NCT #: NCT01671956

CLINICAL STUDY PROTOCOL

A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multi-Center Study Designed to Evaluate the Safety, Efficacy, Pharmacokinetic and Pharmacodynamic Profile of Bertilimumab in Patients with Active Moderate to Severe Ulcerative Colitis

Study Product:	Bertilimumab
Indication:	Active Moderate to Severe Ulcerative Colitis
Protocol Number	Immune/BRT/UC-01
Phase:	2a
Principal Investigator:	[redacted] Israel
Name and Address of Sponsor:	Immune Pharmaceuticals Inc. 550 Sylvan Avenue Suite 101 Englewood Cliffs, New Jersey 07632 USA Tel: 201-464-2677 Fax: 201-608-5103
GCP Statement:	This study will be performed in compliance with GCP, including the archiving of essential documents.
Version Number and Date:	Version 8.0 May 23, 2018

PROTOCOL SIGNATURE PAGE

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multi-Center Study Designed to Evaluate the Safety, Efficacy, Pharmacokinetic and Pharmacodynamic Profile of Bertilimumab in Patients with Active Moderate to Severe Ulcerative Colitis
Protocol Number:	Immune/BRT/UC-01
Study Phase:	2a
Sponsor:	Immune Pharmaceuticals, Inc.

Sponsor Representative:

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the trial and that the protocol is in compliance with International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines.

Name, Title	Signature	Date

Principal Investigator

By signing below, I, the Investigator, approve the protocol and agree to conduct the clinical trial according to all stipulations of the protocol as specified in both the clinical and administrative sections, CRF and any protocol-related documents. I agree to comply with the ICH-GCP, World Medical Association Declaration of Helsinki (and relevant updates) and applicable local regulations. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Immune Pharmaceuticals Inc. I understand that the study may be terminated or enrollment suspended at any time by the Sponsor, or by me, at my center, if it becomes necessary in my opinion, to protect the best interests of the study subjects.

Name	Investigator Signature	Date

Center's Name	City, Country

PROTOCOL VERSION HISTORY

Version	Main Changes
1	Original **Submitted to Shaare Tzedek only**
2.0	• Study changed from 24 subject, dose escalation design exploring three bertilimumab dose levels vs placebo, to 42 subject, randomized, placebo-controlled study with 2:1 randomization ratio exploring a single bertilimumab dose level (7 mg/kg).
2.1	**Submitted to Shaare Tzedek only** • Protocol number changed to Immune/BRT/UC-01 from C2a/BRT/UC-01 to reflect Sponsor name • Sponsor name (Immune Pharmaceuticals Inc/Ltd.) and address updated to reflect offices in USA and Israel • Sponsor representative changed to [redacted] • Criteria for statistical evaluations changed throughout from a one-sided alpha level of 0.10 to a two-sided alpha level of 0.05. • Consequent increase in sample size to 105 evaluable subjects randomized 2:1 to active vs placebo, with 80% power to detect improvement of 30% in clinical response for active treatment over placebo. • Addition of 10-12 clinical sites in Europe and 2-4 in the US with flexibility to recruit additional sites in the event of slow recruitment • Clarification of study objectives • Clarification of allowed/prohibited pre-treatment and concomitant medications in exclusion criteria and sections 6.9.1 and 6.9.2 • Addition of diverticulitis/diverticulosis and systemic fungal infection to exclusion criterion 16 • Deletion of AUC from list of derived PK parameters • Incorporation of flexibility in visit dates • Addition of screening test for fecal calprotectin and Clostridium difficile toxin • Randomization of eligible subjects to treatment groups moved from Visit 2 to screening period for logistical reasons • Addition of information regarding randomization list, treatment allocation and emergency access to randomization codes to section 4.3 • Clarification of definition of screen failure • Reduction of sampling time points for eosinophil shape change assay during treatment period • Screen for active/latent TB to be performed using Interferon Gamma Release Assay • Amendment to classification terminology of infusion site reactions • Clarification of procedure for collection of colonic biopsies during endoscopy at screening and on Day 42 • Introduction of central endoscopy reading • Addition of details for analysis of eotaxin-1 and eosinophil count in biopsy tissue • Addition of pharmacy instructions for preparation of bertilimumab/matching placebo to section 6.6 • Addition of section 6.8 describing blinding and randomization • Sponsor contact for notification of SAEs changed to [redacted] • Section 8.2.2 deleted to allow for the possibility of an interim analysis • Section 10 updated due to incorporation of electronic data capture system • Appendix A, Schedule of Activities, updated to reflect changes in protocol

	• Addition of Appendix D, Changes to the Protocol in Version 2.1 • Definitions for additional acronyms added to the glossary • Typographical, punctuation and grammatical errors corrected throughout • Reference to "subjects" changed to "patients" throughout including study title • The order of some words, sentences and lists have been modified for consistency
3.0	• Sponsor addresses updated to reflect new offices in USA and Israel • Sponsor representative changed to [redacted] • Deletion of Appendix D and replacement with Protocol Version History • Return to sample size to up to 42 subjects, randomized 2:1 to active treatment vs placebo • Amendment of statistical sections throughout to exploratory study with descriptive statistics and no pre-determined hypothesis for study success • Return to number of clinical sites specified in version 2.0 • Increase of bertilimumab dose level to 10 mg/kg • Stratification of enrolled subjects for prior anti-TNF treatment • Addition of UCEIS as efficacy measure • Minor reclassification of efficacy and pharmacodynamic outcome measures • Amendment to pharmacy instructions • Appendix A, Schedule of Activities, updated to reflect changes in protocol • Addition of Appendix C, Ulcerative Colitis Endoscopic Index of Severity • Deletion of Appendix C, Declaration of Helsinki • Minor wording change to the protocol title and study objectives. • Definitions of additional acronyms added to the glossary • Typographical, punctuation and grammatical errors have been corrected throughout • The order of some words, sentences and lists have been modified for consistency
4.0	• Change in title of Sponsor Representative • Addition of flexibility to include European clinical sites in the event of slow recruitment (synopsis, sections 3.0, 9.2 and 11.1) • Visit 7 moved from Day 60 to Day 56 (8 weeks) • Timepoint for post-treatment endoscopy and measurement of primary and secondary efficacy endpoints moved from Visit 6 (Day 42) to Visit 7 (Day 56) • Removal of reference to 5 mg/kg bertilimumab dose from section 1.3
5.0	• Deletion of inclusion criterion 6 and addition of exclusion criterion 6 to exclude young, childless males or those planning to have more children in the future. • Amended exclusion criterion 9 to remove discrepancy with exclusion criterion 20 (Hb level). • Administrative changes to sections 4.3 and 6.8 to remove erroneous reference to three treatment arms. • Administrative changes throughout to clarify stratification according to previous anti-TNF treatment. • Clarification in synopsis (Study Design section) and section 5.1 regarding collection of serology sample – previously only referred to in Schedule of Assessments. • Updated Appendix C to latest version of UCEIS.
6.0	• Change of the lead PI • Change in Sponsor Representative • Amended exclusion criterion 9 (Hb level)

	• Removal of drug preparation instructions from section 6 and insertion of reference to pharmacy manual.
7.0	• Modification of criteria regarding male reproduction to allow for entry of males as long as they use effective contraception for the duration of the study and for four months following completion of the study. • Addition of exclusion criteria to exclude subjects treated with integrin blockers (e.g., vedolizumab) within 60 days of the screening visit. • Updated Immune Pharmaceuticals Representative contact details for SAE reporting.
7.1	• Correction to Declaration of Helsinki version. Version only distributed in Russia.
7.2	• Screening period extended from up to 14 days to up to 28 days

8.0	• Cover page updated to include corrected Sponsor Address and contact information
	• Page 2- Protocol Signature Page- updated with new Sponsor representative information
	• SAE Reporting to Sponsor Representative contact information updated
	  • Addition of a prophylactic pre-medication regimen to be administered prior to study drug (active or placebo) administration on Day 0, 14 and 28, to minimize the risk of infusion reactions. The pretreatment regimen for infusion reaction prophylaxis is as follows:
	  o Dexamethasone 10 mg PO 24-18 hours prior to administration of study drug.
	  o Acetaminophen 1000 mg PO 1 hour prior to administration of study drug.
	  o Loratadine 10 mg PO or cetirizine 10 mg PO one hour prior to the administration of study drug.
	  In the event that dexamethasone was not administered previously, then 10 mg dexamethasone IV may be administered one to three hours prior to study drug administration.
	• Addition of specific instructions for management of study drug infusion in the event of an infusion reaction.
	• Addition of hypersensitivity to any of the components of the pretreatment regimen as an exclusion criterion.
	• Removal of injection site reaction assessments (and grading) after each dosing (and the time frames for these assessments) and replacement with the more relevant assessment of general infusion reaction and a grading schedule for infusion reactions.
	• Clarification that the study drug and placebo formulations include the addition of polysorbate, a non-ionic surfactant added to prevent protein aggregation. This surfactant has always been part of the bertilimumab and placebo formulations delivered to the subject; its inclusion, however, is now clearly noted in the protocol
	• Inclusion of more liberal time guidelines for various study procedure assessments (ex: blood sampling, EKG, vital signs, etc) to more closely reflect the clinical reality of executing multiple study tasks within a compressed time-frame
	• The threshold for the eotaxin-1 level (inclusion criterion #3) in colonic biopsy tissue is lowered to 50 pg/mg protein to more closely reflect the data in the observational study (I*mportance of Intestinal Eotaxin-1, Adar T. et al, Dig*

	Disease Sci, July 2016)[22] upon which this criterion is based, and allow otherwise eligible subjects to enroll. The data for eotaxin-1 can be stratified by screening levels to assess the treatment effect (the relevant article has been added to the list of references). • Deletion of the eosinophil shape change assay and replacement with the eosinophil cationic protein (ECP) assay. • Addition of Cortiment (budesonide) as allowed concomitant study medication at screening and throughout the study owing to its limited systemic absorption • Clarification and correction of several study procedures to be more accurately described. This includes the mechanism for SAE reporting; statistical methodology to be employed; randomization code unblinding; direct data entry of source documents; assessment of study UCEIS and Mayo scores as compared to screening (not baseline) values; provision of study drug on an "as-needed basis" as subjects are enrolled and not to be provided to the sites as stock inventory; clarification of requirement for male contraception throughout the study and for 4 months following the last treatment; and removal of erroneously cited central assay laboratories. • Technical and editorial changes: replaced "patients" with the more study relevant term "subjects" throughout the document, as appropriate; added Appendix D for grading of infusion reactions; updated Corticosteroid Comparison Table; updated List of Abbreviations, as appropriate; and removal of LTD from Sponsor name.

PROTOCOL SYNOPSIS

Study Title	A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multi-Center Study Designed to Evaluate the Safety, Efficacy, Pharmacokinetic and Pharmacodynamic Profile of Bertilimumab in Patients with Active Moderate to Severe Ulcerative Colitis
Protocol No.	Immune/BRT/UC-01
Clinical Sites	Up to 10-12 sites in Israel. Additional sites in Europe may be added in the event of slow recruitment.
Study Phase	2a
Indication	Active moderate to severe ulcerative colitis (UC)
Study Objectives	**Primary Objectives:** • To evaluate, in patients with active moderate to severe UC, the safety and clinical efficacy of bertilimumab administered as 3 intravenous (IV) infusions over 4 weeks. **Secondary Objectives:** • To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of bertilimumab in patients with active moderate to severe UC.
Study Design	This is a randomized, double blind, placebo-controlled, parallel group multi-center study in adult patients with active moderate to severe UC[a]. Eligible subjects will be randomly assigned in a 2:1 ratio to one of two treatment groups, bertilimumab 10 mg/kg or matching placebo, respectively. The study will consist of three periods: a screening period of up to four weeks, a 4-week double-blind treatment period (three IV infusions at 2-week intervals), and a safety and efficacy follow-up period of approximately 9 weeks. **Screening Period – Visit 1 (Days -28 to -1)** Following signing of informed consent, subjects will be screened for study eligibility. The following assessments will be performed: demographic data, medical history, prior medications, physical examination, height and weight, vital signs, ECG, screening for active/latent tuberculosis (TB), screening for *Clostridium difficile* toxin in stool, flexible sigmoidoscopy with biopsies, Ulcerative Colitis Endoscopic Index of Severity (UCEIS), Mayo score[b], eotaxin-1 levels and eosinophil count in tissue, calprotectin in fecal sample and laboratory evaluations (hematology, biochemistry, serology and serum pregnancy test [for females of childbearing potential]). The screening visit may be conducted over multiple days. Subjects who meet all the inclusion criteria and none of the exclusion criteria will be randomized to treatment groups.

[a] A Mayo Score of 6 to 12 (inclusive); Endoscopic evidence of active UC (i.e., Mayo Endoscopic Finding Sub-score of ≥2) as assessed by flexible sigmoidoscopy unless colonoscopy is clinically indicated; Mayo Rectal Bleeding Sub-score of ≥1; Physician's Global Assessment (PGA) of at least moderate disease (Mayo Sub-score ≥2).

[b] Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, et al. (2005 Dec) Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 8;353(23):2462-76.

