Official Protocol Title:	An open label, single group assignment design study to correlate soluble ST2 with clinical, endoscopic and histological activity in moderate to severe Ulcerative Colitis patients under golimumab
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Investigator Signature Page

Abbreviated Title	**EVOLUTION study**
Title	**An open label, single group assignment design study to correlate soluble ST2 with clinical, endoscopic and histological activity in moderate to severe Ulcerative Colitis patients under golimumab** (Phase 4; Protocol No. MK-8259-022-03)
Sponsor	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Trial Physician	PPD
Date of Finalization of This Current Version of the Protocol	Amendment No 3, 13Mar2017
Previous Version(s) of the Protocol	Amendment No 2, 20Jan2016 Amendment No 1, 17Jun2015 Initial Protocol, 06Aug2014_v1.6

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PPD _____ _____
Medical Director ***dd MMM yyyy***

I have read Protocol No. MK 8259-022-03 dated 13 March 2017, including all appendices, and agree to conduct the trial in accordance with the protocol. The amendment to the protocol and trial documents must also be approved by the IRBs/IECs and regulatory authorities as appropriate, before implementation at the site. I agree to implement the amendment to the protocol and trial documents only after all necessary approvals have been obtained and the sponsor has confirmed that it is acceptable to do so.

_____ _____ _____
Name, Degree, full mailing address of Investigator ***Site Number*** ***dd MMM yyyy***

1.0 TITLE PAGE

Abbreviated Title	EVOLUTION study
Title	**An open label, single group assignment design study to correlate soluble ST2 with clinical, endoscopic and histological activity in moderate to severe Ulcerative Colitis patients under Golimumab** MK 8259-022-03
Sponsor	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Sponsor's Address	One Merck Drive P.O. Box 100 Whitehouse Station, NJ 08889-0100, U.S.A.
IND No.	Not Applicable
EudraCT No.	2014–003262–25
Trial Physician	PPD
Phase	4
Date of Finalization of This Current Version of the Protocol	Amendment No 3, 13Mar2017
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Protocol Template Approval Date	26 Nov 2013

C O N F I D E N T I A L

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2.0 SYNOPSIS

TITLE OF TRIAL: An open label, single group assignment design study to correlate soluble ST2 with clinical, endoscopic and histological activity in moderate to severe Ulcerative Colitis patients under Golimumab

(Phase 4; Protocol No. MK 8259-022-03)

ABBREVIATED TITLE: Evolution study

OBJECTIVES: Evaluate soluble ST2 as a surrogate marker of clinical, endoscopic and histological activity in moderate to severe ulcerative colitis patients under treatment with golimumab sc.

Primary Trial Objectives:

- To evaluate the correlation of serum soluble ST2 levels with endoscopic activity (endoscopic Mayo score) at week 6 in moderate to severe UC subjects under golimumab treatment.
- To evaluate the correlation of serum soluble ST2 with histological activity (Geboes index) at week 6 in moderate to severe UC subjects under golimumab treatment.

Secondary Trial Objectives:

- To evaluate the correlation of serum soluble ST2 levels with endoscopic activity (endoscopic Mayo score) at week 16 in moderate to severe UC subjects under golimumab treatment.
- To evaluate the correlation of serum soluble ST2 levels with histological activity (Geboes index) at week 16 in moderate to severe UC subjects under golimumab treatment.
- To correlate serum soluble ST2 levels with fecal calprotectin, at week 6 and week 16 in moderate to severe UC subjects under golimumab treatment.
- To correlate serum soluble ST2 with clinical activity (total Mayo score) at week 6 and week 16 in moderate to severe UC subjects under golimumab treatment.
- To evaluate the potential of serum soluble ST2 as a predictor of endoscopic response (endoscopic Mayo score) to golimumab in moderate to severe UC subjects.
- To evaluate the correlation between serum soluble ST2 levels with maintenance of endoscopic response (endoscopic Mayo score) to golimumab.
- To correlate Mayo endoscopic score with UCEIS overall score at week 6 and week 16 in moderate to severe UC subjects under golimumab treatment.

Exploratory Objectives:

To evaluate the relationships of serum levels of golimumab and the presence of anti-golimumab antibodies with clinical, endoscopic, and histological activities and with biomarker levels in subjects with moderate to severe UC

Trial Design

Overview: This is an exploratory, multi-site, nonrandomized, open label, prospective, interventional, single-arm, study to evaluate the correlation of serum soluble ST2 levels with clinical, endoscopic and histological activity in subjects with moderate to severe active UC who received golimumab. After signing the informed consent, subjects will enter a screening period of up to 42 days. After confirmation of eligibility criteria, subjects will initiate treatment with golimumab according to SmPC (Baseline – V2). Subjects will be followed for a period of 16 weeks for clinical assessments and data collection. Biomarker samples (ST2 and fecal calprotectin) will be collected at baseline and at all subsequent visits. All subjects will be evaluated for endoscopic (fibrosigmoidoscopy) and histologic activity at screening, week 6 and week 16.

Number of Trial Centers: Approximately 10

Duration of Participation: Each subject will participate in the trial for approximately 22 weeks from

TITLE OF TRIAL: An open label, single group assignment design study to correlate soluble ST2 with clinical, endoscopic and histological activity in moderate to severe Ulcerative Colitis patients under Golimumab (Phase 4; Protocol No. MK 8259-022-03)
ABBREVIATED TITLE: Evolution study
the time the subject signs the Informed Consent Form (ICF) until the final contact. After a screening period of up to 6 weeks, each subject will initiate golimumab according to the Summary of Product Characteristics and will be followed for a period of 16 weeks.
Duration of Trial: The trial will require approximately 2 years from the beginning to the end of the overall trial (first subject signing informed consent to last contact with last subject).
Key Inclusion/Exclusion Criteria: Subjects with a diagnosis of moderate to severe ulcerative colitis will be selected to participate in the trial. Inclusion criteria: Age 18 years or older at time of enrollment; diagnosis of moderate to severe ulcerative colitis at inclusion (defined as a clinical Mayo score ≥6) including endoscopy that shows inflammation as judged by a Mayo endoscopy score ≥2; subject is eligible to receive golimumab as per product monograph; signed the informed consent Exclusion criteria: as per golimumab's product monograph; history of asthma, autoimmune diseases, hypertension.
INVESTIGATIONAL PRODUCT, DOSE, MODE OF ADMINISTRATION **Investigational Product:** Golimumab (SIMPONI) sc as per product monograph
Reference Product: Not applicable
STATISTICAL METHODS: All quantitative variables will be summarized through descriptive statistics namely mean, median, standard deviation and range (minimum and maximum) and qualitative variables through absolute (n) and relative frequencies (%) and 95% confidence intervals (if applicable). The statistical analysis will be performed through frequency tables for qualitative variables and tables with descriptive statistics for quantitative variables. The association between two quantitative variables will be performed through Pearson correlation coefficient or Spearman correlation coefficient, in case the normality assumption was not verified. The association of two categorical variables will be tested through the Chi-Square test or Fisher Exact test (if applicable). Cohen's kappa coefficient will be performed. The comparison of two independent samples in respect to quantitative variables will be performed through t-test for independent samples or the Mann-Whitney non-parametric test, according to the assumption validations of the statistical test. ROC curve analysis will be performed as well as sensitivity, specificity, and positive and negative predictive values.
Data Set(s) to be Analyzed: The primary analysis is to be performed on the Full Analysis Set, defined as all subjects who had received study medication and had at least one valid post baseline assessment for the primary endpoint that correlates ST2 with endoscopic activity. In addition, a Per Protocol Set is defined as subjects receiving treatment, who meet key eligibility and evaluability criteria. Sensitivity analyses will be based on this Per Protocol Set. All safety analyses will be performed on the All Treated Set, comprising all subjects who received at least one dose of study medication.
Sample Size: Based on the recruitment capacity of sites it is expected to include a total of 37 subjects for analysis. With this sample size there is a probability of 80% that the lower limit of a one-sided 95% confidence interval is higher than 0.50, if the observed correlation coefficient is at least

TITLE OF TRIAL: An open label, single group assignment design study to correlate soluble ST2 with clinical, endoscopic and histological activity in moderate to severe Ulcerative Colitis patients under Golimumab

(Phase 4; Protocol No. MK 8259-022-03)

ABBREVIATED TITLE: Evolution study

0.75.

Study Analysis:

The primary analysis is to investigate the correlation between serum soluble ST2 and:

- endoscopic activity of disease (measured by endoscopy Mayo subscore) at 6 weeks in UC subjects receiving golimumab;
- histological activity (measured by Geboes index score) at 6 weeks in UC subjects receiving golimumab.

For both analyses the Spearman correlation coefficient will be used.

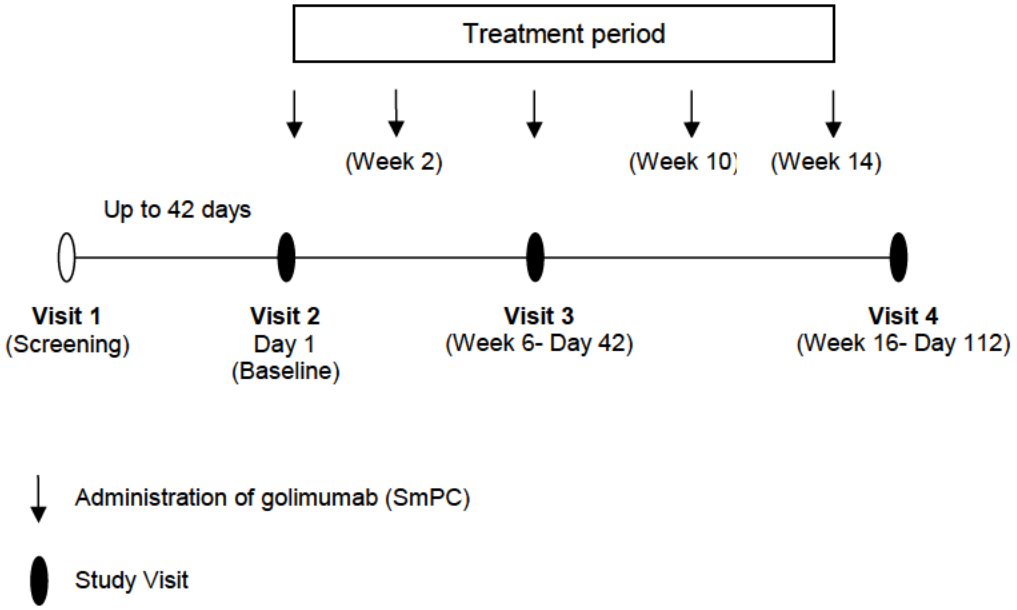
For the key secondary endpoints the following analysis will be performed:

- The correlation between serum soluble ST2 with endoscopic activity of disease (measured by endoscopy Mayo subscore) at 16 weeks in UC subjects receiving golimumab, through the Spearman correlation coefficient;
- The correlation between serum soluble ST2 histological activity (measured by Geboes index score) at 16 weeks in UC subjects receiving golimumab, through the Spearman correlation coefficient.
- Serum soluble ST2 levels at baseline, Week 6 and Week 16 will be correlated with fecal calprotectin levels at baseline, week 6 and week 16 through Pearson correlation coefficient or Spearman correlation coefficient in case the normality assumption is not verified. The two biomarkers will be categorized by the cut-offs and Cohen's kappa coefficient will be obtained.
- Serum soluble ST2 levels at baseline, week 6 and week 16 will be correlated with clinical activity (total Mayo score), through Spearman correlation coefficient.
- Comparative analyses of means (active disease versus inactive disease at week 6) with serum ST2 at baseline and change between baseline and week 6.
- Comparative analyses of subjects who achieved response at week 6 and maintained through week 16 versus subjects who did not maintain response, regarding serum soluble ST2 at baseline, week 6 and change between baseline and week 6. ROC curve analysis of the serum soluble ST2 at week 6 regarding maintenance of response between week 6 and 16 will be performed. This exploratory analysis will detect the cut-off levels of the serum soluble ST2 at week 6 associated with maintenance of response.

