

All efficacy data will be analyzed using the analysis visits. The analysis visit windowing rules will be defined based on study days of post-baseline. The details of analysis visit windowing rules will be described in Section 3.4.

Day 1 will be defined as the day of first investigational product administration. For any variable, unless otherwise defined, the baseline value is the last non-missing assessment

taken prior to the first investigation product administration. The change from baseline will be calculated by subtracting the baseline values from the individual post-baseline values. If either the baseline or post-baseline value is missing, the change from baseline is set to missing.

For the purpose of statistical analyses, the data from DB treatment period (induction and maintenance periods) and OL treatment period will be analyzed separately. Unless otherwise stated, all efficacy analyses will be conducted with a two-sided test at a significance level of $\alpha = 0.10$. Nominal p-values will be provided without multiplicity adjustment.

In addition, the following conventions will be applied to all data presentations and analyses.

- For continuous endpoints, arithmetic mean, and median will be formatted to one more decimal place than the measured value. SD will be formatted to two more decimal place than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value. Confidence limits will be presented to the same decimal places as the point estimate.
- For categorical variables, the count and percentage of responses will be presented in the form XX (XX.X%) where the percentage is in the parentheses.
- Nominal p-values will be rounded to three decimal places using the following algorithm. If the fourth digit of the p-value is less than or equal to 4 the p-value will be rounded down. If the fourth digit of the p-value is greater than or equal to 5, the p-value will be rounded up. All p-values rounded to 0.000 will be presented as "<0.001" and p-values rounded to 1.000 will be presented as ">0.999".
- Data analyses will be conducted using SAS® version 9.3 (SAS Institute Inc., Cary, NC) or higher in UNIX platform.

3.2 Analysis Populations

The analysis populations are defined in Table 3.2-1.

Table 3.2-1 Analysis Populations

Population	Description
Intent-to-treat (ITT) population	The Intent-to-Treat (ITT) Population includes all subjects who are randomized into the study and receive at least one dose of investigational product for the 28-week, double-blind, placebo-controlled treatment period. Subjects will be analysed according to their randomized treatment group, regardless of whether they receive an investigational product that is different from what they were randomized to.
As-treated population	The As-treated Population includes all subjects who receive at least one dose of investigational product. Subjects will be analyzed according to the actual treatment received during the placebo-controlled, double-blind treatment period even if it is different from what the subject is randomized to.
Open-label population	Open-label population includes all subjects who are enrolled in the open-label treatment period and have at least one dose of open-label MEDI2070 210 mg SC treatment.
PK population	The Pharmacokinetics (PK) Population includes all subjects who receive at least one dose of investigational product and have at least one PK sample containing detectable MEDI2070.

3.3 Handling of Dropouts and Missing Data

Subjects may be missing specific data points for a variety of causes. In general, data may be missing due to a subject's early withdrawal from study, a missed visit, or inability to evaluate an endpoint at a particular point in time. The general procedures outlined below describe what will be done when a data point is missing. Missing safety endpoints will not be imputed.

3.3.1 Missing and Incomplete Dates

For any listings, missing or incomplete dates will be listed as is.

In the case where the start or stop date of an event or medication is missing or incomplete, the following rules will be applied in the analysis:

Table 3.3.1-1 Missing Dates Imputation Rules

	Missing	Imputation	Exception
Start date (Medical History, Adverse Events, concomitant medication)	Day	01	Default to Study Day 1 if an event starts the same year and month as Study Day 1 and Stop date is after Study Day 1
	Day/Month	01JAN	Default to Study Day 1 if an event started the same year as Day 1 and Stop date is after Study Day 1
	Day/Month/Year	No imputation	
Stop date (concomitant medication)	Day	Last day of the month	Default to the End of Study Date or the primary analysis cut-off date for ongoing subjects if the concomitant medication stopped the same year and month as the End of Study Date or primary analysis cut-off date
	Day/Month	31DEC	Default to the End of Study Date or the primary analysis cut-off date for ongoing subjects if the concomitant medication stopped the same year as the End of Study Date or primary analysis cut-off date
	Day/Month/Year	No imputation	

3.3.2 Missing Baseline Evaluation

For any endpoint, unless otherwise defined, the baseline value is the last non-missing assessment taken prior to the first investigational product administration. If the baseline is still missing following above definition, the baseline evaluation will not be imputed and will be considered as missing.

3.3.3 Missing Efficacy Evaluations

Through the end of the DB period (induction and maintenance periods), the missing efficacy data will be handled as described below:

- Missing data for dichotomous endpoints will be handled using the non-responder imputation method, i.e. any subject with missing information on the endpoint will be assumed as a non-responder. In addition, subjects with a clinically meaningful increase in steroid use will also be assumed to be a non-responder for the primary

analysis perspective. Clinical meaningful increase in steroid dose is defined as an increase of at least 5 mg/day for at least 3 days of prednisone, or equivalent, or an increase of at least 3mg/day for at least 3 days of budesonide.

- Missing data for continuous measures will not be imputed. The continuous measures will be analyzed using the repeated measure mixed effects model adjusting for prior anti-TNFα agent use and baseline covariate, assuming the missing at random mechanism. Other missing data imputation method (e.g. multiple imputation) may be explored.
- Missing data for PRO components (e.g. IBDQ, CD-PRO) will be handled according to the scoring algorithm as described in corresponding sections. If the score is still missing, no further imputation will be done.

Through the end of the OL period, the missing efficacy data will be handled as described below:

- Missing data for dichotomous endpoints will be handled using the non-responder imputation method in a similar way of the DB period.
- Missing data for continuous measures will not be imputed and will be summarized as observed.
- Missing data for PRO components (e.g. IBDQ, CD-PRO) will be handled in the same way as the DB period.

3.4 Analysis Visit Windowing Rules

The actual visit for a subject may not exactly coincide with their targeted visit date. The actual visit date will be mapped to the study visit following the analysis visit windowing rules below. Unless specified otherwise, all efficacy and safety analyses will be based on the analysis visits. If there are multiple records fall within the same defined analysis visit window, the non-missing record closest to the target day will be considered for the analysis.

If two non-missing assessment actual dates are equidistant from the target day, the later visit will be considered for analysis.

Composite endpoints (e.g. CDAI score) will be calculated for each date at which individual components are being measured before applying the analysis visit windows rather than to calculate visit window based individual component.