	Treatment Period[c] – Visit 2 (Day 0), Visit 3 (Day 14), Visit 4 (Day 28) At Visit 2, inclusion and exclusion criteria will be reviewed. The following assessments will be performed at each treatment visit pre-dose: physical examination, vital signs, ECG, partial Mayo score, eosinophil count, serum eotaxin-1, high-sensitivity C-reactive protein (hs-CRP), eosinophil cationic protein (ECP), pre-dose blood samples for PK (bertilimumab concentration), calprotectin in fecal samples, urine pregnancy test (for females of childbearing potential) and safety laboratory evaluations (hematology, biochemistry, antibodies to bertilimumab). A regimen for infusion reaction prophylaxis, described below (see section "Prophylaxis for Prevention of Infusion Reaction"), will be administered. At each treatment visit, following completion of the pre-dose assessments, and administration of the pre-treatment regimen according to the timeframes noted, bertilimumab/matching placebo will be administered by IV infusion over 30 minutes. Vital signs will be recorded at 15 minutes (during infusion), 30 (+15) minutes (immediately post infusion), 2 hr (±20 minutes) and 4 hr (±20 minutes) following initiation of study drug infusion. ECG will be performed at 30 (+15) minutes (immediately post infusion). Blood samples for bertilimumab concentration (PK analysis) will be collected 30 (+15) minutes and 4 hours (±20 minutes) following initiation of study drug infusion. I Adverse events (AE) and concomitant medications will be recorded. **Follow-Up Period[d] – Visit 5 (Day 35), Visit 6 (Day 42), Visit 7 (Day 56) and Visit 8 (Day 90)** The following assessments will be performed at the follow-up visits: physical examination, vital signs, ECG, AE and concomitant medication recording, partial Mayo score (Visits 5, 6 and 8), safety laboratory evaluations (hematology, biochemistry, antibodies to bertilimumab), blood samplescollection for bertilimumab concentration (PK analysis), ECP, eosinophil count, serum eotaxin-1 and hs-CRP. Calprotectin will be evaluated in fecal samples. Visit 7 (Day 56) will also include flexible sigmoidoscopy with biopsies, and evaluation of UCEIS, Mayo score, eotaxin-1 and eosinophil count in tissue samples.
Study Duration	Study duration for each subject will be approximately 118 days ±12 days (~16-19 weeks) as follows: Screening period: Up to 28 days Treatment period: 28 days (±3 days) Follow-up period: 62 days (±9 days)
Planned Sample Size	Up to 42 subjects are planned to be recruited to this study, randomized to the two arms using a 2:1 active drug to placebo ratio and stratified by previous anti-TNF treatment. Investigators are encouraged to recruit subjects who have not received previous anti-TNF treatment.
Inclusion Criteria	1. Males or females, 18 to 70 years of age inclusive. 2. Diagnosed with active moderate to severe UC per standard diagnostic criteria for a minimum of 3 months The subject must present with the following at the screening visit: • Mayo score of 6-12 (inclusive).

[c] Visits 3 and 4 during the Treatment Period have a ±2 day window.

[d] Visits during the Follow-Up Period have a ±3 day window.

	• Endoscopic evidence of active mucosal disease, as assessed by flexible sigmoidoscopy, with an Endoscopic Finding Sub-score of ≥2 (assessed centrally). • Rectal Bleeding Sub-score of ≥1. • Physician's Global Assessment (PGA) Sub-score of ≥2. 3. Levels of eotaxin-1 in biopsied colon tissue of ≥50 pg/mg protein. 4. Adequate cardiac, renal and hepatic function as determined by the Investigator and demonstrated by screening laboratory evaluations and physical examination results; these findings must all be within normal limits or judged not clinically significant by the Investigator. 5. Females of childbearing potential must agree to use effective contraception consistently throughout the study (such as hormonal contraception or two forms of barrier contraception) and have a negative serum pregnancy test at screening and a negative urine pregnancy test before administration of each study treatment. 6. Males of childbearing potential must agree to use effective contraception consistently throughout the study and for a period of four months following the last treatment 7. Willing and able to adhere to the study visit schedule and other protocol requirements. 8. Willing and able to provide voluntary written informed consent.
Exclusion criteria	1. History of colonic or rectal surgery other than hemorrhoidal surgery or appendectomy. 2. Currently receiving total parenteral nutrition (TPN). 3. Positive *Clostridium difficile* toxin stool assay. 4. Tested positive for active/latent mycobacterium tuberculosis (TB) infection. 5. Pregnant or breast-feeding, or plan to become pregnant during the study. 6. Known hypersensitivity to bertilimumab or any of the drug excipients, or to any components of the pretreatment regimen. 7. History of infection requiring administration of any IV antibiotic, antiviral or antifungal medication within 30 days of Screening or any oral anti-infective agent within 14 days of Screening. 8. Acute or fulminant UC requiring immediate surgery or severe UC evidenced by the following signs of toxicity: toxic megacolon, abscess, heart rate >100 beats/min at rest, temperature >38.2°C, hemoglobin <8.0 g/dL. 9. Ulcerative proctitis, defined as disease limited to less than 15 cm from the anal verge. 10. Received a vaccine or other immunostimulator within 4 weeks prior to screening. 11. Use of >4.8 g mesalazine or equivalent within 2 weeks prior to the screening visit. Mesalazine ≤4.8 g is allowed if the dose during the 2 weeks prior to the screening visit was stable. 12. Use of systemic corticosteroids exceeding the equivalent of 20 mg/day of prednisone within four weeks prior to the screening visit (see Section 6.9.1).

	13. Change in dose of immunosuppressive drugs (e.g., corticosteroids, 6-mercaptopurine [6-MP], azathioprine) within four weeks prior to the screening visit. 14. Use of TNF-blockers (e.g., infliximab or adalimumab) within 60 days of the screening visit. 15. Use of integrin blockers (e.g., vedolizumab) within 60 days of the screening visit. 16. Use of chronic non-steroidal anti-inflammatory (NSAID) therapy. Occasional use of NSAIDs or acetaminophen for headache, arthritis, myalgias, menstrual cramps, etc., or daily use of low dose (81-162 mg) aspirin for cardiovascular prophylaxis is allowed. 17. Subjects diagnosed with: • Crohn's disease. • Diverticulitis or diverticulosis. • Indeterminate colitis (inability to distinguish between UC and Crohn's disease [as assessed by the Investigator]). • Microscopic colitis (collagenous or lymphocytic colitis). • Ischemic or infectious colitis. • Clostridium difficile colitis within 90 days of the screening visit. • Parasitic disease within 90 days of the screening visit. • Systemic fungal infection within 90 days of the screening visit. 18. Current or history of positive serology of hepatitis B or C, or human immunodeficiency virus (HIV) infection. 19. Congenital or acquired immunodeficiency (e.g., common variable immunodeficiency, organ transplantation). 20. Clinically significant abnormal laboratory test results, unless regarded by the Investigator as related to UC, including but not limited to: • Hemoglobin level <10.0 g/dL. • White blood cell count < 3 x 10^3/µL. • Lymphocyte count < 0.5 x 10^3/µL. • Platelet count <100 x 10^3/µL or >1200 x 10^3/µL. • Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × the upper limit of normal (ULN). • Alkaline phosphatase >3 × ULN. • Serum creatinine >2 × ULN. 21. Active abuse of alcohol or drugs. 22. Known malignancy or history of malignancy that could reduce life expectancy. 23. Any condition, which in the opinion of the Investigator, would place the subject at an unacceptable risk if participating in the study protocol. 24. Participation in a clinical trial of an investigational (unapproved) product within 1 month of the screening visit.

Investigational Product, Route and Dosage Form	Bertilimumab is a recombinant human IgG_4 monoclonal antibody that neutralizes human eotaxin-1 (eotaxin). The drug product consists of bertilimumab formulated in phosphate buffered saline (PBS) at a concentration of 10 mg/mL, presented as a sterile, clear, colorless solution in 10 mL clear glass vials. Polysorbate 20, a non-ionic surfactant to prevent protein aggregation, is added to the study drug vial during manufacture or to the saline infusion bag prior to subject dosing. Bertilimumab 10 mg/kg will be administered by IV infusion over 30 minutes.
Reference Therapy	A matching phosphate buffered saline (PBS) placebo containing polysorbate 20 will be administered by IV infusion over 30 minutes.
Prophylaxis for Prevention of Infusion Reactions	Subjects will be administered a pre-treatment regimen consisting of dexamethasone 10 mg PO 18-24 hours prior to administration of study drug (i.e., bertilimumab or placebo). One hour prior to administration of study drug, subjects will receive acetaminophen 1000 mg PO and either loratadine 10 mg PO or cetirizine 10 mg PO. In the event that dexamethasone was not administered previously, then 10 mg dexamethasone IV may be administered one to three hours prior to study drug administration.

Outcome Measures	**EFFICACY ENDPOINTS**
	Primary Endpoint
	• Change in Mayo Score from screening to Day 56 (Visit 7), where clinical response at Day 56[e] is defined as:
	  • A decrease from the pre-treatment screening Mayo score of at least 3 points and at least 30%
	  AND
	  • Either a decrease from the pre-treatment screening sub-score for rectal bleeding of at least 1 point, or Rectal Bleeding Sub-score of 0 or 1.
	Secondary Endpoints
	• Change in UCEIS score from screening to Day 56.
	• Clinical remission at Day 56, defined as a total Mayo score of 2 points or lower, with no individual sub-score exceeding 1 point.
	• Mucosal healing at Day 56, defined as an absolute sub-score for endoscopy of 0 or 1.
	• Change in partial Mayo score from Day 0 to all scheduled measurement timepoints (efficacy follow up).
	PHARMACOKINETICS (PK) ENDPOINTS
	• PK analysis for bertilimumab concentration: blood samples will be collected on dosing days (pre-dose and at 30 minutes (+ 15 minutes) and 4 hours (± 20 minutes) following initiation of study drug infusion) and at the follow-up visits. The following PK parameters will be calculated, to the degree possible given the number of timepoints: C_{max}, T_{max}, C_{avg}, C_{min} and $t_{1/2}$. Additional standard and exploratory PK parameters will be calculated if deemed necessary.
	PHARMACODYNAMIC (PD) ENDPOINTS

[e] This and all other follow-up visits have a window of ±3 days.

	• Fecal calprotectin change from Day 0 (baseline) to all scheduled measurement timepoints. • Change in eosinophil count, ECP, serum eotaxin-1 and hs-CRP from Day 0 to all scheduled measurement timepoints. • Change in eotaxin-1 concentration and eosinophil count in biopsy tissue from Screening to Day 56. **SAFETY ENDPOINTS** Safety will be evaluated on the basis of the following parameters: • Adverse events (AE) • Infusion reactions • Physical examination • Vital signs (blood pressure, heart rate, temperature and respiratory rate) • ECG • Concomitant medications • Laboratory evaluation (hematology, biochemistry, anti-bertilimumab antibodies).
Statistical Methods	**Analysis Sets** Analysis in this trial include safety, modified intent-to-treat (mITT) and per-protocol (PP). **General Analysis Methods and Data Display** All measured variables and derived parameters will be listed individually. Outcomes will be summarized by treatment group, depending on their nature, as follows: For dichotomous variables: Categorization into success/failure-like categories; then incidence of failure and relative risk of failure in the active group compared to placebo with 95% confidence interval. For numeric continuous endpoints: Descriptive statistics and summary tables will include sample size, arithmetic mean, standard deviation, median, minimum and maximum, and 95% Confidence Interval (CI) for mean at the relevant time points by treatment and placebo corrected for the active treatment group. For ordered categories endpoints: incidences in the different categories and, after dichotomization into success/failure-like categories, incidence of failure and relative risk of failure in the active group towards placebo with 95% confidence intervals. This is an exploratory trial whose main analyses will be descriptive in nature. Where statistical testing will be applied, an alpha of 0.1 will be considered significant. At the same time, this being an exploratory trial, there will be no correction for overall Type I Error. The data will be analyzed using the SAS® 9.1 (or higher) software package (SAS Institute, Cary, North Carolina). **Safety Endpoint Analysis** Safety endpoint analysis will be descriptive in nature and done on the safety anlysis set. **Effiacy Endpoints Analysis** Analysis of all efficacy endpoints will be performed on the mITT set. The PP set will be used as supplementary analyses to test the robustness of the results.

TABLE OF CONTENTS

GLOSSARY

Abbreviation/Term	Definition
5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
AE	Adverse event
ALT	Alanine aminotransferase
ASI	Application Setup Instructions
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification)
C_{avg}	Average bertilimumab serum concentration
CDM	Clinical Data Management
CDMoP	Clinical Data Monitoring Plan
CFR	Code of Federal Regulations
CI	Confidence interval
C_{max}	Maximum serum concentration
C_{min}	Minimum serum concentration
CRF	Case report form (also eCRF for electronic CRF)
CRO	Contract research organization
CV%	Coefficient of variance
DEHP	Di (2-ethyl hexyl) phthalate also known as Di-octyl phthalate (DOP)
DM	Data Management
EDC	Electronic Data Capture
ECP	Eosinophil cationic protein
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
Hr	Hour
hs-CRP	High sensitivity C-reactive protein
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
LOCB	Last observation carried backward
LOCF	Last observation carried forward
MedDRA®	Medical Dictionary for Regulatory Activities
mg	Milligram
MI	Multiple imputation
mITT	Modified intent to treat
mL	Milliliter

Abbreviation/Term	Definition
mM	Millimolar
MOH	Ministry of Health
NSAID	Non-steroidal anti-inflammatory
PBS	Phosphate buffered saline
PD	Pharmacodynamic
PGA	Physician's Global Assessment
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per protocol
PPD	Purified protein derivative
PVC	Polyvinyl chloride
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOP	Standard operating procedures
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
$T_{1/2}$	Half-live of bertilimumab in serum
TEAE	Treatment emergent adverse event
T_{max}	Time to reach maximum bertilimumab serum concentration
TNF	Tumor necrosis factor
TPN	Total parenteral nutrition
UC	Ulcerative colitis
UCEIS	Ulcerative Colitis Endoscopic Index of Severity
ULN	Upper limit of normal
WHO	World Health Organization
WMA	World Medical Association

1. INTRODUCTION

1.1 ULCERATIVE COLITIS

Ulcerative colitis (UC) is a chronic and relapsing inflammatory disease characterized by diffuse mucosal inflammation limited to the colon and rectum without evidence of any specific causative pathogens [1]. The disease course is characterized by exacerbations (including symptoms of diarrhea, abdominal pain, and rectal bleeding) and remissions [2, 3]. The worldwide incidence rates of UC range between 1.25 to 20.3 new cases per 100,000/year, with approximately 10–12 new cases per 100,000/year in North America and Europe [4-7].

The goal of the medical treatment in UC is to rapidly induce a steroid-free remission while at the same time preventing complications of the disease itself and its treatment. The choice of treatment depends on severity, localization and the course of the disease. More extensive or severe disease is treated with oral and local 5-ASA compounds and corticosteroids to induce remission. Patients who do not respond to this treatment require hospitalization, intravenous (IV) steroids or, when refractory, calcineurin inhibitors (cyclosporine, tacrolimus), tumor necrosis factor-α antibodies (infliximab, adalimumab) or immunomodulators (6-mercaptopurine [6-MP], azathioprine) [3, 8-10].