Safety Analysis: Adverse events and laboratory tests will be analyzed through descriptive statistics.

Interim Analysis: No formal interim analyses are planned

2.1 Trial Design Diagram



2.2 Trial Flow Chart

Visit Title Visit Number Scheduled Day Scheduling Window	Screening Visit 1 Days -42 thru 0	Baseline Visit 2 Day 1	Week 6 Visit 3 Day 42 ±3 days	Week 16 [16] Visit 4 Day 112 ±3 days	Early Discontin. [16]
Informed Consent	X				
Demography/Medical History	X				
Prior/Concomitant Medications	X	X	X	X	X
Review of Entry Criteria	X	X			
Physical Examination (partial Mayo Score and Montreal Classification)	X[1]	X	X	X	X
Vital signs (SBP, DBP, heart rate, weight and body temperature)	X	X	X	X	X
Chest X-ray	X[2]				
QuantiFERON-TB Gold test [3]	X				
TB evaluation [4]	X	X	X	X	X
Fibrosigmoidoscopy (UC activity assessed by endoscopy Mayo subscore and UCEIS)	X[1,5]		X	X	X
Histology	X[1,6]		X	X	X
Mayo score		X[7]	X	X	X
Serum Pregnancy Test (β-hCG) [8]	X[1]				
Urine pregnancy test [8]			X	X	X[9]
Fecal calprotectin [10]		X	X	X	X[17]
Serum ST2 sampling [11]		X	X	X	X[17]
Measurement of golimumab levels and anti-golimumab antibodies[19]			X	X	X
Plasma for Future Biomedical Research[18]		X		X	X[17]
CRP (local laboratory)		X	X	X	X
Routine Laboratory [12]	X[1]		X	X	X
(Serious) Adverse Events	X	X	X	X	X
Stool negative for enteric pathogens	X[13]				
Dispensing of Subject Identification Card	X[14]				
Dispense Trial Medication[15]		X	X		
Trial Medication Accountability			X	X	X
Dispensing of subject diary		X			
Review of subject diary			X	X	X

All assessments must be completed prior to study product administration unless otherwise specified.

1 This procedure must be performed **within 2 weeks** prior to baseline (V2)

2 If historical Chest-X-ray is not available within 3 months prior to study inclusion, this exam (both posterior-anterior and lateral views) should be performed at the Screening visit.

3 If historical QuantiFERON-TB Gold test result is not available within 2 months prior to study inclusion, this exam should be performed at the Screening Visit.

4 If not available within 2 months prior to study inclusion, latent TB must be evaluated at screening by specialized, trained, and licensed personnel, either at the participating trial site or at an external unit (e.g. Lung Disease Diagnostic Centers (CDPs)), as according to local guidelines. When this evaluation is performed at any site other than the investigator's facility, the results must be made available in written form as source documentation. If TB is suspected at any time during the study, chest x-ray and QuantiFERON-TB Gold test should be performed and latent TB must be re-evaluated.

5 Fibrosigmoidoscopy must be performed **within 2 weeks** prior to baseline (V2). Colonoscopy will replace fibrosigmoidoscopy if screening for polyps or dysplasia is necessary. A screening biopsy will be performed even if a prior biopsy consistent with the diagnosis of UC is available. In the presence of adenomatous polyps these must be removed prior to visit 2 and this should be reported in subject's Medical History if procedure was executed as planned or the condition did not worsen.

6 Histological data from screening will be used to calculate Geboes index baseline score. At all visits, samples will be prepared and sent to Central laboratory for histological assessment

7 Baseline Mayo score will be calculated using the endoscopic subscore assessed during the screening

8 Female subjects of childbearing age

9 If judged necessary by the investigator

10 Fecal biomarkers will be collected prior to study drug administration. Sample will be sent to a certified central laboratory for analysis.

11 Serum biomarkers will be collected prior to study drug administration. Sample will be sent to a certified central laboratory for analysis.

12 The routine laboratory tests include: Hematology (basophils, eosinophils, hematocrit, hemoglobin, lymphocytes, monocytes, neutrophils, platelets, RBC, WBC); Blood chemistry (total bilirubin, ALT, AST, alkaline phosphatase, albumin, total protein, calcium, phosphate, sodium, potassium, chloride, urea and creatinine and CRP; Urinalysis (proteins, glucose, nitrates, WBC, ketone bodies, hemoglobin, urobilinogen, bilirubin). If historical serology results of HIV, HCV and HBV are not available within 3 months prior to study inclusion, these tests must be performed at the screening visit.

13 Stool culture and *Clostridium difficile* assay for toxin must be performed at screening or in the case of episode exacerbation as long as taken during the 4 months prior to inclusion.

14 The Subject Identification Card will be dispensed after the subject provides written informed consent and will be retrieved at the last visit.

15 Study medication will be dispensed at visit 2 and visit 3 for the following planned administrations. After study completion, and if physician finds it beneficial to the subject, golimumab will continue to be dispensed according to SmPC.

16 Prior to termination of study participation, all subjects should complete assessments indicated at Week 16 or Early Discontinuation.

17 Samples of ST2,calprotectin, and plasma for future biomedical research will only be collected at the Early Discontinuation visit in case the investigator discontinued the subject due to golimumab's lack of efficacy

18 Informed consent for plasma samples for future biomedical research must be obtained before the plasma samples are drawn. Plasma samples for analysis should be obtained pre-dose at Baseline/Day 1 and at Week 16 as the last sample drawn, on enrolled subjects only.

19 Golimumab levels and anti-golimumab antibodies will be measured in blood sample collected prior to study drug administration. Sample will be sent to a certified central laboratory for analysis.

3.0 TABLE OF CONTENTS

3.1 List of Tables

3.2 List of Appendices

4.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
ANCA	Anti-neutrophil cytoplasmic antibodies
Anti-OmpC	anti-Outer membrane of porin C
ASCA	Anti-Saccharomyces cerevisiae antibodies
AST	Aspartate aminotransferase (SGOT)
AZA	azathioprine
CHF	chronic heart failure
CO	Country Operations; a local, country-wide, representative of the sponsor
CRF	Case Report Form
CRP	C-reactive protein
CSR	Clinical Study Report
DBP	Diastolic blood pressure
ECI	Events of Clinical Interest
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EU	European Union
FDA	Food and Drug Administration, USA
GCP	Good Clinical Practice
hCG	Human Chorionic Gonadotropin
IBD	Inflammatory bowel disease
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
ICMJE	International Committee of Medical Journal Editors
IL	Interleukin
IL-1RL1	Interleukin-1 receptor like 1
IMP	Investigational Medicinal Product
IND	Investigational New Drug Application; legal instrument in the USA that allows trial of unapproved, investigational new drugs in human subjects
Investigational Product	The drug, biologic, and/or device being investigated in the current trial
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
NA, N/A	Not applicable

Term	Definition
RBC	Red Blood Cell
RSI	Reference Safety Information
SAE	Serious Adverse Event
(S)AE	All Adverse Events, including Serious Adverse Events
SBP	Systolic blood pressure
sc	subcutaneous
SGOT	Serum Glutamic Oxaloacetic Transaminase (AST)
SGPT	Serum Glutamic Pyruvic Transaminase (ALT)
SmPC	Summary of Product Characteristics
sST2	Serum human Suppression of Tumorigenicity 2
ST2	human Suppression of Tumorigenicity 2
TB	Tuberculosis
TNF	Tumor necrosis factor
UC	Ulcerative colitis
UCEIS	Ulcerative Colitis Endoscopic Index of Severity
USA	United States of America
WBC	White Blood Cell

5.0 INTRODUCTION

5.1 Therapeutic Rationale

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) causing continuous mucosal inflammation of the colon without granulomas characterized by a relapsing and remitting course (Silverberg et al., 2005). Currently, the classification of IBDs is based on clinical parameters (activity, localization and phenotype). However, due to the high percentage of non-classifiable IBD (10%-15%) and the difficulty of a differential diagnosis, it has become necessary to search for new markers for these diseases (Díaz-Jiménez et al., 2011).

Ideally, a biomarker should be able to identify individuals at risk of developing the disease, detect the activity, monitor the effect of the treatment and, finally, have a prognostic value for the reactivation of the disease (Tibble and Bjarnason, 2001; Gisbert et al., 2007). Current biomarkers for IBD include serological levels of specific antibodies (ASCA, ANCA, anti-OmpC, anti-Cbir, antiglycans), serum C-reactive proteins (CRP) and cytokines and fecal proteins (calprotectin and lactoferrin). Nevertheless, the majority of these markers show a low sensitivity and/or specificity, and they cannot reflect the real intestinal damage (Díaz-Jiménez et al., 2011).

IL-33 is the newest identified member of the IL-1 family and exerts its biological effects through binding of its receptor, ST2 (human Suppression of Tumorigenicity 2).ST2 belongs to IL-1 receptor like 1 (IL-1RL1) super family, is coded by chromosome 2 and expressed mainly as 2 splice variants, namely transmembrane bound receptor, ST2L, that activates downstream signalling upon IL-33 recognition, and a serum soluble protein, sST2. Complex formation of IL-33 with sST2 leads to cytokine inactivation, suggesting a role for this variant form as a decoy receptor (Beltrán et al., 2010). The IL-33/ST2 axis is a intracellular signalling system that participates in processes as varied as the antigen/allergen response, autoimmunity, organ fibrosis and cardiac failure. Several studies reported an increase in plasma levels of sST2 in patients with inflammatory processes, including asthma, autoimmune, cardiovascular diseases, trauma and sepsis (Kuroiwa et al., 2001; Oshikawa et al., 2001; Weinberg et al., 2003; Brunner et al., 2004). Soluble ST2 protein was recently identified as a new and reliable biomarker of heart failure (Kohli et al., 2012).

