NCT Number: NCT03169894

PROTOCOL

PRODUCT NAME/NUMBER:	MDGN-002
PROTOCOL NUMBER:	MDGN-002-CD-101
IND NUMBER:	[redacted]
DEVELOPMENT PHASE:	Phase 1b
PROTOCOL TITLE:	Phase Ib Escalating Dose, Open-Label, Signal-Finding Study to Evaluate the Safety, Tolerability, and Short-Term Efficacy of the Anti-Light Monoclonal Antibody MDGN-002 in Adults with Moderate to Severe Active Crohn's Disease (CD) or Ulcerative Colitis (UC) who have Failed Prior Treatment with an Anti-TNFα Agent
PROTOCOL DATE:	23 July 2021 (Version 11.0)
COORDINATING/PRINCIPAL INVESTIGTOR:	[redacted]
SPONSORED BY:	Aevi Genomic Medicine, LLC (formerly known as Aevi Genomic Medicine, Inc., and Medgenics, Inc.) 1500 Liberty Ridge Drive, Suite 321 Wayne, PA 19087 Phone: 610-254-4201 Fax: 443-304-8001

1. APPROVAL SIGNATURES

PROTOCOL NUMBER: MDGN-002-CD-101

PROTOCOL TITLE: Phase Ib Escalating Dose, Open-Label, Signal-Finding Study to Evaluate the Safety, Tolerability, and Short-Term Efficacy of the Anti-Light Monoclonal Antibody MDGN-002 in Adults with Moderate to Severe Active Crohn's Disease (CD) or Ulcerative Colitis who have Failed Prior Treatment with an Anti-TNFα Agent

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

2. EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must e-mail the Serious Adverse Event Form within 24 hours to the Pharmacovigilance Contract Research Organization (CRO), at one of the methods noted below. The Investigator should also the Aevi Medical Monitor.
For questions on SAE reporting, please call the drug safety helpline noted below.

[redacted]

All medical personnel and their contact details can be found in the site study documentation (study binder). For protocol, safety-related and emergency issues please first contact the Aevi Medical Monitor using the contact details below.

[redacted]

3. REASON FOR AMENDMENT AND SUMMARY OF CHANGES

The protocol was amended to clarify study procedures and conduct detail. Substantive changes include:

- Revised the study title to reflect the expansion of the study population to include subjects with Ulcerative Colitis (UC) who have failed prior treatment with an anti-TNFα agent.
- Increased the sample size to 14, adding 6 subjects with UC to the 3 mg/kg cohort.
- Clarified that prior documentation of histological confirmation is acceptable.
- Revised the exclusion criteria pertaining to a positive test for C. difficile infection to clarify that this would be exclusionary if this was reported despite an adequate course of treatment.
- Revised the exclusion criteria pertaining to prior treatment with natalizumab (Tysabri®, Biogen) to include a timeframe of within 5 years of Visit 1.
- Added a new section of Inclusion and Exclusion Criteria for subjects with UC
- Added background information on Inflammatory Bowel Disease (IBD) and UC.
- Revised the saliva sample for genotyping to apply only to Crohn's disease (CD) subjects.
- Removed the reference to -14 weeks as the maximum screening period, and added that extensions of the screening window are allowed with approval of the medical monitor.
- Clarified that the diary must be completed for a minimum of 7 days prior to Visit 2 and that Visit 2 should be scheduled >7 days (e.g., Day 8) after the initiation of the diary.
- Revised the CDAI assessment to be collected for CD patients only.
- Added the Modified Mayo Score for UC patients only.
- Clarified that the washout period is the time between when the subject received their last dose of biologic and when they can proceed to Visit 2.
- Added stool frequency and rectal bleeding as the information that will be captured in the daily diary for UC patients.
- Added that a stable dose of 5-aminosalicylic acid (5-ASA) is allowed if taken for at least 2 weeks prior to Visit 1.
- Added that concomitant use of ustekinumab (Stelara®, Jannsen) and vedalizumab (Entyvio™, Takeda) is prohibited.
- Added that treatment with tofacitinib (Xeljanz®, Biogen) within 2 weeeks prior to Visit 1 is exclusionary.
- Added that use of an investigational medicine (non-biologic) within 2 weeks of Visit 1 and/or an investigational medicine that is a biologic within 8 weeks of Visit 1 is exclusionary.
- Added the definitions of primary and secondary non-responders for patients with UC.
- Removed references to sites in Israel and Colombia.

- Revised statistical analyses to include UC efficacy endpoints.
- Removed reference to an ex-US diary.
- Updated the list of references.
- Updated the study timelines.
- Updated the list of abbreviations.

4. SYNOPSIS

Name of Sponsor/Company:
Aevi Genomic Medicine, LLC. (formerly Aevi Genomic Medicine, Inc., and Medgenics, Inc.)

Name of Investigational Product:
MDGN-002

Name of Active Ingredient:
MDGN-002

Title of Study:
Phase Ib Escalating Dose, Open-Label, Signal-Finding Study to Evaluate the Safety, Tolerability, and Short-Term Efficacy of the Anti-Light Monoclonal Antibody MDGN-002 in Adults with Moderate to Severe Active Crohn's disease (CD) or Ulcerative Colitis who have Failed Prior Treatment with an Anti-TNFα Agent

Study Center: Up to 20 centers located in the United States

Principal Investigator:
[redacted]

Studied period (years):	**Phase of development:** Ib
Estimated date first subject enrolled: 2Q2017 Estimated date last subject completed: 3Q2022	

Objectives:

Primary:

Evaluate the safety and tolerability of MDGN-002 administered by subcutaneous (SQ) injection to adults with moderate to severe, active Crohn's disease (CD) or Ulcerative Colitis (UC) who have failed prior treatment with an anti-tumor necrosis factor alpha (TNFα) agent.

Secondary:

- Estimate plasma concentrations of MDGN-002 administered by SQ injection to adults with moderate to severe, active CD or UC.
- Evaluate response to treatment with MDGN-002 administered by SQ injection to adults with moderate to severe, active CD or UC.

Methodology:

This is a Phase 1b, open-label, dose-escalation, signal-finding, multi-center study. The study will evaluate the safety, tolerability, pharmacokinetics and short-term efficacy of MDGN-002 in adults with moderate to severe, active CD or UC who have previously failed anti-tumor necrosis factor alpha (anti-TNFα) treatment. The study is a pilot study using a dose-escalation design to characterize the safety and tolerability of 2 different doses of MDGN-002 (1.0 mg/kg and 3.0 mg/kg) in the CD, and 3.0 mg/kg in the UC population. All subjects will receive a total of 4 doses of MDGN-002 by SQ injection at 14-day intervals. The study will consist of a screening period, an open-label treatment period and a safety follow-up visit.

The total duration of participation is approximately 26 weeks. Subjects will be required to visit the study center up to 12 times inclusive of 1 additional follow-up safety visit. During the study, subjects will participate in safety and efficacy assessments as well as pharmacokinetic blood sampling; DcR3 genotyping (CD only); measurement of LIGHT (**L**ymphotoxin-like, exhibits **I**nducible expression, and competes with Herpes Virus **G**lycoprotein D for **H**erpesvirus Entry Mediator, a receptor expressed by **T** lymphocytes), selected cytokines; ribonucleic acid (RNA) sequencing; flow cytometry of peripheral blood leukocytes; and quality of life assessment. Subjects currently receiving treatment with biologic therapies will be required to participate in a wash-out period, during which biologic treatment will be discontinued.

Number of patients (planned):

Approximately 14 total subjects will be enrolled as follows:

- 4 subjects with CD in the 1 mg/kg cohort
- 4 subjects with CD in the 3 mg/kg cohort
- 6 subjects with UC in the 3 mg/kg cohort

Diagnosis and main criteria for inclusion:

Inclusion criteria - Crohn's Disease:

1. Subject is able to speak English fluently and has provided written informed consent for this study.
2. Subject is male or female, ≥18 to ≤75 years of age.
3. Subject has a documented diagnosis of CD via endoscopy/colonoscopy and histological confirmation. Prior documentation of histological confirmation is acceptable.
4. Subject has moderate to severe, active CD as evidenced by Simple Endoscopy Score for Crohn's Disease (SES-CD) score of ≥7.
5. Subject has failed treatment with an approved therapeutic dose of an anti-TNFα monoclonal antibody treatment with either no initial response (primary non-responder) or an initial response to induction with subsequent lost response (secondary non-responder) as defined in the protocol.
6. Subject can be receiving concurrent treatment with an oral corticosteroid, and/or azathioprine or 6-mercaptopurine (6-MP) or methotrexate (MTX) as defined in the protocol.
7.
8. Subject agrees to be genotyped at the DcR3 locus.

Exclusion criteria - Crohn's Disease:

1. Subject has a diagnosis of ulcerative colitis (UC) or indeterminate colitis.
2. Subject is unable to tolerate or unwilling to undergo study procedures including endoscopy and biopsy during the study.
3. Subject with signs or symptoms of bowel obstruction with small bowel imaging supporting obstruction.
4. Subject has short bowel syndrome as determined by the investigator.
5. Subject has a current functional colostomy or ileostomy.
6. Subject has had a surgical bowel resection within the past 6 months prior to screening or is planning any resection during the study period.
7. Clinical suspicion of intra-abdominal abscesses exists, in the opinion of the investigator.
8. Subject has concurrent bowel dysplasia or a history of bowel dysplasia in the 5 years prior to screening.

9. Subject has a known, active and/or positive test for C. difficile infection despite an adequate course of treatment.
10. Subject has history of or current diagnosis of any cancer excluding cancers that have been cured by surgical excision (e.g., non melanoma skin cancers).
11. Subject has a history of a lymphoproliferative disorder, including lymphoma, or signs and symptoms suggestive of lymphoproliferative disease at any time.
12. Subject has history of or active tuberculosis (TB) infection or positive TB testing at screening.
13. Subject has known concurrent viral hepatitis, or acquired immune deficiency syndrome (AIDS) or known human immunodeficiency virus (HIV) infection.
14. Subject has been treated with natalizumab (Tysabri®, Biogen) within the past 5 years.
15. Subject who has not completed his/her primary vaccination series (particularly hepatitis B, varicella, measles/mumps/rubella) unless immunity is documented with blood titers.
16. Subject has received any live attenuated vaccine, such as varicella-zoster, oral polio, or rubella, within 3 months prior to the baseline visit.
17. Subject has any of the following abnormal screening laboratory test results:
    a. Clinically significant electrocardiographic (ECG) abnormalities;
    b. Aspartate transaminase (AST), alanine transaminase (ALT) or total bilirubin > ULN;
    c. Hemoglobin < 10g/dL
    d. Absolute neutrophil count < 1500 cell/mm^3, or
    e. Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2.
18. Subject has abnormal vital signs during Screening (Visit 1) or prior to enrollment at the baseline visit (Visit 2), as defined in the protocol.
19. Subject is pregnant or a nursing mother.
20. Subject is sexually active and not using effective contraception as defined in the protocol.
21. Subject has a history of drug abuse that would inhibit participation in the clinical trial.
22. Subject has a current or recent history (within 6 months prior to screening) of significant and severe renal, hepatic, hematological, gastrointestinal (other than CD or conditions outlined above), endocrine, pulmonary, cardiac, or neurological disease.
23. Subject has any other clinically significant mental or physical illness or infection that, in the opinion of the investigator, might confound the results of the study, pose additional risk to the subject by their participation, or prevent or impede the subject from completing the study.
24. There is any concern on the part of the investigator regarding the subject's safety, compliance, or suitability with respect to his/her participation in the study.

Inclusion criteria - Ulcerative Colitis:

1. Subject is able to speak English fluently and has provided written informed consent for this study.
2. Subject is male or female, ≥18 to ≤75 years of age.
3. Subject has received a diagnosis of UC for 90 days or greater prior to Visit 1, confirmed by endoscopy during the Screening Period, with exclusion of current infection, dysplasia and/or malignancy. Appropriate documentation of biopsy results consistent with the diagnosis of UC, in the opinion of the Investigator, must be available.

4. Subject has moderately to severely active UC, as defined by a Modified Mayo Score (excluding the PGA component) of 5 to 9 points at Visit 1.
5. Subject has a Modified Mayo Endoscopic Score of ≥2 at Visit 1 as confirmed by central reader.
6. Subject has a Modified Mayo Rectal Bleeding Score of ≥1 at Visit 1.
7. Subject has failed treatment with an approved therapeutic dose of an anti-TNFα monoclonal antibody treatment with either no initial response (primary non-responder) or an initial response to induction with subsequent lost response (secondary non-responder) as defined in the protocol.
8. Subject can be receiving concurrent treatment with an oral corticosteroid, and/or azathioprine or 6-mercaptopurine (6-MP) or methotrexate (MTX) as defined in the protocol.
9. Subject who is currently taking 5-aminosalicylic acid (5-ASA) has been on a stable dose for at least 2 weeks prior to Visit 1.

Exclusion criteria - Ulcerative Colitis:

1. Subject has a diagnosis of CD or indeterminate colitis.
2. Subject is unable to tolerate or unwilling to undergo study procedures including endoscopy and biopsy during the study.
3. Subject with signs or symptoms of bowel obstruction with small bowel imaging supporting obstruction.
4. Subject has short bowel syndrome as determined by the investigator.
5. Subject has a current functional colostomy or ileostomy.
6. Subject has had a surgical bowel resection within the past 6 months prior to screening or is planning any resection during the study period.
7. Clinical suspicion of intra-abdominal abscesses exists, in the opinion of the investigator.
8. Subject has concurrent bowel dysplasia or a history of bowel dysplasia in the 5 years prior to screening.
9. Subject has a known, active and/or positive test for C. difficile infection despite an adequate course of treatment.
10. Subject has history of or current diagnosis of any cancer excluding cancers that have been cured by surgical excision (e.g., non melanoma skin cancers, cervical cancer).
11. Subject has a history of a lymphoproliferative disorder, including lymphoma, or signs and symptoms suggestive of lymphoproliferative disease at any time.
12. Subject has history of or active tuberculosis (TB) infection or positive TB testing at screening.
13. Subject has known concurrent viral hepatitis, or acquired immune deficiency syndrome (AIDS) or known human immunodeficiency virus (HIV) infection.
14. Subject has been treated with natalizumab (Tysabri®) within 5 years of Visit 1.
15. Subject who has not completed his/her primary vaccination series (particularly hepatitis B, varicella, measles/mumps/rubella) unless immunity is documented with blood titers.
16. Subject has received any live attenuated vaccine, such as varicella-zoster, oral polio, or rubella, within 3 months prior to the baseline visit.
17. Subject has received an investigational medicine (non-biologic) within 2 weeks of Visit 1 and/or an investigational medicine that is a biologic within 8 weeks of Visit 1.

18. Subject has any of the following abnormal screening laboratory test results:
    a. Clinically significant electrocardiographic (ECG) abnormalities;
    b. Aspartate transaminase (AST), alanine transaminase (ALT) or total bilirubin > ULN;
    c. Hemoglobin < 10g/dL
    d. Absolute neutrophil count < 1500 cell/mm^3, or
    e. Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2.
19. Subject has abnormal vital signs during Screening (Visit 1) or prior to enrollment at the baseline visit (Visit 2), as defined in the protocol.
20. Subject is pregnant or a nursing mother.
21. Subject is sexually active and not using effective contraception as defined in the protocol.
22. Subject has a history of drug abuse that would inhibit participation in the clinical trial.
23. Subject has a current or recent history (within 6 months prior to screening) of significant and severe renal, hepatic, hematological, gastrointestinal (other than UC or conditions outlined above), endocrine, pulmonary, cardiac, or neurological disease.
24. Subject has any other clinically significant mental or physical illness or infection that, in the opinion of the investigator, might confound the results of the study, pose additional risk to the subject by their participation, or prevent or impede the subject from completing the study.
25. There is any concern on the part of the investigator regarding the subject's safety, compliance, or suitability with respect to his/her participation in the study.