1.1.1 The Role of Eotaxin and Eosinophils in Inflammatory Bowel Disease

Eotaxin-1 is an eosinophil-selective chemokine that is constitutively expressed in the intestine and various other tissues [11]. It is produced by a variety of cell types including eosinophils, epithelial cells, fibroblasts, endothelial cells, T-lymphocytes, monocytes and macrophages following induction by pro-inflammatory mediators [12]. Eotaxin is known to play a significant role in the tissue accumulation of eosinophils that accompanies allergic inflammation. While eosinophils are an important component of innate immunity, the accumulation of eosinophils in tissues can be detrimental. Eosinophil degranulation products have significant cytotoxic effects on tissues, and cytokines known to be released by eosinophils enhance inflammatory signaling.

An association between eosinophils and the initiation of mucosal injury and clinical relapse in UC [13, 14] and Crohn's disease [15] has been documented, and serum eotaxin levels are increased in patients with these diseases [16, 17]. These studies provide strong rationale for the use of therapeutic agents targeting eosinophils and molecules that regulate eosinophil function such as eotaxin-1 in the treatment of UC.

1.2 INVESTIGATIONAL THERAPY

Bertilimumab is a human monoclonal immunoglobulin G (IgG) 4 antibody that neutralizes human eotaxin-1 and inhibits its function. The product is manufactured in a mammalian cell line engineered using recombinant DNA technology to produce the antibody.

1.2.1 Nonclinical Studies

A single-dose toxicity study with bertilimumab was conducted in Rhesus monkeys (6 per dose group). Monkeys were administered a single IV infusion of bertilimumab at a dose of 10 or 100 mg/kg and observed for 28 and 7 days, respectively. No effects on morbidity or mortality were observed. Body weights and food consumption were not impacted by bertilimumab treatment and all clinical chemistry and hematological parameters examined were unaffected. In a repeat-dose toxicity study, Rhesus monkeys (6 per dose group) were administered 10, 30 or 100 mg/kg bertilimumab twice weekly by IV infusion for 28 days. There were no deaths or significant morbidity following treatment with bertilimumab. No effects on clinical chemistry, ophthalmoscopic or hematological parameters or body weight

were observed. At sacrifice (end of study period), there were no treatment-related changes in organ weight or macroscopic/microscopic observations. For detailed information on pre-clinical studies, please refer to the Investigator's Brochure.

1.2.2 Clinical Studies

Three clinical studies of bertilimumab were conducted in Europe: a Phase 1 study in healthy volunteers (study CAT-213-0101), and Phase 2 studies in patients with allergic rhinitis and allergic conjunctivitis (studies CAT-213-0103 and CAT-213-0203, respectively). Ninety-nine (99) individuals have received bertilimumab: 45 via the intravenous (45/99, 45%), eight (8) via the intranasal (8/99, 8%), and 46 via the topical ocular (46/99, 46%) route of administration. Thirteen individuals received IV bertilimumab at doses ≥500 mg (maximum dose administered: 770 mg). In these studies, bertilimumab was well tolerated and no dose-related adverse events (AEs) were noted. To date, no clinical studies of bertilimumab have been conducted in patients with UC. For additional information on these clinical studies, please refer to the Investigator's Brochure.

1.3 STUDY RATIONALE

Bertilimumab is the first monoclonal antibody to specifically neutralize human eotaxin-1. Bertilimumab has been shown to interrupt the eotaxin-stimulated migration of cells and may therefore be useful in the treatment of human diseases such as UC, where eosinophil accumulation is an important feature.

The purpose of this study is to evaluate the safety and efficacy of bertilimumab compared to placebo in adult patients with active moderate to severe UC. The treatment period will include three IV infusions of bertilimumab (10 mg/kg) or placebo at two-week intervals, on study Days 0, 14 (±2 days) and 28 (±2 days). Subjects will be followed for an additional 9 weeks after the end of treatment on study Days 35, 42, 56 and 90 (±3 days per follow-up visit). The study design will allow evaluation of the safety and efficacy of bertilimumab over the treatment and follow-up periods using validated assessment tools. In addition, the pharmacokinetics (PK) and pharmacodynamics (PD) of bertilimumab will be assessed throughout the study.

1.3.1 Rationale for Dose Selection

Immune Pharmaceuticals has chosen to evaluate an IV dose of 10 mg/kg bertilimumab every 2 weeks based on the following safety, PK and PD data:

- No safety concerns were identified in Study CAT-213-0101, in which subjects received a single IV bertilimumab dose of up to 10 mg/kg (corresponding to absolute doses of 570 to 770 mg in four subjects), or in Study CAT-213-0103, in which subjects received a single IV bertilimumab dose of up to 500 mg.
- The PD endpoint in Study CAT-213-0101, eotaxin-induced eosinophil shape change, was inhibited by serum from all subjects who received bertilimumab doses of 1 mg/kg and higher, with nearly 100% inhibition in the 5 mg/kg and 10 mg/kg dose groups. A shape change in eosinophils is considered a requisite process in chemotaxis, and can be taken as evidence of an impending migratory response. Maximum inhibition occurred at concentrations of ~40 µg/mL. At 35 days post-dose, high levels of inhibition were still observed despite low concentrations of bertilimumab, suggesting that the PD response was prolonged when compared with the bertilimumab plasma concentrations.
- In Study CAT-213-001, after a single dose of 5 mg/kg, unbound bertilimumab had a mean half-life of 211 hours (CV% 30.5); the mean half-life after a single 10 mg/kg

dose was 194 hours (CV% 27.1). The half-life of total bertilimumab (bound plus unbound) is estimated to be 16-20 days. The data from this study also suggest dose proportionality in bertilimumab exposure between these two doses.

- No antibodies to bertilimumab were detected in any of the three previous single-dose clinical trials.

Systemic markers of bertilimumab activity (peripheral blood eosinophil count, serum levels of eotaxin-1, ECP, and hs-CRP), as well as eosinophil count and eotaxin level in intestinal tissue, and their correlation with the therapeutic response in UC patients will be also assessed.

1.3.2 Allergic and Infusion Reactions

Monoclonal antibodies, including fully human antibodies, can cause allergic or non-allergic infusion reactions when administered intravenously, and three subjects in bertilimumab clinical trials have experienced infusion reactions, one serious. Accordingly, several precautions have been instituted in the protocol to decrease the risk of infusion reactions and possible anaphylaxis, including the administration of study drug[f] in a controlled setting with ready availability of antihistamines, fluids, epinephrine, and staff trained in the management of anaphylaxis and a pre-study drug regimen with antihistamines, acetaminophen and corticosteroids.

Grading of infusion reactions will be made according to the criteria set forth in Appendix D, as are criteria for anaphylaxis, by definition, a grade 4 reaction. Management of-study drug infusion in the event of an infusion reaction is set forth in Appendix D as well; if additional interventions beyond interruption of- study drug infusion are indicated, then the investigator should manage the reaction according to his or her clinical judgement and any applicable institutional protocols.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 STUDY OBJECTIVES

Primary Objective

- To evaluate, in patients with active moderate to severe UC, the safety and clinical efficacy of bertilimumab administered as 3 IV infusions over 4 weeks.

Secondary Objectives

- To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of bertilimumab in patients with active moderate to severe UC.

2.2 STUDY ENDPOINTS AND OUTCOMES

2.2.1 Efficacy Endpoints

Primary

- Change in Mayo Score from screening to Day 56 (Visit 7). Clinical response at Day 56[g] will be defined as:
    - A decrease from the pre-treatment screening Mayo score of at least 3 points and at least 30%

      AND

[f] In this protocol, "study drug" refers to either bertilimumab or placebo.

[g] This and all other follow-up visits have a window of ±3 days.

- Either a decrease from the pre-treatment screening sub-score for rectal bleeding of at least 1 point, or Rectal Bleeding Sub-score of 0 or 1.

Secondary

- Change in UCEIS score from screening to Day 56.
- Clinical remission at Day 56, defined as a total Mayo score of 2 points or lower, with no individual sub-score exceeding 1 point.
- Mucosal healing at Day 56, defined as an absolute sub-score for endoscopy of 0 or 1.
- Change in partial Mayo score from Day 0 to all scheduled measurement timepoints (efficacy follow up).

2.2.2 Pharmacokinetic Endpoints

- Blood samples will be collected on dosing days (pre-dose and at 30 minutes (+ 15 minutes) and 4 hours (±20 minutes) following the initiation of study drug infusion) and at the follow-up visits. The following PK parameters will be calculated: C_{max}, T_{max}, C_{avg}, C_{min}, and $t_{1/2}$. Additional standard and exploratory PK parameters will be calculated if deemed necessary.

2.2.3 Pharmacodynamic Endpoints

- Fecal calprotectin change from Day 0 (baseline) to all scheduled measurement timepoints.
- Change in eosinophil count, serum eotaxin-1,hs-CRP and ECP from Day 0 to all scheduled measurement timepoints.
- Change in eotaxin-1 concentration and eosinophil count in biopsy tissue from Screening to Day 56.

2.2.4 Safety Endpoints

Safety will be evaluated on the basis of the following parameters:

- Adverse events (AE)
- Infusion reactions
- Physical examination
- Vital signs (blood pressure, heart rate, temperature and respiratory rate)
- ECG
- Concomitant medications
- Laboratory evaluation (hematology, biochemistry, anti-bertilimumab antibodies).

3. STUDY DESIGN

This is a randomized, double blind, placebo-controlled, parallel group multi-center study in adult patients with active moderate to severe UC[h]. Eligible subjects will be randomly assigned in a 2:1 ratio to one of two treatment groups, bertilimumab 10 mg/kg or matching placebo, stratified by previous anti-TNF treatment. Approximately the same proportion of subjects who received previous anti-TNF treatment will be included in each arm. The study

[h] A Mayo Score of 6 to 12 (inclusive); Endoscopic evidence of active ulcerative colitis (i.e., Endoscopic Finding Sub-score of ≥2) as assessed by flexible sigmoidoscopy unless colonoscopy is clinically indicated; Rectal Bleeding Sub-score of ≥1; Physician's Global Assessment (PGA) of at least moderate disease (Mayo Sub-score ≥2).

will consist of three periods: a screening period of up to four weeks, a 4-week double-blind treatment period (three IV infusions at two-week intervals), and a safety and efficacy follow-up period of approximately 9 weeks. A schedule of events for this study is shown in Appendix A. The total duration of subject participation will be ~16-19 weeks. The study will be conducted in up to 10-12 sites in Israel. Additional sites in Europe may be added in the event of slow recruitment.

4. STUDY POPULATION

The study will be conducted in patients aged 18 to 70 years diagnosed with active moderate to severe UC. Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be randomized to treatment groups.

4.1 INCLUSION CRITERIA

1. Males or females, 18 to 70 years of age inclusive.
2. Diagnosed with active moderate to severe UC per standard diagnostic criteria for a minimum of 3 months. The subject must present with the following at the screening visit:
   - Mayo score of 6-12 (inclusive).
   - Endoscopic evidence of active mucosal disease, as assessed by flexible sigmoidoscopy, with an Endoscopic Finding Sub-score of ≥2 (assessed centrally).
   - Rectal Bleeding Sub-score of ≥1.
   - Physician's Global Assessment (PGA) Sub-score of ≥2.
3. Levels of eotaxin-1 in biopsied colon tissue of ≥50 pg/mg protein.
4. Adequate cardiac, renal and hepatic function as determined by the Investigator and demonstrated by screening laboratory evaluations and physical examination results; these findings must all be within normal limits or judged not clinically significant by the Investigator.
5. Females of childbearing potential must agree to use effective contraception consistently throughout the study (such as hormonal contraception or two forms of barrier contraception) and have a negative serum pregnancy test at screening and a negative urine pregnancy test before administration of each study treatment.
6. Males of childbearing potential must agree to use effective contraception consistently throughout the study and a period of four months following the end of the study treatment-
7. Willing and able to adhere to the study visit schedule and other protocol requirements.
8. Willing and able to provide voluntary written informed consent.

4.2 EXCLUSION CRITERIA

1. History of colonic or rectal surgery other than hemorrhoidal surgery or appendectomy.
2. Currently receiving total parenteral nutrition (TPN).
3. Positive *Clostridium difficile* toxin stool assay.
4. Tested positive for active/latent mycobacterium tuberculosis (TB) infection.
5. Pregnant or breast-feeding, or plan to become pregnant during the study.
6. Known hypersensitivity to bertilimumab or any of the drug excipients or to any components of the pretreatment regimens.

7. History of infection requiring administration of any IV antibiotic, antiviral or antifungal medication within 30 days of Screening or any oral anti-infective agent within 14 days of Screening.
8. Acute or fulminant UC requiring immediate surgery or severe UC evidenced by the following signs of toxicity: toxic megacolon, abscess, heart rate >100 beats/min at rest, temperature >38.2°C, hemoglobin <8.0 g/dL.
9. Ulcerative proctitis, defined as disease limited to less than 15 cm from the anal verge.
10. Received a vaccine or other immunostimulator within 4 weeks prior to screening.
11. Use of>4.8 g mesalazine or equivalent within 2 weeks prior to the screening visit. Mesalazine ≤4.8 g is allowed if the dose during the 2 weeks prior to the screening visit was stable.
12. Use of systemic corticosteroids exceeding the equivalent of 20 mg/day of prednisone (see Section 6.9.1) within four weeks prior to the screening visit.
13. Change in dose of immunosuppressive drugs (e.g., corticosteroids, 6-MP, azathioprine) within four weeks prior to the screening visit.
14. Use of TNF-blockers (e.g., infliximab, adalimumab) within 60 days of the screening visit.
15. Use of integrin blockers (e.g., vedolizumab) within 60 days of the screening visit.
16. Use of chronic non-steroidal anti-inflammatory (NSAID) therapy. Occasional use of NSAID and acetaminophen for headache, arthritis, myalgias, menstrual cramps etc., daily use of low-dose (81-162 mg) aspirin for cardiovascular prophylaxis is permitted.
17. Subject diagnosed with:
    - Crohn's disease
    - Diverticulitis or diverticulosis
    - Indeterminate colitis (inability to distinguish between UC and Crohn's disease [as assessed by the Investigator])
    - Microscopic colitis (collagenous or lymphocytic colitis)
    - Ischemic or infectious colitis
    - *Clostridium difficile* colitis within 90 days of the screening visit
    - Parasitic disease within 90 days of the screening visit
    - Systemic fungal infection within 90 days of the screening visit.
18. Current or history of positive serology of hepatitis B or C, or human immunodeficiency virus (HIV) infection.
19. Congenital or acquired immunodeficiency (e.g., common variable immunodeficiency, organ transplantation).
20. Clinically significant abnormal laboratory test results, unless regarded by the Investigator as related to UC, including but not limited to:
    - Hemoglobin level < 10.0 g/dL
    - White blood cell count < 3 x 10^3/µL
    - Lymphocyte count < 0.5 x 10^3/µL
    - Platelet count < 100 x 10^3/µL or > 1200 x 10^3/µL
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 × the upper limit of normal (ULN)

- Alkaline phosphatase >3 × ULN
- Serum creatinine > 2 × ULN.