3.4.1 DB Treatment Period

DB Period Study Day 1 is defined as the first day of DB IP administration. For subjects who are randomized but not dosed after randomization, the Day 1 is defined as the date of randomization.

DB Period Study Day is defined as the number of days from the Double-Blind Period Study Day 1.

- Before DB Period Study Day 1:

Double-Blind Period Study Day = (Date of Interest – Date of DB Period Study Day 1)

- On or After DB Period Study Day 1:

DB Period Study Day = (Date of Interest – Date of DB Period Study Day 1) + 1

Unless otherwise specified, all efficacy analysis will apply the analysis visit window rules as defined in [redacted]

[redacted]

[redacted]

[redacted]

3.4.2 OL Treatment Period

OL Period Study Day 1 is defined as the first day of OL IP administration. OL Period Study Day is defined as the number of days from OL Period Study Day 1.

- Before OL Period Study Day 1:

Open-Label Period Study Day = (Date of Interest – Date of OL Period Study Day 1)

- On or After OL Period Study Day 1:

OL Period Study Day = (Date of Interest – Date of OL Period Study Day 1) + 1.

[redacted]

[redacted]

3.5 Study Subjects

3.5.1 Subject Disposition and Completion Status

A summary of subject disposition throughout the study with respect to completion of double-blind induction and maintenance periods and open-label period will be provided. The number and percentage will be provided by treatment groups and overall using the ITT population and OL population, respectively. The timing of and reasons for early withdrawal from treatment and from study will be tabulated and listed.

3.5.2 Demographics and Baseline Characteristics

Subject demographics and baseline characteristics will be listed for each subject. Following demographics and baseline characteristics will be summarized by treatment groups and overall using the ITT population and OL population, respectively. A summary of baseline disease characteristics may include, but not be limited to:

- Age
- Age (< 40 years, ≥ 40 years)
- Sex (Male, Female)
- Race (White, Black/African American, Asian, Other)
- Race (White, Non-white)
- Region (US, Non-US)
- Disease duration of CD (years)
- Disease duration (< 2 years, ≥ 2 years)
- Disease duration (< 5 years, ≥ 5 years)
- Ethnic group (Hispanic or Latino, Other)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)

- Baseline disease location (ileum, not colon; colon, not ileum; or ileo-colonic, as observed at baseline ileocolonoscopy)
- Baseline CDAI score
- Baseline weekly abdominal pain score
- Baseline weekly loose/liquid stool count
- Baseline SES-CD score
- Baseline SES-CD score by baseline disease location subgroup (per subgroup of subjects with ileum, not colon; colon, not ileum; or ileo-colonic disease)
- Baseline CRP (mg/L)
- Baseline CRP (< 5 mg/L, ≥ 5 mg/L)
- Baseline fecal calprotectin (µg/g)
- Baseline fecal calprotectin (< 250 µg/g, ≥ 250 µg/g)
- Baseline fecal calprotectin (< 200 µg/g, ≥ 200 µg/g)
- Baseline IL22 (unit)
- [redacted]
- Baseline IBDQ score
- Alcohol status(Never, Current and Former)
- Number of prior use of anti-TNF agents (1, > 1)
- Number of prior use of anti-TNFα agents (1, 2, ≥ 3)
- Prior use of vedolizumab (Yes, No)
- Use of 5-aminosalicylatesat baseline (Yes, No)
- Use of corticosteroids at baseline (Yes, No)
- Use of immunomodulators at baseline (Yes, No)
- Smoking status at baseline (Never, Current, Former)

3.5.3 Study Drug Exposure

Descriptive statistics for extent of exposure (in days) will be presented for the as-treated population and the OL population during the specified treatment period.

For DB period, the following summaries will be provided using for the as-treated population:

- Duration of exposure in the DB period

- Number of doses received
- Number and percentage of subjects received the entire dose

For OL period, the following summaries will be provided using the OL population:

- Duration of exposure in the OL period
- Number of doses received
- Number and percentage of subjects received the entire dose by visit

Additionally, descriptive statistics for the cumulative exposure for overall MEDI2070 will be provided. If a subject entered both the DB period and OL period, the subject will be considered as the same subject and the exposure data will be combined from both periods.

3.5.4 Prior and Concomitant Medications

Prior medication refers to all medications that were started prior to the start of the first dose of investigational product.

Concomitant medication refers to all medications taken during the treatment period of the DB period and the OL period. Concomitant medications include medications continued from pre-treatment. Medications with missing start and stop dates will be counted as concomitant medications. Medications with partial start or stop dates will be handled as described in Section 3.3.1. Medications with start and stop dates which bracket the first dose date will be summarized as both prior and concomitant medications.

All prior and concomitant medications data will be coded by Medimmune approved drug dictionary (AstraZeneca Drug Dictionary or WHODrug) and listed for each subject by treatment groups. The number and percentage of subjects taking at least one prior or concomitant medication will be presented by Preferred Term (PT) and treatment group for the DB and OL treatment periods using the ITT population and the OL population, respectively. The following summary tables will be provided for the prior and concomitant medications:

- Prior disease related treatments
- Concomitant medication taken for CD
- Concomitant medications for reason other than CD
- Disallowed concomitant medications

In addition, the number and percentage of subjects receiving the following selected medications: 5- aminosalicylates, prednisone, and immunomodulators (e.g. methotrexate, azathioprine, and 6-mercaptopurine) will be summarized for each treatment group as coded. The dose level of oral corticosteroid will be summarized by visit.

3.5.5 CD History

The CD history will be summarized descriptively using the ITT population. In particular,

- Summary of Crohn's location by category for current, at the original diagnosis, and at any past time. The Crohn's location categories include Colon, not ileum; Ileocolonic (ileum and colon); Ileum, not colon; Extra-intestinal.
- Summary of subjects with anti-TNF use
    - Number and percentage of subjects with anti-TNF use
    - Number and percentage of subjects with prior use of following anti-TNF: Infliximab, Adalimumab, Certolizumab pegol, Golimumab.
    - Descriptive summary of time since first use of anti-TNF by type of anti-TNF
    - Number and percentage of subjects by primary reason for stopping prior anti-TNF: Primary failure, Secondary failure, Intolerance, Not applicable, Other
- Summary of subjects with biologics agents other than anti-TNF agents
    - Number and percentage of subjects with biologics agents other than anti-TNF agents
    - Number and percentage of subjects with prior use of Vedolizumab
    - Number and percentage of subjects by primary reason for stopping prior Vedolizumab: Primary failure, Secondary failure, Intolerance, Not applicable, Other
- Summary of subjects with immunomodulator
    - Number and percentage of subjects with prior immunomodulator
    - Number and percentage of subjects with prior use of following immunomodulator: Methotrexate, Azathioprine, 6-mercaptopurine,Other
    - Descriptive summary of time since first use of immunomodulator
- Summary of subjects with fistula and stricture/obstruction
    - Number and percentage of subjects with history of fistula
    - Number and percentage of subjects with fistula at baseline
    - Number and percentage of subjects with stricture/obstruction

3.5.6 Medical and Surgical History

The MedDRA Preferred Term (PT) in the medical history and surgical history will be summarized by the number and percentage of subjects for each treatment group and overall using the ITT population.