There is an established role of IL-1 family members (such IL-1β and IL-18) in inflammatory bowel disease. Since 2010, several studies reported elevated expression of IL-33 in UC inflamed intestinal mucosa vs. healthy controls. Mucosal expression of IL-33 is mostly localized to non-hematopoietic cells, particularly to intestinal epithelial cells and myofibroblasts (Beltrán et al., 2010; Kobori et al., 2010; Pastorelli et al., 2010; Seidelin et al., 2011).In mucosal tissue, levels of IL-33 showed to correlate positively with the severity of gut inflammation (Pastorelli et al., 2010). Similary, the expression of its receptor, ST2, was shown to be increased in both colonic wall and serum of UC patients (Beltrán et al., 2010; Pastorelli et al., 2010). In IBD, there is a recruitment of ST2 positive cells into the lamina propria,

while epithelial-derived ST2 expression is lost /decreased and redistributed. It was suggested that the global increase in ST2 in IBD represents the sST2 protein, produced by mucosal lamina propria mononuclear cells, intestinal epithelial cells and circulating mononuclear cells. ST2 could also be involved in a negative feedback mechanism to control inflammation (Beltrán et al., 2010).The IL-33/ST2 axis seems to have a dual and dichotomous role in the pathogenesis of IBD. On one hand, pro-inflammatory cytokine stimuli, such as TNF, result in the increase of IL-33 in epithelial cells. On the other hand, IL-33 may be released by injured epithelial cells to induce pro-inflammatory cytokines production through activation of ST2L, in mast cells, macrophages, eosinophils and neutrophils. IL-33 may function as an endogenous danger signal or alarmin, to alert immune system of cell or tissue danger (Pastorelli et al., 2010).

Recent data showed that sST2 levels correlate positively with the severity of colonic mucosal disease and inflammatory cytokines (IL-6, IL-33 and TNF) (Beltrán et al., 2010; Pastorelli et al., 2010; Díaz-Jiménez et al., 2011). Diaz-Jimenez and his group demonstrated that sST2 has a good performance for discriminating between active and inactive UC in TNF inhibitors naïve patients, based on clinical, endoscopic and histopathological characteristics: active UC = 235.8 pg/mL (90.65-367.90); inactive UC = 33.19 pg/mL (20-65.32), for a cut-off value of 74.87 pg/mL (sensitivity=83%, specificity=83%; AUC=0.92 [0.86-0.97, $p<0.0001$]). This study also showed that sST2 serum levels from UC patients significantly correlate to endoscopic Mayo score ($r=0.76$, $p<0.0001$) as well as histopathological score ($r=0.67$, $p<0.0001$) (Díaz-Jiménez et al., 2011).

Treatment with TNF inhibitors modulates circulating IL-33 and sST2 levels. In a small cohort of IBD patients, Pastorelli and his group evaluated Infliximab's acute and long term effects and observed a decrease of IL-33 and an overall decrease in the IL-33/sST2 ratio, with a greater impact in UC patients (Pastorelli et al., 2010).

In a rheumatoid arthritis study, serum levels of IL-33 were shown to decrease significantly in responders to TNF inhibitors vs. non responders, and sustained elevation of serum and/or synovial levels of IL-33 were suggested to have a possible association with poor response to TNF inhibitors (Matsuyama et al., 2012).

TNF inhibitors have improved outcomes of patients with moderate to severe ulcerative colitis, in spite some patients do not respond to treatment. Approximately one third of IBD patients are primary non-responders and fail to improve after therapy induction. In UC, mucosal healing is one of the most important clinical targets in order to maintain long-term remission. As mucosal healing has become a goal of treatment in IBD, endoscopy is the "gold standard" for the assessment of inflammation of intestinal mucosa. Surrogate markers that reflect the severity of mucosal inflammation and could potentially replace endoscopy are being investigated. Fecal calprotectin levels correlate significantly with endoscopic disease activity in IBD and is currently the best surrogate marker for the presence of intestinal inflammation. Still, the use of nonsteroidal anti-inflammatory drugs (NSAIDs), occurrence of intercurrent intestinal infection and the presence of malignancy may cause elevation of calprotectin levels in the absence of IBD.

A simple, rapid, sensitive, specific, inexpensive, non-invasive marker to detect and monitor intestinal inflammation is still needed. If such biomarker could also predict the clinical response to therapeutic regimens, its importance and impact for the patient would be greater.

Golimumab is a fully human anti-TNFα monoclonal antibody that binds with high affinity to human TNFα and inhibits TNFα bioactivity. A study recently conducted with 1228 patients (Sandborn et al., 2014a) has shown that golimumab induces clinical response in 51% of patients with moderate to severe UC at week 6, with remission and mucosal healing being achieved by 18% and 42% of patients, respectively. Among those patients on clinical response after induction with golimumab, 47-50% were able to maintain response through week 54 (50-100mg). At both week 30 and week 54, 23-28% of patients were in remission and 42-42% had mucosal healing (50-100mg). (Sandborn et al ., 2014b)

No research so far correlated the levels of ST2 with endoscopic and histological activity in UC patients receiving anti-TNF-α therapy.

This is an exploratory study aiming to evaluate the potential of serum soluble ST2 as a surrogate biological marker of disease outcome and therapeutic response, in subjects with moderate to severe active UC who have an inadequate response to conventional therapies and who will start treatment with golimumab according to the SmPC.

5.2 Subject Population Rationale

This study will include adult subjects with a diagnosis of moderate to severe active ulcerative colitis eligible for use of anti-TNF-α therapy, i.e., subjects who had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Details about specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying SmPC and Informed Consent documents.

5.3 Dose and Administration Rationale

Golimumab will be used in this indication according to the SmPC.

5.4 Rationale for Future Biomedical Research

Merck will conduct Future Biomedical Research on plasma specimens collected during this clinical trial. Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and

identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The details of this Future Biomedical Research sub-trial are presented in Appendix 6: Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Appendix 7.

6.0 TRIAL OBJECTIVES

6.1 Primary Trial Objectives

- To evaluate the correlation of serum soluble ST2 levels with endoscopic activity (endoscopic Mayo score) at week 6 in moderate to severe UC subjects under golimumab treatment.
- To evaluate the correlation of serum soluble ST2 with histological activity (Geboes index) at week 6 in moderate to severe UC subjects under golimumab treatment.

6.2 Secondary Trial Objective(s)

- To evaluate the correlation of serum soluble ST2 levels with endoscopic activity (endoscopic Mayo score) at week 16 in moderate to severe UC subjects under golimumab treatment.
- To evaluate the correlation of serum soluble ST2 levels with histological activity (Geboes index) at week 16 in moderate to severe UC subjects under golimumab treatment.
- To correlate serum soluble ST2 levels with fecal calprotectin at week 6 and week 16 in moderate to severe UC subjects under golimumab treatment.
- To correlate serum soluble ST2 with clinical activity (total Mayo score) at week 6 and week 16 in moderate to severe UC subjects under golimumab treatment.
- To evaluate the potential of serum soluble ST2 as a predictor of endoscopic response (endoscopic Mayo score) to golimumab in moderate to severe UC subjects.
- To evaluate the correlation between serum soluble ST2 levels with maintenance of endoscopic response (endoscopic Mayo score) to golimumab.
- To correlate Mayo endoscopic score with UCEIS overall score at week 6 and week 16 in moderate to severe UC subjects under golimumab treatment.

6.3 Exploratory Objective(s)

- To evaluate the relationships of serum levels of golimumab and the presence of anti-golimumab antibodies with clinical, endoscopic, and histological activities and with biomarker levels in subjects with moderate to severe UC

7.0 INVESTIGATIONAL AND ANALYSIS PLAN

7.1 Overall Trial Design

This is an exploratory, multi-site, nonrandomized, open label, prospective, interventional, single-arm, study to evaluate the correlation of serum soluble ST2 levels with clinical, endoscopic and histological activity in subjects with moderate to severe active UC who received golimumab. During this study, golimumab will be used according to the SmPC.

The overall study design is illustrated in the trial design diagram presented in **Section 2.1**. Study procedures are outlined by visit in the trial flow chart in **Section 2.2.**

After signing the informed consent, subjects will enter a screening period of up to 42 days. After confirmation of eligibility criteria, subjects will initiate treatment with golimumab according to SmPC (Baseline Visit – V2). Subjects will be followed for a period of 16 weeks for clinical assessments and data collection. Biomarker samples (ST2 and fecal calprotectin) will be collected at baseline and at all subsequent visits. All subjects will be evaluated for clinical, endoscopic (fibrosigmoidoscopy) and histologic activity at screening, week 6 and week 16.

The trial design is appropriate for the indication studied. Validated methods of data collection, analysis, and evaluation will be used for the trial.

The method of assessment of serum soluble ST2 is described in **Section 7.6**.

In addition it will be evaluated the correlation between ST2 levels with fecal calprotectin, which is currently the best surrogate marker for the presence of intestinal inflammation. Fecal calprotectin has been demonstrated to be a sensitive and specific marker in identifying intestinal inflammation and response to treatment in subjects with IBD.

The Geboes index is a validated instrument for evaluating histologic disease activity in UC (Geboes et al., 2000) - see more detailed information in **Section 7.7.2.2**. This index will be applied at screening, week 6 and week 16 in order to determine if a correlation exists between its overall score and serum soluble ST2 levels at the respective time points.

Ulcerative Colitis Endoscopic Index of Severity (UCEIS) is a 3-item validated tool for assessing endoscopic severity of UC (Travis et al., 2011) - see more detailed information in **Section 7.7.2.2** and Appendix 4. This tool will be applied at screening, week 6 and week 16 in order to determine if a correlation exists between its overall score and the endoscopic Mayo score at the respective time points.

At this moment, little is known about the benefit of measuring golimumab serum concentrations in daily practice. In the pivotal PURSUIT Induction trial, an exposure-response relationship was observed for the change from baseline in Mayo score and rates of clinical response and clinical remission, with patients in the highest serum golimumab concentration quartiles having greater improvement in median Mayo scores and greater rates of clinical response and clinical remission when compared with those in the lower quartiles at week 6 (Sandborn et al., 2014a). A second study, also including UC patients from PURSUIT (Sandborn et al., 2016a and Sandborn et al., 2016b), assessed golimumab pharmacokinetics and exposure-response relationship. It was observed that serum golimumab concentrations are approximately dose proportional, and a positive serum golimumab concentration-efficacy relationship exists during induction/maintenance golimumab treatment of adult UC patients (Adedokun et al., 2016).

On the other hand, the presence of anti-drug antibodies may also be associated with low response to anti-TNFs since it is thought that anti-drug antibodies can neutralize the therapeutic antibodies or induce their rapid elimination (Vincent et al., 2013)To investigate these findings, comparisons of serum golimumab levels and the presence of anti-golimumab antibodies with clinical response and remission, endoscopic activity, fecal calprotectin and histological activity will be analysed as exploratory endpoints.