Investigational product, dosage, and mode of administration:

MDGN-002 will be supplied in vials of 150 mg/mL. MDGN-002 will be administered by SQ injection in the abdomen in a zone of 4 to 10 cm from the umbilicus with the injection site rotated with each subsequent dose. The dose MDGN-002 will be administered every 14 days at 1 of 2 dose levels: 1.0 mg/kg or 3.0 mg/kg.

Duration of treatment:

Duration of treatment will be approximately 56 days

Reference therapy, dosage and mode of administration:

None

Criteria for evaluation:

Safety: Adverse events, clinical laboratory, and urinalysis tests, vital signs, ECGs, and physical examinations

Pharmacokinetics: Sparse pharmacokinetic blood sampling

Efficacy: SES-CD, abdominal pain assessment, loose/watery stool frequency assessment, Modified Mayo Score (excluding the PGA component), stool frequency and rectal bleeding assessment, and CDAI (CD only)

Statistical methods:

This is the first use of MDGN-002 in patients with CD or UC who have failed treatment with anti-TNFα monoclonal antibodies. The sample size of the study is based on feasibility and not on formal hypothesis testing.

Descriptive statistics will be used to summarize all safety, pharmacokinetic, efficacy, and quality of life variables. Continuous variables will be summarized using N, mean and/or median, standard deviation, and range. Categorical variables will be summarized using frequencies and percentages.

Detailed descriptions of data summaries and listings will be provided in the Statistical Analysis Plan.

5. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF ABBREVIATIONS

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Explanation
ADA	anti-drug antibody
ADL	activities of daily living
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALT	alanine transaminase
Anti-TNFα	anti-tumor necrosis factor alpha
AST	aspartate transaminase
AUC	area under the curve
AUC_{last}	last observed concentration
$AUC_{0-\infty}$	area under the sum concentration versus time curve from time zero to infinity
βhCG	beta human chorionic gonadotropin
BP	blood pressure
C_{max}	maximum observed serum concentration
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CRA	Clinical Research Associate
CRO	Contract Research Organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DcR3	decoy receptor 3
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EU	European Union
FasL	Fas ligand
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase

Abbreviation	Explanation
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HVEM	Herpes Virus Entry Mediator
IBD	inflammatory bowel disease
IBD-Q	Inflammatory Bowel Disease Questionnaire
ICH	International Conference on Harmonisation
IgG4	immunoglobulin G4
IP	Investigational Product
IRB	Institutional Review Board
LIGHT	**L**ymphotoxin-like, exhibits **I**nducible expression, and competes with Herpes Virus **G**lycoprotein D for **H**erpesvirus Entry Mediator, a receptor expressed by **T** lymphocytes
LTβR	lymphotoxin beta receptor
MTX	methotrexate
NF-κB	Nuclear factor kappa B
PI	Principal Investigator
PK	pharmacokinetic
QFT	QuantiFERON-TB Gold
q14	every 14 (days)
RNA	ribonucleic acid
RR	respiration rate
SAE	serious adverse event
SES-CD	Simple Endoscopy Score for Crohn's Disease
SOC	system organ class
SQ	subcutaneous
TB	tuberculosis
TEAEs	treatment-emergent adverse events
TL1A	TNF-like ligand 1A
t_{max}	time to the maximum observed serum concentration
TNF	tumor necrosis factor
TNFα	tumor necrosis factor alpha
$t_{1/2}$	Apparent terminal half-life
UC	ulcerative colitis
5-ASA	5-aminosalicylic acid

Abbreviation	Explanation
6-MP	6-mercaptopurine

6. INTRODUCTION

6.1. Inflammatory Bowel Disease

Crohn's Disease (CD) and ulcerative colitis (UC) are the two major phenotypes of chronic idiopathic inflammatory bowel disease (IBD), and they afflict over 3 million patients in the US (Dahlhamer et al., 2015). Both diseases carry significant risk for serious complications and the need for surgical interventions. The etiology of IBD involves an interplay between the immune system, the microbiome, and genetic factors. The immune system in the intestinal tract includes various epithelial cells, myeloid cells, and lymphocytes all producing a wide variety of molecules that mediate and regulate the inflammatory response, with imbalance of this network driving the pathophysiology of IBD (Abraham and Cho, 2009; Giles et al., 2018).

6.1.1. Pediatric-Onset Crohn's Disease

The incidence of pediatric CD is rapidly increasing worldwide (Kappelman et al, 2013). The treatment of pediatric CD poses several particular challenges compared to adult-onset disease. First, the extent of disease is more widespread among children, with pediatric CD often involving both the small and large intestines as well as organ systems outside the gastrointestinal tract (de Bie et al, 2013; Dotson et al, 2010). As such, children tend to have a more aggressive disease course and many will require surgical resections (Freeman, 2014). Second, growth failure is a problem unique to pediatric CD. Without optimized treatment, the inflammatory burden caused by CD can result in delayed onset of puberty and shorter adult height (Sanderson, 2014).

The tumor necrosis factor alpha (TNFα) inhibitors infliximab and adalimumab are effective at inducing and maintaining remission in pediatric CD. However, at least 12% of children with CD will never respond to infliximab therapy (Hyams et al, 2007). Even among patients with initial response, sustained efficacy is complicated by loss of response, with nearly 50% of pediatric CD patients losing response to infliximab within 5 years (Assa et al, 2013). Additionally, in approximately 20% of children, infusion reactions and other adverse events (AEs) require treatment cessation (Vahabnezhad et al, 2014). As a result, a large percentage of pediatric CD patients are unable to sustain durable response with these conventional therapies.

6.1.2. Ulcerative Colitis

Anti-inflammatory agents and immunosuppressants are used as first line treatment of UC. TNFα inhibitors are used in the setting of first line treatment failure or intolerance to gain control of the disease. Unfortunately, available agents such as infliximab, adalimumab, and golimumab often face primary and secondary loss of response (Pouillon et al, 2016). Primary non-response rates for infliximab have been reported up to 30% for IBD (Ben-Horin et al, 2014), with about 50% of these patients requiring colectomy within 2 years (Papamichael et al, 2016). In the setting of rescue therapy for adult patients with severe acute UC, while 84% had an initial clinical response to infliximab within the first week, 54% had failed treatment and 21% required colectomy within 14 weeks (Laharie et al, 2012). For TNFα inhibitors overall, about 30–40% of patients may fail to demonstrate a primary response, and about 30–40% of patients lose response over time or may become intolerant to TNFα inhibitors (Papamichael et al, 2015). As such there remains an unmet

medical need for alternate or second-line treatment options for UC patients with severe relapsing disease.

6.2. MDGN-002

6.2.1. Description and Mechanism of Action

MDGN-002 is a fully human anti-lymphotoxin-like, exhibits inducible expression, and competes with Herpes Virus Glycoprotein D for Herpes virus entry mediator (HVEM), a receptor expressed by T lymphocytes (LIGHT) antibody which binds specifically to LIGHT, preventing binding of LIGHT with its receptors. It has a modified human immunoglobulin G4 (IgG4) backbone. LIGHT is a member of the tumor necrosis factor (TNF) superfamily which binds to 3 distinct receptors: HVEM, lymphotoxin-β receptor (LTβR), and decoy receptor 3 (DcR3). LIGHT expression is restricted to natural killer cells, monocytes, immature dendritic cells, and activated T cells where expression is inducible and transient in nature.

LIGHT has a role as an important mediator in mucosal inflammation and inflammatory bowel disease (IBD) pathogenesis (Cohavy et al, 2004; Ware, 2005; Cohavy 2005; Wang et al, 2005). The human LIGHT gene maps to chromosome 19p13.3, a region that has been implicated in the pathogenesis of CD (Granger et al, 2001; Rioux et al, 2000). The concept that LIGHT provides a critical pro-inflammatory signal during cellular immune responses is reinforced by studies in IBD patients. LIGHT messenger ribonucleic acid (RNA) is upregulated in biopsies from inflamed areas of small bowel (Cohavy et al, 2005).

Decoy receptor 3 belongs to the TNF superfamily (TNFRSF6B) (Yu et al, 1999). It acts as a decoy receptor that competes with death receptors for ligand binding and is postulated to play a regulatory role in suppressing Fas ligand (FasL)- and LIGHT-mediated cell death and T cell activation as well as to induce angiogenesis via neutralization of TNF-like ligand 1A (TL1A) (Yu et al, 2009). Decoy receptor 3 is over-expressed in the epithelial layer of ileum specimens in patients with CD, both at actively inflamed and non-active sites. Decoy receptor 3 serum levels are significantly elevated in patients with active and non-active CD compared with healthy controls. The expression of DcR3 in intestinal epithelial cells is induced by TNFα. Increased DcR3 expression is associated with activation of nuclear factor kappa B (NF-κB) and results in protection of intestinal epithelial cells and lamina propria T cells from CD95L-induced apoptosis (Funke et al, 2009). Defective variants of DcR3 have recently been observed in patients with pediatric onset IBD which further suggests an important protective role for DcR3 (Cardinale et al, 2013), potentially by moderating the effects of TNF and LIGHT.

6.2.2. Non-Clinical Data

[redacted]

[redacted]

6.2.3. Clinical Data

[redacted]

6.3. Rationale for Present Study

The roles of LIGHT and DcR3 in the pathogenesis of IBD, as described in Section 6.2.1, provide a rationale for the study of MDGN-002 in CD patients with or without loss-of-function mutations in DcR3. This first study will provide insight into the safety, tolerability, and possible efficacy of MDGN-002 in the target indication.

Non-clinical and clinical safety data (described in Sections 6.2.2 and 6.2.3, respectively) support the MDGN-002 dose proposed as the dose for the first cohort of adult subjects with CD in the present study (ie, 1.0 mg/kg). Dose escalation in a subsequent cohort (to 3.0 mg/kg) will proceed only if there are no clinically important safety findings in the first dose cohort. Additionally, 6 patients with UC will be enrolled in the 3.0 mg/kg dose cohort. The dose-escalation design allows for the preliminary evaluation of the safety and PK of and response to MDGN-002 in the intended indications.

7. STUDY OBJECTIVES AND PURPOSE

7.1. Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of MDGN-002 administered by SQ injection to adults with moderate to severe, active CD or UC who have failed prior treatment with an anti-tumor necrosis factor alpha (anti-TNFα) agent.

7.2. Secondary Objectives

The secondary objectives of this study are to:

- Estimate plasma concentrations of MDGN-002 administered by SQ injection to adults with moderate to severe, active CD or UC.
- Evaluate response to treatment with MDGN-002 administered by SQ injection to adults with moderate to severe, active CD or UC.

8. INVESTIGATIONAL PLAN

8.1. Overall Study Design

This is a Phase 1b, multi-center, open-label, dose-escalation, signal-finding study to evaluate the safety, tolerability, PK and short-term efficacy of MDGN-002 in adults with moderate to severe, active CD or UC who have previously failed anti-TNFα treatment.

Four subjects with Crohn's disease who satisfy all eligibility criteria will be enrolled in each of 2 dose cohorts. The first cohort will receive MDGN-002 1.0 mg/kg SQ every 14 (q14) days. Dose escalation will proceed after all subjects in the first cohort have been enrolled and reached Visit 4 (Day 14 ±3 days), the safety data from those subjects has been reviewed by the Data Monitoring Committee, and a decision has been made to progress to the second cohort (see Section 8.4). The estimated dose escalation for the second cohort is 3.0 mg/kg SQ q14 days, if permitted by safety data review. After dose escalation has taken place 6 additional patients with UC will also be enrolled in the 3 mg/kg cohort.

Each subject's participation will include a screening period, which if required includes a wash-out period for subjects who have received biologic treatment within 12 weeks of the Screening Visit. With the exception of subjects requiring wash-out of the biologic certolizumab pegol (Cimzia), only those subjects without detectable biologic levels after 8 weeks of wash-out will be allowed to enter the study after confirmation of undetectable levels; all other subjects (including those receiving certolizumab pegol [Cimzia]) will be required to complete a full 12-week wash-out period. The wash-out period includes the time period from the last dose received prior to the Screening Visit. Subjects not requiring a biologic wash-out period will be allowed to enter the study after review and confirmation of eligibility at screening. Screening is followed by an 8-week, open-label treatment period, and a safety follow-up visit approximately 4 weeks after the last dose. The maximum study duration is 26 weeks.

Study visits will occur at screening and on Days 0, 7, 14, 21, 28, 35, 42, 49 and 56. The safety follow-up visit will occur on Day 84. The Schedule of Assessments is shown in Table 1.

Table 1 Schedule of Assessments

	Screening Period				Open-Label Treatment Period										Safety Follow-up
					Visit 2[c]										
Assessment or Procedure	Visit 1	Initial Phone Contact[a]	Visit for Testing Previous Biologics (if required)	Wash-out Phone Contact[b]	Pre-dose Day 0	Dosing and Post-dose Day 0	Visit 3 Day 7	Visit 4 Day 14	Visit 5 Day 21	Visit 6 Day 28	Visit 7 Day 35	Visit 8 Day 42	Visit 9 Day 49	Visit 10 / ET Visit Day 56	Visit 11 Day 84 or 28 days after ET visit
Informed consent	X														
Inclusion/ exclusion criteria review	X	X			X										
Testing for Previous Biologics			X[q]												
Genotyping for DcR3 genes (CD only)	X														
Demographics / medical history[d]	X														
Physical examination, incl. weight[e]	X				X			X		X		X		X	
Vital signs (BP, pulse, RR, T)[f]	X				X	X		X		X		X		X	
TB testing[g]	X														
12-lead ECG	X									X				X	
Clinical laboratory assessments[h]	X				X			X		X		X		X	

	Screening Period				Open-Label Treatment Period										Safety Follow-up
					Visit 2[c]										
Assessment or Procedure	Visit 1	Initial Phone Contact[a]	Visit for Testing Previous Biologics (if required)	Wash-out Phone Contact[b]	Pre-dose Day 0	Dosing and Post-dose Day 0	Visit 3 Day 7	Visit 4 Day 14	Visit 5 Day 21	Visit 6 Day 28	Visit 7 Day 35	Visit 8 Day 42	Visit 9 Day 49	Visit 10 / ET Visit Day 56	Visit 11 Day 84 or 28 days after ET visit
PK blood sampling[i]					X		X	X	X	X	X	X	X	X	X
Blood draws for exploratory analyses[j]					X					X				X	
Anti-drug antibody assessment					X			X		X				X	X
Urinalysis	X				X					X				X	
Pregnancy testing (females of childbearing potential)[k]	X				X					X				X	
Urine drug screen[l]	X														
Stool sample[m]	X									X				X	
Modified Mayo score (UC only)[r]	X													X	
CDAI (CD only)	X				X			X		X		X		X	
IBD-Q	X				X									X	
Endoscopy with biopsy and histology[n]	X													X	

	Screening Period				Open-Label Treatment Period										Safety Follow-up
					Visit 2[c]										
Assessment or Procedure	Visit 1	Initial Phone Contact[a]	Visit for Testing Previous Biologics (if required)	Wash-out Phone Contact[b]	Pre-dose Day 0	Dosing and Post-dose Day 0	Visit 3 Day 7	Visit 4 Day 14	Visit 5 Day 21	Visit 6 Day 28	Visit 7 Day 35	Visit 8 Day 42	Visit 9 Day 49	Visit 10 / ET Visit Day 56	Visit 11 Day 84 or 28 days after ET visit
Adverse event monitoring[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Provide/re-confirm access to subject diary	X				X		X	X	X	X	X	X	X	X	
Subject diary reviewed for completeness					X		X	X	X	X	X	X	X	X	
Assess individual subject stopping criteria						X	X	X	X	X	X	X	X	X	
MDGN-002 administration (on-site)[p]						X		X		X		X			

[a] Telephone visit is conducted for confirmation of eligibility. If the subject is not currently receiving biologic treatment, they will begin completing the subject diary and have visit 2 scheduled >7 days from the diary being initiated. The diary should be completed up to the time of the visit.