21. Active abuse of alcohol or drugs.
22. Known malignancy or history of malignancy that could reduce life expectancy.
23. Any condition, which in the opinion of the Investigator, would place the subject at an unacceptable risk if participating in the study protocol.
24. Participation in a clinical trial of an investigational (unapproved) product within 1 month of the screening visit.

4.3 SUBJECT IDENTIFICATION AND TREATMENT ALLOCATION

At screening, all subjects who signed informed consent will be identified by a screening number, their initials and birth date. Subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized to treatment groups. Subjects will be block randomized centrally (i.e., not within each center) and stratified by previous anti-TNF treatment. Specifically, the randomization scheme will ensure that approximately equal proportions of subjects who received previous anti-TNF treatment will be in each of the two treatment arms.

The randomization list specifying treatment assignments will be generated by the Clinical Research Organization (CRO). Within each anti-TNF treatment strata, each eligible subject will be assigned a treatment corresponding to the randomization number specified on the randomization list in the order in which they are enrolled; i.e. separate block randomization sequences will be generated for each anti-TNF strata and each subject will be given a randomization number in sequence within his or her strata. The randomization number assigned to the subject will be recorded by the pharmacist on the infusion bag when the dose is prepared.

In the event of a medical emergency requiring knowledge of the study drug assignment, the Investigator will be provided access to the randomization code in the secured database by the data management team.

4.4 SCREENING FAILURES

Subjects who fail to meet the eligibility criteria at any stage prior to randomization are defined as screen failures. All screen failures will be documented on the screening log, which documents the screening number, subject's initials, birth date and reason(s) for screen failure. The screening log will be kept in the Investigator's Site File. Screen failure subjects will not be enrolled in the study and will receive the local standard-of-care.

4.5 REMOVAL, REPLACEMENT, OR EARLY DISCONTINUATION OF SUBJECTS FROM THERAPY OR ASSESSMENT

Subjects are free to discontinue their participation in the study at any time and without prejudice to further treatment. The Investigator must withdraw any subject from the study if that subject requests to be withdrawn, or if it is determined that continuing in the study would result in a significant safety risk to the subject. Withdrawn subjects will not be replaced.

The subject's participation in this study may be discontinued due to the following reasons:

- Subject withdraws consent.
- Intolerable adverse event (any subject experiencing a grade 3 or 4 infusion reaction will be withdrawn from the study).
- Subject's need for medication prohibited by the protocol.

- The Investigator decides that continuing in the study would not be in the subject's best interest.
- The subject is noncompliant with the protocol.
- The subject becomes pregnant.
- Upon the decision of relevant Regulatory Authorities and/or the Institutional Review Board/Independent Ethics Committee (IRB/IEC).

Subjects who progress and/or relapse will be withdrawn from the study at the Investigator's discretion and will be able to receive local standard-of-care.

4.5.1 Handling of Early Discontinuation

If a subject is withdrawn from the study, either at his or her request or at the Investigator's discretion, or fails to return, every effort should be made to determine the reason. This information will be recorded on the subject's case report form (CRF). All subjects who withdraw from the study prematurely, regardless of cause, should undergo Early Discontinuation Study Visit (see Section 5.4). It is important to obtain follow-up data for any subject withdrawn due to an AE or abnormal laboratory test finding. In any case, every effort must be made to undertake safety follow-up procedures.

4.5.2 Adverse Events

Any serious AE (SAE) must be reported to the Sponsor or Sponsor's designee (by telephone/ fax/text/email) as well as by inputting to the EDC within 24 hours; the IRB/IEC must be notified as required, according to site's regulations (for SAE notification procedures, refer to 7.4).

In the event of any AEs considered to be clinically significant by the Investigator, subjects will be followed up with appropriate medical management until the outcome is determined or stabilized, according to the Investigator's clinical judgment. All follow-up information will be recorded in the subject's CRF until resolution of the AE. Subsequent follow-up will be documented in the subject's personal file.

4.6 SPONSOR'S TERMINATION OF STUDY

The Sponsor reserves the right to discontinue the study at any time at the participating centers for any reason. Regulatory Authorities also have the right to terminate the study for any reason.

5. STUDY PROCEDURES AND ASSESSMENTS

The schedule of events for this study is shown in Appendix A. No protocol related procedures, including cessation of prohibited concomitant medications should be performed before subjects provide written informed consent. Study related events and activities including specific instructions, procedures, concomitant medications, dispensing of study medication and descriptions of AEs should be recorded in the appropriate source documents and CRF. The total amount of blood drawn during this study and by study visit is detailed in the Laboratory Manual.

5.1 SCREENING PERIOD (VISIT 1, DAY -28 TO DAY -1)

The purpose and procedures of the study will be fully explained to participating subjects. Those wishing to enroll in the study will sign a written informed consent prior to initiating any study related evaluations or procedures.

The following assessments will be done at the screening visit, up to 28 days before initiation of treatment (Day 0):

- Review and sign Informed Consent
- Assign screening number
- Inclusion and Exclusion Criteria
- Medical history and demographic data
- Prior and concomitant medications
- Physical examination (including vital signs, height and weight measurements)
- ECG
- Screen for active/latent tuberculosis (Interferon Gamma Release Assay)
- Screen for *C. Difficile* toxin in stool sample
- Flexible sigmoidoscopy with biopsies. At least 3 tissue samples are required from area of active inflammation. Additional biopsy samples may be obtained at the Investigator's discretion for histological assessment.
- Mayo score
- UCEIS
- Eotaxin-1 in tissue will be measured using two of the biopsy samples
- Eosinophil count in tissue will be measured histologically using the remaining biopsy sample
- Calprotectin in fecal sample
- Laboratory evaluations: hematology, biochemistry, serology and serum pregnancy test for females of childbearing potential.
- Eligible subjects will be randomized in a 2:1 ratio to one of two treatment arms, bertilimumab 10 mg/kg or matching placebo.

The screening visit may be conducted over multiple days. Screening visit data (Mayo score, UCEIS, eotaxin-1 and eosinophil count in tissue sample) will be considered baseline data for statistical analysis purposes.

5.2 TREATMENT PERIOD[i]: VISIT 2 (DAY 0), VISIT 3 (DAY 14) AND VISIT 4 (DAY 28)

At Visit 2 (Day 0), inclusion exclusion criteria will be reviewed.

The following assessments will be performed at each treatment visit (Day 0, Day 14 and Day 28) pre-dose:

- Physical examination
- Vital signs
- ECG
- Partial Mayo score
- Safety laboratory evaluations: hematology, biochemistry, antibodies to bertilimumab.
- Blood samples for eosinophil count[j], serum eotaxin-1, hs-CRP[k] and ECP

[i] Visits 3 and 4 during the Treatment Period have a ±2 day window.

[j] Done using the hematology blood sample.

[k] Done using the biochemistry blood sample.

- Blood samples for bertilimumab (PK analysis)
- Calprotectin in fecal samples
- Urine pregnancy test (for females of childbearing potential)

Subjects will receive a pretreatment regimen for infusion reaction prophylaxis. The regimen is as follows:

- Dexamethasone 10 mg PO 24-18 hours prior to administration of study drug.
- Acetaminophen 1000 mg PO 1 hour prior to administration of study drug.
- Either loratadine 10 mg PO or cetirizine 10 mg PO one hour prior to the administration of study drug.

In the event that dexamethasone was not administered previously, then 10 mg dexamethasone IV may be administered 1-3 hours prior to study drug administration.

Following completion of pre-dose assessments and administration of pretreatment regimen according to the appropriate timelines above, study drug will be administered by IV infusion over 30 minutes.

Subjects will remain in the clinic for up to 4 hours following completion of the 30 minutes IV infusion for PK assessment and safety follow-up. The following procedures will be conducted post-dose:

- Vital signs: 15 minutes (during infusion), 30 (+ 15) minutes (immediately post-infusion), 2 hr (±20 minutes) and 4 hr (±20 minutes) following initiation of study drug infusion.
- ECG at 30 (+15) minutes after initiation of study drug infusion.
- Blood samples for bertilimumab (PK analysis) at 30 (+15) minutes (immediately post-infusion) and 4 hours (±20 minutes) following initiation of study drug infusion.
- Recording of AEs (including post-infusion reactions, if applicable) and concomitant medications.

5.3 FOLLOW-UP PERIOD[l]: VISIT 5 (DAY 35), VISIT 6 (DAY 42), VISIT 7 (DAY 56) AND VISIT 8 (DAY 90)

Subjects will be followed for 3 months post first study drug administration. The following assessments will be performed at the follow-up visits:

- Physical exam
- Vital signs
- ECG
- AE and concomitant medication recording
- Partial Mayo score (at Visits 5, 6 and 8)
- Safety laboratory evaluations: hematology, biochemistry, antibodies to bertilimumab
- Blood samples for eosinophil count, serum eotaxin-1[i], hs-CRP[j] and ECP
- Blood samples for bertilimumab (PK analysis)
- Calprotectin in fecal samples
- Flexible sigmoidoscopy with biopsies. On Day 56 (or early discontinuation visit), at least 3 tissue samples are required from the same region where the Screening

[l] Visits during the Follow-Up Period have a ±3 day window.

biopsies were obtained. Additional biopsy samples may be obtained at the Investigator's discretion for histological assessment.

- Eotaxin-1 in tissue will be measured using 2 of the biopsy samples (Visit 7 only)
- Eosinophil count in tissue will be measured histologically using the remaining biopsy sample (Visit 7 only).
- Mayo score (Visit 7 only)
- UCEIS (Visit 7 only)

5.4 EARLY DISCONTINUATION STUDY VISIT

An early discontinuation study visit will be performed for subjects who withdraw from the study for the reasons specified in Section 4.5.

All reasons for treatment discontinuation will be documented in the source documents as well as the CRF. Only one reason (the most severe) for early discontinuation should be recorded in the CRF. If one of the reasons for discontinuation is an AE – this should be chosen as the reason. Every effort should be made to follow-up these subjects for resolution of AE.

At this visit, flexible sigmoidoscopy with biopsies will be done in addition to the activities relating to the study period at which time the subject discontinuation visit will be performed. That is, if the subject discontinues during the Treatment period, the visit activities will be similar to those described in Section 5.2; likewise, if the subject discontinues during the Follow-up Period, the visit activities will be similar to those described in Section 5.3. Activities may include (but not limited to): AEs, concomitant medications, laboratory tests, vital signs, and physical examination. Appropriate procedures and evaluations will be completed as deemed necessary by the Investigator.

This visit may be performed on the same day as an originally scheduled visit or could be conducted separately. Data collection at these visits should primarily be guided according to principles to protect subject safety and well-being.

5.5 UNSCHEDULED VISIT

An unscheduled visit may be performed at any time during the study at the subject's request or as deemed necessary by the Investigator. The date and reason for the unscheduled visit will be recorded. AE monitoring and concomitant medication recording will be performed by the Investigator. Appropriate procedures and evaluations will be completed as deemed necessary by the Investigator and may include (but not limited to) laboratory tests, vital signs and physical examination.

5.6 SAFETY ASSESSMENTS

Safety assessments will be based on changes from Baseline of AEs (either reported by the subject or observed by the Investigator), concomitant medication use, treatment compliance (e.g., dropouts due to AEs), vital signs, ECG, physical examination and laboratory assessments (hematology, blood chemistry, anti-bertilimumab antibodies).

5.6.1 Adverse Events (AEs)

Adverse events will be assessed throughout the study. Any AE that occurs will be recorded.

Any new AE that occurs between scheduled visits should be brought to the attention of the Investigator and recorded in the subject's medical file and on the appropriate CRF page.

AEs will be coded by Data Management using Medical Dictionary for Regulatory Activities (MedDRA®) version 14.0 or higher (see section 10.4 for more details).

5.6.2 Concomitant Medications

Recording of concomitant medication use will be conducted at all study visits.

5.6.3 Vital Signs

Vital signs will be measured at all study visits. On dosing days, vital signs will be measured pre-dose and at 15 minutes (during infusion), 30 (+ 15) minutes (immediately post infusion), 2 hr (± 20 minutes) and 4 hr (± 20 minutes) following initiation of study drug administration.

Vital signs will include blood pressure, pulse rate, oral temperature and respiration rate after at least 5 minutes rest as per standard practice at the investigational site. Significant findings noticed after the start of study drug, which meet the definition of an AE must be recorded on the AE CRF module.

5.6.4 Electrocardiogram

ECG will be performed at all study visits. On dosing days, ECG will be performed pre-dose, and at 30 minutes (+ 15 minutes) following initiation of study drug administration (immediately post-infusion). The subject should rest for at least 10 minutes before measurement is taken.

The ECG will be evaluated by the Investigator (signed and dated) and the printout should be kept in the source documentation file. When potentially clinically significant findings are detected by the site Investigator, a cardiologist should be consulted for a definitive interpretation and treatment administered based on medical need. All communications and diagnoses should be filed in the source documentation file. The Investigator/local cardiologist is responsible to determine whether the ECG findings are of clinical significance. All abnormalities will be closely monitored until stabilized or resolved.

5.6.5 Physical Examination

Physical examination will be conducted at all study visits. On dosing days, physical examination will be performed pre-dose. Height will be recorded at Visit 1 (screening). Physical examination will include weight measurements, assessment of head, lungs, cardiovascular system, abdomen, musculoskeletal system, skin, lymph nodes, central nervous system and, where appropriate, other body systems as indicated in the study schedule.