3.5.7 Physical, Neurological and Visual Examination

All data related to physical, neurological and visual examination will be listed for each subject.

The physical and neurological examination will be summarized by visit and treatment groups using the ITT population and the OL population respectively. Frequency count and percentages will be presented.

The visual examination will include following parameters:

- Best corrected near vision (Right eye, Left eye)
- Best corrected distance vision (Right eye, Left eye)

Summary statistics of best corrected near and distance vision for both eyes will be presented using the decimal format of the acuity notation. The visual acuity notation conversions can be found in Appendix. Change from baseline will be calculated and categorized as < 0 (worsened vision), 0 (no change) and > 0 (improved vision). Frequency count and percentages based on the defined categories will be presented.

3.5.8 Protocol Deviations

Protocol deviations (PDs), will be recorded and are classified as major and minor deviation under following categories:

- Did not fulfil eligibility criteria
- Developed discontinuation criteria but continued IP treatment
- Received incorrect investigational treatment/dose
- Received prohibited concomitant medication
- Protocol-required procedure not adhered to
- Other

Tabulation of major protocol deviations by category will be provided by treatment group. The number of percentage of subjects who had at least one major protocol violation or deviation will be summarized in total and by treatment group. A supporting data listing will be provided as well.

3.6 Efficacy Analyses

Efficacy data from the DB treatment period and the OL treatment period will be analyzed separately. All efficacy endpoints will be summarized by treatment group.

3.6.1 Primary Efficacy Endpoint(s) and Analyses

3.6.1.1 Primary Efficacy Endpoint(s)

The primary efficacy endpoint is Crohn's Disease Activity Index (CDAI) remission at Week 8. CDAI remission is defined as a CDAI score of < 150. Refer to Appendix 6.1 for detail on CDAI score.

3.6.1.2 Primary Efficacy Analysis

The primary analysis will be conducted in the ITT population. The primary efficacy endpoint is CDAI remission at Week 8 of the induction period. The null and alternative hypotheses for the primary endpoint are:

H_0: There is no difference between the proportions of CDAI remission in MEDI2070 high dose group and placebo at Week 8 for subjects with moderate to severe CD who have failed or are intolerant to anti-TNFα therapy.

versus

H_1: There is difference between the proportion of CDAI remission in MEDI2070 high dose group and placebo at Week 8 for subjects with moderate to severe CD who have failed or are intolerant to anti-TNFα therapy.

The primary comparison of interest will be MEDI2070 high-dose group versus placebo. The comparisons between MEDI2070 high-medium dose group versus placebo, low-medium dose group versus placebo, and MEDI2070 low dose group versus placebo will also be conducted. Nominal p-values will be presented without multiplicity adjustment.

P-values for comparisons between any MEDI2070 dose group and placebo will be obtained from a logistic regression model adjusting for prior anti-TNFα use (1 versus >1). In the

event the number of remissions is too small (i.e. < 5), the exact logistic regression will be performed instead. The statistical significant treatment effect will be tested against 2-sided alpha level of 0.10. The odds ratio and associated 90% confidence interval from the aforementioned logistic regression model will be presented.

In addition, the difference in CDAI remission rates at Week 8 between MEDI2070 dose groups and placebo group and associated 90% confidence interval will be provided using the logistic regression with delta method approach (Ge et al, 2011). In the event the number of remission is too small (i.e. < 5), the unconditional exact confidence interval for the difference in CDAI remission at Week 8 between MEDI2070 dose groups and placebo group will be provided using Agresti and Ming (2001)'s approach via STATXACT. The pseudo SAS code can be found in the SPP.

3.6.1.3 Additional Analyses of the Primary Efficacy Endpoint

The following sensitivity analyses will be performed for the primary efficacy endpoints in the ITT population using the non-responder imputation:

1. A sensitivity analysis for the primary efficacy endpoint will be performed by extending the logistic regression model planned above via adjusting for baseline CDAI score. The odds ratio between each MEDI2070 dose group and placebo and associated 90% confidence interval will be presented.

2. A stratified Cochran-Mantel-Haenszel (CMH) row mean score test adjusting for prior anti-TNFα use (1 versus > 1) will be conducted for the primary efficacy endpoint using the ITT population. In the event of small number of remissions (i.e. < 5), the stratified conditional exact test will be performed via STATXACT. P-value, point estimate of common odds ratio and associated 90% mid-p corrected exact confidence interval will be presented.

3. Other baseline covariates will be explored by extending the logistic regression model via adjusting for baseline CDAI score and/or other baseline covariates. The following baseline covariates may be assessed and the final model will only include the significant baseline covariates ($p < 0.10$). The odds ratio between each MEDI2070 dose group and placebo and associated 90% confidence interval from the logistic regression model will be presented.