[b] Telephone visit is conducted for confirmation whether additional wash-out time is required following receipt and review of the laboratory results. If the concentration level is not detectable, the subject will have their visit scheduled >7 days from the time the subject started completing the diary. If the concentration level is detectable, the subject will complete the full 12 week wash-out. The diary should be completed up to the time of the visit.

[c] After Day 0 (Visit 2), visits at which MDGN-002 is administered should occur every 14 ± 3 days. These visits should be scheduled relative to Day 0 (Visit 2), which is the baseline visit.

[d] Medical history will include details regarding all UC/CD-related surgical procedures and hospitalizations.

[e] A complete physical examination will be performed at Visits 1, 2, 6, and 10/ET. Brief physical examinations will be done at Visits 4 and 8. Height will be measured at V2 only.

[f] Vitals will be taken pre-and post-dose on Visit 2, 4, 6 and 8. Post-dose vitals should be taken at least 60 minutes post-dose, immediately prior to discharge.

[g] TB testing will include QuantiFERON-TB Gold (QFT) blood testing or PPD skin testing. If the subject's PPD tine skin test is ≥ 5 mm, a chest x-ray will also be employed for TB assessment.

[h] Clinical laboratory assessments at Visits 1, 6, and 10/ET include: CBC with differential, hematology, serum albumin, CRP, liver panel, GGT. Anti-drug antibodies will be measured at Visits 2, 6 and 10. Clinical laboratory assessments at Visits 2, 4, and, 8 include hematology and serum albumin.

[i] Pre-dose PK blood samples will be obtained within 60 minutes prior to dose at Visits 2, 4, 6 and 8.

j Exploratory analyses will examine LIGHT, cytokines, RNA sequencing, and flow cytometry.

[k] Serum β-hCG will be conducted at Visit 1 and Urine β-hCG tests will be conducted on Visits 2, 6 and 10.

[l] Screening for amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, cannabinoids, propoxyphene, and methadone as warranted.

[m] Stool samples will be obtained at Visits 1, 6 and 10/ET. C.difficile test will be performed only at Visit 1. Fecal calprotectin will be measured at all specified visits.

[n] Histological confirmation of disease is performed only at Visit 1. Documentation will be provided to site for confirmation or prior documentation of histological confirmation is acceptable. Exploratory biomarker histology will be completed for samples provided to study central laboratory provider.

[o] Adverse event monitoring begins at the time informed consent is signed.

[p] Subjects will be required to remain in the clinic for at least 60 minutes after MDGN-002 administration for adverse event monitoring.

[q] Subjects requiring wash-out will have a blood test performed at 8 weeks after the start of the wash-out period to confirm the previous biologic therapy is undetectable. If there is no previous biologic therapy detected, subjects will be able to continue onto Visit 2 and will not be required to complete the full 12-week wash-out. If there are detectable levels of the previous biologic therapy, then subjects will complete the full 12-week wash-out before proceeding to Visit 2. For subjects receiving certolizumab pegol (Cimzia) a 12-week wash-out is required.

[r] The Modified Mayo Score includes stool frequency, rectal bleeding, and the appearance of mucosa upon endoscopy. This score will be calculated at Visit 1 and Visit 10 using the endoscopy score from the central reader, self reported data on stool frequency and rectal bleeding from the period prior to the subject being screened for Visit 1 and data from the patient diary for Visit 10.

BP=blood pressure; CBC=complete blood count; CDAI=Crohn's Disease Activity Index; CRP=C-reactive protein; DcR3=decoy receptor 3; GGT=gamma-glutamyl transferase; ECG=electrocardiogram; ET=early termination; hCG=human chorionic gonadotropin; LIGHT=Lymphotoxin-like, exhibits Inducible expression, and competes with Herpes Virus Glycoprotein D for Herpesvirus Entry Mediator, a receptor expressed by T lymphocytes; PK=pharmacokinetic; PPD = purified protein derivative; RR=respiration rate; T=temperature; TB=tuberculosis; TNFα=tumor necrosis factor alpha.

8.2. Study Periods

The study includes a screening period, an open-label treatment period, and a safety follow-up visit. Each cohort will complete the study periods described below. Following a review of the safety data, a decision will be made whether or not to escalate to the 3 mg/kg as described in Section 8.4.

8.2.1. Screening Period

During the screening period, all subjects will be evaluated for their eligibility to participate in the study. At Visit 1, subjects will sign the informed consent form before any study-related procedures or evaluations are conducted.

Demographic information will be obtained along with medical history, including CD/UC diagnostic information, CD/UC-related procedures/surgeries and medication use history. Any existing conditions reported at the screening visit will be recorded in the electronic case report form (eCRF); current medications will also be recorded on the eCRF. Prior CD/UC therapies (lifetime recall) will be recorded in the eCRF with dates reflecting prior use. All safety assessments will be conducted, including physical examinations (with weight measurements), vital signs (blood pressure, pulse, respiration rate and temperature), 12-lead ECGs, clinical laboratory tests, stool sample and urinalysis. A urine drug screening test (as warranted) and tuberculosis (TB) testing defined as either a purified protein derivative (PPD) skin reaction test or QuantiFERON-TB Gold (QFT) blood test, and as required by protocol, chest x--ray, will be administered to all subjects. A serum β-human chorionic gonadotropin (β-hCG) test will be administered to females of childbearing potential. The CDAI and the Inflammatory Bowel Disease Questionnaire (IBD-Q) will be administered. Subjects will undergo an endoscopy with biopsy and histology during the screening period. Subjects with CD will be provided access to a study diary to record their daily assessment of well-being, abdominal pain and stool frequency including loose and watery stools. Subjects with UC will be provided access to a study diary to record their daily assessment of their stool frequency and rectal bleeding. The diary must be completed for a minimum of 7 days prior to initiation of open-label treatment as described in Table 1. Finally, adverse events (AEs) will be monitored.

Subjects who are currently taking a biologic treatment or who have received biologic treatment within 12 weeks of the Screening Visit but who are otherwise eligible for study participation based on review of all screening evaluations and results will begin a wash-out period for these medications. Washout is the period between when the subject received their last dose of biologic and when they are eligible to proceed to Visit 2. With the exception of subjects requiring wash-out of the biologic certolizumab pegol (Cimzia), a blood test will be administered to subjects undergoing wash-out 8 weeks after their last dose of biologic treatment to ensure that serum levels of any previous biologic treatments are below the level of detection. If it is confirmed that the levels of previous biologic treatment are undetectable, then the subject will proceed to Visit 2. If the test results indicate that the previous biologic treatment is detectable, the subject will be required to complete a full 12-week wash-out period before proceeding to Visit 2. For subjects receiving the biologic certolizumab pegol (Cimzia) a 12-week wash-out is required.

8.2.2. Open-label Treatment Period

Eligible subjects will return to the clinic after the screening period (and wash-out period, if applicable) on Visit 2, which is Day 0 of the 8-week, open-label treatment period. Physical examinations including weight and vital sign assessments, clinical laboratory tests, urinalysis, and the CDAI (CD only) will be performed. A urine β-hCG test will be administered to females of childbearing potential. Any AEs and concomitant medications will be recorded. Blood will be drawn for PK, ADA and exploratory analyses (including LIGHT, cytokines, RNA sequencing, and flow cytometry). Subjects with CD will record their daily assessment of well-being, abdominal pain and stool frequency including loose and watery stools daily in their study diary. Subjects with UC will record stool frequency and rectal bleeding daily in their study diary. Diary data will be reviewed for completeness during each visit. Subjects will be re-evaluated to determine whether they meet all inclusion criteria and do not satisfy any of the exclusion criteria.

Eligible subjects will then be enrolled in the study and receive their first dose of MDGN-002 in the clinic. Subjects will receive MDGN-002 as a SQ injection in the abdomen in a zone of 4 to 10 cm from the umbilicus with the injection site rotated with each subsequent dose. The dose of MDGN-002 will be administered every 14 days (± 3 days) for 8 weeks. Subjects will be monitored for AEs during the administration of each dose and for 60 minutes after dosing.

Subjects will return to the clinic every 14 (± 3) days (Visits 4, 6, 8, and 10) after the first MDGN-002 dose for assessment of safety, PK, and efficacy and to receive the next dose of investigational product, as shown in Table 1. Additional weekly visits between dosing visits (Visits 3, 5, 7, and 9) will occur at which time blood will be drawn for PK analyses, subjects will be provided access to a study diary for diary data collection, and AEs and concomitant medication use will be recorded.

Prior to enrolling subjects in the second dose cohort, all subjects in the first cohort will have reached Visit 4 (Day 14 ±3 days) in the study and safety data from those subjects will be reviewed by the Data Monitoring Committee (DMC; as described in Section 8.4). A recommendation will be provided by the DMC and a decision by the Sponsor whether subjects can be enrolled in the next dose cohort.

8.2.3. Safety Follow-up Visit

Approximately 28 days after the final dose, subjects will have a safety follow-up visit. The safety follow-up visit will be conducted in the clinic with the subject. Any AEs that occurred in the time since the subject's last MDGN-002 dose will be recorded, along with any concomitant medication use.

8.3. Safety Data Review

Each investigator will review all available safety data collected at their site on a weekly basis, and communicate any safety concerns to the sponsor medical monitor. The sponsor medical monitor will review all relevant safety findings with the coordinating principal investigator and DMC as needed.

Special attention will be paid to adverse drug reactions observed in the MDGN-002 preclinical study as well as other common adverse reactions seen with other biologic treatments which include:

MDGN-002 preclinical observation:

- Injection site reactions

Adverse reactions observed with other biologic treatments:

- Potential for increased infection including opportunistic infections (such as tuberculosis)
- Hypersensitivity reactions (including anaphylaxis)
- Immunogenicity
- Malignancy
- Impaired immunization
- CD exacerbation

8.4. Data Monitoring Committee

An external, independent Data Monitoring Committee (DMC) comprising physicians, scientists and a biostatistician will review the study data at a meeting after all subjects in the first cohort have been enrolled and reached Visit 4 (Day 14 ±3 days), and after completion of the second cohort. Additionally, ad hoc meetings to assess individual exacerbations of CD or UC meeting Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or greater as defined in Section 8.5 may be held. The DMC's role is to protect the interests of the subjects in the study and those still to be entered in the study by reviewing information such as safety, tolerability, pharmacokinetic and efficacy data. The DMC's meeting schedule may be adjusted based on recommendations made by the DMC, the amount of incremental safety data, and other practical considerations. The data provided to the DMC may not be monitored and will not be considered "clean" until the database is locked at the completion of the study.

Possible outcomes of the DMC review can include one of the following recommendations:

- Study can continue
- Study can continue with modifications
- Study is to be terminated

Data Monitoring Committee recommendation will be documented in meeting minutes which will include, at a minimum:

- List of meeting participants
- Summary of data considered during the meeting
- Summary of the DMC recommendation regarding further dose cohorts, including any concerns raised

The sponsor is responsible for the decision to continue, modify or terminate the study. A copy of the DMC meeting recommendation and sponsor decision will be sent to the study sites upon completion and prior to administration of the next subject dose in the second cohort.

8.5. Individual Subject and Study Stopping Criteria

8.5.1. Individual Subject Stopping Criteria

The following individual subject stopping criteria will be used during the study and will be assessed starting post-dose at Visit 2:

- A subject develops a CTCAE Grade 3 or higher of the following:
    - Injection site reactions
    - Opportunistic infections (i.e. tuberculosis)
    - Hypersensitivity reactions (e.g. allergic reactions, anaphylaxis or cytokine release syndrome)
    - Malignancy
    - Decreased white blood cell count
    - Decrease neutrophil count
    - Decreased platelets
    - Colonic or ileal hemorrhage
    - Colonic, ileal or small intestine obstruction
    - Colonic, ileal or small intestine perforation
    - Colonic, ileal or small intestine stenosis
- A subject will also be stopped if liver enzymes are:
    - ALT or AST >8x ULN
    - ALT or AST >5x ULN for more than 2 consecutive weeks or
    - A single subject ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and or eosinophilia (>5%).

    Note: subjects who exhibit ALT or AST >3x ULN without appearance of any of the above symptoms must have repeat testing within 48-72 hours to confirm abnormality and determine direction (increase or decrease) from the original value.
- A subject will be stopped if Hy's Law is detected (i.e. ALT or AST >3x ULN and total bilirubin >2x ULN and no other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury).

8.5.2. Study Stopping Criteria

The following study stopping criteria will be used during the study:

- The study will be stopped if two or more subjects develop the same CTCAE Grade 3 or if one subject develops a CTCAE Grade 4 of the following:
    - Injection site reactions
    - Opportunistic infections (i.e. tuberculosis)
    - Hypersensitivity reactions (e.g. allergic reactions, anaphylaxis or cytokine release syndrome)
    - Malignancy

  - Decreased white blood cell count
  - Decrease neutrophil count
  - Decreased platelets

- The study will be stopped if two individual subjects develop any of the following liver toxicities:
  - ALT or AST >8x ULN
  - ALT or AST >5x ULN for more than consecutive 2 weeks or
  - ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and or eosinophilia (>5%).

- The study will be stopped if one subject meeting Hy's Law is detected (i.e. ALT or AST >3x ULN and total bilirubin >2x ULN and no other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury).

- Individual reports of exacerbations of Crohn's disease CTCAE Grade 3 or greater, such as:
  - Colonic or ileal hemorrhage
  - Colonic, ileal or small intestine obstruction
  - Colonic, ileal or small intestine perforation
  - Colonic, ileal or small intestine stenosis

will be reviewed by the DMC at the first available date after report to determine if modifying the study or stopping the study is recommended.

8.6. Study Design Rationale

This is the third study in which MDGN-002 is being administered to human subjects and the first study in subjects with treatment-resistant CD or treatment resistant UC. The study is a pilot study using a dose-escalation design to characterize the safety and tolerability of 2 different doses of MDGN-002 (1.0 mg/kg and 3.0 mg/kg) in the target population. The dose escalation design allows for the evaluation of safety and tolerability in small numbers of subjects before proceeding to the next dose level. The open-label administration of MDGN-002 to all enrolled subjects minimizes the number of subjects exposed to the study procedures. The inclusion of PK blood draws and efficacy assessments allows for preliminary assessments of plasma levels and efficacy, respectively.

No specific hypotheses are being tested in this pilot study. All data will be summarized using descriptive statistics as appropriate (see Section 13).

8.7. Number of Subjects

Four subjects with CD will be enrolled in each of the 2 planned dose cohorts for a maximum of 8 study subjects with CD. Additionally, 6 subjects with UC will be enrolled in the 2nd dose cohort. Subjects who withdraw from the study prematurely prior to a third dose may be replaced.

8.8. Treatment Assignment

The first cohort of subjects will be assigned to the 1.0 mg/kg dose of MDGN-002. Subjects will be assigned to the second dose cohort, after the DMC review of the safety data from the first cohort, as described in Section 8.4, provided study stopping criteria have not been met as described in Section 8.5.2 and a decision is made by the Sponsor that enrolment can continue.

8.9. Criteria for Study Termination

The study may be terminated at the sponsor's discretion at any time and for any reason.

9. SELECTION AND WITHDRAWAL OF SUBJECTS

A screening log of potential study candidates and an enrollment log of enrolled subjects must be maintained at each study site.

9.1. Subject Inclusion Criteria – Crohn's Disease

Subjects with CD must meet all of the following inclusion criteria in order to be eligible for enrollment in the study:

1. Subject is able to speak English fluently and has provided written informed consent for this study.
2. Subject is male or female, ≥18 to ≤ 75 years of age.
3. Subject has a documented diagnosis of CD via endoscopy/colonoscopy and histological confirmation. Prior documentation of histological confirmation is acceptable
4. Subject has moderate to severe, active CD as evidenced by Simple Endoscopy Score for Crohn's Disease (SES-CD) score of ≥7.
5. Subject has failed treatment with an approved therapeutic dose of an anti-TNFα monoclonal antibody treatment with either no initial response (primary non-responder) or an initial response to induction with subsequent lost response (secondary non-responder) as defined in Appendix 18.2.
6. Subject can be receiving concurrent treatment with an oral corticosteroid, and/or azathioprine or 6-mercaptopurine (6-MP) or methotrexate (MTX) as defined in Section 10.2.1.
7. Subject agrees to be genotyped at the DcR3 locus.