Information about the physical examination must be present in the source documentation at the study site. Significant findings that are present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions CRF. Significant findings made after the start of study drug, which meet the definition of an AE must be recorded on the AE CRF.

5.6.6 Infusion Reactions

Infusion reactions to monoclonal antibody administration are not uncommon and are typically mild to moderate in intensity. They can develop during the infusion or several hours thereafter, and, are most commonly associated with a complex of chills, fever, nausea, asthenia, headache, skin rash or pruritus. However, infusion reactions in a small percentage of patients, may also present with a variety of signs and symptoms of severe hypersensitivity characterized by the acute onset of bronchospasm, hypotension, urticaria and/or cardiac arrest. Therefore, all subjects in the study will be pre-medicated with a prophylactic regimen prior to study treatment on each of the dosing days (Days 0, 14 and 28) to prevent potential infusion reactions and will be closely monitored for up to 4 hours post-infusion.

5.6.7 Safety Laboratory Assessments

Clinical laboratory assessments will be performed by a central laboratory. Investigators at each site will review these laboratory data for safety considerations. Hematology and biochemistry will be conducted at all study visits. Screen for active/latent mycobacterium tuberculosis (TB) infection and *Clostridium difficile* toxin stool assay will be conducted at screening only. Anti-bertilimumab antibodies will be evaluated from Day 0 until the end of the study. Pregnancy test for women of childbearing potential will be conducted at Screening (serum) and before each study drug infusion (urine).

Safety laboratory sampling will be performed as follows by a central laboratory:

Evaluations	Parameters
Hematology	Hematocrit, hemoglobin, platelet count, red blood cell count, reticulocytes, white blood cell count with differential count
Biochemistry	Alanine aminotransferase, alkaline phosphatase, α-amylase, aspartate aminotransferase, calcium, cholesterol, creatinine, gamma-glutamyl transferase, glucose, potassium, sodium, total bilirubin, triglycerides, urea/BUN
Immunology*	Anti-bertilimumab antibodies
Pregnancy test	Serum β-hCG pregnancy test at Screening Urine β-hCG on dosing days (pre-dose)

The volume of blood to be drawn for each subject and processing and storage of samples are detailed in the Laboratory Manual.

All laboratory tests with values that became abnormal and are considered clinically significant after drug administration will be repeated as clinically indicated until the values return to normal, or until the etiology has been determined and the condition considered stable. Abnormal laboratory test results that are considered to be clinically important by the Investigator will be reported as an AE in the AE CRF. A laboratory abnormality will not be considered an AE unless:

- Intervention is required
- Changes in dose are required (decrease, discontinued, interrupted)
- Other treatment/therapy is required
- It is associated with other diagnoses.

Laboratory results will be reported to the Investigator who will review abnormal laboratory findings for clinical significance. The Investigator will note any laboratory test results of clinical concern, or values that were outside normal ranges and provide details of the relationship to investigational product and the action taken. If a change in a laboratory value represents a medical condition, the medical condition will be listed in the AE CRF page. If no correlation is possible, the direction of change (increase or decrease) in addition to the actual value will be recorded.

5.7 EFFICACY ASSESSMENTS

5.7.1 Sigmoidoscopy

Flexible sigmoidoscopy with biopsies will be performed at Screening (Visit 1) and Day 56 (Visit 7) or early discontinuation visit. At least 3 tissue samples are required from an area of active inflammation at Screening. On Day 56 (or early discontinuation visit), at least 3 tissue samples are required from the same region where Screening biopsies were obtained.

Additional biopsy samples may be collected at the Investigator's discretion for histological assessment.

The Endoscopic Finding Sub-score grading is provided in Appendix B. The UCEIS grading is provided in Appendix C. Each site will perform sigmoidoscopy at Screening (Visit 1) to evaluate eligibility (see Inclusion/Exclusion criteria). For efficacy evaluation, all endoscopic images (Visits 1 and 7 [or early discontuation visit]) will be reviewed centrally according to the procedure provided by the Institution conducting the central reading.

5.7.2 Mayo score

The Mayo Scoring System (Appendix B) for assessment of UC activity will be used for efficacy evaluation. The score will be determined at Screening (Visit 1) and Day 56 (Visit 7).

The Mayo Score is a discrete ordinal scale ranging from 0 (normal or inactive disease) to 12 (severe disease) and is a composite of 4 sub-scores: Stool Frequency Sub-score, Rectal Bleeding Sub-score, Endoscopic Finding Sub-score and Physician's Global Assessment Sub-score, each of which ranges from 0 (normal) to 3 (severe disease) [18]. The sub-scores are summed to give a total score that ranges from 0–12.

The partial Mayo Score is a 9-point scale that excludes the Endoscopic Finding Sub-score. It will be used for assessment of disease activity on Day 0 (Visit 2), Day 14 (Visit 3), Day 28 (Visit 4), Day 35 (Visit 5), Day 42 (Visit 6) and Day 90 (Visit 8).

5.8 PD ASSESSMENTS

5.8.1 Fecal calprotectin

Calprotectin is a cytosolic protein in neutrophilic granulocytes that correlates with neutrophilic infiltration of the intestinal mucosa [19, 20]. Fecal calprotectin is a marker of intestinal inflammation in UC. Fecal samples for analysis of calprotectin level will be collected at every study visit. On treatment days, samples will be collected pre-dose. Analysis will be conducted by a central laboratory.

5.8.2 Eosinophil count, serum eotaxin-1, hs-CRP and ECP

Blood samples for eosinophil count[i], eotaxin-1, hs-CRP and ECP[j] will be collected at every study visit (excluding screening visit). On treatment days, samples will be collected pre-dose. Processing and storage of the samples are detailed in the Laboratory Manual. Analysis will be conducted by a central laboratory.

5.8.3 Eosinophil count and eotaxin-1 concentrations in biopsy tissue

Biopsy tissue samples for analysis of eotaxin-1 concentrations and eosinophil count will be collected at screening (Visit 1) and on Day 56 (Visit 7) or early discontinuation.

Analysis of eotaxin-1 and eosinophil count in biopsy tissue will be conducted by a central laboratory and the handling, storage, processing and analysis procedures will be described in the Laboratory Manual.

5.9 PK ASSESSMENTS

PK outcome is study drug (bertilimumab) concentration in the serum. PK parameters will include:

C_{max}	Maximum bertilimumab serum concentration
T_{max}	Time to C_{max} (peak exposure)
C_{avg}	Average bertilimumab serum concentration

C_{min}	Minimum bertilimumab serum concentration
λ_z	Elimination rate constant
$t_{1/2}$	Elimination half-life, calculated as $0.693/\lambda_z$.

Additional PK parameters may be calculated if deemed necessary.

PK blood samples will be collected at every study visit (excluding screening). On dosing days, blood samples will be collected pre-dose and at 30 (+15) minutes (immediately post-infusion) and 4 hours (±20 minutes) following the initiation of study drug administration. The actual sampling times will be recorded.

Processing and storage of the samples are detailed in the Laboratory Manual. PK analysis will be conducted by a central laboratory using a validated method.

6. INVESTIGATIONAL PRODUCT

6.1 IDENTITY OF INVESTIGATIONAL PRODUCT

Bertilimumab is a recombinant human IgG_4 monoclonal antibody that neutralizes human eotaxin-1 (eotaxin). The drug product consists of bertilimumab formulated in phosphate buffered saline (PBS) at pH 7.2 and at a concentration of 10 mg/mL, presented as a sterile, clear, colorless solution in 10 mL clear glass vials.

The formula for the PBS is sodium chloride 77 mM, monosodium phosphate 17 mM and disodium phosphate 50 mM.

Matched placebo glass vials will contain PBS.

Polysorbate 20, a non-ionic surfactant to prevent protein aggregation, is added to the bertilimumab or placebo formulationat the time of vialing or to the saline infusion bag prior to dosing. The Pharmacy Manual will indicate whether polysorbate 20 is to be added prior to dosing.

6.2 STUDY DRUG ADMINISTRATION AND DOSAGE

Bertilimumab (10 mg/kg) or placebo will be administered by intravenous infusion over 30 minutes. A pretreatment prophylactic regimen (as detailed in section 5.2) will be administered prior to dosing on each treatment dosing day (Days 0, 14 and 28) to reduce the likelihood of an infusion reaction.

6.3 MANUFACTURING OF STUDY MEDICATION

A cGMP vendor will perform the drug product and placebo manufacturing and release.

6.4 PACKAGING AND LABELLING OF STUDY MEDICATION

Bertilimumab vials or matching placebo will be packaged and labeled in compliance with GCP and local health authority guidelines. Each study center's hospital pharmacy facility will be responsible for handling and preparation of the study drug.

6.5 DISTRIBUTION AND SHIPMENT OF STUDY MEDICATION

Study drug will be packed and shipped in appropriate boxes. If, upon arrival at the clinical investigation site, the study drug appears to be damaged, the study monitor should be contacted immediately.

Each shipment of study drug supplies for the study will be accompanied by a shipment form describing the contents of the shipment, acknowledgement of receipt and other appropriate

documentation. The shipment form will assist in maintaining current and accurate inventory records. The study staff will confirm the receipt of clinical supply to the study monitor.

All study supplies should arrive at the Pharmacy/Investigational site in sufficient quantity and in time to enable dosing as scheduled. The Sponsor or its representative must notify the principal Investigator prior to dispatch of drug supplies with the anticipated date of their arrival.

6.6 STORAGE AND INSTRUCTIONS FOR PREPARATION AND INFUSION OF THE INVESTIGATIONAL PRODUCT

The study medication will be stored in each study center's hospital pharmacy facility. The study drug (bertilimumab or placebo) will be stored in glass vials under refrigeration at 2-8°C. The polysorbate 20, if not included during vialing and necessary for inclusion to the saline infusion bags prior to subject dosing, will be provided to the center's hospital pharmacy facility where it is to be stored, under frozen (-20°C) conditions.

Records should be kept by the pharmacist as to how much study drug was used by each subject. The study monitors must periodically check the study drug supplied to ensure expiry date and sufficient amount of study drug, and be sure that drug accountability is being performed at each visit, and the drug accountability logs (for study drug/placebo and polysorbate) are maintained.

All investigational products must be kept in a locked area with access to the study drug limited to designated study personnel.

Preparation of the study drug dose for administration must be carried out by a trained medical professional at the study center's hospital pharmacy using aseptic technique according to the Pharmacy Manual. The number of vials used as well as the study drug volume dispensed per dose will be recorded in the study logbook.

Only trained personnel under the supervision of either the Investigator or the local pharmacist are authorized to administer study drug to participating subjects.

6.7 ACCOUNTABILITY AND COMPLIANCE OF INVESTIGATIONAL PRODUCT

Each delivery must be acknowledged by the hospital pharmacist (or authorized study team member responsible for the investigational medicinal product) by filling in the receipt record form and returning it by fax to delegated CRO. Accurate, complete, and timely documentation for all distribution to the study staff and subjects will be maintained by the pharmacy and the study staff of the investigational site which may include confirmation of receipts of clinical supply, drug accountability logs, and other forms.

The hospital pharmacist (or authorized study team member responsible for the investigational medicinal product) is responsible for ensuring the supervision of the storage and allocation of these supplies, which will be forwarded to the Investigator at the appropriate time before administration. The Investigator may dispense investigational drug only to subjects enrolled in the study.

Drug accountability records must be maintained by the clinical investigation site at all times. At the last study visit, all used and unused investigational drug will be collected and drug accountability performed by the study staff. The study monitor will check these regularly during monitoring visits.

Unused drug supplies will be returned to the Sponsor. At the end of the study, all the clinical supply and the corresponding accountability forms must be returned to the Sponsor, the study

monitor or designee for reconciliation and destruction. A photocopy of these records must be kept at the clinical investigation site.

The inventory will be made available to the study monitor who will verify accountability and verify dose during the course of the study.

Study drug orders, records of study drug receipts, dispensing records, and inventory forms located at the site will be examined and reconciled by the study monitor periodically during and at the end of the study.

6.8 BLINDING AND RANDOMIZATION

Subjects will be block randomized centrally (i.e., not within each center), stratified by previous anti-TNF treatment to ensure that approximately equal proportions of subjects who received previous anti-TNF treatment will be in each of the two treatment arms.

A CRO will be responsible to assign and track the treatment randomization for each enrolled subject and to provide the randomization number to the sites. The randomization assignment for a subject will be made available to the pharmacist at the study site but not to any other person on the study staff nor to any of the Sponsor's personnel or blinded monitors.

However, if the identity of the test medication administered needs to be known in order to manage the subject's condition, the Principal Investigator may be allowed access to the database treatment emergency code for that subject and the test medication identified. All such occurrences should be documented in the study file. Treatment emergency codes should not be broken except in emergency situations and, if possible, the Sponsor should be contacted before the emergency code is accessed.

Whenever disclosure of the identity of the test medication is necessary, adequate procedures will be in place to ensure integrity of the data. Any unblinding will be documented in the study report with date, reason for identifying the drug and the name of all the person(s) who had to be unblinded.

6.9 CONCOMITANT THERAPY

At the screening visit, relevant treatments currently received by the subject will be recorded on the subject's CRF including treatment's name, indication, dose, total daily dose and start and stop dates. Any medications (including prescription, over-the-counter, herbal supplements and other health store-type products) to be taken during the study must be approved by the Investigator and recorded in the CRF.

6.9.1 Allowed Medications

The following concomitant medications/therapies will be allowed during the treatment period:

- Occasional use of NSAID and acetaminophen for headache, arthritis, myalgia, menstrual cramps etc., and daily use of low-dose (81-162 mg) aspirin for cardiovascular prophylaxis is permitted
- Mesalazine ≤ 4.8 g is allowed if the dose during the 2 weeks prior to the screening visit was stable; subject is to remain on stable dose through Visit 6 (Study Day 42).
- Systemic corticosteroids not exceeding the equivalent of 20 mg/day of prednisone (see Corticosteroid Comparison Chart below) are allowed if the dose during the 4 weeks prior to the screening visit was stable; subject is to remain on stable dose through Visit 6 (Study Day 42), excluding corticosteroid used in pretreatment prophylaxis.