    - Region (US, Non-US)
    - Disease duration

- Baseline CDAI score
- Baseline IL22
- [redacted]
- Baseline CRP
- Baseline weekly abdominal pain score
- Baseline weekly loose/liquid stool count
- Baseline SES-CD score
- Baseline fecal calprotectin
- Smoking status at baseline

3.6.2 Secondary Efficacy Endpoint(s) and Analyses

3.6.2.1 Secondary Efficacy Endpoint(s)

Remission and response will be assessed by both clinical and patient reported outcomes (PRO) measures. The following definitions will be used to define the secondary efficacy endpoints:

- CDAI clinical response: Decrease from baseline in the CDAI of ≥ 100 points
- SES-CD remission: Total SES-CD score ≤ 4, with:
  - No subscore > 2, and
  - Segments scored at baseline that cannot be observed on a subsequent examination will be scored with an imputed value unchanged from baseline
- SES-CD response: Decrease from baseline in SES-CD ≥ 50%; segments scored at baseline that cannot be observed on a subsequent examination will be scored with an imputed value unchanged from baseline.
- PRO2 remission (loose/liquid stool frequency/abdominal pain): Remission achieved for both abdominal pain and loose/liquid stool frequency
- PRO2 response: (loose/liquid stool frequency/abdominal pain): Remission or response in one symptom (either abdominal pain or stool frequency) plus response in the other
  - Abdominal pain remission: On an 11-point (0 to 10) pain scale: During 1 week, no daily score > 2
  - Abdominal pain response: On an 11-point (0 to 10) pain scale: ≥ 30% reduction in weekly pain score from baseline

- Loose/liquid stool frequency remission: Counting stools identified as Type 6 or 7 on Bristol Stool Scale, during 1 week, each daily loose loose/liquid stool count ≤ 3
- Loose/liquid stool frequency response: Counting stools identified as Type 6 or 7 on Bristol Stool Scale, ≥ 30% reduction in weekly loose/liquid stool count compared to baseline

Refer to Appendix 6.1 and Appendix 6.2 for details on CDAI score and SES-CD score.

Table 3.6.2.1-1 List of Secondary Endpoints

	Secondary Efficacy Endpoints	
Induction Period		
Week 8	PRO2 Remission Abdominal pain remission Loose/liquid stool frequency remission [redacted]	PRO2 Response Abdominal pain response Loose/liquid stool frequency response CDAI clinical Response
Week 16	SES-CD Remission PRO2 Remission CDAI clinical remission Abdominal pain remission Loose/liquid stool frequency remission	SES-CD Response PRO2 Response CDAI clinical response Abdominal pain response Loose/liquid stool frequency response
Maintenance Period		
Week 28	CDAI clinical remission SES-CD Remission PRO2 Remission Abdominal pain remission Loose/liquid stool frequency remission	CDAI clinical response SES-CD Response PRO2 Response Abdominal pain response Loose/liquid stool frequency response
Other	CDAI Modified sustained clinical remission at Week 8 and 28 [redacted]	

3.6.2.2 Secondary Efficacy Analyses

The efficacy data from the DB induction and maintenance treatment periods will be summarized descriptively and displayed graphically by treatment group and by visit using the ITT Population.

The secondary efficacy endpoints with dichotomous outcomes will be analyzed similarly as the primary analysis of the primary efficacy endpoint using the ITT population. The following sensitivity analysis will be performed for the selected secondary endpoints (e.g. SES-CD and PRO2 endpoints, CDAI remission) in the DB induction period:

1. A logistic regression model with treatment, randomization stratification factor and corresponding baseline score (e.g., baseline SES-CD score, baseline CDAI score, baseline weekly abdominal pain score, baseline weekly loose/liquid stool count) will be performed.

2. A stratified Cochran-Mantel-Haenszel (CMH) row mean score test adjusting for prior anti-TNFα use (1 versus > 1) will be conducted. In the event of small number of remissions (i.e. < 5), the stratified conditional exact test will be performed via STATXACT.

3. Other baseline covariates will be explored by extending the logistic regression model via adjusting for baseline CDAI score and/or other baseline covariates. The following baseline covariates may be assessed and the final model will only include the significant baseline covariates ($p < 0.10$).

    - Region (US, Non-US)
    - Disease duration
    - Baseline CDAI score
    - Baseline IL22
    - [redacted]
    - Baseline CRP
    - Baseline weekly abdominal pain score
    - Baseline weekly loose/liquid stool count
    - Baseline SES-CD score
    - Baseline fecal calprotectin
    - Smoking status at baseline

3.6.2.3 Predictive Biomarker Analyses

To evaluate the predictive biomarkers, serum IL-22 and serum [redacted] for their value in predicting MEDI2070's efficacy for induction and maintenance of response and remission, two types of the analyses will be performed for the following efficacy endpoints at the DB treatment period.

Table 3.6.2.3-1 List of Efficacy Endpoints for Predictive Biomarker Analyses

DB Treatment Period	Efficacy Endpoints
Induction	CDAI clinical remission at Week 8
	CDAI clinical remission at Week 16
	SES-CD remission at Week 16, SES-CD response at Week 16
	PRO2 remission at Week 8, PRO2 response at Week 8
	PRO2 remission at Week 16, PRO2 response at Week 16
Maintenance	SES-CD remission at Week 28, SES-CD response at Week 28
	CDAI modified sustained clinical remission at Week 8 and Week 28
	[redacted]
	[redacted]

[redacted]