Serum golimumab levels and the presence of anti-golimumab antibodies will be evaluated at week 6 and week 16 using an ELISA (enzyme-linked immunosorbent assay) technique (IDKmonitor® Golimumab drug level ELISA and IDKmonitor® golimumab free ADA ELISA, from Immundiagnostik AG, Germany). These analyses will be done at the end of the study and will not be available to the investigators during subjects' participation in the study.

Considering these study aims, there is no justification for including a comparative arm.

7.2 Beginning and End of the Trial

Each subject is considered to be enrolled in the trial when he/she (or the subject's legal representative) has provided written informed consent.

Each subject is considered to have ended participation in the trial when he/she has completed the last protocol-specified contact (e.g., visits or telephone contacts) or prematurely discontinues from the trial.

A subject is considered to have discontinued after he/she has withdrawn consent or has been discontinued under the conditions specified in **Section 7.3.3.**

A subject is considered to have been lost to follow-up if he/she is unable to be contacted by the investigator. The end of participation for a subject lost to follow-up is the last known contact (e.g., visit or telephone contact).

Subjects may be rescreened one time only, and only for the reason of initially failing to meet the Visit 1 inclusion/exclusion criteria related with the severity of the disease.

The overall trial begins when the first subject is enrolled (i.e., signs the informed consent form). The overall trial ends when the last remaining subject has ended participation in the trial, by completing the trial, being discontinued from the trial, or being lost to follow-up.

Each subject will be monitored for the occurrence of AEs immediately after he/she has signed informed consent and until the last protocol-specified visit. Follow-up procedures related to pregnancy or SAEs may continue beyond the end of the clinical trial.

Each subject will participate in the trial for approximately 22 weeks from the time the subject signs the Informed Consent Form (ICF) until the final protocol-specified contact. After a screening phase of up to 6 weeks each subject will receive golimumab (**Section 7.4.1.1**) for 16 weeks.

7.3 Trial Population

Adult subjects with a diagnosis of moderate to severe active ulcerative colitis who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies, and are considered candidates to TNF inhibitors, will be selected to participate in the trial.

7.3.1 Subject Inclusion Criteria

To be eligible for the study, subjects must meet all of the following criteria:

1. Are men or women of any race, ≥ 18 and ≤ 65 years of age;
2. Had UC diagnosed prior to screening, based on results from a biopsy collected at an endoscopy procedure;
3. Have moderate to severe active UC with total Mayo score of 6 to 12, inclusive at baseline, AND endoscopic Mayo subscore (fibrosigmoidoscopy), greater than or equal to 2;
4. Regarding prior or current medication for UC:

4.1 Subjects must have responded inadequately to corticosteroids (at least 40mg) with or without 5-ASA, or subjects must be steroid-dependent (unable to reduce steroids below 10mg within 3 months of starting steroids and/or have relapsed within 3 months of stopping steroids)

AND

4.2 Subjects must have responded inadequately to AZA or 6-MP (must have been receiving it for the last 12 weeks) or are intolerant or have medical contraindications to these agents

5. Subjects must be naïve to TNF inhibitors;

6. Subjects must be eligible to start golimumab treatment according to SmPC;

7. All subjects must either have had a colonoscopy to assess for the presence of adenomatous polyps within 5 years of study inclusion or a colonoscopy to assess for the presence of adenomatous polyps at the screening visit. The adenomatous polyps must be removed prior to the first administration of golimumab;

8. All subjects who have had extensive colitis for ≥ 8 years, or disease limited to the left side of the colon for ≥10 years, must either have had a colonoscopy to assess the presence of dysplasia within 1 year prior study inclusion or a colonoscopy to assess the presence of malignancy at the screening visit;

9. The investigator has discussed with the subject the information contained in the informed consent regarding anti-TNF therapies and the potential risk of cancer, and has reviewed with the subject country-specific guidance (local practice) on cancer screening and the impact of life-style choices (e.g., smoking) on the risk of developing cancer.

10. Have an acceptable Tuberculosis Assessment:

10.1. Have no history of untreated latent or active tuberculosis (TB) prior to screening. An exception is made for subjects who have a history of latent TB and are currently receiving treatment for latent TB, or who will initiate treatment for latent TB prior to first administration of study agent, or have documentation of having completed appropriate treatment for latent TB within 5 years prior to the first administration of study agent. It is the responsibility of the investigator to verify the adequacy of previous anti-tuberculous treatment and provide appropriate documentation.

10.2. Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.

10.3. Have had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluations and receive appropriate treatment for latent TB prior to the first administration of study agent.

10.4. Within 2 months prior to study inclusion, have a negative result for QuantiFERON-TB Gold test; or have a newly identified positive result for QuantiFERON-TB Gold test in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated prior to the first administration of study agent.

- The QuantiFERON®-TB Gold test is not required at screening for subjects with a history of latent TB and ongoing treatment for latent TB or documentation of having completed adequate treatment as described above; Subjects with documentation of having completed adequate treatment as described above are not required to initiate additional treatment for latent TB.

10.5. Have a chest radiograph (both posterior-anterior and lateral views) within 3 months prior to study inclusion and read by a qualified radiologist, with no evidence of current, active TB or old, inactive TB.

11. Have negative stool results for enteric pathogens (including *Clostridium difficile* stool culture and toxin assay)

12. During the study and for 6 months after receiving the last administration of golimumab, women of childbearing potential or men capable of fathering children must agree to use adequate birth control measures (eg, abstinence, oral contraceptives, intrauterine device, barrier method with spermicide, surgical sterilization). Women of childbearing potential must test negative for pregnancy at screening (V1).

13. Have screening detailed laboratory test results:

a. White blood cells	≥ 2.5 x 10^3 cells/μL	(SI: ≥ 2.5 x10^9 cells/L)
b. Neutrophils	≥ 1.5 x 10^3 cells/μL	(SI: ≥ 1.5 x10^9 cells/L)
c. Platelets	≥ 100 x 10^3 cells/μL	(SI: ≥ 100 x10^9 cells/L)
d. Serum creatinine	≤ 1.5 mg/dL	(SI: ≤ 133 μmol/L)
e. Serum ALT and AST levels not exceeding 2 times the ULN		

14. Must be able and willing to adhere to the study visit schedule and comply with other protocol requirements.

15. Are capable of providing informed consent, which must be obtained prior to any study-related procedures. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research

7.3.2 Subject Exclusion Criteria

A subject meeting any of the exclusion criteria listed below must be excluded from participating in the trial:

1. Any contraindication as specified in golimumab's SmPC,
2. Have severe extensive colitis as evidenced by:
    a) Investigator judgment that the subject is likely to require a colectomy within 12 weeks of baseline (V2).

       OR

    b) Symptom complex at screening (V1) or baseline visit (V2) that includes at least 4 of the following:
        I. diarrhea with ≥ 6 bowel movements/day with macroscopic blood in stool
        II. focal severe or rebound abdominal tenderness
        III. persistent fever (≥ 37.5°C)
        IV. tachycardia (> 90 beats/minute)
        V. anemia (hemoglobin < 8.5 g/dL)
3. Presence of symptomatic colonic or small bowel obstruction, confirmed by objective radiographic or endoscopic evidence of a stricture with resulting obstruction (dilation of the colon or small bowel proximal to the stricture on barium radiograph or an inability to traverse the stricture at endoscopy).
4. History of colonic mucosal dysplasia in flat mucosa.
5. Presence on screening endoscopy of adenomatous colonic polyps, if not removed prior to study entry, or history of adenomatous colonic polyps that were not removed.

Concomitant or previous medical therapies received:

6. Have ever received biologic therapy targeted at TNFα.
7. Have received natalizumab within 12 months prior to study inclusion.
8. Have received agents that deplete B or T cells (e.g., rituximab, alemtuzumab, or visilizumab) within 12 months prior to study inclusion, or continue to manifest depletion of B or T cells more than 12 months after completion of therapy with lymphocyte-depleting agents.
9. Have received cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil (MMF) within 8 weeks prior to study inclusion. .

10. Have a known hypersensitivity to human immunoglobulin proteins or other components of golimumab.

11. Have used any investigational drug within 4 weeks prior to prior to study inclusion or within 5 half-lives of the investigational drug, whichever is longer.

12. Have used apheresis (i.e., Adacolumn apheresis) within 2 weeks prior to study inclusion.

13. Have rectal corticosteroids or 5–ASA compounds administered to the rectum or sigmoid colon via foam or enema or suppository within 2 weeks prior to study inclusion.

Infection or predisposition to infections:

14. Have a history of latent or active granulomatous infection, histoplasmosis, or coccidioidomycosis, prior to screening (for TB refer to inclusion criteria 10).

15. Have a history of, or ongoing, chronic or recurrent infectious disease, including but not limited to, chronic renal infection, chronic chest infection (e.g., bronchiectasis), sinusitis, recurrent urinary tract infection (e.g., recurrent pyelonephritis, chronic cystitis), an open, draining, or infected skin wound, or an ulcer.

16. Have immune deficiency syndrome (eg, severe combined immunodeficiency syndrome [SCIDS], T cell deficiency syndromes, B cell deficiency syndromes, and chronic granulomatous disease).

17. Are known to be infected with HIV, hepatitis B, or hepatitis C.

18. Have had a Bacille Calmette-Guerin (BCG) vaccination within 12 months of screening.

19. Have had a nontuberculous mycobacterial infection or opportunistic infection (e.g., cytomegalovirus, Pneumocystis carinii, aspergillosis) within 6 months prior to screening.

20. Have a chest radiograph within 3 months prior to study inclusion that shows an abnormality suggestive of a malignancy or current active infection, including TB.

21. Have received, or are expected to receive, any live virus or bacterial vaccination within 3 months prior to study inclusion, or during the study,

22. Have had a serious infection (e.g., hepatitis, pneumonia, or pyelonephritis), have been hospitalized for an infection, or have been treated with parenteral antibiotics for an infection within 2 months prior to study inclusion. Less serious infections (e.g., acute upper respiratory tract infection, simple urinary tract infection) need not be considered exclusionary at the discretion of the investigator.

Malignancy or increased potential for malignancy:

23. Presence or history of any malignancy within 5 years of screening (with exception of nonmelanoma skin cancer that has been treated with no evidence of recurrence).

24. Presence or history of lymphoproliferative disease including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy of unusual size or location (e.g., nodes in the posterior triangle of the neck, infraclavicular, epitrochlear, or periaortic areas), or clinically significant hepatomegaly or splenomegaly.

Coexisting medical conditions or past medical history of:

25. Concomitant diagnosis or history of chronic heart failure (CHF), including medically controlled asymptomatic CHF.

26. Have signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, hematologic, endocrine, pulmonary, cardiac, neurologic, psychiatric, or cerebral diseases.