- Cortiment (budesonide) up to a daily dose of 9 mg is allowed during the screening period and throughout the study owing to limited systemic absorption.

Table 1: Corticosteroid Comparison Chart

	Approximate Equivalent Dose, mg	Relative Potency
Hydrocortisone	20	1.0
Cortisone Acetate	25	0.8
Prednisone	5	4.0
Prednisolone	5	4.0
Methylprednisolone	4	5.0
Dexamethasone	0.75	30-150

Reference: Welsh GA, Manzullo EF and Nieman LK. The surgical patient taking glucocorticoids. 2007 UpToDate® www.uptodate.com.

Additional medications/therapies may be allowed at the discretion of the Investigator in consultation with the Sponsor. All concomitant medications used to treat AEs will be recorded in the subject's medical file and on the appropriate CRF page.

6.9.2 Prohibited Prior and Concomitant Medication

Medications having the potential to interfere with the study assessments are excluded throughout the trial and include:

- Use of vaccines or other immunostimulator within 4 weeks prior to screening or any time during the study.
- Use of >4.8 g mesalazine or equivalent within 2 weeks prior to the screening visit.
- Use of systemic corticosteroids exceeding the equivalent of 20 mg/day of prednisone within four weeks prior to the screening visit.
- Change in dose of immunosuppressive drugs (e.g., corticosteroids, 6-mercaptopurine [6-MP], azathioprine) within four weeks prior to the screening visit.
- Use of TNF-blockers (e.g., infliximab or adalimumab) within 60 days of the screening visit.
- Use of oral or parenteral antibiotics within two weeks prior to the screening visit.
- Use of chronic non-steroidal anti-inflammatory (NSAID) therapy.

In the interests of patient safety, and acceptable standards of medical care, the Investigator may prescribe treatment(s) at his/her discretion, which will be recorded on the subject's CRF.

7. SAFETY AND PHARMACOVIGILANCE

7.1 ADVERSE EVENT

An adverse event (AE) is any adverse change from the subject's baseline condition, whether or not considered investigational product related. This includes any subjective signs, symptoms or diagnosis, clinical significant deviation from baseline laboratory values or vital signs, or worsening (more severe, more frequent or increased in duration during the investigational product treatment) of the concomitant disease present at baseline visit (after initiation of investigational product treatment). Stable chronic conditions that are present prior to study entry and do not worsen during the study will not be considered AEs. Disease-related adverse events will not be considered AEs only if they worsen beyond what would be

expected in the normal progression of the disease. In all cases, the etiology should, as much as possible, be identified and the Sponsor notified.

An abnormal result of diagnostic procedures including abnormal laboratory or vital sign findings will be considered an AE if it:

- Results in subject's withdrawal by the Investigator
- Is associated with clinical signs or symptoms
- Is considered by the physician to be of clinical significance.

Adverse events reported by the subject or observed by the Investigator will be individually listed on an AE form in the CRF as follows: the specific event or condition, whether the event was present pre-study, the dates and times of occurrence, duration, severity, relationship to study medication, specific countermeasures and outcome.

The intensity or severity of the AE will be characterized as:

- Mild: Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
- Moderate: Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required.
- Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required; hospitalization possible.

The Investigator will document in his/her opinion the relationship of the AE to the investigational product (study medication) using the following criteria:

Category	Definition
Unrelated	Clearly due only to extraneous causes, and does not meet criteria listed under possible or probable.
Unlikely	Does not follow a reasonable temporal sequence from administration. May have been produced by the subject's clinical state or by environmental factors or other therapies administered.
Possible	Follows a reasonable temporal sequence from administration, but may have been also produced by the subject's clinical state, environmental factors or other therapies administered.
Probable	Clear-cut temporal association with administration with improvement on cessation of investigational medicinal product or reduction in dose. Reappears upon rechallenge. Follows a known pattern of response to the investigational medicinal product.

7.2 SERIOUS ADVERSE EVENT

A **serious** adverse event (SAE) is any adverse event occurring at any dose that suggest a significant hazard or side effect, regardless of the Investigator or Sponsor's opinion on the relationship to the investigational product and that results in, but may not be limited to, any of the following outcomes:

- death (regardless of the cause)
- a life-threatening adverse drug experience
- inpatient hospitalization or prolongation of existing hospitalization (any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility)
- a persistent or significant disability/incapacity

- a congenital anomaly or birth defect.

Important medical events that may not result in death, be life-threatening or require hospitalization may be **serious** when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Hospitalization for elective treatment of a pre-study condition that did not worsen while on study and hospitalizations for treatment of non-adverse events (e.g., cosmetic surgery) are not considered serious adverse events.

Significant medical events are those, which may not be immediately life-threatening, but may jeopardize the subject and may require intervention to prevent one of the other serious outcomes listed 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; resulting in an adverse event will normally be considered serious by this criterion.

Inpatient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of AE, or that they occurred as a consequence of the event. Hospitalization for elective treatment of a pre-study condition that did not worsen while on study and hospitalizations for treatment of non-adverse events (e.g., cosmetic surgery or diagnostic procedure) are not considered serious adverse events.

Any new SAE that occurs after the study period and is considered to be related (possibly/probably) to the investigational product or study participation should be recorded and reported immediately.

A **life-threatening** adverse drug experience is any adverse event that places the subject, in the view of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

7.3 DEFINITION OF AN UNEXPECTED ADVERSE EVENT

An **unexpected** adverse drug experience (event) is any adverse event, the specificity or severity of which is not reported in the current Investigator's brochure.

7.4 NOTIFICATION ABOUT SERIOUS OR UNEXPECTED ADVERSE EVENTS

All SAEs must be reported **immediately** to the Immune Pharmaceuticals representative as soon as it becomes known to the Investigator and not later than within 24 hours of their knowledge of the occurrence of an SAE. The notification will occur via data entry to the EDC with phone/fax/text/email notification to the Sponsor.
Immune Pharmaceuticals Representative:

[redacted]
Phone: [redacted], ext: [redacted]
Mobile: [redacted]
Fax: [redacted]
E-mail: [redacted]

These preliminary reports will be followed within 24 hours by detailed descriptions that will include a completed SAE form, copies of hospital case reports, autopsy reports and other documents, when requested and applicable.

In addition, all AEs / SAEs / Suspected Unexpected Serious Adverse Reaction (SUSARs) will be reported to the local EC and regulatory authorities as required by local regulations and ICH-GCP guidelines.

Minimal information should include:

- An identifiable subject (e.g., Subject randomization number)
- An identifiable reporting source
- All related adverse events
- The suspect medicinal product
- Follow-up of SAEs / SUSARs
- Follow-up of SAEs / SUSARs that occur during the study will continue until their satisfactory resolution or stabilization.

If, when supplementary information is available, a follow-up SAE Report Form must be completed by the site and data entry inputted to the EDC with follow-up phone/fax/text/email to Sponsor within 24 hours.

The contact information for follow up SAE reporting is the same as for initial SAE reports (see above section).

The paper copy of the SAE form and accompanying documentation should be placed in the SAE section of the Investigator's file. If supplementary information on a SAE has to be sent, the SAE form has to be used marked as "follow-up report."

Follow-Up Reports on non-serious AEs

All AEs must be followed until resolution or stabilization. In outstanding cases, it may be defined as "ongoing without further follow-up" by the Investigator and Sponsor's decision.

8. PLANNED STATISTICAL ANALYSES AND METHODS

A statistical analysis plan (SAP) will be written and finalized before the study closure, i.e., database closure and unblinding of the randomization code. The SAP will provide full details of the analyses, the data displays and the algorithms to be used for data derivations. The SAP will include the definition of major and minor protocol deviations and the link of major protocol deviations to the analysis sets.

8.1 DESIGN CONSIDERATIONS

This is a two-arm, parallel control, double-blind, multi-center trial comparing three doses of bertilimumab 10 mg/kg to placebo in subjects with active moderate to severe UC. Subjects will be block randomized centrally (over all centers) in a 2:1 ratio (bertilimumab to placebo) and stratified by previous anti-TNF treatment, with approximately equal proportion of subjects with previous anti-TNF history included in each arm. Additionally, to reduce bias, the Mayo score and UCEIS will be evaluated by a central reader blind to subject identifier.

8.2 DETERMINATION OF SAMPLE SIZE

This is the first study investigating clinical outcome of treatment with bertilimumab in UC patients, and is therefore exploratory. Consequently, this trial's analyses are descriptive in nature and whose sample size has been chosen, in consultation with physicians in the field and based on studies with similar objectives in the literature[m], to provide reasonable precision

[m] Parikh, A. et al. Vedolizumab for the treatment of ulcerative colitis: a randomized controlled phase II dose-ranging study. Inflammatory Bowel Disease, 2012; *18*:1470-1479.

in initial estimation of the drug's clinical effect at one dose level. Specifically, up to 42 subjects will participate in this trial.

8.3 STATISTICAL METHODS

All measured variables and derived parameters will be listed individually. Outcomes will be summarized by treatment group, depending on their nature, as follows:

- For dichotomous variables: Categorization into success/failure-like categories; then incidence of failure and relative risk of failure in the active group compared to placebo with 95% confidence interval.
- For numeric continuous endpoints: Descriptive statistics and summary tables will include sample size, arithmetic mean, standard deviation, median, minimum and maximum, and 95% Confidence Interval (CI) for mean at the relevant time points by treatment.
- For ordered categories endpoints: incidences in the different categories and, after dichotomization into success/failure-like categories, incidence of failure and relative risk of failure by treatment with 95% confidence intervals.

All tests applied will be two-tailed, and p value of 0.1 or less will be considered statistically significant. Since this is an exploratory trial, there will be no Alpha-correction for multiple testing. The data will be analyzed using the SAS® 9.1 software package or higher (SAS Institute, Cary, North Carolina).

8.3.1 Analysis Sets

8.3.1.1 Safety Analysis Set

The Safety Analysis Set will include all subjects who were exposed to any of the study treatments.

8.3.1.2 Modified Intent to Treat Analysis Set

The modified intent to treat (mITT) analysis set will include all randomized subjects who received at least one dose of study treatment (placebo or bertilimumab), and had at least a full Mayo score at screening and at least one post-baseline partial Mayo score from visit 3 onward. Excluded from mITT will be subjects with major entry violations as determined by blind review.

Missing primary efficacy data in mITT will be imputed as follows:

Full Mayo Score at Visit 7:

- Subjects with a Full Mayo Score post-screening prior to Visit 7 (and none at Visit 7) will have their Visit 7 score imputed by last observation carried forward (LOCF).
- Subjects with a Full Mayo Score after Visit 7 (and none at Visit 7) will have their Visit 7 score imputed by last observation carried backward (LOCB).
- Subjects with only partial Mayo score(s) from Visit 3 onward will have their Full Mayo Score at Visit 7 imputed by multiple imputation (MI), using a model that includes screening data, treatment and partial Mayo Score.[n]

UCEIS (a secondary endpoint that will be analyzed in mITT as well)

[n] a) The continuous Full Mayo Score will be imputed using MI, after which clinical response will be computed and b) Should there be variables causing the MI model not to converge, these will be excluded from the model.

- Subjects with UCEIS post-screening prior to Visit 7 (and none at Visit 7) will have their Visit 7 score imputed by last observation carried forward (LOCF).
- Subjects with UCEIS after Visit 7 (and none at Visit 7) will have their Visit 7 score imputed by last observation carried backward (LOCB).
- Subjects with no post-screening endoscopy will have their UCEIS at Visit 7 imputed by MI using screening data, treatment and partial Mayo Score (from Visit 3 onward).[o]

8.3.1.3 Per Protocol Analysis Set

The per protocol (PP) analysis set will be a subset of mITT subjects who had no major protocol violations likely to affect outcome as determined by blind review and who received at least 2 of 3 study treatments (placebo or bertilimumab) and who had a full Mayo score at screening and at visit 7. Only observed data will be used in PP; primary data will not be imputed.

8.3.2 Subject Disposition

Major and minor protocol deviations will be identified by medically trained staff before the study closure. All screened subjects will be accounted for; enrolled subjects will be followed to completion. Protocol violations determining the belonging of subjects to the different analysis sets will be summarized. A full disposition tree will be generated displaying the number of subjects reaching the different phases of the study (screening, randomization/treatment, end of treatment, end of study) and the main reasons for exclusion.

8.3.3 Demographics and Baseline Characteristics

Baseline demographics and disease characteristics will be summarized for the safety analysis. Continuous demographic variables and baseline/screening disease characteristics will be summarized by mean, median, standard deviation, minimum and maximum. Qualitative demographic characteristics and baseline/screening disease characteristics will be summarized by counts and percentages. Other subject characteristics (medical history, clinical findings, inclusion/exclusion checklist, etc.) will be listed only.

These variables will be compared between the treatment groups in a descriptive fashion; no formal statistical testing will be performed.

Previous and concomitant medications will be coded according to the WHO drug code and the ATC class code. They will be summarized by type (e.g., previous, concomitant, for AE) by tabulating the number and percentages of subjects having received each treatment.

8.3.4 Efficacy Endpoints Analysis

Analysis of all efficacy endpoints will be performed on the mITT set. The PP set will be used as supplementary analyses to test the robustness of the results. If deemed appropriate, supportive analyses using multiple imputations for missing data will be performed on the primary and secondary endpoints. Additional exploratory data-driven analyses could be performed with the caveat that any statistical inference will not have any confirmatory value. Because this is an exploratory study, alpha will be set at 0.1 for comparisons between groups.

8.3.4.1 Primary Endpoint Analysis

This study's primary endpoint analyses will be descriptive, providing proportion of Mayo Score Clinical Response separately by treatment group, including two-sided 95% Exact

[o] a) The continuous UCEIS will be imputed using MI, after which clinical response will be computed and b) Should there be variables causing the MI model not to converge, these will be excluded from the model.

Binomial confidence intervals. Exploratory statistical testing will be done by comparing Bertilimumab treatment arm to placebo.

8.3.4.2 Secondary Endpoint Analyses

a. Primary endpoint analysis described in the preceding section will be repeated in PP.
b. Secondary endpoints will be analysed in both mITT and PP analysis sets.