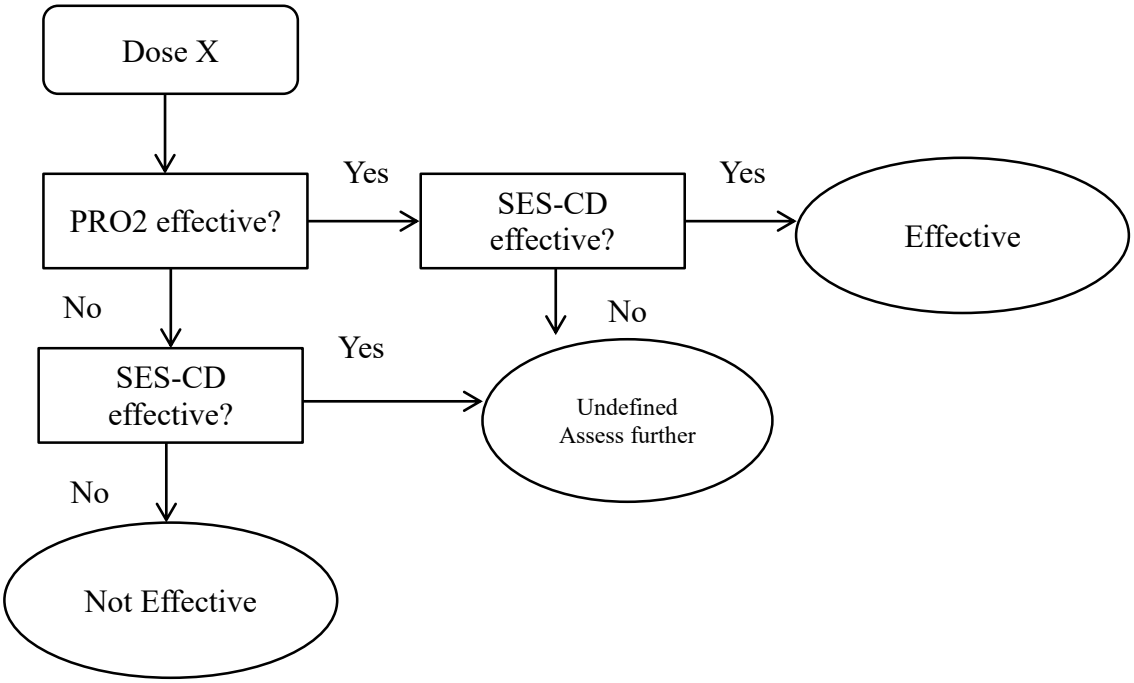


Figure 3.6.2.3-1 Effective Dose Determination Diagram

[redacted]

[redacted]

3.6.3 Exploratory Efficacy Endpoint(s) and Analyses

3.6.3.1 Exploratory Efficacy Endpoint(s)

Induction Period Exploratory endpoints:

Table 3.6.3.1-1 List of Exploratory Efficacy Endpoints

DB Treatment Period	Efficacy Endpoints
Induction	Change from baseline in IL-22 at [redacted] Week 16
	[redacted]
	[redacted]

DB Treatment Period	Efficacy Endpoints
	[redacted]
	[redacted]
	[redacted]
	[redacted]
Maintenance	Change from baseline in IL-22 at Week 28
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]

3.6.3.2 Analyses of Exploratory Endpoints

Serum IL-22 and [redacted] concentrations will be summarized by treatment group and by visit. Efficacy data over time during the DB induction and maintenance periods will be summarized and plotted by visit and by treatment.

Patient reported outcomes endpoints [redacted] will be described in Section 3.6.

The exploratory efficacy endpoints with continuous or ordinal outcomes [redacted] will be analyzed using a mixed effects repeated measures model with fixed terms for treatment group, visit, treatment-by-visit interaction, stratification factor of prior anti-TNFα use (1 versus >1), and corresponding baseline values, and subject as a random effect with unstructured covariance structure for the observed data up to Week 28. Comparisons between any MEDI2070 dose group and placebo will be performed by visit. Point estimate of the difference between each MEDI2070 dose group and placebo and associated 90% CI will be provided.

Distributional assumptions underlying the model will be assessed by visual inspection of residual plots. The assumption of normality will be assessed by examination of the normal probability plot. The assumption of homogeneity of variance will be assessed by plotting the residuals versus the predicted values from the model. If assumptions appear to be grossly violated, the data will be log-transformed or alternative analyses such as Wilcoxon rank-sum test will be performed.

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Table 3.6.4.1-1 Candidate Dose-response Models

Model	$f(d,\theta) = \theta_0 + \theta_1 f^0(d, \theta^0)$	$f^0(d, \theta^0)$	**Pre-specified θ^0**
Linear log-dose	$E_0 + \delta \log(d + c)$	$\log(d + c)$	NA
EMax	$E_0 + E_{max} d/[\, ED_{50} + d]$	$d/[\, ED_{50} + d]$	ED_{50} =105, 210
Sigmoid EMax	$E_0 + E_{max} d^h/\, [\, {ED_{50}}^h + d^h]$	$d^h/\, [\, {ED_{50}}^h + d^h]$	ED_{50} =105, 210 h =0.5

Model	$f(d,\theta) = \theta_0 + \theta_1 f^0(d, \theta^0)$	$f^0(d, \theta^0)$	**Pre-specified θ^0**
Logistic	$E_0 + E_{max}/\{1 + \exp[(ED_{50} - d)/\delta]\}$	$1/\{1 + \exp[(ED_{50} - d)/\delta]\}$	ED_{50} =105, 210 δ =45

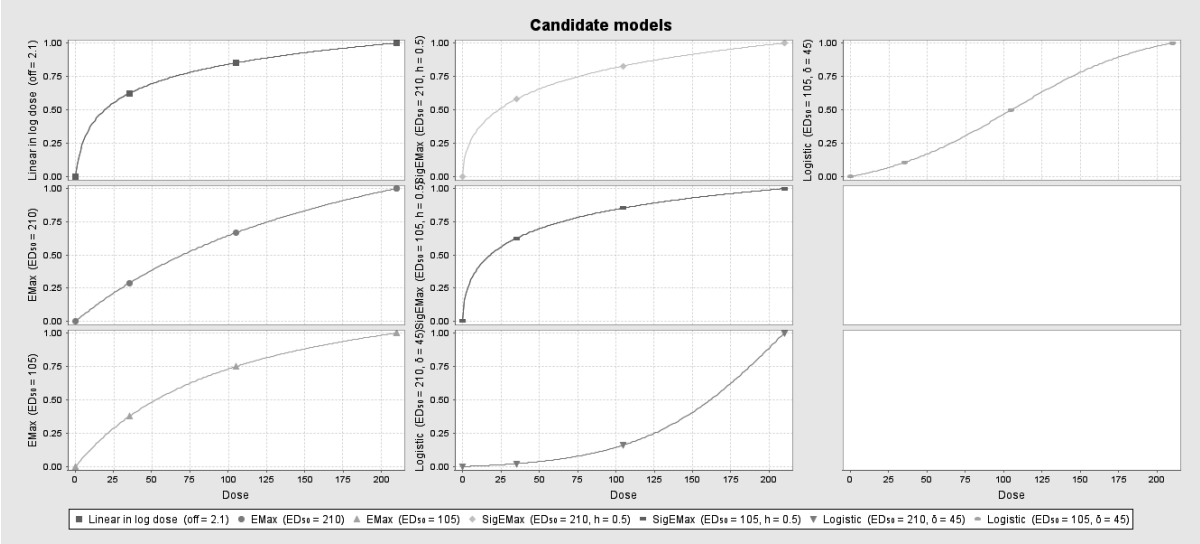


Figure 3.6.4.1-1 Dose-response Shape for the Selected Candidate Models

3.6.4.2 Efficacy Analysis for OL Treatment Period

The efficacy data from the OL treatment period will be summarized descriptively by randomized treatment group in the DB period and by visit using the OL population. The efficacy data from the DB treatment and OL treatment period will be combined and displayed graphically by visit and by the randomized treatment group in DB treatment period using the OL population.