9.2. Subject Exclusion Criteria – Crohn's Disease

Subjects with CD who meet any of the following exclusion criteria will not be eligible for enrollment in the study:

1. Subject has a diagnosis of ulcerative colitis (UC) or indeterminate colitis.
2. Subject is unable to tolerate or unwilling to undergo study procedures including endoscopy and biopsy during the study.
3. Subject with signs or symptoms of bowel obstruction with small bowel imaging supporting obstruction.
4. Subject has short bowel syndrome as determined by the investigator.
5. Subject has a current functional colostomy or ileostomy.
6. Subject has had a surgical bowel resection within the past 6 months prior to screening or is planning any resection during the study period.
7. Clinical suspicion of intra-abdominal abscesses exists, in the opinion of the investigator.
8. Subject has concurrent bowel dysplasia or a history of bowel dysplasia in the 5 years prior to screening.

9. Subject has a known, active and/or positive test for C. difficile infection despite an adequate course of treatment.
10. Subject has history of or current diagnosis of any cancer excluding cancers that have been cured by surgical excision (e.g., non melanoma skin cancers).
11. Subject has a history of a lymphoproliferative disorder, including lymphoma, or signs and symptoms suggestive of lymphoproliferative disease at any time.
12. Subject has history of or active TB infection or positive TB testing at screening.
13. Subject has known concurrent viral hepatitis, or acquired immune deficiency syndrome (AIDS) or known human immunodeficiency virus (HIV) infection.
14. Subject has been treated with natalizumab (Tysabri®) within the past 5 years.
15. Subject who has not completed his/her primary vaccination series (particularly hepatitis B, varicella, measles/mumps/rubella) unless immunity is documented with blood titers.
16. Subject has received any live attenuated vaccine, such as varicella-zoster, oral polio, or rubella, within 3 months prior to the baseline visit.
17. Subject has any of the following abnormal screening laboratory test results:
    - Clinically significant ECG abnormalities;
    - Aspartate transaminase (AST), alanine transaminase (ALT) or total bilirubin > ULN;
    - Hemoglobin < 10g/dL
    - Absolute neutrophil count <1500 cell/mm^3, or
    - Estimated glomerular filtration rate <60 mL/min/1.73 m^2.
18. Subject has abnormal vital signs during Screening (Visit 1) or prior to enrollment at the baseline visit (Visit 2), as defined in Section 12.3.1.2.
19. Subject is pregnant or a nursing mother.
20. Subject is sexually active and not on effective contraception as defined in Section 10.2.3.
21. Subject has a history of drug abuse that would inhibit participation in the clinical trial.
22. Subject has a current or recent history (within 6 months prior to screening) of significant and severe renal, hepatic, hematological, gastrointestinal (other than CD or conditions outlined above), endocrine, pulmonary, cardiac, or neurological disease.
23. Subject has any other clinically significant mental or physical illness or infection that, in the opinion of the investigator, might confound the results of the study, pose additional risk to the subject by their participation, or prevent or impede the subject from completing the study.
24. There is any concern on the part of the investigator regarding the subject's safety, compliance, or suitability with respect to his/her participation in the study.

9.3. Subject Inclusion Criteria – Ulcerative Colitis

Subjects with UC must meet all of the following inclusion criteria in order to be eligible for enrollment in the study:

1. Subject is able to speak English fluently and has provided written informed consent for this study.
2. Subject is male or female, ≥18 to ≤ 75 years of age.
3. Subject has received a diagnosis of UC for 90 days or greater prior to Visit 1, confirmed by endoscopy during the Screening Period. Appropriate documentation of biopsy results consistent with the diagnosis of UC, in the assessment of the Investigator, must be available.
4. Subject has moderately to severely active UC, as defined by a Modified Mayo Score (excluding the PGA component) of 5 to 9 points.
5. Subject has a Modified Mayo Endoscopic Score of ≥2 at Visit 1 as confirmed by central reader.
6. Subject has a Modified Mayo Rectal Bleeding Score of ≥1 at Screening Visit 1.
7. Subject has failed treatment with an approved therapeutic dose of an anti-TNFα monoclonal antibody treatment with either no initial response (primary non-responder) or an initial response to induction with subsequent lost response (secondary non-responder) as defined in Appendix 18.2.
8. Subject can be receiving concurrent treatment with an oral corticosteroid, and/or azathioprine or 6-mercaptopurine (6-MP) or methotrexate (MTX) as defined in Section 10.2.1.
9. Subject who is currently taking 5-aminosalicylic acid (5-ASA) has been on a stable dose for at least 2 weeks prior to Visit 1.

9.4. Subject Exclusion Criteria – Ulcerative Colitis

Subjects with UC who meet any of the following exclusion criteria will not be eligible for enrollment in the study:

1. Subject has a diagnosis of CD or indeterminate colitis.
2. Subject is unable to tolerate or unwilling to undergo study procedures including endoscopy and biopsy during the study.
3. Subject with signs or symptoms of bowel obstruction with small bowel imaging supporting obstruction.
4. Subject has short bowel syndrome as determined by the investigator.
5. Subject has a current functional colostomy or ileostomy.
6. Subject has had a surgical bowel resection within the past 6 months prior to screening or is planning any resection during the study period.
7. Clinical suspicion of intra-abdominal abscesses exists, in the opinion of the investigator.

8. Subject has concurrent bowel dysplasia or a history of bowel dysplasia in the 5 years prior to screening.
9. Subject has a known, active and/or positive test for C. difficile infection despite an adequate course of treatment.
10. Subject has history of or current diagnosis of any cancer excluding cancers that have been cured by surgical excision (e.g., non melanoma skin cancers, cervical cancer).
11. Subject has a history of a lymphoproliferative disorder, including lymphoma, or signs and symptoms suggestive of lymphoproliferative disease at any time.
12. Subject has history of or active TB infection or positive TB testing at screening.
13. Subject has known concurrent viral hepatitis, or acquired immune deficiency syndrome (AIDS) or known human immunodeficiency virus (HIV) infection.
14. Subject has been treated with natalizumab (Tysabri®, Biogen) within the past 5 years.
15. Subject who has not completed his/her primary vaccination series (particularly hepatitis B, varicella, measles/mumps/rubella) unless immunity is documented with blood titers.
16. Subject has received any live attenuated vaccine, such as varicella-zoster, oral polio, or rubella, within 3 months prior to the baseline visit.
17. Subject has received an investigational medicine (non-biologic) within 2 weeks of Visit 1 and/or an investigational medicine that is a biologic within 8 weeks of Visit 1.
18. Subject has received Tofacitinib within 2 weeks of Visit 1.
19. Subject has any of the following abnormal screening laboratory test results:
    - Clinically significant ECG abnormalities;
    - Aspartate transaminase (AST), alanine transaminase (ALT) or total bilirubin > ULN;
    - Hemoglobin < 10g/dL
    - Absolute neutrophil count <1500 cell/mm^3, or
    - Estimated glomerular filtration rate <60 mL/min/1.73 m2.
20. Subject has abnormal vital signs during Screening (Visit 1) or prior to enrollment at the baseline visit (Visit 2), as defined in Section 12.3.1.2.
21. Subject is pregnant or a nursing mother.
22. Subject is sexually active and not on effective contraception as defined in Section 10.2.3.
23. Subject has a history of drug abuse that would inhibit participation in the clinical trial.
24. Subject has a current or recent history (within 6 months prior to screening) of significant and severe renal, hepatic, hematological, gastrointestinal (other than CD or conditions outlined above), endocrine, pulmonary, cardiac, or neurological disease.

25. Subject has any other clinically significant mental or physical illness or infection that, in the opinion of the investigator, might confound the results of the study, pose additional risk to the subject by their participation, or prevent or impede the subject from completing the study.
26. There is any concern on the part of the investigator regarding the subject's safety, compliance, or suitability with respect to his/her participation in the study.

9.5. Screen Failure

Subjects who fail inclusion and/or exclusion criteria may be rescreened for the study with the prior approval of the Aevi Genomic Medicine, LLC medical monitor. In the event of a rescreening, the first screening visit will be entered into the eCRF as the Screening Visit (Visit 1) and the repeat assessments entered into the eCRF as an unscheduled visit.

9.6. Subject Withdrawal Criteria

All subjects will be advised that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. Every reasonable attempt should be made by the investigator to keep subjects in the study; however, subjects must be withdrawn from the study if they withdraw consent to participate. For subjects who fail to attend scheduled visits, the investigator must attempt to contact them by telephone or other means to exclude the possibility of an AE being the cause of withdrawal. Should this be the cause, the AE must be documented, reported, and followed as described in Section 12.3.1.6.

The sponsor reserves the right to request the withdrawal of a subject due to protocol violations or other reasons.

The investigator also has the right to withdraw subjects from the study at any time for lack of therapeutic effect that is intolerable or otherwise unacceptable to the subject, for intolerable or unacceptable AEs, intercurrent illness, for meeting the individual subject stopping criteria (Section 8.5.1), noncompliance with study procedures, administrative reasons, or in the investigator's opinion, to protect the subject's best interests.

If a subject is withdrawn before completing the study, the reason for withdrawal and the date of discontinuation will be recorded on the appropriate eCRF. Whenever possible and reasonable, the evaluations that were to be conducted at the completion of the open-label treatment period (ie, Visit 10) should be performed at the time of early termination.

Subjects who withdraw prior to receiving the third dose of study drug may be replaced.

All samples will be retained according to applicable rules and regulations. Blood and biopsy samples may be stored and used for further analysis related to this research. As applicable, saliva samples may also be used for purposes related to this research. Samples will be given a unique code that will include no information that will name the subject. Any remaining DNA sample will be stored for future biomarker studies.

10. TREATMENT OF SUBJECTS

10.1. Description of Investigational Product

A description of the investigational product is provided in Section 11.1

Subjects in each dose cohort will receive the investigational product as a single SQ injection in the abdomen in a zone of 4 to 10 cm from the umbilicus with the injection site rotated with each subsequent dose. The dose of MDGN-002 will be administered on Days 0, 14, 28, and 42. After Day 0, injections must occur within ± 3 days of the scheduled 14-day intervals.

Subjects in the first dose cohort will receive MDGN-002 1.0 mg/kg for the entire 8-week, open-label treatment period. Data from this cohort will be reviewed by the Data Monitoring Committee as described in Section 8.4 before subjects in the second dose cohort can be treated.

Eligible subjects in the second dose cohort will receive MDGN-002 3.0 mg/kg for the entire 8-week, open-label treatment period. Data from the second cohort will be reviewed, as described in Section 8.4, after all subjects have completed the treatment period and its associated assessments.

Any quality issue noticed with the receipt or use of an investigational product provided by the sponsor (deficiency in condition, packaging, appearance, pertaining documentation, labeling, expiration date, etc.) should be promptly communicated to the sponsor, who will investigate.

A potential defect in the quality of investigational product provided by the sponsor may be subject to initiation of a recall procedure by the sponsor. In this case, the investigator will be responsible for promptly addressing any request made by the sponsor, in order to recall the investigational product and eliminate potential hazards.

10.2. Permitted and Prohibited Therapies

All prior lifetime CD and UC therapies as well as concomitant medications used (including over-the-counter medications and herbal supplements) will be recorded in the source document and on the appropriate eCRF.

10.2.1. Permitted Therapies

Subjects can be receiving concurrent treatment with an oral corticosteroid, and/or azathioprine, 6-MP or MTX. Subjects may not have their dose of these medications increased during the study. If a dose increase of a concomitant permitted therapy is required, the subject must be discontinued from the study utilizing the Early Termination visit procedures. Concurrent treatment with an oral corticosteroid, and/or azathioprine, 6-MP, MTX or 5-ASA is defined as follows:

- Oral corticosteroid – Prednisone dose not exceeding 40 mg/day, with a stable dose for at least 2 weeks prior to baseline.
- Azathioprine or 6-MP – Azathioprine dose of at least 2 mg/kg/day or 6-MP dose of 1 to 1.5 mg/kg/day rounded to the nearest available tablet formulation, or a dose that is the highest tolerated for the subject, in the opinion of the investigator, for at least 8 weeks prior to baseline with a stable dose for at least 4 weeks prior to baseline.

- MTX dose of 25 mg/week during study, either SQ, intramuscularly, or orally, for at least 8 weeks prior to baseline with a stable dose for at least 4 weeks prior to baseline.
- A stable dose of 5-ASA for at least 2 weeks prior to Visit 1

Doses of these therapies may be decreased during the study; however, all doses must be within the combinations and dose ranges specified above. These changes must be recorded on the concomitant medication eCRF.

For subjects on corticosteroids at the time of study enrollment, weaning during the study may be done according to the rules below:

Corticosteroid dose	Maximum taper rate per week
≥20mg	10mg
10 to <20mg	5mg
<10mg	2.5mg

If a deviation from the permitted concomitant therapy combinations, dose ranges or weaning schedule is necessary, the subject must be withdrawn from study participation.

10.2.2. Prohibited Therapies

Concomitant use of biologic treatments during the study is prohibited including use of anakinra, (Kineret®, Amgen), abatacept (Orencia®, Bristol-Myers Squibb), ustekinumab (Stelara®, Jannsen), vedolizumab (Entyvio™, Takeda), or tocilizumab (Actemra®, Genentech). A wash-out period of up to 12 weeks is required prior to study enrollment (Visit 2) and after confirmation of eligibility from screening procedures performed at Visit 1 for all biologic treatments received within 12 weeks of the Screening Visit. Treatment with tofacitinib (Xeljanz®, Pfizer) within 2 weeks of Visit 1 or prior treatment with natalizumab (Tysabri®, Biogen) with 5 years of Visit 1 would exclude subjects from participation. Dosing with an investigational medicine (non-biologic) within 2 weeks of Visit 1 and/or an investigational medicine that is a biologic within 8 weeks of Visit 1 would also exclude subjects from participation.

Vaccination with live or attenuated virus 3 months prior to screening and at any time during the study is prohibited.

10.2.3. Contraceptive Methods

Sexually active study participants must agree to the use of effective contraceptive methods during the study and for the defined period after the end of study visit. Approved methods require double barrier according to the following algorithm: condom plus intra-uterine device or condom plus hormonal contraceptive. Should any subject be sterilized, the procedure for sterilization is required to have been completed more than 3 months prior to study screening visit.

A sexually active male participant must use one of the above-described double barrier contraceptive methods during the study and for 3 months after the end-of-study visit. A sexually

active female participant must use one of the above-described double barrier contraceptive methods during the study and for 1 month after the end-of-study visit.

Male subjects must also have to agree not to donate sperm for the duration of the study and for up to 3 months after the end-of-study visit.

Study participants who are abstinent at the time of study entry must agree to use the approved methods described in this section should they become sexually active during the study.

10.3. Treatment Compliance

Treatment with MDGN-002 will be administered by study center personnel under direct medical supervision, and an appropriate record will be made in the source data by the investigator or his/her delegate. The investigator or designee will record the dosing information on the appropriate eCRF page. It is the investigator's responsibility to ensure that an accurate record of the administration of the investigational product is maintained.

10.4. Randomization and Blinding

All subjects will receive MDGN-002 in an open-label manner.

10.5. Treatment after End of Study

After successful enrollment and subsequent completion of or early termination from the study, each subject will be treated according to standard clinical practice. In order to support the subject's transition from the clinical trial, after care medical expenses such as co-pays and out of pocket medical/treatment associated costs will be covered in the total amount of $5,000.00 which may be used up to a total 6 months post-study exit. Aftercare payments will be administered by a third-party vendor contracted by the Sponsor.

11. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

11.1. Investigational Product

The following table provides a description of the investigational product used in this study.