27. History of systemic lupus erythematosus.

28. Have a transplanted organ (with the exception of a corneal transplant performed > 3 months prior to study inclusion).

29. History of demyelinating disease, such as multiple sclerosis or optic neuritis.

30. Have or have had a substance abuse (drug or alcohol) problem within the previous 3 years.

31. Are participating in another study with an investigational product or procedure.

32. Are pregnant, nursing, or planning pregnancy (both men and women) within 6 months following the last administration of investigational product.

33. Coexisting medical conditions or medical history of: hypertension, asthma.

34. The subject or a family member is among the personnel of the investigational or sponsor staff directly involved with this trial.

7.3.3 Subject Discontinuation Criteria

A subject may discontinue from the clinical trial at any time for any reason.

It is the right and the duty of the investigator or sub investigator to stop treatment in any case in which emerging effects are of unacceptable risk to the individual subject. In addition, the investigator or sub investigator is to stop treatment of any subject with unmanageable factors that may interfere significantly with the trial procedures and/or the interpretation of results.

Discontinuation is “permanent”: once a subject is discontinued, he/she shall not be enrolled again.

At a minimum, collect the following information when a subject discontinues:

1. The reason the subject discontinued;
2. The date of the last dose of test product from the trial;
3. The date of the last assessment and/or contact. A follow-up contact (telephone or visit) will be arranged as appropriate;
4. (Serious) Adverse events;
5. Compliance with the test product administration as specified in this protocol;
6. Final Assessments:
7. Every effort should be made to ensure that all procedures and evaluations scheduled for the Early Discontinuation visit is performed (**Section 2.2**, Trial Flow Chart). Samples of ST2 and calprotectin will only be collected at the Early Discontinuation visit in case the investigator discontinued the subject due to golimumab’s lack of efficacy.
8. Retrieve all investigative product(s) and test articles from the subject.

A subject must be discontinued from the trial for any of the following reasons:

1. The subject or legal representative (such as a parent or legal guardian) withdraws consent;
2. The subject shows lack of compliance with the trial or treatment evaluations.
3. Lost to follow-up
4. Reaction resulting in bronchospasm with wheezing and/or dyspnea requiring ventilatory support, or symptomatic hypotension that occurs following the administration of investigational product.
5. Reaction resulting in myalgia and/or arthralgia with fever and/or rash (suggestive of serum sickness and not representative of signs and symptoms of other recognized clinical syndromes) occurring 1-14 days after injection of investigational product. These may be accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache
6. Opportunistic infection
7. Malignancy, excluding nonmelanoma skin cancer
8. Pregnancy, or pregnancy planned within the study period or within 6 months after the last study agent administration

9. CHF
10. Demyelinating disease
11. Subject is deemed ineligible according to the following TB screening criteria:
    - 11.1 A diagnosis of active tuberculosis is made
    - 11.2 A subject receiving treatment for latent TB who discontinues prematurely or is non-compliant
    - 11.3 A subject has symptoms suggestive of active TB
    - 11.4 A subject with active TB
12. Initiation of protocol prohibited medications (thalidomide or related agents, tacrolimus or sirolimus, investigational products, other immunomodulators biologic agents: anakinra, rituximab, natalizumab, vedolizumab, etanercept, adalimumab, infliximab)

7.3.3.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by writing to the principal investigator for the main trial. If medical records for the main trial are still available, the Investigator will contact the Sponsor using the designated mailbox PPD , and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the bio repository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the Investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory agencies to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

7.3.4 Replacement of Subjects

A subject who discontinues from the study without performing at least one valid post baseline assessment for the primary endpoint correlating ST2 with endoscopic activity may be replaced at the discretion of the sponsor.

7.4 Treatments

7.4.1 Trial Treatments

Golimumab (Simponi; CNTO-148) is a high affinity, fully humanised monoclonal antibody, directed against tumour necrosis factor-α (TNF-α). Golimumab inhibits the interaction between TNF-α and the p55 and p75 cell surface receptors, neutralising its biological effects.

Golimumab has been shown to be effective to treat moderate to severe UC (Sandborn et al., 2014ab).

The treatment with golimumab will follow the SmPC.

7.4.1.1 Treatments Administered

The first dose of subcutaneous (sc) golimumab will be administered at the trial site at Visit 2 (Day 1). Subsequent dosing will be done by the subject (i.e., unsupervised at his/her home) at week 2 and every 4 weeks thereafter (approximately the same time as the first administration), according to SmPC.

7.4.1.2 Method of Treatment Assignment, Randomization, and/or Stratification

This is a single-arm study. No stratification based on age, sex, or other characteristics will be performed.

7.4.1.3 Selection and Timing of Dose for Each Subject

7.4.1.3.1 Selecting the Dose for Each Subject

The rationale for the selection of induction and maintenance doses to be used in this trial is presented in golimumab's SmPC.

7.4.1.3.2 Determining the Timing of Dose Administration for Each Subject

The rationale for the selection of timings of doses to be used in this trial is presented in golimumab's SmPC.

7.4.1.4 Blinding Trial Treatments

This will be an open label trial.

7.4.1.5 Investigational Medicinal Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, handling, storage, distribution, and usage of these materials in accordance with the protocol and any applicable laws and regulations.

7.4.1.5.1 Identity of Investigational Medicinal Product

The Investigational Medicinal Product to be used in this trial is as follows:

- Golimumab 50mg/0.5 mL in a single-use, ready-to-use autoinjector

7.4.1.5.2 Source

The sponsor will provide the investigational medicinal product as described above in Section 7.4.1.5.1.

7.4.1.5.3 Labelling

The carton containing the pre-filled pen autoinjector will be labeled in accordance with local regulations.

7.4.1.5.4 Packaging

Each clinical supply device will be packaged into a medication kit.

7.4.1.5.5 Storage

Trial treatment supplies must be stored in a secure, limited-access location under the storage conditions specified on the supply label. Site storage conditions should be monitored by the site personnel for adherence to label specifications and reviewed during site visits.

7.4.1.5.6 Dispensing

The investigator or qualified designee(s) will dispense trial treatments at the designated site(s) to subjects who have provided written informed consent and have met the entry criteria. Clinical supplies may not be used for any purpose other than that which is stated in this protocol.

See the Trial Flow Chart in **Section 2.2** for a schedule of when clinical supplies are to be dispensed to the subjects. First administration of golimumab will be performed at the trial site during Baseline (V2), under supervision of the investigator or qualified designee(s). At this visit golimumab will dispensed to the subject, for self-injection two weeks after the first administration. At week 6 (V3) golimumab will be dispensed in order to be administrated at the day of this visit and at weeks 10 and 14, according to SmPC. Each subject will be instructed by the investigator or designee to return all unused and partially used investigational product to the site at week 6 (V3) and week 16 (V4). After study completion, and if physician finds it beneficial to the subject, golimumab will continue to be dispensed according to SmPC.

7.4.1.5.7 Replacement of Investigational Product

Clinical supplies provided by the sponsor will be replaced, where required. Provisions that govern this activity extend to clinical supplies that have short expiration dating, and/or inadequate inventory levels. The sponsor and investigator should monitor the clinical supplies for adequate inventory levels and/or expiration date.

7.4.1.5.8 Investigational Medicinal Product Accountability

Accurate and current accounting of the dispensing and return of investigational product will be maintained on an ongoing basis by a member of the trial site staff:

- Investigational medicinal product dispensed to each site will be recorded in the trial-specific Site Investigational Medicinal Product (IMP) Accountability Log (or equivalent document approved by the sponsor);
- Investigational medicinal product dispensed to each subject will be recorded in the trial-specific Subject IMP Accountability Log (or equivalent document approved by the sponsor).

The Site IMP Accountability Log and Subject IMP Accountability Log will be verified by the sponsor's trial monitor. The original Site IMP Accountability Log and Subject IMP Accountability Log will be approved by the investigator and retained at the trial site and a copy supplied to the sponsor when the trial is complete.

Each subject will be instructed by the investigator or designee to return all unused and partially used test articles to the site at all protocol-specified visits.

The sponsor's trial monitor will instruct the site on the return of all investigational product(s) supplies. A final inventory of the total amount of investigational product(s) received at each trial site against the amount used and returned must be recorded in the Site IMP Accountability Log. Inventory records must be readily available for inspection by the trial monitor and/or auditor, and open to government inspection at any time.

7.4.2 Non-Trial Treatments

7.4.2.1 Prior and Concomitant Medications

7.4.2.1.1 Medications, Supplements, and Other Substances Prohibited Prior to Screening and During the Trial

The subject must not take the treatments listed in table 1 during the trial after the Screening visit (V1).

Table 1 Medications, Supplements, and Other Substances Prohibited During the Trial

Protocol No. MK 8259-022-03

Topical 5-ASA and topical corticoids
Thalidomide or related agents, investigational products
Tacrolimus or sirolimus
Other immunomodulators biologic agents: anakinra, rituximab, natalizumab, vedolizumab, etanercept, adalimumab, infliximab tacrolimus or sirolimus

The medications, supplements, and other substances prohibited prior to Screening are listed in **Section 7.3.2** with the subject exclusion criteria.

7.4.2.1.2 Concomitant Medications, Supplements, and Other Substances Allowed During the Trial

The following medications, supplements, and other substances are allowed during the trial:

Table 2 Medications, Supplements, and Other Substances Allowed During the Trial

Protocol No. MK 8259-022-03

Oral 5-ASA: Dose must be maintained throughout the study according to clinical practice
AZA or 6-MP
Oral Corticosteroids - Subjects in clinical response to golimumab who were receiving oral corticosteroids should begin tapering the daily dose of corticosteroids by 5mg per week after 6 week. In case of clinical relapse corticosteroids can be re-initiated or the dose increased

Note that the use of any concomitant medication must relate to the documented medical history, prophylaxis, or an adverse event of the subject.

7.4.2.2 Other Treatments

None.

7.4.3 Procedures for Monitoring Subject Compliance With Administration of Trial Treatments

At all protocol-specified visits, the investigator or qualified designee is to record whether treatment had been taken per protocol in the preceding interval. If not, the date(s) and reason for each dosing noncompliance must be recorded.

A diary will be dispensed to the subject at Baseline (V2), with the expected dates for next golimumab administrations provided by the investigator or designee. In this diary the subject will record/confirm the date of golimumab administration. The subject should be instructed to return the diary at each study visit for investigator or designee to check compliance with defined administrations.

7.5 Trial Schedule

The visit-by-visit schedule of trial activities is provided in the Trial Flow Chart in **Section 2.2**.

The timing of each visit is relative to Day 1, which is defined as the baseline and corresponds to the administration of the first dose of trial medication, Visit 2 (**Section 7.4.1.1**).

All visits should be performed within the windows specified in **Section 2.2** (Trial Flow Chart). Every attempt should be made to have each subject attend each visit as scheduled. However, if a subject is unable to attend a visit within the specified

windows, the visit should be scheduled as closely as possible to these windows. A subject should not miss a protocol-specified visit due to scheduling difficulties.