3.6.5 Subgroup Analysis

This section applies to the following selected efficacy endpoints outlined in Table 3.6.5-1. The subgroup analyses will be focusing on the effective dose(s) only. If there is more than one effective dose, the effective doses may be combined for the purpose of subgroup analysis.

Table 3.6.5-1 List of Efficacy Endpoints for Subgroup Analysis

DB Treatment Period	Efficacy Endpoints
Induction	CDAI clinical remission at Week 8
	CDAI clinical remission at Week 16
	SES-CD remission at Week 16
	PRO2 remission at Week 8
	PRO2 remission at Week 16
Maintenance	CDAI clinical remission at Week 28
	SES-CD remission at Week 28
	PRO2 remission at Week 28

Table 3.6.5-2 List of Subgroups of Interest

Subgroups of Interest	Subgroup Categories
Prior anti-TNF failure reason	intolerance, primary or secondary failure
Prior anti-TNF failure reason	intolerance, primary failure, secondary failure
Prior Vedolizumab failure reason	intolerance, primary or secondary failure
Prior Vedolizumab failure reason	intolerance, primary failure, secondary failure
Number of prior use of anti-TNFα agents	1 versus > 1
Region	USA, Non-USA
Disease duration	< 5 years, ≥ 5 years
Disease duration	< 2 years, ≥ 2 years
Baseline CRP	< 5 mg/L, ≥ 5 mg/L
Baseline FCP	< 200 μg/g, ≥ 200 μg/g
[redacted]	[redacted]
[redacted]	[redacted]

Difference in proportions between MEDI2070 dose groups and placebo and associated 90% confidence interval will be provided for each subgroup. The results will be tabulated and the corresponding forest plots for the subgroup analyses will be presented as well. In addition, the interaction effect between treatment group and subgroups may be explored. SIDES may

be used for the subgroups with differential treatment effect. SIDES may also be applied to search for differential subgroups for baseline disease duration, CRP, and FCP.

3.7 Patient Reported Outcomes

The study will utilize several PRO instruments. The sequence in which scoring instruments that contain PRO components (CDAI) or PROs will be collected at a given study visit will be the following order:

- CDAI
- [redacted]
- [redacted]
- PGIC-IBD (Visits 7 and 10 only)
- Cognitive Patient Interview (selected subjects, Visit 10 or Early Termination Visit only)

Data from PGIC-IBD and cognitive patient interview will be analyzed and reported separately (i.e. not in the clinical study report).

The PRO data may be further explored. A separate (supplementary) SAP for the endpoint development process and responder remitter definitions may be developed by Quintiles and the associated results will be reported separately (i.e. not in the clinical study report).

3.7.1 CDAI score

The two items from CDAI, “total number of liquid or very soft stools over past week” and “total abdominal pain score over past week”, will be descriptively summarized and plotted over time. Further explorations on the 2-item CDAI data may be described in the supplementary SAP and reported separately.

[redacted]

[redacted]

[redacted]

3.8 Summary of Analyses

In summary, the primary, secondary and exploratory endpoints in the DB induction and maintenance treatment periods will be analyzed using the methods specified in Table 3.8-1.

Table 3.8-1 Summary of Efficacy Endpoints and Analyses

Endpoints	Primary Analysis	Secondary/Sensitivity Analyses
Primary Efficacy Endpoint		
CDAI Clinical Remission at Week 8	1. Summary statistics using non-responder imputation 2. Logistic regression (or exact logistic regression) with treatment and prior anti-TNFα use as covariates using non-responder imputation	1. Logistic regression model adjusting for baseline CDAI score 2. CMH test or exact stratified test 3. Logistic regression model adjusting other baseline covariates 4. Predictive biomarker analysis 5. Cochran-Armitage trend test 6. MCP-Mod analysis
Secondary Efficacy Endpoints for DB induction period		
SES-CD remission at Week 16 PRO2 remission at Week 8 PRO2 remission at Week 16	1. Summary statistics using non-responder imputation 2. Logistic regression (or exact logistic regression) with treatment and prior anti-TNFα use as covariates using non-responder imputation	1. Logistic regression model adjusting for baseline SES-CD or PRO2 score 2. CMH test or exact stratified test 3. Logistic regression model adjusting other baseline covariates. 4. Predictive biomarker analysis 5. Cochran-Armitage trend test 6. MCP-Mod analysis

Endpoints	Primary Analysis	Secondary/Sensitivity Analyses
SES-CD response at Week 16 PRO2 response at Week 8 PRO2 response at Week 16 CDAI clinical remission at Week 16	1. Summary statistics using non-responder imputation 2. Logistic regression (or exact logistic regression) with treatment and prior anti-TNFα use as covariates using non-responder imputation	1. Logistic regression model adjusting for baseline CDAI, SES-CD or PRO2 score 2. CMH test or exact stratified test 3. Logistic regression model adjusting other baseline covariates 4. Predictive biomarker analysis 5. Cochran-Armitage trend test
CDAI clinical response at Week 8	1. Summary statistics using non-responder imputation 2. Logistic regression (or exact logistic regression) with treatment and prior anti-TNFα use as covariates using non-responder imputation	1. Logistic regression model adjusting for baseline CDAI, SES-CD or PRO2 score 2. CMH test or exact stratified test 3. Logistic regression model adjusting other baseline covariates 4. Cochran-Armitage trend test
CDAI clinical response at Week 16 Abdominal pain remission at Week 8 Abdominal pain response at Week 8 Abdominal pain remission at Week 16 Abdominal pain response at Week 16	1. Summary statistics using non-responder imputation 2. Logistic regression (or exact logistic regression) with treatment and prior anti-TNFα use as covariates using non-responder imputation	1. Logistic regression model adjusting for baseline CDAI or PRO2 score 2. CMH test or exact stratified test 3. Logistic regression model adjusting other baseline covariates.
Secondary efficacy endpoints for DB maintenance period		
SES-CD remission at Week 28 SES-CD response at Week 28 CDAI modified sustained remission SES-CD modified sustained remission PRO2 modified sustained remission	1. Summary statistics using non-responder imputation 2. Logistic regression (or exact logistic regression) with treatment and prior anti-TNFα use as covariates using non-responder imputation	1. Predictive biomarker analysis
CDAI clinical remission at Week 28	1. Summary statistics using non-responder imputation	