Table 2 Investigational Product

Product Name:	MDGN-002
Dosage Form:	150 mg/mL solution
Unit Dose	1.0 mg/kg or 3.0 mg/kg
Route of Administration	SQ injection in the abdomen in a zone of 4 to 10 cm from the umbilicus with the injection site rotated with each subsequent dose.
Physical Description	[redacted]
Manufacturer	[redacted]

11.2. Packaging and Labeling

All packaging and labeling operations will be performed by the sponsor or designee according to Good Manufacturing Practice and Good Clinical Practice (GCP) rules. The investigational product will be sent to the study site by the sponsor or designee. Labeling will be in the local language and dependent upon local regulations.

11.2.1. Packaging

MDGN-002 (150 mg/mL) vials containing nominally 2 mL will be packaged separately into bulk, open-labeled cartons.

11.2.2. Labeling

The vial and the carton will have affixed a label that meets the applicable regulatory requirements.

The investigator will be asked to save all unused or partially used medication vials and all empty packaging for final disposition locally or by the sponsor. Syringes used for dosing must be treated as biologic waste and disposed of properly.

11.3. Storage

All investigational product must be stored between 2° and 8°C and protected from light.

Investigators or other authorized persons (e.g., pharmacists) are responsible for storing the investigational product provided by the sponsor in a secure and safe place in accordance with local regulations, labeling specifications, institutional policies and procedures.

Control of storage conditions for the investigational product provided by the sponsor, especially control of temperature (e.g., refrigerated storage) and daily temperature monitoring, and information on in-use stability and instructions for handling the investigational product must be managed according to the rules provided by the sponsor in the Pharmacy Manual.

11.4. Preparation

Preparation of syringes will be described in the Pharmacy Manual.

11.5. Administration

MDGN-002 will be administered by SQ injection in the abdomen in a zone of 4 to 10 cm from the umbilicus with the injection site rotated with each subsequent dose.

11.6. Accountability

The investigator must maintain adequate records showing the receipt, administration, or other disposition of the investigational product including the date, lot identifier, dosage, volume administered to each subject, and identification of subjects (subject number and initials) who received the investigational product. The investigator will not supply the investigational product to any other location or person except those named as sub-investigators on the Form FDA 1572, designated study personnel, and subjects in this study. The investigator will not dispense the investigational product from any study sites other than those listed on Form FDA 1572. If any of the investigational product is not dispensed; is lost, stolen, spilled, unusable; or is received in a damaged container, this information must be documented and reported to Aevi Genomic Medicine and appropriate regulatory agencies, as required.

Upon completion of the study, unused investigational product must be left in the original packaging for final disposition locally or by the sponsor. Any partially used investigational product and all empty packaging (e.g., vials) must also be saved for final disposition locally or returned to the sponsor's designee for destruction.

11.7. Handling and Disposal

Investigational product reconciliation must be performed at the site by the investigator and the monitoring team using treatment log forms and documented on the site's investigational product inventory countersigned by the investigator and the monitoring team.

After reconciliation authorization by the sponsor, all used, partially used, and unused vials and all original packaging will be disposed of locally (as required) or by the sponsor. This process will be provided to the site by the sponsor's designee.

12. STUDY PROCEDURES AND ASSESSMENTS

Subjects will provide written informed consent before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

For the timing of assessments and procedures throughout the study, refer to the Schedule of Assessments (see Table 1). Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the schedule of events for each subject. Visits performed after the Visit 2 baseline visit should be scheduled relative to Visit 2 in order to maintain 56 days of open-label treatment and administration every 14 days (± 3 days). If a subject misses a study visit for any reason, the visit should be rescheduled as soon as possible. Each study visit window after Visit 2 is ± 3 days. Visit procedures should be performed in the order shown however adjustments may be made to the order to accommodate site-specific requirements.

12.1. Study Periods and Visits

12.1.1. Screening (Visit 1)

The subject must be screened within 14 weeks before enrollment in the study. The following procedures will be performed at screening:

1. Obtain written informed consent
2. Review inclusion/exclusion criteria
3. Conduct genotyping for DcR3 genes (CD only)
4. Collect demographic information
5. Record medical and medication history
6. Perform a complete physical examination, including measurements of weight
7. Collect vital signs, including systolic and diastolic blood pressures, pulse, respiration rate and temperature
8. Perform 12-lead ECG
9. Collect blood samples for clinical laboratory tests
10. Perform QuantiFERON-TB Gold (QFT) blood test, or PPD tuberculosis skin test. If the subject's PPD tine skin test is ≥ 5 mm, a confirmatory chest x-ray is required.
11. Collect blood sample for β-hCG test (for females of childbearing potential only)
12. Collect stool sample for C. difficile and fecal calprotectin analyses
13. Collect urine sample for urinalysis
14. Collect urine sample for drug testing as warranted
15. Administer the CDAI (CD only)
16. Administer the IBD-Q questionnaire
17. Conduct the endoscopy with biopsy

18. Assess and record any AEs and concomitant medications
19. Provide access to patient diary to record daily assessment of the following:
    a) Abdominal pain, general well-being and number of stools including loose or watery stool (e.g., 6 or 7 on Bristol stool form scale) and daily abdominal pain severity (scale of 0 to 10) for CD patients.
    b) Stool frequency and rectal bleeding for UC patients.
20. Calculate the Modified Mayo Score (excluding the PGA component) using the endoscopy score from the central reader and self-reported data on stool frequency and rectal bleeding from the period prior to the subject being screened.

NOTE: Stool samples may be obtained at any time during the visit. Subjects who fail to meet clinical laboratory entry requirements may be re-tested as part of the screening period. Extensions of the screening window to accommodate clinical laboratories re-testing timeframes (excluding endoscopy with biopsy) are permitted as agreed with medical monitor.

12.1.2. Eligibility Check/Wash-Out Period

Each subject will receive a telephone call to confirm continued subject eligibility. For subjects not requiring a wash-out period the subject may return for Visit 2 once the diary has been completed for a minimum of 7 days immediately prior to dosing. Visit 2 should be completed no sooner than Day 8 from the time diary completion was initiated. Any changes in concomitant medication use and any newly occurring AEs since the last evaluation will be recorded.

With the exception of subjects who most recently received the biologic certolizumab pegol (Cimzia), subjects requiring a wash-out will have a blood test administered 8 weeks after their last dose of biologic treatment to ensure that serum levels of any previous biologic treatments are below the level of detection. If it is confirmed that the levels of previous biologic treatment are undetectable and the subject has completed the diary for a minimum of 7 days immediately prior to dosing, the subject may return for Visit 2. Visit 2 should be completed no sooner than Day 8 from the time diary completion was initiated. If the test results indicate that the previous biologic treatment is detectable, the subject will be required to complete a full 12-week wash-out period. For subjects receiving the biologic certolizumab pegol (Cimzia) a 12-week wash-out is required. The diary should be completed up to the time of the visit. Any changes in concomitant medication use and any newly occurring AEs since the last evaluation will be recorded.

If the subject is not eligible, the subject should have any changes in concomitant medication use and any newly occurring AEs since the last evaluation recorded and should be removed from screening.

12.1.3. Open-Label Treatment Period

12.1.3.1. Baseline Visit (Visit 2, Day 0)

12.1.3.1.1. Before Dosing

Prior to administration of the first dose of investigational product on Day 0, the following procedures will be performed:

1. Review inclusion/exclusion criteria to confirm continued eligibility or screen failure status.

   NOTE: If the subject continues to be eligible for the study, the subsequent procedures should be performed. If the subject is not eligible, the subject should have any changes in concomitant medication use and any newly occurring AEs since the last evaluation recorded and should be removed from screening.
2. Perform a complete physical examination, including measurements of height and weight
3. Collect vital signs, including systolic and diastolic blood pressures, pulse, respiration rate and temperature
4. Collect blood sample for clinical laboratory tests
5. Collect blood sample for plasma MDGN-002 concentration and PK analysis
6. Collect blood sample for plasma ADA analysis
7. Collect blood sample for exploratory analyses as defined in Table 1
8. Collect urine sample for urinalysis
9. Collect urine sample for urine β-hCG test (for females of childbearing potential only)
10. Administer the CDAI (CD only)
11. Administer the IBD-Q
12. Review diary completion
13. Assess and record concomitant medications and newly occurring AEs since the last evaluation

In addition, ongoing AEs from the previous visit will be assessed and any change in their status will be recorded.

12.1.3.1.2. Dosing and 60 Minutes Post-Dosing

After completing the assessments shown in Section 12.1.3.1.1, subjects will receive MDGN-002 by SQ injection in the abdomen in a zone of 4 to 10 cm from the umbilicus with the injection site rotated with each subsequent dose. Vital sign assessments will be conducted within 60 minutes post-dosing.

Subjects will remain in the clinic for 60 minutes after the investigational product has been administered. During this time, the following details will be recorded:

1. Any AEs occurring after dosing
2. Any concomitant medications administered after dosing
3. Assess subject response and available results against individual stopping rules criteria defined in Section 8.5.1.

After completion of the post-dosing assessments, the subject may leave the clinic.

12.1.4. Visit 3 (Day 7 [± 3 days])

Subjects will return to the clinic on Day 7 (± 3 days), at which time the following procedures will be performed:

1. Collect blood samples for plasma MDGN-002 concentration and PK analyses
2. Assess and record any AEs and concomitant medications
3. Review diary completion

Assess subject response and available results against individual stopping rules criteria defined in Section 8.5.1. In addition, ongoing AEs from the previous visit will be assessed and any change in their status will be recorded.

12.1.5. Visit 4 (Day 14 [± 3 days])

Subjects will return to the clinic on Day 14 (± 3 days), at which time the following procedures will be performed prior to dosing:

1. Perform a brief physical examination, including measurement of weight
2. Collect vital signs, including systolic and diastolic blood pressures, pulse, respiration rate and temperature
3. Collect blood sample for clinical laboratory tests
4. Collect blood samples for plasma MDGN-002 concentration, PK and ADA analyses
5. Administer the CDAI (CD only)
6. Review diary completion
7. Assess and record concomitant medication use and any newly occurring AEs since the last evaluation

In addition, ongoing AEs from the previous visit will be assessed and any change in their status will be recorded.

After completing these assessments, subjects will receive MDGN-002 by SQ injection in the abdomen in a zone of 4 to 10 cm from the umbilicus with the injection site rotated with each subsequent dose. Vital sign assessments will be conducted within 60 minutes post-dosing.

Subjects will remain in the clinic for 60 minutes after the investigational product has been administered. During this time, the following details will be recorded:

1. Any AEs occurring after dosing
2. Any concomitant medications administered after dosing.

After completion of the post-dosing assessments, the subject may leave the clinic.

12.1.5.1. Visit 5 (Day 21 [± 3 days])

Subjects will return to the clinic on Day 21 (± 3 days), at which time the following procedures will be performed:

1. Collect blood sample for plasma MDGN-002 concentration and PK analysis

2. Assess and record any AEs and concomitant medications
3. Review diary completion
4. Assess subject response and available results against individual stopping rules criteria defined in Section 8.5.1.

In addition, ongoing AEs from the previous visit will be assessed and any change in their status will be recorded.

12.1.5.2. Visit 6 (Day 28 [± 3 days])

Subjects will return to the clinic on Day 28 (± 3 days), at which time the following procedures will be performed prior to dosing:

1. Perform a complete physical examination, including measurement of weight
2. Collect vital signs, including systolic and diastolic blood pressures, pulse, respiration rate and temperature
3. Perform 12-lead ECG
4. Collect blood sample for clinical laboratory tests
5. Collect blood samples for plasma MDGN-002 concentration, PK and ADA analyses
6. Collect blood sample for exploratory analyses as defined in Table 1
7. Collect stool for fecal calprotectin analysis
8. Collect urine sample for urinalysis
9. Collect urine sample for urine β-hCG test (for females of childbearing potential only)
10. Administer the CDAI (CD only)
11. Review diary completion
12. Assess and record concomitant medication use and any newly occurring AEs since the last evaluation

In addition, ongoing AEs from the previous visit will be assessed and any change in their status will be recorded.

After completing these assessments, subjects will receive MDGN-002 by SQ injection in the abdomen in a zone of 4 to 10 cm from the umbilicus with the injection site rotated with each subsequent dose. Vital sign assessments will be conducted within 60 minutes post-dosing.

Subjects will remain in the clinic for 60 minutes after the investigational product has been administered. During this time, the following details will be recorded:

1. Any AEs occurring after dosing
2. Any concomitant medications administered after dosing.

NOTE: Stool samples may be obtained at any time during the visit

3. Assess subject response and available results against individual stopping rules criteria defined in Section 8.5.1.

After completion of the post-dosing assessments, the subject may leave the clinic.

12.1.5.3. Visit 7 (Day 35 [± 3 days])

Subjects will return to the clinic on Day 35 (± 3 days), at which time the following procedures will be performed:

1. Collect blood sample for pharmacokinetic analysis
2. Assess and record any AEs and concomitant medications
3. Review diary completion
4. Assess subject response and available results against individual stopping rules criteria defined in Section 8.5.1.

In addition, ongoing AEs from the previous visit will be assessed and any change in their status will be recorded.

12.1.5.4. Visit 8 (Day 42 [± 3 days])

Subjects will return to the clinic on Day 42 (± 3 days), at which time the following procedures will be performed prior to dosing:

1. Perform a brief physical examination, including measurement weight
2. Collect vital signs, including systolic and diastolic blood pressures, pulse, respiration rate and temperature
3. Collect blood sample for clinical laboratory tests
4. Collect blood sample for plasma MDGN-002 concentration and PK analysis
5. Administer the CDAI
6. Review diary completion
7. Assess and record any AEs and concomitant medications

In addition, ongoing AEs from the previous visit will be assessed and any change in their status will be recorded.

After completing these assessments, subjects will receive MDGN-002 by SQ injection in the abdomen in a zone of 4 to 10 cm from the umbilicus with the injection site rotated with each subsequent dose. Vital sign assessments will be conducted within 60 minutes post-dosing.

Subjects will remain in the clinic for 60 minutes after the investigational product has been administered. During this time, the following details will be recorded:

1. Any AEs occurring after dosing
2. Any concomitant medications administered after dosing.
3. Assess subject response and available results against individual stopping rules criteria defined in Section 8.5.1.

After completion of the post-dosing assessments, the subject may leave the clinic.

12.1.5.5. Visit 9 (Day 49 [± 3 days])

Subjects will return to the clinic on Day 49 (± 3 days), at which time the following procedures will be performed:

1. Collect blood sample for plasma MDGN-002 concentration and PK analysis
2. Assess and record any AEs and concomitant medications
3. Review diary completion

In addition, ongoing AEs from the previous visit will be assessed and any change in their status will be recorded

12.1.5.6. Visit 10 (Day 56 [± 3 days])

Subjects will return to the clinic on Day 56 (± 3 days), at which time the following procedures will be performed:

1. Perform a complete physical examination, including measurement of weight
2. Collect vital signs, including systolic and diastolic blood pressures, pulse, respiration rate and temperature
3. Perform 12-lead ECG
4. Collect blood sample for clinical laboratory tests
5. Collect blood samples for plasma MDGN-002 concentration, PK and ADA analysis
6. Collect blood sample for exploratory analyses as defined in Table 1
7. Collect stool for fecal calprotectin analysis
8. Collect urine sample for urinalysis
9. Collect urine sample for urine β-hCG test (for females of childbearing potential only)
10. Administer the CDAI (CD only)
11. Review diary completion
12. Administer IBD-Q questionnaire
13. Conduct the endoscopy and biopsy
14. Calculate the Modified Mayo Score (excluding the PGA component) using the endoscopy score from the central reader and the diary data on stool frequency and rectal bleeding (UC only)
15. Assess and record any AEs and concomitant medications
16. Assess subject response and available results against individual stopping rules criteria defined in Section 8.5.1.

In addition, ongoing AEs from the previous visit will be assessed and any change in their status will be recorded.

NOTE: Stool samples may be obtained at any time during the visit.