8.3.5 Pharmacokinetic Analysis

To the degree possible given the limited number of sampling timepoints, PK parameters will include AUC, T_{max}, C_{max}, C_{avg}, C_{min}, and $t_{1/2}$. The PK parameters will be summarized by descriptive statistics (i.e., mean, standard deviation, standard error, geometric mean, median, minimum and maximum) by treatment group and by timepoint. Additional analyses may be performed if deemed necessary.

8.3.6 Pharmacodynamic Analysis

Descriptive statistics will be provided by change from baseline and percentage change from baseline as appropriate for:

- Fecal calprotection
- Eosinophil count, serum eotaxin-1,hs-CRP and ECP
- Change in eotaxin-1 concentration and eosinophil count in biopsy tissue from Screening to Day 56.

8.3.7 Safety Analysis

The evaluation of safety endpoints will be carried out on the Safety set. Safety will be assessed by evaluation of adverse events and changes from baseline in vital signs, physical examination, infusion reactionand clinical laboratory safety test results. Individual subject listing will be provided. The observation period for all the safety endpoints spans from start of study medication up to study day 90.

8.3.7.1 Adverse Events

Adverse events will be coded to system organ class and preferred term using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) and are graded by the Investigator in terms of severity and relation to study treatment. All data will be listed by subject. Only treatment emergent AEs (TEAEs) will be presented in summary tables.

TEAEs are the adverse events that occur during the observation period, and the pre-treatment adverse events or pre-existing medical conditions that worsen in intensity after start of study medication and within the observation period.

TEAEs will be summarized by treatment arm in terms of crude incidence rates. For each event the crude incidence rate is defined as the number of subjects experiencing the event divided by the number of subjects initially exposed to study drug, regardless of duration of exposure to study drug. In addition, for each event the worst severity grade and the "worst" Investigator's judgment on study drug relationship is considered for each subject and frequency tables by worst severity grade and by worst study drug relation are provided. In this analysis, a subject having experienced more than once events classified under the same preferred term (body system) will be counted only once in the number of subjects with that preferred term (body system).

Summaries of TEAEs will be presented by body system and by preferred term within each body system (MedDRA™ Terminology). The percentage of subjects who experienced AEs coded with the same term will be tabulated by treatment group in descending order according to the incidence of AEs in the active treatment groups.

All reported adverse events will be listed independently of their onset date. Serious Adverse Events, causes of death and AEs leading to premature discontinuation of study drug will be summarized similarly and listed. Reasons for premature discontinuation of study drug will be listed and summarized by frequency tables on all analysis sets.

8.3.7.2 Clinical Laboratory

All laboratory data will be listed in original and standardized units; abnormal results will be flagged, depending on the direction of the change with respect to below or above the normal ranges, as high or low.

Treatment-emergent laboratory abnormalities (those that newly emerge during the observation period) will be summarized by treatment arm in terms of crude incidence rates.

Algorithms for the standardization of numeric values obtained from different laboratories and/or using different normal ranges will be defined in the SAP. In the evaluation of laboratory abnormalities, missing baseline values for subjects who had other assessments will be imputed by the mean of the normal range boundaries.

Numeric laboratory variables, transformed to standard units, as assessed at baseline, at each scheduled time point during the observation period and at the last available timepoint during the observation period will be summarized by descriptive statistics (i.e., mean, median, standard deviation, standard error, quartiles, minimum and maximum) by treatment group both for observed values and for changes from baseline. In this evaluation, subjects will be included who had the baseline and the relevant assessment.

8.3.7.3 Evaluation of Anti-Bertilimumab Antibodies

Occurrence of anti-bertilimumab antibodies above the predefined threshold will be summarized by treatment arm in terms of crude incidence rate.

8.3.7.4 ECG

ECG parameters as assessed at baseline (i.e., pre-dosing, Day 0), at each scheduled time point during the observation period and at the last available timepoint during the observation period will be summarized by descriptive statistics (i.e., mean, median, standard deviation, standard error, quartiles, minimum and maximum) by treatment group both for observed values and for changes from baseline. In this evaluation, subjects will be included who had the baseline and the relevant assessment. Treatment-emergent ECG abnormalities (those that newly emerge during the observation period) will be summarized by treatment arm in terms of crude incidence rates.

8.3.7.5 Vital Signs

Vital signs as assessed at baseline (i.e., pre-dosing, Day 0), at each scheduled time point during the observation period and at the last available time point during the observation period will be summarized by descriptive statistics (i.e., mean, median, standard deviation, standard error, quartiles, minimum and maximum) by treatment group both for observed values and for changes from baseline. Subjects who had the baseline and the relevant assessment will be included in this evaluation.

8.3.7.6 Physical Examination

The data collected on the physical examination form at baseline (i.e., pre-dosing, Day 0) and each study visit will be tabulated by frequency count and percentage for each organ system.

8.3.8 Interim Analysis

No interim analysis is planned in this trial.

9. ETHICS

9.1 INSTITUTIONAL REVIEW BOARD OR INDEPENDENT ETHICS COMMITTEE

Prior to initiation of the study, the Principal Investigator will submit the study protocol and amendments, sample Informed Consent Form (ICF), and any other documents that may be requested to the IRB/IEC for review and approval. The Investigator will request that the IRB/IEC provide written approval of the study and will keep on file records of approval of all documents pertaining to this study. The Investigator will not begin the study until the protocol and ICF have been approved by the IRB/IEC. The Investigator must agree to make any required progress reports to the IRB, as well as reports of SAEs, life-threatening conditions or death.

9.2 ETHICAL CONDUCT OF THE STUDY

All clinical work conducted under this protocol is subject to GCP guidelines. This includes an inspection by Sponsor or its designee, health authority or IRB/IEC representatives at any time. The Investigator must agree to the inspection of study-related records by health authority representatives and/or Sponsor or its designee.

The study will be conducted in accordance with the following guidelines:

- GCP: Consolidated Guideline (International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use, May 1996).
- Declaration of Helsinki: Fortaleza, Brazil, October 2013.
- Israeli MOH guidelines (February 2016).
- Guidelines from the country-specific National Competent Authority as appropriate.

9.3 PROTOCOL REVISIONS AND/OR DEVIATIONS

Changes to the protocol may be made only by the Sponsor. All protocol modifications must be submitted to the IRB/IEC in accordance with local requirements and, if required, to Regulatory Agencies, either as an amendment or a notification. Approval for amendments must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial study subjects, or when the changes involve only logistical or administrative aspects of the trial. No approval will be required for notifications.

9.4 STUDY SUBJECT INFORMATION AND CONSENT

Prior to screening for the study, each potential subject will be informed in detail about the study drugs to be administered, and the nature of the clinical investigation with its risks and discomforts to be expected. The basic elements of informed consent as specified by the FDA (21 CFR 50.25) and ICH-GCP will be followed. Written consent will be obtained from each subject to be involved in the clinical trial by using the IRB/IEC-approved Informed Consent Form (ICF) prior to the conduct of any study-related activity. Each subject will be given a copy of the written ICF. Subjects will also be instructed that they are free to withdraw their

consent and discontinue their participation in the study at any time without prejudice. Each subject's chart will include the signed ICF for study participation. When the study treatment is completed and the CRF has been monitored, the ICF will be kept in the Investigator's central study file for the required period. Regulatory authorities may check the existence of the signed ICF in this central study folder if not having done so during the study.

9.5 STUDY SUBJECT INSURANCE

The Sponsor has an insurance policy for the total duration of the study covering the subjects and Investigators in respect of the risks involved in conducting this study according to this protocol. The certificate of insurance will be filed in the Investigator's file or can be made available to the Investigator and to the IRB/IEC upon request.

9.6 PERSONAL DATA PROTECTION

The Sponsor complies with the principle of subject's right to protection against invasion of privacy. Throughout this trial, all data will be identified only by an identification number and subject initials. The data will be blinded in all data analyses. The subject must be informed and consent is required that authorized personnel of the Sponsor and/or designee (Study Monitor, Auditor, etc.) and relevant health regulatory agency will have direct access to personal medical data to assure a high quality standard of the study.

10. QUALITY CONTROL AND QUALITY ASSURANCE

10.1 AUDITS AND INSPECTIONS

The Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor or its designees or to regulatory authority inspectors after appropriate notification. The verification of the CRF data must be by direct inspection of source documents. These audits or inspections may take place at any time, during or after the study, and are based on the national regulations, as well as ICH guidelines.

10.2 STUDY MONITORING

Monitoring of the study is the responsibility of the Sponsor and may be delegated to a CRO or a contract monitor. The study monitor will advise the Investigator regarding the practical conduct of the study and maintaining compliance with the protocol, GCP and all applicable regulatory requirements. Throughout the course of the study, the study monitor will oversee the conduct and the progress of the study by frequent contacts with the Investigator. This will include telephone calls and on-site visits. During the on-site visits, the CRF will be reviewed for completeness with corresponding source documents. As part of the data audit, source documents will be made available for review by the study monitor. The study monitor will also perform drug accountability checks and may periodically request review of the Investigator's study file to ensure completeness of documentation in all respects of clinical study conduct.

Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate period. The Investigator or appointed delegate will receive the study monitor during these on-site visits, cooperate in providing the documents for inspection and respond to inquiries.

10.2.1 Source Data and Records

Source data/records contain all the information, which is necessary for the reconstruction and evaluation of the study. Source data/records are 1) original records, 2) certified copies of

original records, 3) observations, 4) laboratory reports, 5) paper Case Report Forms (CRFs) and/or data sheets, 6) data entered directly into the eCRF. Source data/records are to be kept within the control of the Investigator until the end of the regulatory retention period. The Investigator will permit study-related monitoring, audit(s), IRB review(s) and regulatory inspection(s), with direct access to all the required source records.

In this study, at the time of the office visit, study specific original data elements may be entered directly into a web-based system without first being transcribed on other media such as paper. These original electronic data will be stored with Target e*CTR® (electronic Clinical Trial Record) Viewer in a central server prior to being transmitted to the electronic data capture (EDC) database. Access to these electronic original data are controlled by the Investigator or designee.

10.2.2 Original Records

This study may use direct data entry of clinical trial data into the Target e*CRF® (EDC) system, using the Target e*CTR® (Target e*Clinical Trial Record) process. This process allows a clinical study site to perform direct data entry of original data into Target e*CRF®, and to store these original data in PDF format in the Target e*CTR Viewer, an independent repository controlled by the clinical Investigator, prior to the data being recorded in the Target e*CRF® database.

10.2.3 Target e*CRF® (Electronic Data Capture)

Clinical trial data will be entered by the Investigator, or a designee into Target e*CRF®, a validated 21 CFR Part 11 compliant Internet-based EDC system. Changes to the clinical trial data can only be performed by the Investigator or designee through the change management methodology that is subject to a full audit trail.

The Investigator and staff will be trained on Target e*CRF® prior to enrollment of the first subject. A list of the status of each user, including an audit trail of status changes will be maintained. In addition, the user module of Target e*CRF® maintains the original status and an audit trail of any changes.

At the end of the study, the completed online eCRF must be reviewed and signed electronically by the Investigator named in the study protocol or by a designated sub Investigator authorized to sign. A certification must be obtained from all authorized persons to sign electronically indicating that their electronic signature is equivalent to their hand-written signature. In order to sign electronically, the signer must log in with their username and password and reenter their password on the page(s) requiring a signature(s).

10.2.4 Target e*CTR® Viewer (Target e*Clinical Trial Record Viewer)

Target e*CTR® Viewer is a validated 21 CFR Part 11 compliant Internet-based software system. The original subject data PDF files are read-only. Users' access to the Target e*CTR® Viewer is granted by the Investigator, or a designee. The Investigator can download a bookmarked PDF copy of original records of individual subjects or all subjects, including an audit trail of changes and electronic signatures.

10.2.5 Certified Copies of Original Data

In the event there is no access to the Internet for direct data entry at the time of the study visit, the site should record original data using paper records or equivalent. Once the Internet is available, these original data must be entered into Target e*CRF®. If these original data are then designated as Certified Copies within Target e*CRF®, the paper records may be discarded as long as:

1. This process is supported by written procedures

2. The site is trained on these procedures, including instructions to visually check the transcribed data prior to certification.

10.3 QUALITY LABORATORY STANDARDS

Laboratory tests or evaluations described in this protocol will be conducted in accordance with quality laboratory standards as described in the SOPs of the local institution laboratory and central laboratories.

10.4 DATA MANAGEMENT

A Clinical Data Monitoring Plan (CDMoP) is created to specifically identify how data management will be performed for the study. The following summarizes the CDMoP:

The clinical database is held and managed by Target Health during the lifetime of the study. Target e*CRF® will be used for online edit checks, batch edit checks and query management. In order to build the EDC application, an Application Setup Instructions (ASI) document is created. The ASI document contains the specific instructions to both the EDC and data management (DM) programmers.

Data validation is performed according to the specifications in the Data Validation Plan (DVP). Within the DVP, there are 3 types of validation checks:

- Online checks performed by the EDC system during data entry. Target Health is responsible for programming and resolving any hits based on these checks.
- Batch edit checks. Target Health is responsible for programming and resolving any hits based on these checks.
- Manual checks performed by the monitor and Target Health Clinical Data Management (CDM). The data manager (DM) is responsible for providing listings to monitors to be used for manual checks.

Queries are handled within the Target e*CRF® application. The monitors and DMs are the only persons who can generate a query. Under direction of the Investigator, the site Coordinator addresses the query. If the query is due to a data entry error, the Coordinator can immediately make the corrections in the applicable eCRF pages. If the query needs clarification, the Coordinator contacts the Investigator for resolution. The Coordinator then enters the correct value or submits an answer to the query without modifying the data. The monitor then reviews the corrected eCRF pages and/or answer. If the data are changed correctly or the answer is acceptable, the monitor closes the query. If the answer is not acceptable, the monitor submits an additional query for clarification. All changes to the database require a "Reason for Change" and are subject to an audit trail. The audit trails identifies the changed data, reason(s) for change, who changed the data and the time and date of the change (based on the Target e*CRF® server's time).