Endpoints	Primary Analysis	Secondary/Sensitivity Analyses
CDAI clinical response at Week 28 PRO2 remission at Week 28 PRO2 response at Week 28 Abdominal pain remission at Week 28 Abdominal pain response at Week 28 Loose/liquid stool frequency remission at Week 28 Loose/liquid stool frequency response at Week 28	2. Logistic regression (or exact logistic regression) with treatment and prior anti-TNFα use as covariates using non-responder imputation	
Exploratory Efficacy Endpoints		
Change from Baseline in IL22 [redacted]	1. Summary statistics by visit 2. Repeated measures analysis using observed data only (up to Week 28)	
[redacted]		
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	

3.9 Safety Analyses

The analysis of safety endpoints will include TEAEs, laboratory values, vital signs, and ECG. Safety data from the 28-week placebo-controlled, DB treatment period will be analyzed using the as-treated population with the actual treatment received. Safety data from

the OL treatment period will be analyzed in a similar way using the OL population. No statistical comparisons will be performed for the safety data.

3.9.1 Adverse Events and Serious Adverse Events

Adverse events (AE) will be coded by MedDRA version (17.0 or higher) and the type incidence, severity and relationship to study investigational product will be summarized. Specific adverse events will be counted once for each subject for calculating percentages. In addition, if the same adverse event occurs multiple times within a particular subject, the highest severity and level of relationship observed will be reported. If any associations of interest between adverse events and baseline characteristics are observed, additional stratified results may be presented. All AEs and SAEs collected in the database (including those starting prior to first dose of study drug) will be listed. Any other information collected (e.g. relatedness to study drug, action taken etc.) will be listed as appropriate.

3.9.1.1 Pre-treatment AEs

The AEs with onset prior to the administration of the first dose of investigational product (MEDI2070 or placebo) will be considered as pre-treatment AEs for the DB treatment period. Pre-treatment AEs will be summarized with number of subjects and percentages by SOC and PT for each treatment group.

3.9.1.2 Treatment-Emergent AEs during DB Treatment Period

For subjects entering the OL treatment period, the TEAE will be defined as any AE with onset on or after the administration of the first dose of blinded investigational product up to the day prior to administration of the first OL SC dose. For subjects not entering the OL treatment period, the TEAE will be defined as any AE with onset on or after the administration of the first dose of blinded investigational product up to and including 28 weeks post last blinded dose.

All TEAEs including TESAEs, AESIs, and TEAEs leading to permanent discontinuation of investigational product will be summarized overall as well as categorized by MedDRA System Organ Class (SOC) and Preferred Term (PT). The TEAEs with severity grades will be summarized by grades assigned by National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE) V4.0. Tabular summaries of the TEAEs during the DB treatment period will be provided as follows:

- Incidence rate of TEAEs by SOC and PT
- Incidence rate of TEAEs by severity and relationship to the investigational product

- Incidence rate of fatal TEAEs, TESIs, TESAEs, TEAEs leading to permanent discontinuation of investigational product, treatment-related TESAEs by SOC and PT
- Incidence rate of TEAE and infectious TEAEs occurring in at least 5% of the subjects in any treatment group by PT in descending order of frequency
- Incidence rate of TESAEs occurring in at least 1% of the subjects in any treatment group

3.9.1.3 TEAEs during OL Treatment Period

TEAE for the OL treatment period will be defined as any AE with onset on or after the administration of the first open-label SC dose of MEDI2070 up to and including 28 weeks post-last dose. Similar tabular summaries will be prepared for the OL treatment period using the OL population.

3.9.2 Adverse Events of Special Interest (AESI)

An AESI is one of scientific and medical interest specific to understanding of the investigational product and requires close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. Identification of TESIs through search criteria (Standardized MedDRA Query (SMQ) etc.) will be an ongoing task throughout the study and latest convention will be used to summarize by SOC and PT in each category. In particular, the time to onset of surgery for CD complications will be summarized for each treatment group.

Table 3.9.2-1 AESIs Categories

AESI Category	Description
Hepatic Function Abnormality (Hy's Law)	The Hy's law is defined in the protocol Section5.6.2. AEs meeting the Hy's law criteria will be identified using MedDRA SMQ.
Infusion/injection site Reactions	AEs with PT "infusion reaction" will be captured under this category.
Infections	An event recorded on the AEs eCRF that is coded to the MedDRA SOC of "Infections and Infestations."
Systemic Hypersensitivity	e.g. anaphylaxis
Malignancies	
Major Cardiac Events (MACE)	AEs defined as myocardial infarction, stroke, or cardiovascular death
Ocular AEs	Including cataracts

3.9.3 Deaths and Treatment Discontinuations due to Adverse Events

Deaths and treatment discontinuation due to AEs will be listed and summarized by treatment groups.

[redacted]	[redacted]	[redacted]
	[redacted]	

[redacted]

3.9.4.1 Vital Signs

Vital signs parameters, including blood pressure, temperature, pulse rate and respiration rate, will be obtained according to study schedule procedures. All vital signs parameters (blood pressure, temperature, pulse rate, and respiration rate) will be listed. Abnormal vital sign values will be flagged.

Vital signs parameter values will be collected before, during, and after completion of the IV administration and before and after the completion of the SC administration at each visit. Change from baseline for each vital signs parameter to each scheduled visit will be summarized by treatment group using descriptive statistics. For vital sign assessments collected on the dosing day, the vital sign data will be summarized by time points of interest as well. The time points of interest are as follows:

- pre-dose assessment,
- the 1st set of assessment after dosing, and
- the last set of assessment before discharge from site.

The results for the DB treatment period and the OL treatment period will be presented using the as-treated population and OL population respectively.

3.9.4.2 Electrocardiogram

12-lead Electrocardiogram (ECG) measurements will be performed according to the study schedule. The ECG data will be listed. The overall interpretation of the ECG results (Normal; Abnormal, not Clinically Significant; and Abnormal, Clinically Significant) will be summarized using frequency count and percentages by visit and treatment groups. The results for the DB treatment period and the OL treatment period will be presented separately using the as-treated population and the OL population respectively.