12.1.6. Early Termination

If a subject is withdrawn from the study for any reason, every effort must be made to conduct all Day 56 (Visit 10) procedures and assessments (see Section 12.1.5.6).

12.1.7. Safety Follow-Up

12.1.7.1. Visit 11 (Day 84 [± 3 days])

Subjects will return to clinic 28 days (± 3 days) after Visit 10 or the early termination visit for a safety follow-up visit, as appropriate. Subject will have blood collected for plasma MDGN-002 concentration, PK and ADA analyses. Any concomitant medications and newly occurring AEs since the last visit will be recorded. In addition, ongoing AEs from the previous visit will be assessed and any change in their status will be recorded.

12.2. Study Duration

The overall study duration is expected to be approximately 26 weeks (including up to 14 weeks of screening [inclusive of wash-out of up to 12 weeks, if required], 56 days of open-label treatment, and a follow-up visit approximately 28 days after the final dose of investigational product).

The planned sequence and maximum duration of the study periods will be as follows:

1. Screening period: approximately 2 weeks
2. Wash-out period, if applicable: Up to 12 weeks from the subject's last dose of biological treatment
3. Open-label treatment period: 56 days (beginning on Day 0 with doses administered q14 days)
4. Follow-up: 28 days after the last dose of investigational product.

The maximum study duration for each subject is approximately 26 weeks.

The maximum treatment duration for each subject is approximately 56 days, with SQ injections beginning on Day 0 and continuing every 14 (± 3) days through Day 42.

Note: Extensions of the screening window to accommodate clinical laboratory re-testing timeframes (excluding endoscopy with biopsy) are permitted as agreed with medical monitor.

12.3. Assessments

12.3.1. Safety Assessments

Safety assessments will include monitoring of AEs, clinical laboratory tests, vital signs measurements, physical examinations (including measurement of weight) and 12-lead ECG parameters, as described below. Demographic information and medical and medication histories will be obtained at the screening visit.

All safety assessments are to be recorded on the appropriate eCRF.

The Investigator's Brochure is the reference document for safety information pertaining to this study and is provided under separate cover.

12.3.1.1. Demographic/Medical History

Demographic information, a complete medical history (which includes surgical history), and medication history will be collected at the screening visit by appropriate site staff as delegated by the PI and reviewed and verified by a qualified licensed physician, physician's assistant, or a nurse practitioner. The medical history will be reviewed and recorded, including:

- Date of birth
- Sex
- Race and ethnicity
- Recent use of non-CD/UC medication within 30 days of Visit 1
- CD/UC past and ongoing treatments (recall past year)
- CD/UC-related surgical procedures and hospitalizations
- History of respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, psychiatric, and other diseases; history of surgical procedures

12.3.1.2. Vital Signs

Vital signs, including systolic and diastolic blood pressure, pulse, and respiration rate, will be collected as shown in the Schedule of Assessments (see Table 1). Vital signs must be within the ranges listed below during Screening (Visit 1) and prior to enrollment at Visit 2:

- Blood Pressure: 80/50 to 140/90 mm/Hg
- Respiratory Rate: 8-20 breaths per minute
- Pulse: 50-120 beats per minute
- Temperature: 97.8°F to 99.1°F (36.5°C to 37.3°C)/average 98.6°F (37°C)

Vital signs will be taken pre- and post-dose at Visits 2, 4, 6 and 8. Pre-dose vital signs should be taken within 60 minutes before dosing. Post-dose vital signs should be taken at least 60 minutes after dosing, prior to discharge. Additional blood pressure and pulse measurements may be performed, as determined by the investigator, in order to ensure appropriate monitoring of subject safety and accurate recording of vital sign measurements. Any changes from baseline deemed clinically significant by the investigator are to be recorded as AEs.

The same method of blood pressure measurement (auscultatory or oscillometric) should be used and documented throughout the study for all subjects. In addition, the conditions of vital signs measurements should be controlled and as consistent as possible in order to minimize variability of the readings. It is advised that measurements be collected at a comfortable room temperature with little to no background noise, using the same (appropriately sized) cuff placed at the same location on the same arm. The cuff should have a bladder length that is 80% and a width that is at least 40% of arm circumference (a length-to-width ratio of 2:1).

The subject should be asked to remove all clothing that covers the location of cuff placement. The subject should not have exercised or consumed caffeine, alcohol, or nicotine within 30 minutes of collection. The subject should be comfortably seated, with the legs uncrossed, with feet flat on the floor, and the back and arm supported, such that the middle of the cuff on the upper arm is at the level of the right atrium (the mid-point of the sternum). The subject should be instructed to relax as much as possible for at least 5 minutes prior to collection. The subject should remain quiet during this time and throughout the measurement.

The bladder should be deflated (calibrated for oscillometric method or manually by auscultatory method) at a rate of 2-3 mmHg/sec (and the first and last audible sounds recorded as systolic and diastolic pressures) after at least 5 minutes of rest.

The use of automated devices for measuring pulse is acceptable, although, when done manually, pulse should be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, blood pressure and pulse should be obtained prior to the nominal time of the blood collection.

12.3.1.3. Physical Examination

A complete physical examination, including measurements of weight, will be conducted by a qualified licensed physician, physician's assistant, or a nurse practitioner at the screening visit and at Visits 2 (Day 0), 6 (Day 28) and 10 (Day 56). Brief physical examinations, including measurements of weight, will be conducted at Visits 4 (Day 14), and 8 (Day 42) (see Table 1).

The complete physical examination will include a review of the following body systems:

- General appearance
- Skin
- Head, eyes, ears, nose, and throat
- Spine/neck/thyroid
- Musculoskeletal
- Respiratory
- Cardiovascular
- Neurological
- Abdomen (including liver and kidneys)

Any abnormalities or changes in intensity from baseline noted during the review of body systems should be documented in the medical record and reported on the appropriate eCRF. If a new clinically significant abnormal finding is reported after the baseline examination, it must be captured as an AE and documented on the appropriate AE eCRF. In addition, resolution of any abnormal findings during the study will be noted in the medical record and eCRF if clinically significant.

The brief physical examination will include a review of general appearance, skin, head, eyes, ears, nose, and throat, abdomen, joints and perianal area at a minimum, with other systems reviewed as medically needed. Measurement of weight will also be collected.

Subjects will remove their shoes before measurements of weight (in kg) are taken.

12.3.1.4. Electrocardiogram

A standard 12-lead ECG will be conducted by appropriate site staff as delegated by the PI and the results will be reviewed and verified by the PI or a qualified licensed physician delegated by the PI as shown in the Schedule of Assessments (see Table 1).

The 12-lead ECG will be performed after the subject has been supine for approximately 5 minutes. All ECG recordings will be identified with the subject number, subject initials, date, and time of the recording and will be included in the subject's study file.

The subject should be asked to remove all clothing that covers the location of lead placement. The subject should not have exercised or consumed caffeine, alcohol, or nicotine within 30 minutes prior to collection.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. One complete recording, including a 10-second rhythm strip, should be taken at each time point. It should be immediately assessed as a valid recording and if not valid, it should be repeated. All ECGs collected are to be entered in the eCRF.

All ECGs will be performed using the equipment supplied by the site. ECG recordings will be collected and a copy provided to the study sponsor.

The following parameters will be recorded on the appropriate eCRF: heart rate, PR, respiration rate (RR), QRS, and QT interval; corrected QT intervals using both the Bazett (QTcB) and Fridericia (QTcF) formulas will also be recorded. The investigator's assessment of the ECG tracing as normal or abnormal must be documented, and if abnormal, his/her determination of whether the abnormality is clinically significant will be documented on the tracing and recorded in the eCRF.

All ECG values that, in the investigator's opinion, show clinically relevant or pathological changes during or after termination of the investigational product are to be discussed with the medical monitor and reported as AEs and followed, as described in Section 12.3.1.6.2.

12.3.1.5. Clinical Laboratory Assessments

12.3.1.5.1. Clinical Laboratory Tests

Samples for the following clinical laboratory tests will be collected at the time points specified in the Schedule of Assessments (see Table 1).

Hematology	Hemoglobin, hematocrit, red blood cell count, red blood cell indices, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count (or estimate), and white blood cell count including differential
Serum chemistry	Albumin, total bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, blood urea nitrogen, creatinine, creatine kinase, glucose, sodium, potassium, chloride, bicarbonate, lactate dehydrogenase, uric acid, eGFR, and C-reactive protein
Other	ADAs; LIGHT, cytokines (e.g. IL-1 beta, IL-6, IL-8, and TNF-alpha, and other exploratory cytokines), flow cytometry analysis of peripheral blood leukocytes and RNA sequencing
Fecal chemistry	Fecal calprotectin, C. difficile
Urinalysis	pH, specific gravity, hemoglobin, white blood cells, red blood cells, glucose, casts, protein, ketones, epithelial cells, crystals, mucous threads, bacteria, yeast, color, and appearance
Serum & Urine β-hCG test	For women of childbearing potential only
Urine drug screen (screening visit only as warranted)	Amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, cannabinoids, propoxyphene and methadone.
Testing for previous biologics (for subjects requiring wash-out)	Commercial test to detect the serum concentrations of four of the common biologic drugs and biosimilars (infliximab [Remicade], infliximad-adba [Renflexis], infliximab-dyyb [Inflectra], adalimumab [Humira], adalimumab-adbm [Cyltezo], adalimumab-atto [Amjevita] vedolizumab [Entyvio] and ustekinumab [Stelara]). **Note: Testing is not required for certolizumab pego1 (Cimzia) as there is no commercially available test to determine serum concentration.**

Laboratory specimens will be collected and analyzed at the laboratories specified in the study Laboratory Manual(s) or guidelines.

12.3.1.5.2. Sampled Blood Volume

The sampled blood volume to be taken from each subject is shown in Table 3. (See Section 12.3.2.1 for details regarding pharmacokinetic blood sampling.)

Table 3 Blood Samples Taken from Each Subject

Assessment		Sample Volume (mL)	Number of Samples	Total Volume (mL)
Safety	Hematology	2.0	6	12.0
	Clinical chemistry	3.5	6	21.0
MDGN-002 concentration and PK analysis (Pre-dose Day 0)		2.0	2	4.0
MDGN-002 concentration and PK analysis		2.0	9	18.0
Anti-drug Antibodies (ADA)		2.0	5	10.0
Flow Cytometry		3.0	3	9.0
RNA sequencing		2.5	3	7.5
Cytokines		3.5	3	10.5
LIGHT		2.0	3	6.0
Testing for previous biologics		6.0	1	6.0
Total mL		--	--	104.0

12.3.1.5.3. Tuberculosis (TB) testing

All subjects will be screened for tuberculosis using QuantiFERON-TB Gold (QFT) blood test, or tuberculin skin reaction test (PPD skin test) at screening. If the subject's PPD tine skin test is ≥ 5 mm, a chest x-ray is required to be performed to rule out active or latent pulmonary TB infection. Subjects will be excluded from the study if they have active or latent TB as demonstrated by any of the following:

- A positive QFT test result or a positive PPD skin test reaction ≥10 mm.
- Chest x-ray in which active or latent pulmonary TB cannot be ruled out.

12.3.1.5.4. Genotyping for Decoy Receptor 3

For patients with CD, 2 mL of saliva for genotyping will be collected in a designated collection vehicle according to the manufacturer's instructions.

Deoxyribonucleic acid (DNA) is isolated from the saliva samples from each study subject and then evaluated for genetic alteration in TNFRSF6B encoding for the protein DcR3 or alterations in at least one DcR3 network gene. All genotyping will be performed in a CLIA certified laboratory specified in the laboratory manual(s) and guidance(s). Any remaining DNA samples will be stored for future biomarker studies.

12.3.1.5.5. LIGHT, Cytokines, RNA Sequencing and Flow Cytometry Exploratory Analyses

Blood samples will be collected for exploratory analyses. Exploratory analyses may include but are not limited to of LIGHT biomarker, cytokines (e.g. IL-1 beta, IL-6, IL-8,TNF-alpha, and other exploratory cytokines), ribonucleic acid (RNA) sequencing; flow cytometry of peripheral blood leukocytes at visits specified in Table 1. Exploratory biomarker analyses will be performed at the laboratories specified in the laboratory manual(s) and guidance(s).

12.3.1.5.6. Testing for Previous Biologics

An adequate wash-out period is required to avoid the potential for confounding the effects related to dosing with MDGN-002 following the prior use of other biologics. In order to allow for a shorter wash-out period, commercial tests available to identify the serum concentrations of biologics will be utilized. With the exception of Cimzia, a blood test will be administered to subjects undergoing wash-out 8 weeks after their last dose of biologic treatment to ensure that serum levels of any previous biologic treatments are below the level of detection. If the serum concentration of biologic treatment is undetectable (i.e., below the level of quantification) according to the respective, CLIA-validated commercial test, then the subject is deemed to have completed the wash-out period and will be able to proceed to Visit 2. If biologic treatment is detected, then the subject will complete a full 12-week wash-out period prior to proceeding to Visit 2. For subjects receiving the biologic certolizumab pegol (Cimzia) a 12-week wash-out is required.

12.3.1.5.7. Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles, blood or blood products and/or laboratory specimens. Consequently, appropriate blood, body fluid and specimen precautions should be employed by all study personnel involved in the collection and handling of specimens in both the clinic and laboratory settings. Refer to current recommendations of the appropriate authorities.

In addition to appropriate handling of subject samples, specific regulations exist regarding the shipment of biologic samples. Procedures and regulations for the packaging and shipping of infectious samples are outlined in the study Laboratory Manual(s). The investigator is responsible for ensuring that all study samples that are to be transported to another location are appropriately packed and shipped according to the applicable regulations.

12.3.1.5.8. Evaluation of Laboratory Values

The normal ranges of values for the clinical safety laboratory assessments will be provided by the responsible laboratory and submitted to Aevi Genomic Medicine, LLC prior to the beginning of the study. They will be regarded as the reference ranges upon which clinical decisions will be made.

If a laboratory value is out of the reference range, it is not necessarily clinically relevant, with the exception of those defined as exclusionary per Section 9.2. The investigator must evaluate the out-of-range values and record his/her assessment of their clinical relevance in the appropriate eCRF.

All laboratory values which, in the investigator's opinion, show clinically relevant or pathological changes during or after termination of the treatment are to be discussed with the medical monitor and reported as AEs and followed, as described in Section 12.3.1.6.2.

12.3.1.6. Adverse Events

12.3.1.6.1. Adverse Event Collection

The investigator is responsible for the detection and documentation of events meeting the criteria and definitions of an AE (Section 12.3.1.6.2) or SAE (Section 12.3.1.6.6) described below. At each visit, the subject will be allowed time to spontaneously report any issues since the last visit or evaluation. At each visit, the investigator will then monitor, ask about, and/or evaluate AEs using non-leading questions, such as:

- "How are you feeling?"
- "Have you experienced any issues since your last visit?"
- "Have you taken any new medications since your last visit?"

Any clinically relevant observations made during each visit will also be considered AEs.

12.3.1.6.2. Definition of Adverse Events, Period of Observation and Recording of Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease, temporally associated with the product, whether or not related to the product.

All AEs are collected from the time of the informed consent is signed until the final safety follow-up visit (described in Section 8.2.3). This includes events occurring during the screening phase of the study, regardless of whether investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE eCRF and in source documents. In addition to AEs, unexpected benefits outside the investigational product indication should also be captured in the source documents and AE eCRF.

All AEs must be followed to closure (ie, the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization is achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of an event(s) can be documented.

12.3.1.6.3. Severity of Adverse Events

The severity of AEs must be recorded during the course of the event, including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events after initiation of the investigational product must be recorded as new AEs. For example, if the subject experiences mild, intermittent headaches prior to dosing with investigational product and the headache intensity increases to moderate after the

first dose of investigational product, a new AE of moderate intermittent headaches is to be recorded in the source documents and eCRF.