7.6 Trial Procedures

The Trial Flow Chart in **Section 2.2** summarizes the trial procedures to be performed at each visit. Individual trial procedures are described below.

In order to minimize variability of evaluations, it is preferred that the same individuals perform the same types of evaluations for all subjects at each trial site.

1. **Explain Trial and Obtain Written Informed Consent**

   The investigator or qualified designee will explain the trial to the subject, answer all of his/her questions, and obtain written informed consent before performing any trial-related procedure. A copy of the informed consent will be given to the subject (see **Section 9.1.2** for further description of the Informed Consent).

2. **Consent and Collection of Specimens for Future Biomedical Research**

   The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

3. **Issue or Collect Subject Identification Card**

   The investigator or qualified designee will provide the subject with a Subject Identification Card after the subject provides written informed consent. The investigator or qualified designee will retrieve the card from the subject at the last contact (see **Section 9.1.3** for further description of the Subject Identification Card).

4. **Obtain Demography and Medical History**

   Demographic information and medical history will be obtained by the investigator or qualified designee.

5. **Review Inclusion/Exclusion Criteria**

   The inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

6. **Review Prior Medications**

   Review of appropriate prior medications, including the necessary washout times, with the subject. A record of prior medication taken by the subject within 6 months before starting the trial is to be obtained.

7. **Record Concomitant Medications**

   A record of medication taken by the subject during the trial is to be obtained.

8. **Record (Serious) Adverse Events**

   See **Section 7.7.2.4**, for instructions on the assessment and reporting of (Serious) Adverse Events and **Section 7.7.2.5** for instructions on the reporting of (Serious) Adverse Events to the sponsor.

9. **Physical Examination**

   A partial physical examination will be performed. Ulcerative colitis clinical activity will be assessed by partial Mayo score and Montreal classification (Silverberg et al., 2005) of extent of ulcerative colitis performed at every study visit. If the subject is discontinued for any reason during the treatment phase, every attempt should be made to perform a final physical examination.

10. **Sigmoidoscopies**

    Fibrosigmoidoscopies will be performed at the visits indicated in the study Flowchart. The subject preparation for the exam should be done only with water. Endoscopic activity will be assessed by Endoscopic Mayo score and UCEIS index at every study visit indicated.

11. **Histology**

    Four biopsies will be collected from distinct areas (2 rectum and 2 sigmoid) from each subject at every study visit indicated. The samples will be prepared and sent to Central Laboratory. The formalin fixed and Hematoxylin & Eosin-stained specimens will be assessed according to the Geboes index (Geboes et al., 2000) – see Appendix 5

12. **Pregnancy Assessment**

    Assess whether a subject is pregnant with a medically acceptable test (Serum Pregnancy Test - Beta-hCG at Screening visit and urine hCG at visits 3 and 4).

13. **Tuberculosis Evaluation**

    For this protocol, a chest X-ray and QuantiFERON-TB Gold test are mandatory. All subjects must at least perform a postero-anterior and lateral chest x-rays (unless a chest x-ray has been performed within 3 months prior to study inclusion), and QuantiFERON-TB Gold test (unless performed within two months of study inclusion).

    If not available within 2 months prior to study inclusion, latent TB must be evaluated at screening by specialized, trained, and licensed personnel, either at the participating trial site or at an external unit (e.g. Lung Disease Diagnostic Centers (CDPs)), as according to local guidelines. When this

evaluation is performed at any site other than the investigator's facility, the results must be made available in written form as source documentation.

If TB is suspected at any time during the study, chest x-ray and QuantiFERON-TB Gold test should be performed and latent TB must be re-evaluated.

14. Laboratory Tests

- Laboratory tests for hematology, blood chemistry, and urinalysis are specified in Table 3. Blood samples for laboratory tests are to be taken prior to investigational product(s) administration. If judged necessary by investigator, laboratory tests may be repeated during Screening period, and results should be obtained prior to first administration of investigational product.
- CRP is a useful marker of inflammation in patients with IBD. CRP will be assayed using a validated, high sensitivity CRP assay. Serum CRP evaluation will be done at the visits indicated.
- Levels of serum soluble ST2 (human Suppression of Tumorigenicity 2). Serum ST2 evaluation will be done at the visits indicated and analysed by a central laboratory.
- Levels of serum golimumab and the presence of anti-golimumab antibodies will be evaluated at the visits indicated and analysed by a central laboratory.
- Stools collection for culture and *Clostridium difficile* assay for toxin must be performed at screening visit (local laboratory) or in the case of episode exacerbation as long as taken during the last 4 months prior study inclusion.
- Stools collection for fecal calprotectin assessments should be performed at the same timings of ST2, according to the study flowchart. Calprotectin will be done at the visits indicated and analysed by a central laboratory.
- Plasma for Future Biomedical Research will be collected pre-dose at Baseline/Day 1 and Week 16 (or Early Discontinuation) from subjects who consent to Future Biomedical Research. See Appendix 6 for further information concerning Future Biomedical Research.

Table 3 Laboratory Tests

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Hematology	Chemistry	Faeces
Basophils	Albumin	calprotectin
Eosinophils	Alkaline phosphatase	Culture and *Clostridium difficile* assay for toxin, if applicable
Hematocrit	ALT (SGPT)	
Hemoglobin	AST (SGOT)	
Lymphocytes	Calcium	
Monocytes	Chloride	
Neutrophils	Creatinine	
Platelets	Phosphate	
RBC	Potassium	
WBC	CRP	
Golimumab levels	Sodium	
Anti-golimumab antibodies	Serum ST2	
	Total Bilirubin	
	Total protein	
	Urea	
	Urinalysis (proteins, glucose, nitrates, WBC, ketone bodies, hemoglobin, urobilinogen, bilirubin)	
	Serum Pregnancy Test - Beta-hCG	

15. Dispensing Diary Card

Each subject will be provided with a diary card to collect the date of each Golimumab administration. This information will be recorded in the card by the subject for all Golimumab doses administered out-of-site, or also by site personnel when Golimumab is administered at the site. The subject must bring his/her diary card at all trial visits. At each visit, the site will collect the diary card, record the new information in the CRF, and return the card to the subject. Subjects will be instructed to return the completed card in their final visit.

7.7 Assessments

7.7.1 Efficacy Assessments

7.7.1.1 Coprimary Efficacy Endpoint(s)

There are no efficacy-related endpoints in this study.

7.7.1.2 Secondary Efficacy Endpoint(s)

There are no efficacy-related endpoints in this study.

7.7.2 Safety Monitoring and Assessments

7.7.2.1 Safety Endpoints

There are no safety-related endpoints in this study.

Hematology and blood chemistry assessments will be performed according to the study schedule of events (**Section 2.2**).

Hematology assessments in this study include: basophils, eosinophils, hematocrit, hemoglobin, lymphocytes, monocytes, neutrophils, platelets, RBC, WBC.

Blood chemistry assessments in this study include: total bilirubin, ALT, AST, alkaline phosphatase, albumin, total protein, calcium, phosphate, sodium, potassium, chloride, urea and creatinine), CRP.

7.7.2.2 Definition of Terms

- Moderate to severe active UC is defined in this study as a total Mayo score of 6 to 12, inclusive.
- The total Mayo Score, is a scale for assessing UC activity, it is the sum of 4 subscores and has values that range from 0 to 12. It includes assessment of Stool frequency (0–3) + Rectal bleeding (0–3) + Physician's global assessment (0–3) + Findings of endoscopy (0–3). Clinical remission: ≤2 points with no individual subscore > 1 ; Mildly active disease: 3-5 points; Moderately active disease: 6-10 points; Severely active disease: 11-12 points
- Endoscopic Mayo score (0-3): 0 = Normal or inactive disease, 1 = Mild disease (erythema, decreased vascular pattern, mild friability); 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions); 3 = Severe disease (spontaneous bleeding, ulceration) - See Appendix 3.

- Partial Mayo score: Mayo score excluding the endoscopy subscore and has values that range from 0 to 9.
- Mucosal healing in this study will be determined by the endoscopy subscore of the Mayo score. Mucosal healing corresponds to endoscopy subscore of 0 or 1.
- Geboes index, is a validated score for evaluating histologic disease activity in UC as follows: grade 0, structural and architectural changes; grade 1, chronic inflammatory infiltrate; grade 2, lamina propria neutrophils and eosinophils; grade 3, neutrophils in the epithelium; grade 4, crypt destruction; grade 5, erosions or ulceration ; a higher score indicating more severe disease. Active histologic disease can be defined as a Geboes score ≥3.1 (presence of epithelial neutrophils with or without crypt destruction or erosions) (Geboes et al., 2000). - See Appendix 5
- Ulcerative Colitis Endoscopic Index of Severity (UCEIS) is a 3-item (vascular pattern, bleeding and erosion/ulceration) validated tool for assessing endoscopic severity of UC. Each item with three or four levels of severity, yielding a 9-point scale that accounts for 94% of the variance between observers in the overall assessment of severity (Travis et al., 2011) - See Appendix 4
- Clinical response is defined as a reduction in the Mayo score of at least 3 points and a decrease of at least 30% from the baseline score, accompanied by a decrease of at least 1 point in the rectal bleeding scale or an absolute rectal bleeding score of 0 or 1.
- Clinical remission is defined as Mayo score ≤ 2, with no individual subscore exceeding 1.

7.7.2.2.1 Adverse Event

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

7.7.2.2.2 Serious Adverse Event

Serious Adverse Event (SAE) is any untoward medical occurrence or effect that at any dose:

Results in death;
Is life-threatening;
Requires hospitalization or prolongation of existing inpatients' hospitalization;
Results in persistent or significant disability or incapacity; and/or
Is a congenital anomaly or birth defect;
Is a cancer;
Is associated with an overdose;
Is an Other Important Medical Event.

Life-threatening in the definition of a serious adverse event refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Medical judgment should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/ reactions that are not immediately life-threatening or do not result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious. These are considered "Other Important Medical Events".

7.7.2.2.3 Events of Clinical Interest

An "Event of Clinical Interest" is a non-serious adverse event or occurrence that is designated to be of special interest and must be reported to the sponsor as though it were a serious adverse event – as described in **Section 7.7.2.5.1**.

The following events are considered events of clinical interest for this trial:

1. An overdose of Sponsor's product, as defined in Section 7.7.2.2.4, Overdose, that is not associated with clinical symptoms or abnormal laboratory results is to be reported as a non-serious ECI, using the terminology "accidental or intentional overdose without adverse effect."

2. An elevated AST or ALT lab value that is ≥3 x the upper limit of normal (ULN) and an elevated total bilirubin lab value that is ≥2 x ULN and, at the same time, an alkaline phosphatase lab value that <2 x ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing is to be reported as a non-serious ECI.

   Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

3. Infections (including serious infections: sepsis, TB (frequently disseminated or extrapulmonary), invasive fungal and opportunistic infections)

4. Demyelinating disorders

5. Lymphoma

6. HBV reactivation

7. CHF

8. Autoimmune processes (lupus-like syndrome)

9. Hypersensitivity reactions

10. Immunogenicity

7.7.2.2.4 Overdose

An overdose is a significant variation above the recommended/scheduled dosage for a product. In this current trial an overdose of the investigational product golimumab is any dose higher than the dose specified in **Section 7.4.1.1** of this protocol.

7.7.2.2.5 Clinical Supply Complaint

A clinical supply complaint is defined as any communication concerning manufacturing, packaging, labelling or distribution (including adverse storage at depots) of a clinical supply that describes a potential defect related to its identity, strength, quality or purity after it is released and left the control of a Merck-approved packaging facility for distribution. A clinical supply GCP inquiry is defined as any

communication of an event taking place at a trial site after the product was satisfactorily received at the trial site, which puts product disposition in question. Examples include adverse storage of product at the trial site and dosing past expiration. Alleged Counterfeit, Diversion and Tampering (CDT), adverse events and trial site errors/issues which do not put product disposition in question should not be reported.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations. This responsibility includes reporting of all clinical supply complaints and/or clinical supply GCP inquiries to the Sponsor.

Clinical supplies complaints and GCP inquiries, as defined above, must be reported to the Sponsor within 1 business day of first becoming aware of the issue. Sponsor Contact information and related reporting details can be found in the Investigator Trial File Binder.

7.7.2.2.6 Incident

A device-related incident is any product complaint that led to or might have led to death or serious deterioration of health/serious injury/serious illness for the user of the product or any other person.

7.7.2.3 Monitoring

7.7.2.3.1 Monitoring Adverse Events

Each subject will be monitored for the occurrence of AEs immediately after the subject has signed informed consent through after the last protocol-specified visit as described in **Section 7.2**.

Subjects will be questioned and/or examined by the investigator or a qualified designee for evidence of AEs. The questioning of subjects with regard to the possible occurrence of adverse events will be generalized such as, "How have you been feeling since your last visit?" The presence or absence of specific AEs should not be elicited from subjects.

Subjects having AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the investigator.

AEs, actions taken as a result of AEs, and follow-up results must be recorded in the Case Report Forms (**Section 9.2.1**), as well as in the subject's source documentation. Follow-up laboratory results should be filed with the subject's source documentation.

For all AEs that require the subject to be discontinued from the trial and SAEs, relevant clinical assessments and laboratory tests will be repeated as clinically appropriate, until final resolution or stabilization of the event(s).

7.7.2.3.2 Monitoring Laboratory Assessments

Serum ST2, fecal calprotectin, serum golimumab levels and anti-golimumab antibodies assessments will be performed by a certified central laboratory selected by the sponsor.

Histological assessment will be performed at a certified laboratory selected by the sponsor.

The routine laboratory tests (hematology, chemistry) will be performed at local certified hospital laboratory in each center.

The routine laboratory tests (hematology, chemistry) and histological assessment will be reported to the investigator by the laboratories and he/she will review them for significance and consideration as an AE.

Serum ST2 and fecal calprotectin assessments will not be provided to the investigator during the clinical trial.

7.7.2.4 Assessment of Adverse Events

7.7.2.4.1 Assessment of Severity

Where the determination of adverse event severity rests on medical judgment, the determination of severity must be made with the appropriate involvement of a medically-qualified investigator.

The severity of AEs will be graded according to the following definitions:

Mild:	awareness of sign, symptom, or event, but easily tolerated;
Moderate:	discomfort enough to cause interference with usual activity and may warrant intervention;
Severe:	incapacitating with inability to do normal daily living activities or significantly affects clinical status, and warrants intervention;

7.7.2.4.2 Assessment of Causality

A medically-qualified investigator must assess the relationship of any AE (including SAEs) to the use of the investigational product using the guidelines listed below:

- Yes, there is reasonable possibility of drug relationship. There is evidence of exposure to test drug. The temporal sequence of the AE onset relative to the administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause.
- No, there is not a reasonable possibility of drug relationship. Subject did not receive the test drug OR temporal sequence of the AE onset relative to administration of the test drug is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

7.7.2.4.3 Reference Safety Information (RSI) for the Assessment of Expectedness of Adverse Events

The Reference Safety Information (RSI) for assessing the expectedness of an adverse event for the investigational product in this current trial is to be the most recent SmPC.

7.7.2.4.4 Known Potential Toxicities of Investigational Products

The following observations are known potential toxicities of the investigational product golimumab:

1. Infections (including serious infections: sepsis, TB (frequently disseminated or extrapulmonary), invasive fungal and opportunistic infections)
2. Demyelinating disorders
3. Lymphoma
4. HBV reactivation
5. CHF
6. Autoimmune processes (lupus-like syndrome)
7. Hematologic reactions
8. Hypersensitivity reactions
9. Immunogenicity

Refer to the approved labelling for additional information on AEs related to toxicities observed to date.

7.7.2.4.5 Known Adverse Events Relating to the Underlying Clinical Condition

Some common AEs associated with ***ulcerative colitis*** include:

1. ulcerative colitis
2. abdominal pain
3. hematochezia
4. diarrhoea

7.7.2.5 Reporting Safety Observations by the Investigator to the Sponsor

7.7.2.5.1 Expedited Reporting of Safety Observations by the Investigator to the Sponsor

Any occurrence of the following events or outcomes in a subject in the trial must be reported by the investigator or qualified designee to the sponsor – either by electronic media or paper – within **24 hours of learning of the event**.

1. SAE (including SAEs associated with pregnancy or exposure during pregnancy or lactation – including the pregnancy of a male subject's female partner who has provided written informed consent to provide information regarding pregnancy);
2. Events of clinical interest;
3. Incidents associated with the device.

If the investigator is unsure about when to report an observation from the lists above, the event or outcome should be reported to the sponsor or designee.

Any observation reported to the sponsor or designee that is also an AE, is to be recorded in the eCRF (**Section 9.2**), as well as in the subject's source documentation, along with any actions taken as a result of AE and follow-up results.

If an autopsy is performed, available results should be provided to the sponsor.

The investigator must assess causality of the event as relative to the investigational product administered in the trial as described in **Section 7.7.2.4.2**.

There will be a follow-up from the Sponsor to the Investigator for all malignancies occurring in patients 30 years of age or younger. This will be done via a dedicated Malignancy Follow-up Questionnaire, which needs to be completed by the Investigator(s) and submitted to the Sponsor within 2 weeks of receipt via a designated fax number. The Investigator must make at least 2 attempts to contact the patient or guardian to complete the Malignancy Follow -up Questionnaire. If the attempts are not successful, the reason for each unsuccessful attempt must be documented (e.g., patient lost-to-follow-up, patient refuses to supply the additional information, etc.).

The Sponsor will review the study AE database for possible premalignant conditions twice a year, occurring in patients 30 years of age or younger. If any are reported, the Sponsor will contact the Investigator with a dedicated follow-up request that needs to be completed. In case a pre-malignant condition has progressed to a malignancy, the Investigator will need to complete the Malignancy Follow-Up Questionnaire.

7.7.2.5.2 Expedited Reporting by the Sponsor to a Regulatory Health Authority

Global Safety will monitor data for safety. The Sponsor will manage the expedited reporting of relevant safety information to concerned health authorities, competent authorities, and IRBs/IECs in accordance with local laws and regulations.

7.7.2.6 Discontinuation, Treatment Interruption, and Unblinding of Blinded Treatment Due to Safety Observations

7.7.2.6.1 Discontinuation

See **Section 7.3.3** for the criteria by which a subject must be discontinued. Should a subject be discontinued from the trial, complete the visit activities as specified for discontinuation in the Trial Flow Chart in **Section 2.2**.

7.7.2.6.2 Temporary Interruption of Treatment for a Subject

A Subject may not temporarily interrupt and then restart treatment. The investigator is to discontinue a subject as necessary according to the criteria provided in **Section 7.3.3**.

7.7.2.6.3 Modification of Dose and/or Administration of Investigational Product for a Subject

The dose and administration to any subject may not be modified. If necessary a subject must be discontinued for the reasons described in **Section 7.3.3**.

7.7.2.6.4 Unblinding Treatment for a Subject During the Trial

No treatments in this current trial are blinded.

7.7.3 Other Endpoints

7.7.3.1 Primary endpoints

- To correlate serum soluble ST2 levels with endoscopic activity of disease (assessed by endoscopy subscore of Mayo score) at week 6 in moderate to severe UC subjects under golimumab treatment.
- To correlate serum soluble ST2 levels with histological activity (assessed by Geboes index) at week 6 in moderate to severe UC subjects under golimumab treatment.

See **Section 7.7.2.2** for the definition of endoscopic and histological activity of disease.

7.7.3.2 Secondary endpoints

- To correlate serum soluble ST2 levels with endoscopic activity (assessed by endoscopy subscore of Mayo score) at week 16 in moderate to severe UC subjects under golimumab treatment.
- To correlate serum soluble ST2 levels with histological activity (assessed by Geboes index) at week 16 in moderate to severe UC subjects under golimumab treatment.
- To correlate serum soluble ST2 levels with fecal calprotectin levels at week 6 and week 16.
- To correlate serum soluble ST2 levels with clinical activity (assessed by total Mayo score) at week 6 and week 16.

- To evaluate the potential of serum soluble ST2 as a predictor of endoscopic response to golimumab by comparing Mayo endoscopic activity (activity [subscore ≥ 2] or no activity [subscore 0 or 1]) with ST2 at baseline and change of ST2 between baseline and Week 6.

- To correlate serum soluble ST2 levels with maintenance of endoscopic response to golimumab by comparing subjects who achieved endoscopic response at week 6 [subscore 0 or 1] and maintained through week 16 versus subjects who did not maintain response throughout the same period, regarding serum soluble ST2 at baseline, week 6 and change between baseline and week 6.

- To correlate Mayo endoscopic score with UCEIS overall score at week 6 and week 16 in moderate to severe UC subjects under golimumab treatment.

7.7.3.3 Exploratory endpoints

- To compare serum golimumab levels with clinical activity (total Mayo score) at weeks 6 and 16.

- To compare serum golimumab levels in subjects with endoscopic active disease (total Mayo score >2) and subjects with inactive disease (total Mayo score ≤2 points with no individual subscore >1) at week 6 and 16.

- To compare the presence of anti-golimumab antibodies (+ or -) and clinical activity (total Mayo score) at weeks 6 and 16.

- To compare the presence of anti-golimumab antibodies in subjects with endoscopic active disease (total Mayo score >2) and subjects with inactive disease (total Mayo score ≤2 points with no individual subscore >1) at week 6 and 16.

- To compare serum golimumab levels with endoscopic activity (endoscopic Mayo score) at weeks 6 and 16.