3.10 Pharmacokinetics and Immunogenicity

Serum MEDI2070 concentration data will be summarized descriptively by visit using the PK population. Individual and mean serum concentration-time profiles of MEDI2070 will be generated. PK data obtained in this study will be combined with all available PK data for MEDI2070 and analyzed using population PK methodology and will be reported separately from the CSR for this study.

In addition, the presence of anti-drug antibodies (ADA) to MEDI2070 in serum will be assessed and reported. Immunogenicity results (binding and, if positive, neutralizing) will be summarized by the number and percentage of subjects who develop detectable ADAs. If possible, the relationship between PK and ADA status will be summarized.

4 INTERIM ANALYSIS

An interim analysis may be conducted when at least 75% of the total planned number of subjects has completed the Week 16 visit or withdrawn prior to the Week 16 visit. Data for the primary and secondary endpoints through Week 16 will be analyzed as part of the interim analysis for internal decision making purposes. To ensure the blinding of each subject's treatment assignment throughout the 28-week placebo-controlled, double-blind period, the interim analysis will be conducted by a limited number of sponsor personnel who are not involved in the conduct of the study. Study site personnel and sponsor personnel directly associated with the conduct of this study and the study subjects will remain blinded to the treatment assignment for individual subjects and to the outcome of interim analysis until the completion of the 28-week placebo-controlled, double-blind period.

Since this is a Phase 2b study, the interim analysis is intended to assist internal decision making and does not include a possibility to stop the study for efficacy or futility. Thus, there will be no alpha level adjustment for the final analysis. Should the sponsor choose to perform

such an interim analysis, the details would be described in an interim unblinding analysis plan prior to unblinding.

The primary analysis will be performed when all subjects complete the initial 16-week induction period. All the data available by the time of primary analysis database snapshot will be included in the analysis, including available data through Week 28 and the open-label period for a certain proportion of subjects. At the time of the primary analysis, selected personnel from the sponsor will be unblinded to individual treatment assignments as will be outlined in an unblinding plan. Study team members who are unblinded to conduct and review the results from the primary analysis will be removed from the blinded study team and the associated study responsibilities.

A further analysis is planned when all subjects complete the maintenance period, at Week 28. The study will be blinded to all subjects, investigators, and sponsor study team through the end of the maintenance period.

The final analysis for the study, including all study periods and all data, will be performed at the end of the study.

Independent Data Monitoring Committee (IDMC) analysis will be performed for the safety data on a regular basis throughout the DB treatment period of the study as set out in the IDMC charter, i.e. until the last subject completes Week 28. A separate IDMC SAP and/or SPP will be prepared.

6 APPENDIX

6.1 CDAI Score

The CDAI is the oldest and most widely used of several multi-item instruments that have been developed and is validated for use in clinical studies to measure disease activity in CD (Best et al, 1976; Sands et al, 2005). The CDAI measures the severity of active disease using symptom scores that are monitored over the previous week and includes subject-reported symptoms, physician-assessed signs, and laboratory markers.

The CDAI score is calculated by summing weighted scores for subjective items (number of liquid or very soft stools, the degree of abdominal pain over a week (on a scale of 0-3, mild

to severe) and general well-being (on scale of 1-4, "Generally well" to "Terrible") recorded by a diary during a 1-week period, and objective items (associated symptoms, taking antidiarrheal such as loperamide/opiates, abdominal mass, hematocrit, daily morning temperature, and body weight). The CDAI scores range approximately from 0 to 600, with higher scores indicating greater disease activity (See Table 3.4.1.1-1 for details).

The CDAI will be calculated at the site in order to determine the eligibility for the study. For statistical analysis, CDAI for all visits will be also calculated based on the data entered in the eCRF.

Table 6.1-1 Items Included in CDAI and Their Weights

Item	× Weight	Total
Total number of liquid or very soft stools over past week	×2	X_1
Total abdominal pain score (rating: 0-3) over past week (range: 0-21)	×5	X_2
Total general well-being score (rating: 1-4) over past week (range: 1-28)	×7	X_3
Sum of presence of following clinical signs over past week: 1. Arthritis/Arthralgia (1=yes, 0=no) 2. Iritis/ uveitis(1=yes, 0=no) 3. Erythema Nodosum/Pyoderma Gangrenosum/Aphthous Stomatitis (1=yes, 0=no) 4. Anal Fissure, Fistula or Abscess (1=yes, 0=no) 5. Other Fistula (1=yes, 0=no) 6. Fever >37.8 C During Past Week(1=yes, 0=no)	×20	X_4
Antidiarrheal use (Eg, Diphenoxylate hydrochloride) (0=none, 1=yes)	×30	X_5
Abdominal mass (none=0, equivocal=2, present=5)	×10	X_6
Deviation of Hematocrit levels (minimum value = 0) 47 - hematocrit (males) 42 - hematocrit (females)	×6	X_7 (if value<0, enter 0)
Weight ratio 100×(1-[Current body weight / standard weight]) Minimum = -10 for overweight subject Maximum = 10 for underweight subject	×1	X_8 (if value<-10, enter -10, if value >10, enter 10)
CDAI score		$\sum_{i=1}^{8} X_i$

In addition, following set of rules will be applied:

- For items 1, 2 and 3, if information is available only for ≤ 3 days, then CDAI score will be set to missing. Otherwise, the sub score for each of these three items will be calculated as mean value of item from available days × 7.
- For all items, if a subject doesn't have score for any of the sub categories, CDAI score will be set to missing.
- Any total CDAI score < 0 will be considered as 0 in the analysis.

Subjects with scores of < 150, 150 to 219, and 220 to 450 represent remission, mild disease, and moderate to severe disease, respectively; whereas subjects with scores of > 450 have very severe disease (Buxton et al, 2007).

6.3 Covariate-adjusted difference of proportion using logistic regression

The fitted logistic regression model is used to predict the response rate for every subject in the study as if they had received the treatment or the control intervention, and the difference in the average of the treated and control rates is computed. The delta method is used to calculate a standard error for the difference and an associated CI. Regarding the strata (covariate) values in the trial as a population distribution (e.g. regarding strata frequencies as fixed, which is also implicit in the weighted mean risk difference estimators), the LR estimator is the maximum likelihood estimator of the risk difference under the logistic model (See the SPP for pseudo SAS codes).

6.4 Visual acuity notation conversions

The visual acuity notation routinely used at different sites may vary. Each site should convert the acuity notation to decimal format to enter onto the electronic case report form (eCRF).