EDC management reports are also available to view the data for consistency. The basic reports are:

- Overall Data Entry Status (By Site/Subject)
- Investigator signature status (By Site/Subject)
- Query Age Report (by Site)
- Query Report (by Site/Subject)
- Query Frequency By Site
- Query Frequency By Edit Check
- Query Frequency by Form
- Subject Visit Status Report (by Site / Subject)

- AE Report (By Site/Subject)
- Concomitant Medication Report (By Site/Subject)
- Serious AE Report (by Site/Subject)
- Subject Status Report (by Site)
- Protocol Violation Report (by Site / Subject)
- Treated (by Site / Subject)
- Subject Tracking Report (Individual)

Additional management reports can be specified and programmed during the course of the study.

Centralized monitoring is performed daily or at an agreed-upon frequency, as defined in the CDMoP. The following are samples of reports that assist in the centralized monitoring process. Study specific reports will be found in Target e*CRF®.

1. System logs and reports to identify when users log in
2. Time from subject visit to data entry
3. Online edit checks
4. Batch edit checks
5. Data listings
6. Subject profiles

Results from the daily monitoring are discussed. Meetings with the clinical research and DM teams are held to review and discuss data quality and data management issues, and minutes of meetings maintained. When necessary, the Monitoring Plan and CDMoP are revised and corrective actions are implemented.

11. STUDY ADMINISTRATION

11.1 PARTICIPATING CENTERS

Approximately 10-12 sites in Israel will participate in this study. Additional sites in Europe may be added in the event of slow recruitment. A list of the Principal Investigators will be maintained in the trial master file.

11.2 REQUIRED DOCUMENTS PRIOR TO STUDY INITIATION

Prior to the start of this study, all pre-investigational requirements must be met by the Investigator and study site. These may include:

- Appropriate local health authority documentation properly signed and dated by the required Investigators (i.e., the submission package)
- Signed copy (original) of the approved protocol
- Completed and signed statement of Investigator
- A signed Clinical Trial Agreement
- Curriculum vitae for the Investigator and sub-Investigators[p]
- IRB/IEC name and address; and membership list
- Letter of approval from the IRB/IEC for both protocol (identified by protocol title and number) and informed consent form (identified by protocol title and number)
- Copy of the IRB/IEC-approved written ICF to be used in the study (that has also been approved by the Sponsor)

[p] Can be collected at Site Initiation Visit

- Provisions for direct access to source/data documents if necessary for trial-related monitoring, audits, IRB/IEC review and regulatory inspection
- Name and location of the laboratory utilized for laboratory assays and other facilities conducting tests, as well as a copy of the laboratory certificate and list of normal laboratory values (can be collected at Site Initiation Visit). In case a laboratory certification is not available, a written statement as to how the laboratory complies with quality assurance should be provided.

Upon satisfactory receipt of all required regulatory documents, Sponsor will arrange the supply of all required infusion and ancillary pharmacy supplies. Study drug (bertilimumab or placebo), will be provided only on an as-needed basis, as subjects are enrolled in the study. - Supply of all other study materials will be the responsibility of the Sponsor and/or designee. Subject entry should not begin until after the required regulatory documents are confirmed as received and the Investigator Meeting/Initiation Meeting has occurred. All personnel expected to be involved in the conduct of the study will undergo orientation to include review of study protocol, instructions for CRF completion, AE reporting, and overall responsibilities including those for drug accountability and study file maintenance.

The Investigator and/or designee (study monitor) will prepare an Investigator's study file. This file should be used for all trial related documents. The Investigator will be responsible for keeping the Investigator's file updated and ensuring that all required documents are filed. The file will be inspected during monitoring visits.

11.3 CLINICAL TRIAL SUPPLIES

The Investigator will be responsible for administrating, inventory and accountability of all clinical trial supplies and exercising accepted medical and pharmaceutical practices. An accurate and timely record of the disposition of all clinical supplies must be maintained. The supplies and inventory record must be made available for inspection upon request. Upon completion or termination of the study, the Investigator will keep the remaining clinical supplies along with a copy of the inventory record and a record of the clinical supplies returned. **Under no circumstances will the Investigator allow the study drugs or other study-related supplies to be used other than as directed by this protocol.**

11.4 INVESTIGATOR SITE FILE

All documents required for the conduct of the study as specified in the ICH-GCP guidelines will be maintained by the Investigator in an orderly manner and made available for monitoring and/or auditing by the Sponsor and regulatory agencies.

11.5 STUDY COMPLETION

This study is expected to end when all required subjects have been enrolled and the last subject has completed the study and the query resolution has been completed. Data and materials that are required before the study can be considered complete and/or terminated are:

- Laboratory findings, clinical data and all special test results from screening through the end of the follow-up period.
- CRF properly completed by appropriate study personnel and signed by the Investigator.
- Completed Drug Accountability Records.
- Statement of outcome for each serious adverse event reported.
- Copies of protocol amendments and IRB/IEC as well as relevant health authority approval/notification (if applicable).

11.6 FINAL REPORT

A final study report will be prepared after the study has been completed and database has been cleaned, locked and analyzed. The report will be prepared according to the ICH E3 guidelines.

11.7 RETENTION OF STUDY RECORDS

The Investigator will retain copies of the approved protocol, completed CRF, informed consent documents, relevant source documents, and all other supporting documentation related to the project for 15 years. If the Investigator is unable to retain the study documents for the required amount of time, Sponsor or designee must be informed of the individual who will be assuming this responsibility.

These files must be made available for inspection upon reasonable request by authorized representatives of Sponsor and/or the relevant regulatory agencies.

11.8 CONFIDENTIALITY AND PUBLICATION

Subject medical information obtained by the study is confidential and disclosure to third parties other than those noted below is prohibited. Throughout the study, all data will be identified only by the subject identification number, and where applicable, the subject's initials and birthdates.

At the subject's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. Personal physician will be notified by site personnel of subject participation in the study.

All information supplied by Immune Pharmaceuticals, Inc. in association with this study and not previously published, is considered confidential information. This information includes, but is not limited to, the Investigator's Brochure, the protocol, CRFs, and other scientific data. Any data collected during the study are also considered confidential. This confidential information shall remain sole property of Immune Pharmaceuticals, Inc., shall not be disclosed to others without the written consent of Immune Pharmaceuticals, Inc. and shall not be used except in the performance of this study.

The information developed during the conduct of this study is also considered confidential, and will be used by Immune Pharmaceuticals, Inc. This information may be disclosed as deemed necessary by Immune Pharmaceuticals, Inc. To allow the use of this information derived from this study, the Investigator is obliged to provide Immune Pharmaceuticals, Inc. with complete test results and all data developed in this study.

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13. APPENDICES

Appendix A Schedule of Activities

Study Procedures	Screening Period	Treatment Period[a]			Early Discontinuation[b]	Follow-up Period[c]			
Visit	**1**	**2**	**3**	**4**	**-**	**5**	**6**	**7**	**8**
Study Day	**-28 to -1**	**0**	**14**	**28**	**-**	**35**	**42**	**56**	**90**
Inclusion/exclusion criteria	X	X							
Informed consent	X								
Demographic & medical history	X								
Physical examination	X	X*	X*	X*	X	X	X	X	X
Vital signs	X	X[d]	X[d]	X[d]	X	X	X	X	X
ECG	X	X[e]	X[e]	X[e]	X	X	X	X	X
Screen for active/latent tuberculosis and fecal sample for *C. difficile* toxin	X								
Randomization	X								
Mayo Score	X				X			X	
Partial Mayo Score	X	X*	X*	X*	X	X	X	X	X
Bertilimumab or Placebo infusion- (after administration of pretreatment regimen)[i]		X	X	X					
Flexible sigmoidoscopy with biopsies[f]	X				X			X	
Ulcerative Colitis Endoscopic Index of Severity	X				X			X	
Adverse events		X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Infusion reaction assessment[g]		X	X	X					
Urine β-hCG		X*	X*	X*					
Hematology and biochemistry	X[h]	X*	X*	X*	X	X	X	X	X
Serology	X								
PK (bertilimumab) blood sampling		X[i]	X[i]	X[i]	X	X	X	X	X
Anti-bertilimumab antibodies		X*	X*	X*	X	X	X	X	X
Eotaxin-1, eosinophil count, eosinophil cationic protein (ECP)-s-CRP		X*	X*	X*	X	X	X	X	X

[a] Visits during the treatment period have a ±2 day window.
[b] At this visit the activities relating to the study period at which time the patient discontinued will be performed.
[c] Visits during the follow-up period have a ±3 day window.
[d] Vital signs will be measured pre-dose and 15 min (during), 30 minutes (+15 minutes), 2 hr (± 20 minutes), and 4 hr (± 20 minutes) following initiation of study drug administration.
[e] ECG will be performed pre-dose, and at 30 (+ 15) minutes following initiation of study drug administration.
[f] At least 3 tissue samples are required from area of active inflammation at Screening. On Day 56 (or early discontinuation visit), at least 3 tissue samples are required from the same region where Screening biopsies were obtained. Additional biopsy samples may be collected at the Investigator's discretion for histological assessment.
[g] Infusion reactions will be monitored for up to 4 hours following study drug administration and graded, as applicable, as appears in Appendix D
[h] Biochemistry will include serum β-hCG at screening.
[i] Blood samples for bertilimumab (PK analysis) will be collected pre-dose, 30 (+15) minutes (immediately post-dose) and 4 hours (± 20 minutes) following initiation of study drug infusion.

Study Procedures	Screening Period	Treatment Period[a]			Early Discontinuation[b]	Follow-up Period[c]			
Visit	**1**	**2**	**3**	**4**	**-**	**5**	**6**	**7**	**8**
Study Day	**-28 to -1**	**0**	**14**	**28**	**-**	**35**	**42**	**56**	**90**
Calprotectin in fecal sample	X	X*	X*	X*	X	X	X	X	X
Eotaxin-1 & eosinophil count in tissue samples	X				X			X	

* Denotes assessment will be done pre-dose.

[j] The pretreatment dosing regimen is as follows:

Dexamethasone 10 mg PO 24-18 hours prior to administration of bertilimumab.

Acetaminophen 1000 mg PO 1 hour prior to administration of bertilimumab

Loratadine 10 mg PO or cetirizine 10 mg PO one hour prior to the administration of bertilimumab.

In the event that dexamethasone was not administered previously, then 10 mg dexamethasone IV may be administered one to three hours prior to bertilimumab administration.

Appendix B Mayo Score

The Mayo score is a discrete ordinal scale ranging from 0 (normal or inactive disease) to 12 (severe disease) and is a composite of 4 sub-scores: Stool Frequency Sub-score, Rectal Bleeding Sub-score, Endoscopic Finding Sub-score, and Physician's Global Assessment Sub-score, each of which ranges from 0 (normal) to 3 (severe disease).

Mayo Scoring System* for Assessment of Ulcerative Colitis Activity	
Stool Frequency Sub-score	
0	Normal number of stools for study patient
1	1 to 2 stools per day more than normal
2	3 to 4 stools more than normal
3	≥5 stools more than normal
Rectal Bleeding Sub-score	
0	No blood seen
1	Streaks of blood with stool less than half the time
2	Obvious blood with stool most of the time
3	Blood alone passes
Endoscopic Finding Sub-score	
0	Normal or inactive disease
1	Mild Disease (erythema, decreased vascular pattern, mild friability)
2	Moderate Disease (marked erythema, lack of vascular pattern, friability, erosions)
3	Severe Disease (spontaneous bleeding, ulceration)
Physician's Global Assessment Sub-score	
0	Normal
1	Mild Disease
2	Moderate Disease
3	Severe Disease

*Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, et al. (2005 Dec) Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 8;353(23):2462-76.

Appendix C Ulcerative Colitis Endoscopic Index of Severity

Descriptor (score most severe lesions)	Likert scale anchor points	Definition
Vascular pattern	Normal (0)	Normal vascular pattern with arborization of capillaries clearly defined or with blurring or patchy loss of capillary margins
	Patchy obliteration (1)	Patchy obliteration of vascular pattern
	Obliterated (2)	Complete obliteration of vascular pattern
Bleeding	None (0)	No visible blood
	Mucosal (1)	Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope that can be washed away
	Luminal mild (2)	Some free liquid blood in the lumen
	Luminal moderate or severe (3)	Frank blood in the lumen ahead of the endoscope or visible oozing from the mucosa after washing intraluminal blood, or visible oozing from a hemorrhagic mucosa
Erosions and ulcers	None (0)	Normal mucosa, no visible erosions or ulcers
	Erosions (1)	Tiny (≤5 mm) defects in the mucosa of a white or yellow color with a flat edge
	Superficial ulcer (2)	Larger (>5 mm) defects in the mucosa, which are discrete fibrin-covered ulcers when compared with erosions but remain superficial
	Deep ulcer (3)	Deeper excavated defects in the mucosa with a slightly raised edge

NOTE. The worst affected area of the colon visible at sigmoidoscopy was scored. Although the original version of the UCEIS[6] gave a score of 1 to the normal appearance of a descriptor, a collective decision was made to change the numbering of the levels with normality awarded a score of 0, so that the simple sum of the UCEIS ranges from 0 to 8.

Appendix D Grading of Infusion Reactions

	Grade			
	1	**2**	**3**	**4**
Signs and symptoms	Transient flushing or rash, drug fever <38º C; asymptomatic bronchospasm	Generalized urticaria responsive to medication; drug fever >38°C; dyspnea or reversible bronchospasm	Bronchospasm requiring medication; symptomatic urticaria persisting with medication; allergy-related edema/angioedema; hypotension; signs and symptoms not rapidly responsive to interruption of infusion	Anaphylaxis (defined below); laryngeal/ pharyngeal edema requiring resuscitation; cardiopulmonary instability requiring ventilatory support or pressors
Intervention	None	Infusion held up to 30 minutes or until symptoms recede; if symptoms recur upon resuming infusion, then discontinue infusion	Discontinue infusion; initiate additional interventions if warranted clinically	Discontinue infusion; urgent intervention indicated

Anaphylaxis criteria (adopted from the NIAAD/FAAN Clinical Criteria for Anaphylaxis, The Second Symposium on the Definition and Management of Anaphylaxis, Sampson *et al.* 2006):

One or both of the following:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   And at least one of the following:

   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)

   b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur minutes to several hours after exposure to a likely allergen for that patient:

   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)

   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)

   c. Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)

   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)