The medical assessment of clinical severity of an AE will be determined using the definitions outlined in Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (Published May 28, 2009 with Version 4.0.3 on June 14, 2010 by the US Department of Health and Human Services, National Institutes of Health, National Cancer Institute):

Grade 1	Mild; asymptomatic or mild symptoms; or clinical or diagnostic observations only; or intervention not indicated
Grade 2	Moderate; or minimal, local or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living (ADL)
Grade 3	Severe or medically significant but not immediately life-threatening; or hospitalization or prolongation of hospitalization indicated; or disabling; or limiting self-care ADL.
Grade 4	Life-threatening consequences; or urgent intervention indicated.
Grade 5	Death related to AE

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria as described in Section 12.3.1.6.6.2.

Please refer to the above-referenced CTCAE document for full description of CTCAE terms and instrumental and self-care ADLs.

12.3.1.6.4. Relationship Categorization

A physician/investigator must make the assessment of relationship to the investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related." Otherwise, the AE should be categorized according to the guidelines below. The causality assessment must be documented in the source document and the eCRF.

Not related	Exposure to Investigational Product (IP) has not occurred; OR The administration of IP and the occurrence of the AE are not reasonably related in time; OR The AE is considered likely to be related to an etiology other than the use of the IP; that is, there are no facts/evidence or arguments to suggest a causal relationship to the IP.
Possibly related	The administration of the IP and the occurrence of the AE are reasonably related in time AND The AE could not be explained equally well by factors or causes other than exposure to IP.
Probably related	The administration of IP and the occurrence of the AE are reasonably related in time AND The AE is more likely explained by exposure to IP than by other factors or causes.

IP=investigational product

12.3.1.6.5. Outcome at the Time of Last Observation

The outcome of an AE at the time of last observation will be classified as:

- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Not recovered/not resolved
- Fatal (see Section 12.3.1.6.6.5)
- Unknown

12.3.1.6.6. Serious Adverse Events

12.3.1.6.6.1. Reporting of Serious Adverse Events

Initial and follow-up SAE reports must be completed by the investigator and sent to the sponsor and the CRO within 24 hours of the first awareness of a SAE.

The investigator must complete, sign and date the appropriate SAE form and verify the accuracy of the information against corresponding source documents. No source documents are to be sent

with the SAE form. This SAE information (form) is to be sent to the CRO pharmacovigilance department, with a copy to the Aevi Genomic Medicine medical monitor by e-mail or fax at one of the methods noted below. For questions on SAE reporting, please call the drug safety helpline noted below.

[redacted]

12.3.1.6.6.2. Definition of Serious Adverse Event

An SAE is any untoward medical occurrence, whether considered to be related to the investigational product or not, that at any dose:

- Results in death
- Is life-threatening

  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization

  NOTE: Inpatient hospitalization is defined as 24 hours in a hospital or an overnight stay. An elective hospital admission to treat a condition present before exposure to the test drug, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE. Further, an overnight stay in the hospital that is only due to transportation, organization, or accommodation problems and without medical background does not need to be considered an SAE.

- Results in persistent or significant disability/incapacity
- Is a congenital anomaly

  NOTE: A congenital anomaly in an infant born to a mother who was exposed to the IP during pregnancy is an SAE. However, a newly diagnosed pregnancy in a subject that has received an IP is not considered an SAE unless it is suspected that the IP(s) interacted with a contraceptive method and led to the pregnancy.

- Is an important medical event

  NOTE: Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

12.3.1.6.6.3. Serious Adverse Event Collection Time Frames

All SAEs, regardless of the relationship to study, are collected from the time the subject signs the informed consent until the subject's last visit (office or telephone contact). The investigator or designee must report all SAEs promptly to the CRO and Aevi Genomic Medicine medical monitor within 24 hours of first becoming aware of the event.

Any SAE(s), regardless of relationship to IP, discovered by the investigator at any interval after the study has completed must be reported to the CRO and Aevi Genomic Medicine medical monitor within 24 hours of the first awareness of the event.

12.3.1.6.6.4. Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria (see Section 12.3.1.6.6.2). The resolution date is the date the event no longer meets serious criteria, the date symptoms resolve or the event is considered chronic. In the case of hospitalization, the hospital admission and discharge dates are considered respectively, the onset and resolution dates of the SAE.

Any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE or following the resolution date of the SAE must be recorded as AEs.

12.3.1.6.6.5. Fatal Outcome

An outcome of "fatal" should only be selected when the AE results in death. If more than 1 AE is possibly related to the subject's death, "fatal" outcome should be indicated for each such AE.

Any AE that results in the subject's death must have "fatal" checked as an outcome with the date of death recorded as the resolution date. Adverse events resulting in death must be reported within 24 hours as SAEs, if not already reported as such.

For other AEs ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered "not resolved" with no resolution date recorded.

12.3.1.6.7. Special Considerations

12.3.1.6.7.1. Adverse Events of Special Interest and Adverse Drug Reactions

There are no events from research to date which qualify as an adverse event of special interest. Adverse drug reactions observed in the MDGN-002 pre-clinical study as well as reactions with other biologic agents include:

[redacted]

Please refer to the Investigator's Brochure for further details on possible risks and adverse drug reactions.

12.3.1.6.7.2. Pregnancy

All females of childbearing potential who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation. Study participants should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted prior to administration of investigational product on every female of childbearing potential. A female who is found to be pregnant at the screening visit will be excluded from the study and considered to be a screening failure.

The investigator must report the pregnancy of any female (study participant or female partner of male study participant) who becomes pregnant during investigational product treatment or within 7 days of discontinuing the investigational product. The pregnancy should be reported within 24 hours of awareness to the CRO via the same fax and email address used for SAE reporting (see Section 12.3.1.6.6.1). The investigator should contact the designated individual(s) who receive SAE notification and record information related to the pregnancy on the designated form provided by the sponsor or its designee.

Early termination visit assessments are required as soon as possible after learning of the pregnancy. The investigator is also responsible for following the pregnancy until delivery or termination. These findings must be reported on the Exposure in Utero form/other designated form and forwarded to the designated individual(s). The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly.

12.3.1.6.7.3. Abuse, Misuse, Overdose and Medication Error

Abuse, misuse, overdose or medication error involving the investigational product, as defined below, must be reported to the sponsor using the SAE reporting procedures outlined in Section 12.3.1.6.6.1 whether or not they result in an AE or SAE. The 24-hour reporting period from time of first awareness does not apply to an abuse, misuse, overdose, or medication error event(s) unless the abuse, misuse, overdose, or medication error event results in a SAE.

Abuse	Persistent or sporadic intentional intake of IP when used for a non-medical purpose (for example, to get high, for potential psychoactive effects) in a manner that would be detrimental to the individual and/or society
Misuse	Intentional use of IP other than as directed or indicated at any dose. This includes where IP is not used as directed at the dose prescribed in the protocol.
Overdose	Intentional or unintentional intake of a dose of IP exceeding the dose prescribed to the subject as part of the study.
Medication error	Error made in prescribing, dispensing, administration and/or use of IP. A medication error is reportable to the sponsor or its designee if it involves: • Administration and/or use of an unassigned treatment (for example, incorrect IP kit used by subject) • Administration and/or use of expired IP

IP=investigational product
NOTE: An abuse, misuse, overdose or medication error event can meet more than 1 category.

Missing doses are not considered medication error events and do not need to be reported.

12.3.1.6.8. Reporting to Regulatory Agency, Institutional Review Board and Site

The sponsor or its designee is responsible for notifying the relevant regulatory authorities of related, unexpected SAEs.

In addition, the sponsor or its designee is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the development program.

The investigator is responsible for notifying the local IRB or the relevant local regulatory authority of all SAEs that occur at his/her site, as required.

12.3.2. MDGN-002 Concentration, Pharmacokinetic and Anti-Drug Antibody Assessments

The name and address of the bioanalytical laboratory for this study is defined in the Laboratory Manual(s) and guidance(s).

Pharmacokinetics will be calculated from the plasma concentrations of MDGN-002.

12.3.2.1. Blood Sample Collection and Analysis

Blood samples will be collected within 60 minutes prior to the administration of MDGN-002 on Days 0, 14, 28 and 42 (Visits 2, 4, 6, and 8 respectively) and at any time on Days 7, 21, 35, 49, 56, and 84 (Visits 3, 5, 7, 9, 10, and 11) and processed to plasma (see laboratory manual). Time of PK samples will be recorded in the electronic CRF. A total of 1.0mL plasma (0.5 mL per PK and ADA sample) will be collected from each subject to measure plasma concentrations of

MDGN-002 or ADA samples. Pharmacokinetic and ADA samples will be processed according to the methods and directions set forward in the Laboratory Manual(s) and guidance(s). Pharmacokinetic and ADA plasma sample analysis will be performed by laboratory defined in the Laboratory Manual(s) and guidance(s), according to their SOPs using a validated enzyme-linked immunosorbent assay (ELISA). Assay and analysis details will be described in the method validation and bioanalytical information.

12.3.3. Assessment of Efficacy

12.3.3.1. Crohn's Disease Activity Index

The CDAI will be completed by a qualified licensed physician, physician's assistant, or a nurse practitioner at the times shown in the Schedule of Assessments (see Table 1). Site personnel conducting the CDAI should use the following link to derive individual and total scores: https://www.thecalculator.co/health/Crohn's-Disease-Activity-Index-(CDAI)-Calculator-1035.html, with standard weights calculated as follows:

- Standard weight for men = (height in m)^2 x 22.1
- Standard weight for women = (height in m)^2 x 20.8

Information on abdominal pain and frequency of loose and watery stools should be taken from subject diary information (see Section 12.3.3.4). The same individual should complete the CDAI for a given subject throughout the study, whenever possible.

The CDAI was developed by the National Cooperative Crohn's Disease Study group and published in 1976 by Best et al (1976) to determine variables that best predicted disease activity. A total of 8 items were identified (abdominal pain, number of liquid stools, general well-being, extraintestinal complication, use of antidiarrheal drugs, abdominal mass, hematocrit, and body weight). Each item is scored on individual parameter criteria. Total CDAI scores can range from 0 to approximately 600 with higher scores indicating more active disease. The CDAI has been the most frequently used efficacy scale for interventional trials in CD (Sostegni et al, 2003).

12.3.3.2. Modified Mayo Score

The Modified Mayo Score (excluding the PGA component) includes stool frequency, rectal bleeding, and the appearance of mucosa upon endoscopy. Stool frequency will be based on a scale of 0 to 3 (0 = normal, 1 = 1 to 2 stools/day > normal, 2 = 3 to 4 stools/day > normal, 3 = > 4 stools/day > normal). Rectal bleeding will be based on a scale of 0 to 3 (0 = none, 1 = streaks of blood, 2 = obvious blood, 3 = blood alone passed). Appearance of mucosa upon endoscopy will be based on a scale of 0 to 3 (0 = normal, 1 = mild friability, 2 = moderate friability, 3 = exudation, spontaneous bleeding). The score consists of the sum of all 3 criteria and can range from 0 to 9, with higher scores indicating more severe disease. This score will be calculated at Visit 1 and Visit 10 using the endoscopy score from the central reader, self-reported data on stool frequency and rectal bleeding from the period prior to the subject being screened for Visit 1 and data from the patient diary for Visit 10.

12.3.3.3. Endoscopy with Biopsy and Histology

All subjects who enroll in the study will undergo an endoscopy with biopsy at screening and again at Day 56 (Visit 10) or at early termination. Screening endoscopies may be performed either as a stand-alone endoscopy for purposes of this protocol or as a clinically-required endoscopy, provided consenting procedures for this study were completed prior to endoscopy.

Endoscopy evaluation for patients with CD will use the SES-CD. The SES-CD is a simple, easy-to-use endoscopic scoring system developed specifically for CD. It assesses 4 variables: size of ulcers, percentage of ulcerated surface, percentage of affected surface and the presence of narrowing across 4 categories per variable on a scale of 0 to 3 (Daperno et al 2004).

Endoscopic evaluation for patients with UC will use the Mayo Endoscopy Score. The Mayo Endoscopy Score is a simple, easy-to-use scoring system in order to evaluate ulcerative colitis stage, based only on endoscopic exploration.

Biopsies taken at screening will be assessed for histological confirmation of disease. Each subject will have screening and Visit 10/ET biopsy samples retained for evaluation of exploratory parameters (which may include but is not limited to DcR3, LIGHT, HVEM and LTβR) which may occur after trial completion. Further information on endoscopic transmission to the central reader and assessment can be found in the endoscopy manual. Information on biopsy collection requirements for exploratory parameters are found in the study sample guidelines.

12.3.3.4. Patient-reported Assessment of Well-being, Abdominal Pain and Stool Frequency (Crohn's Disease Patients)

All CD subjects who enroll in the study will be required to report their daily assessment of well-being, abdominal pain and stool frequency including loose and/or watery stools via a diary (electronic or hard copy). Abdominal pain will be assessed on a scale of 0 to 3 with higher values indicating greater pain severity. The stool frequency including number of loose and/or watery stools per day, equivalent to a score of a 6 or 7 on the Bristol Stool Scale, will be recorded. Loose stools are described as fluffy pieces with ragged edges, a mushy stool. Watery stools are described as watery, no solid pieces (O'Donnell et al, 1990).

12.3.3.5. Patient-reported Assessment of Stool Frequency and Rectal Bleeding (Ulcerative Colitis Patients)

All UC subjects who enroll in the study will be required to report their daily assessment of stool frequency and rectal bleeding via a diary. Stool frequency is to be recorded as an increase from "normal" where normal is the subject's bowel movement pattern when healthy, ideally prior to UC diagnosis or for a 24 hour period during a period of disease remission.

12.3.4. Quality of Life Assessment – Inflammatory Bowel Disease Questionnaire

The IBD-Q is a 32 item questionnaire validated to measure quality of life in CD and UC. The IBD-Q assesses the dimensions of bowel function, emotional status, systemic symptoms and social function (Guyatt G, 1989). The IBD-Q will be completed by all subjects at screening (Visit 1), before dosing (Visit 2), and at the end of the open-label treatment period or early termination (Visit 10/ET) (see Table 1).

13. STATISTICS

Detailed descriptions of data summaries and listings will be provided in the Statistical Analysis Plan, which will be finalized prior to database lock. The sections below provide a summary of the planned statistical methods.

13.1. Statistical Methods

Pharmacokinetic, efficacy and quality of life data will be summarized with traditional descriptive statistics. Continuous variables will be summarized with N, mean, standard deviation, and range. Categorical variables will be summarized by frequencies and percentages.

No formal inferential analyses are planned.

13.1.1. Analysis Populations

The Safety Population will include all subjects who are enrolled in the study and receive any amount of investigational product. The Pharmacokinetic Population will include all subjects who received their assigned dose of MDGN-002 and for whom MDGN-002 plasma concentration data are available. The Efficacy Population will include all subjects who have a baseline and at least 1 post-baseline efficacy score.

13.1.2. Statistical Analyses

Analyses of efficacy will focus on the Efficacy Population. Results of endpoints (e.g., CDAI, SES-CD, abdominal pain and loose/watery stool frequency and IBD-Q (CD only; Modified Mayo Score, stool frequency, rectal bleading, endoscopic appearance, and IBD-Q (UC only) will be summarized by visit for each cohort, both as raw scores and the change from baseline value. For CD, the CDAI individual and total scores will be derived programmatically using recorded data from patient diary, responses to CDAI questions, laboratory tests, and physical exam results.

For UC, the Modified Mayo Score individual and total scores will be derived programmatically using recorded data from patient diary and endoscopy results. Quantitative endoscopy and biopsy results will also be summarized for both the Baseline and End of study visits.

Analyses of safety data will be focused on the Safety Population (as defined in Section 13.1.1).

Safety variables include treatment-emergent AEs (TEAEs), clinical laboratory results, vital signs measurements, ECG results, and physical examination findings.

Adverse events will be coded using Medical Dictionary for Regulatory Affairs (MedDRA). TEAEs are defined as any AE having first onset or worsening in severity after the first administration of IP. TEAEs will be classified by system organ class (SOC) and preferred term and summarized by the number of subjects reporting each event for each cohort and overall.

For clinical laboratory tests, descriptive summaries of actual (absolute) values and change from baseline values will be presented by cohort for each study visit.

Vital signs (systolic and diastolic blood pressure, pulse, and respiratory rate) and ECG results will be summarized by visit and cohort using appropriate descriptive statistics.

Data in this open-label study will be monitored continually and may be analyzed at any time.

13.2. Sample Size Determination

This is the first use of MDGN-002 in the intended population of patients with CD or UC resistant to anti-TNFα monoclonal antibodies. The sample size of the study was based on feasibility.

14. STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of a qualified investigator and appropriate study site, review of protocol procedures with the investigator and associated personnel prior to the study, periodic monitoring visits, and meticulous data management.

14.1. Sponsor and Investigator Responsibilities

14.1.1. Sponsor Responsibilities

The sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 16). The sponsor reserves the right to withdraw a subject from the study (Section 9.6), to terminate participation of a study site at any time (Section 14.5), and/or to discontinue the study (Section14.4).

Aevi Genomic Medicine agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study according to the study protocol.

14.1.2. Investigator Responsibilities, Protocol Adherence and Investigator Agreement

By signing the Investigator's Agreement (Appendix 18.1), the investigator indicates that she/he has carefully read the protocol, fully understands the requirements, and agrees to adhere to the study procedures as detailed in this protocol. The investigator is responsible for enrolling only those subjects who have met the protocol eligibility criteria.

The investigator also agrees to conduct this study in accordance with all laws, regulations, and guidelines of the pertinent regulatory authorities, including and in accordance with the International Conference on Harmonisation (ICH) Guidance for Industry E6 GCP and in agreement with the Declaration of Helsinki. While delegation of certain aspects of the study to subinvestigators and study coordinators is appropriate, the investigator will remain personally accountable for closely overseeing the study and for ensuring compliance with the protocol and all applicable regulations and guidelines. The investigator is responsible for maintaining a list of all persons that have been delegated study-related responsibilities (e.g., subinvestigators and study coordinators) and their specific study-related duties.

The investigator should ensure that all persons who have been delegated study-related responsibilities are adequately qualified and informed about the protocol, investigational products, and their specific duties within the context of the study. The investigator is responsible for providing Aevi Genomic Medicine with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

According to local laws and regulations, the investigator, sponsor or sponsor designee will communicate with the IRB to ensure accurate and timely information is provided throughout the study.

14.2. Study Documents

All documentation and material provided by Aevi Genomic Medicine for this study are to be retained in a secure location and treated as confidential material.

14.2.1. Case Report Forms

By signing the Investigator's Agreement (Appendix 18.1), the investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all subjects who sign an Informed Consent Form.

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific eCRFs used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual subject visits should be completed as soon as possible after the visit. All requested information must be entered in the eCRF according to the completion guidelines provided by the sponsor or its designee. All data will have separate source documentation; no data will be recorded directly into the eCRF.

The eCRFs will be signed by the investigator or a subinvestigator to whom this authority has been delegated. These signatures serve to attest that the information contained in the eCRF is accurate and true.

14.2.2. Recording and Retention of Source Data and Study Documents

All study information must be recorded in the subject's medical records.

Data recorded in the eCRF must be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory reports and notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

14.2.3. Video Recordings

The endoscopic examinations will be recorded to allow for central reading and scoring of CD/UC in study participants. These recordings will be stored at a vendor designated by the Sponsor on a secure computer server and will not be labeled with any information that allows direct identification of the subject.

14.3. Data Quality Control

Aevi Genomic Medicine and its designees will perform quality control checks on this clinical study.

14.3.1. Access to Study and Source Documents

Aevi Genomic Medicine and/or designee will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local authorities, or the IRB, having access to the source data (for

example, subject's medical records, appointment books, original laboratory reports, radiographic exams and reports, etc.)

The assigned clinical research associate(s) (CRA[s]) will visit the investigator and study site at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRA(s) and other authorized Aevi Genomic Medicine personnel access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. While on site, the CRA(s) will review:

- Regulatory documents, directly comparing entries in the eCRF with the source documents
- Informed consent procedures
- Adverse event procedures
- Storage and accountability of investigational product and study materials

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRFs will be described for the study personnel as part of training. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (Appendix 18.1), the investigator agrees to meet with the CRA(s) during study site visits; to ensure that study staff is available to the CRA(s) as needed; to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the investigator agrees to allow Aevi Genomic Medicine or designee auditors or inspectors from the IRB or regulatory agencies to review records and to assist the inspectors in their duties, if requested.

14.3.2. Data Management

Aevi Genomic Medicine or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and designee's standard operating procedures. A comprehensive data management plan will be developed including a data management overview, database contents, annotated eCRF, self-evident correction conventions, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data.

14.3.3. Quality Assurance Audit / Inspection

[redacted]

14.4. Study Termination

The study may be terminated at Aevi Genomic Medicine' discretion at any time and for any reason.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB and provide them with a detailed written explanation. The investigator will either dispose of all unused or partially used medication vials locally (sites in Colombia and Israel) or return to the sponsor (US sites).

14.5. Study Site Closure

At the end of the study, the study sites will be closed. Aevi Genomic Medicine may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines
- Inadequate subject enrollment

14.5.1. Record Retention

It is the investigator's responsibility for maintaining adequate and accurate study and medical records. The investigator shall retain and preserve all data generated in the course of the study, specifically including, but not limited to, those defined by ICH GCP as essential until:

- At least 2 years after the last marketing authorization for the investigational product has been approved or the sponsor has discontinued its research with the investigational product, or
- At least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product

These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

At the end of such period, the investigator must notify the sponsor in writing of her/his intent to move or destroy any study material. The sponsor shall have 30 days to respond to the

investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

14.5.2. Sample Retention

All samples will be retained according to applicable Standard Operating Procedures and regulations. Blood and biopsy samples may be stored and used for further analysis related to this research.

Saliva samples may be used for purposes related to this research. Samples will be given a unique code that will include no information that will identify the subject. They will be stored securely at locations defined in the Laboratory Manual(s) and guidance(s). Clinical information will be held at a separate location.

14.6. Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of Aevi Genomic Medicine, LLC. The protocol amendment must be signed by the investigator and approved by the IRB before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(ies) having jurisdiction over the conduct of the study.

14.7. Use of Information and Publication

All information concerning MDGN-002, Aevi Genomic Medicine' operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information supplied by Aevi Genomic Medicine or designee to the investigator and not previously published, is considered confidential and remains the sole property of Aevi Genomic Medicine. Case report forms also remain the property of Aevi Genomic Medicine. The investigator agrees to use this information for purposes of study execution through finalization.

The information developed in this study will be used by Aevi Genomic Medicine in connection with the continued development of MDGN-002 and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this study is the property of Aevi Genomic Medicine. Publication or other public presentation of MDGN-002 data resulting from this study requires prior review and written approval of Aevi Genomic Medicine. Abstracts, manuscripts, and presentation materials should be provided to Aevi Genomic Medicine for review at least 30 days prior to the relevant submission deadline.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition or publication by the investigator until Aevi Genomic Medicine has reviewed and commented on such a presentation or manuscript for publication.

15. PUBLIC POSTING OF STUDY INFORMATION

Aevi Genomic Medicine is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigator information (e.g., site name, investigator name, site location, site contact information).

16. ETHICAL AND LEGAL CONSIDERATIONS

16.1. Declaration of Helsinki and Good Clinical Practice

This study will be conducted in compliance with the ICH Guidance for Industry E6 GCP (including archiving of essential study documents), the Declaration of Helsinki, and the applicable regulations of the country in which the study is conducted.

16.2. Subject Information and Informed Consent

It is the responsibility of the investigator to ensure that written informed consent is obtained from the subject before any activity or procedure is undertaken that is not part of routine care, including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject is requested to sign and date the subject informed consent form or a certified translation, if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risks, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (such as a complete set of subject information sheets and fully executed signature pages) must be given to the subject. This document may require translation into local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The PI provides the sponsor with a copy of the consent form which was reviewed by the IRB and which received favorable opinion/approval. A copy of the IRB's written favorable opinion/approval of these documents must be provided to the sponsor, prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national requirements) prior to the study start that another party (such as the sponsor or coordinating PI) is responsible for this action. If the IRB requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

16.3. Institutional Review Board or Ethics Committee

A properly constituted, valid IRB according to local laws and regulations must review and approve the protocol, the investigator's informed consent document, and related subject information and any other study materials requiring review (such as recruitment information) before the start of the study.

Until written approval by the IRB has been received by the investigator, no subject may undergo any study procedure solely for determining eligibility for this study. Investigational product will not be released until the sponsor or its designee has received written IRB approval.

Prior to implementing changes in the study, the sponsor and the IRB must approve and provide documentation of favorable opinion/approval of any revisions to informed consent documents and amendments to the protocol unless there is a subject safety issue.

Depending on location (outside the European Union [EU] or inside EU) the IRB will be apprised of the progress of the study and of any changes made to the protocol at least yearly. This may be done by the investigator (outside EU and in some cases, inside EU) or the sponsor (in some cases inside EU). These updates include information on any serious or significant AEs.

Upon study completion, the investigator will provide the IRB with a final report/summary as required.

16.4. Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after where the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from sponsor or subsidiaries such as grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consulting or honoraria; any proprietary interest in the investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 (b) (1998).

16.5. Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the sponsor/contract research organization.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations and guidelines.

After subjects have consented to participate in a study, the sponsor and/or its representatives reviews their medical records and data collected as part of the study. These records and data may be reviewed by others including the monitor/auditor from the sponsor or its representatives, national or local authorities, or the IRB which gave the approval for the study, third parties with whom the sponsor may develop, register or market the investigational product. The sponsor and its representatives will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, the initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of data.

The results of the studies, containing the subjects' unique identifying numbers, relevant medical records and possibly initials and dates of birth, will be recorded. They may be transferred to and used in other countries which may not afford the same level of protection that applies within the countries where the study is conducted. The purpose of such transfer would include supporting regulatory submissions, to conduct new data analyses, to publish or present the study results or to answer questions asked by regulatory or health authorities.

17. LIST OF REFERENCES

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18. APPENDICES

18.1. Investigator's Agreement

PROTOCOL NUMBER:	MDGN-002-CD-101
PROTOCOL TITLE:	Phase Ib Escalating Dose, Open-Label, Signal-Finding Study to Evaluate the Safety, Tolerability, and Short-Term Efficacy of the Anti-Light Monoclonal Antibody MDGN-002 in Adults with Moderate to Severe Active Crohn's Disease (CD) or Ulcerative Colitis (UC) who have Failed Prior Treatment with an Anti-TNFα
FINAL PROTOCOL:	Version 11.0, 23 July 2021

I have read this protocol and agree to conduct this clinical trial as outlined herein. I will ensure that all subinvestigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with Aevi Genomic Medicine, LLC. and their designees during the study. I will adhere to all FDA, ICH, and other applicable regulations and guidelines regarding clinical trials on an investigational product during and after study completion.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

18.2. Definitions of Primary and Secondary Non-responder

1. **Primary non-responder – Crohn's Disease**

A primary non-responder is defined as a subject for whom treatment with infliximab, adalimumab, or certolizumab pegol produced an inadequate initial response. Inadequate initial response symptom details must occur ≥ 2 weeks after the last dose of induction therapy. The algorithm for defining inadequate initial response is shown below. Subjects categorized as primary non-responders must meet both parts of the algorithm. Documentation required includes dates and doses of failed induction therapy and lack of response details around disease activity recorded by a treating clinician.

Algorithm for inadequate initial response to current or prior therapy with infliximab, adalimumab, or certolizumab pegol:

Subject has received induction doses of either:

- infliximab (2 or 3 doses of ≥ 5 mg/kg), OR
- adalimumab (dose of 160 mg followed by a dose of ≥ 80 mg or, dose of 80 mg followed by a dose of ≥ 40 mg), OR
- certolizumab pegol (2 or 3 doses of ≥ 400 mg).

AND

Subject did not initially respond to these induction doses as documented by the presence of at least 1 of the following signs or symptoms related to Crohn's disease activity:

- lack of improvement or worsening in stool frequency
- lack of improvement or worsening in daily abdominal pain
- occurrence, lack of improvement, or worsening of fever associated with Crohn's disease
- recurring drainage from a previously non-draining fistula or development of a new draining fistula
- lack of improvement or worsening in rectal bleeding
- initiation or increase in antidiarrheal medication

2. Secondary non-responder – Crohn's Disease

A secondary non-responder is defined as a subject for whom treatment with infliximab, adalimumab, or certolizumab pegol produced an initial response followed by a loss of response. Loss of response details must occur ≥ 2 weeks after last dose of maintenance therapy. The algorithm for defining loss of response is shown below. Subjects categorized as secondary non-responders must meet both parts of the algorithm. Documentation required includes dates and

doses of induction and maintenance, initial response and subsequent loss of response including details around disease activity recorded by a treating clinician.

Algorithm for loss of response to prior therapy with infliximab, adalimumab, or certolizumab pegol:

Subject responded to induction therapy at doses described above and received at least 2 maintenance doses of:

- infliximab (≥ 5 mg/kg), OR
- adalimumab (dose ≥ 40 mg or, if failed as a pediatric dose of ≥ 20 mg), OR
- certolizumab pegol (≥ 400 mg)

AND

Subject did not respond to these maintenance doses as documented by the presence of at least 1 of the following signs or symptoms related to Crohn's disease activity.

- worsening in stool frequency
- worsening in daily abdominal pain
- occurrence, or worsening of fever associated with Crohn's disease
- recurring drainage from a previously non-draining fistula or development of a new draining fistula
- worsening in rectal bleeding
- initiation or increase in antidiarrheal medication

3. **Primary non-responder – Ulcerative Colitis**

A primary non-responder is defined as a subject for whom treatment with infliximab, adalimumab, certolizumab pegol or golimumab produced an inadequate initial response. Inadequate initial response symptom details must occur ≥ 2 weeks after the last dose of induction therapy. The algorithm for defining inadequate initial response is shown below. Subjects categorized as primary non-responders must meet both parts of the algorithm. Documentation required includes dates and doses of failed induction therapy and lack of response details around disease activity recorded by a treating clinician.

Algorithm for inadequate initial response to current or prior therapy with infliximab, adalimumab, certolizumab pegol or golimumab in patients with UC:

Subject has received induction doses of either:

- infliximab (2 or 3 doses of ≥ 5 mg/kg), OR
- adalimumab (dose of 160 mg followed by a dose of ≥ 80 mg or, dose of 80 mg followed by a dose of ≥ 40 mg), OR
- certolizumab pegol (2 or 3 doses of ≥ 400 mg), OR
- golimumab (dose of 100 mg every 4 weeks).

AND

Subject did not initially respond to these induction doses as documented by the presence of at least 1 of the following signs or symptoms related to UC activity:

- lack of improvement of stool frequency
- lack of improvement of rectal bleeding
- initiation or increase in antidiarrheal medication

4. **Secondary non-responder – Ulcerative Colitis**

A secondary non-responder is defined as a subject for whom treatment with infliximab, adalimumab, certolizumab pegol, or golimumab produced an initial response followed by a loss of response. Loss of response details must occur ≥ 2 weeks after last dose of maintenance therapy. The algorithm for defining loss of response is shown below. Subjects categorized as secondary non-responders must meet both parts of the algorithm. Documentation required includes dates and doses of induction and maintenance, initial response and subsequent loss of response including details around disease activity recorded by a treating clinician.

Algorithm for loss of response to prior therapy with infliximab, adalimumab, certolizumab pegol, or golimumab:

Subject responded to induction therapy at doses described above and received at least 2 maintenance doses of:

- infliximab (dose of 5 mg/kg), OR
- adalimumab (dose of 40 mg or, if failed as a pediatric dose of 20 mg), OR
- certolizumab pegol (dose of 400 mg) OR
- golimumab (dose of 100 mg every 4 weeks)