- To compare the presence of anti-golimumab antibodies (+ or -) and endoscopic activity (endoscopic Mayo score) at weeks 6 and 16.

- To compare serum golimumab levels with faecal calprotectin at weeks 6 and 16.

- To compare the presence of anti-golimumab antibodies (+ or -) and faecal calprotectin at weeks 6 and 16.

- To compare serum golimumab levels with histological activity (Geboes index) at weeks 6 and 16.

- To compare the presence of anti-golimumab antibodies (+ or -) and histological activity (Geboes index) at weeks 6 and 16.

- To compare quartile serum golimumab levels with rates of clinical response and clinical remission
- To compare serum golimumab levels between subjects who achieved response at week 6 and subjects who did not.
- To compare serum golimumab levels among subjects who achieved response at week 16 and subjects who did not.
- To compare the presence of anti-golimumab antibodies among subjects who achieved response at week 6 and subjects who did not.
- To compare the presence of anti-golimumab antibodies who achieved response at week 16 and subjects who did not.
- To compare serum golimumab levels between subjects who achieved remission at week 6 and subjects who did not.
- To compare serum golimumab levels among subjects who achieved remission at week 16 and subjects who did not.
- To compare the presence of anti-golimumab antibodies among subjects who achieved remission at week 6 and subjects who did not.
- To compare the presence of anti-golimumab antibodies who achieved remission at week 16 and subjects who did not.

See **Section 7.7.2.2** for the definitions of interest.

7.8 Criteria for Early Termination of the Trial

There are no pre-specified criteria for terminating the trial early.

In addition, further recruitment in the trial or at (a) particular site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems, or the number of discontinuations for administrative reasons is too high.

8.0 STATISTICAL AND ANALYTICAL PLAN

All quantitative variables will be summarize through descriptive statistics namely mean, median, standard deviation and range (minimum and maximum) and qualitative variables though absolute (n) and relative frequencies (%) and 95% confidence intervals (if applicable). The statistical analysis will be performed through frequency tables for qualitative variables and tables with descriptive statistics for quantitative variables.

The association between two quantitative variables will be performed through Pearson correlation coefficient or Spearman correlation coefficient, in case the normality assumption was not verified.

The association of two categorical variables will be tested through the Chi-Square test or Fisher Exact test (if applicable). Cohen's kappa coefficient will be performed.

The comparison of two independent samples in respect to quantitative variables will be performed through t-test for independent samples or the Mann-Whitney non-parametric test, according to the assumption validations of the statistical test.

ROC curve analysis will be performed as well as sensitivity, specificity, and positive and negative predictive values.

The primary analysis is to investigate the correlation between serum soluble ST2 and:

- endoscopic activity of disease (measured by Endoscopy Mayo subscore) at 6 weeks in UC subjects receiving golimumab, through the Spearman correlation coefficient;
- histological activity (measured by Geboes index score) at 6 weeks in UC subjects receiving golimumab, through the Spearman correlation coefficient.

Additionally, it will be obtained the cut-off of serum soluble ST2 levels at week 6 that optimizes sensitivity and specificity in the identification of disease activity through ROC curve analysis supplemented with analysis of sensitivity, specificity, and positive and negative predictive values. Endoscopic activity will be classified according to endoscopy subscore of Mayo score and histological activity will be classified according to Geboes index score.

For the analysis of the secondary endpoints the following analysis will be performed:

- the correlation between serum soluble ST2 with endoscopic activity of disease (measured by Endoscopy Mayo subscore) at 16 weeks in UC subjects receiving golimumab, through the Spearman correlation coefficient;
- the correlation between serum soluble ST2 histological activity (measured by Geboes index score) at 16 weeks in UC subjects receiving golimumab, through the Spearman correlation coefficient.
- Correlations will also be performed between serum soluble ST2 levels and endoscopic and histological activity at baseline.
- Serum soluble ST2 levels at baseline, Week 6 and Week 16 will be correlated with fecal calprotectin levels at baseline, week 6 and week 16 through Pearson correlation coefficient or Spearman correlation coefficient in case the normality assumption was not verified. The two biomarkers will be categorized by the cut-offs and Cohen's kappa coefficient will be obtained.

- Serum soluble ST2 levels at baseline, week 6 and week 16 will be correlated with clinical activity (total Mayo score), through Spearman correlation coefficient.
- Comparative analyses of means (active disease versus inactive disease at week 6) with serum ST2 at baseline and change between baseline and week 6.
- Comparative analyses of subjects who achieved response at week 6 and maintained through week 16 versus subjects who did not maintain response, regarding serum soluble ST2 at baseline, week 6 and change between baseline and week 6. ROC curve analysis of the serum soluble ST2 at week 6 regarding maintenance of response between week 6 and 16 will be performed. This exploratory analysis will detect the cut-off levels of the serum soluble ST2 at week 6 associated with maintenance of response.
- It will be investigated the correlation of Mayo endoscopic score at baseline, week 6 and week 16 with UCEIS overall score at baseline, week 6 and week 16, through the Spearman correlation coefficient.

For the exploratory endpoints the following analysis will be performed:

- Serum golimumab levels at week 6 and week 16 will be correlated with clinical activity (total Mayo score) at the same time points, through Spearman correlation coefficient.
- Mean serum golimumab levels will be compared between patients with active disease (total Mayo score >2) and patients with inactive disease (total Mayo score ≤2 points with no individual subscore > 1) at week 6 and 16 through T-test for independent groups or Mann-Whitney test according to the assumption validations of the statistical test.
- The association between the presence of anti-golimumab antibodies at week 6 and week 16 and clinical activity (total Mayo score) at the same time points will be tested through t-test for independent samples or the Mann-Whitney non-parametric test, according to the assumption validations of the statistical test.
- Presence of anti-golimumab antibodies will be compared between patients with active disease (total Mayo score >2) and patients with inactive disease (total Mayo score ≤2 points with no individual subscore > 1) at week 6 and 16 through Chi-Square test or Fisher exact test.
- Serum golimumab levels at week 6 and week 16 will be correlated with endoscopic activity (endoscopic Mayo score) at the same time points, through Spearman correlation coefficient.

- The association between the presence of anti-golimumab antibodies at week 6 and week 16 and endoscopic activity (endoscopic Mayo score) at the same time points will be tested through t-test for independent samples or the Mann-Whitney non-parametric test, according to the assumption validations of the statistical test.

- Serum golimumab levels at Week 6 and Week 16 will be correlated with faecal calprotectin levels at the same time points through Pearson correlation coefficient or Spearman correlation coefficient in case the normality assumption was not verified.

- The association between the presence of anti-golimumab antibodies at Week 6 and Week 16 and faecal calprotectin levels at the same time points will be tested through will be tested through t-test for independent samples or the Mann-Whitney non-parametric test, according to the assumption validations of the statistical test.

  Both measurements will be categorized by the cut-offs and Cohen's kappa coefficient will be obtained.

- The correlation between serum golimumab levels at week 6 and 16 and histological activity (measured by Geboes index score) at the same time points will be performed through the Spearman correlation coefficient.

- The association between the presence of anti-golimumab antibodies at week 6 and 16 and histological activity (measured by Geboes index score) at the same time points will be tested through Mann-Whitney non-parametric test.

- Subjects who achieved response / remission at week 6 versus subjects who did not will be compared regarding serum golimumab levels at this time point through T-test for independent groups or Mann-Whitney test according to the assumption validations of the statistical test.

- Subjects who achieved response / remission at week 16 versus subjects who did not will be compared regarding serum golimumab levels at this time point through T-test for independent groups or Mann-Whitney test according to the assumption validations of the statistical test.

- Subjects who achieved response / remission at week 6 versus subjects who did not will be compared regarding the presence of anti-golimumab antibodies at this time point through the Chi-Square test or Fisher Exact test (if applicable).

- Subjects who achieved response / remission at week 16 versus subjects who did not will be compared regarding the presence of anti-golimumab antibodies at this time point through the Chi-Square test or Fisher Exact test (if applicable).

- ROC curve analysis of the serum golimumab levels at week 6 regarding maintenance of response between week 6 and 16 will be performed. This exploratory analysis will allow to detect the cut-off for serum golimumab levels at week 6 associated with maintenance of response.

In addition, CRP at baseline, week 6 and week 16 will be correlated with endoscopic activity (measured by Endoscopy Mayo subscore) and histological activity at the same time points, through Spearman correlation coefficient.

Bivariate correlation analysis will be carried out for ST2, calprotectin, CRP and endoscopy Mayo score.

The incidence of adverse events (percentage of subjects with at least one adverse event) and serious adverse events (overall and with reasonable relationship) will be presented as well as the frequency distribution of AEs and SAEs (overall and with reasonable relationship) by means of total number of observations (n) and relative frequency (%). Frequency distribution of adverse events by grade and relationship with study drug will be summarized by total number of observations (n) and relative frequency (%).

Adverse events will be listed individually with severity, grade, relationship with study drug, duration (for solved AEs and calculated as the difference between end date and start date), measures taken and outcome.

All deaths will be listed, regardless of being caused by adverse events.

Results for hematology (basophils, eosinophils, hematocrit, hemoglobin, lymphocytes, monocytes, neutrophils, platelets, RBC, WBC); blood chemistry (total bilirubin, ALT, AST, alkaline phosphatase, albumin, total protein, calcium, phosphate, sodium, potassium, chloride, urea and creatinine and CRP; urinalysis (proteins, glucose, nitrates, WBC, ketone bodies, hemoglobin, urobilinogen, bilirubin) will be summarized by total number of observations (n), mean, median, standard deviation, minimum and maximum.

Based on the recruitment capacity of sites it is expected to include a total of 37 subjects for analysis. With this sample size there is a probability of 80% that the lower limit of a one-sided 95% confidence interval is higher than 0.50, if the observed correlation coefficient is at least 0.75.

The primary analysis is to be performed on the Full Analysis Set, defined as all subjects who had received study medication and had at least one valid post baseline assessment for the primary endpoint that correlates ST2 with endoscopic activity.

In addition, a Per Protocol Set is defined as subjects receiving study medication, who meet key eligibility and evaluability criteria (without major protocol deviations). Sensitivity analyses will be based on this Per Protocol Set.

All safety analyses will be performed on the All Treated Set, comprising all subjects who received at least one dose of study medication.

No interim analysis is planned.

9.0 ADHERENCE TO ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

The trial must be conducted in accordance with Good Clinical Practice (GCP) as outlined in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, E6 Good Clinical Practice: Consolidated Guidance and other applicable laws and regulations. In addition, the trial must be conducted in accordance with: (i) the USA Code of Federal Regulations (CFR) if the trial is conducted under a USA IND, regardless of the country involved; (ii) the European Union (EU) Clinical Trial Directive (CTD) and local regulations if the trial is conducted in the EU; and (iii) any specific local regulations if the trial is conducted elsewhere.

9.1 Ethical Conduct of the Trial

9.1.1 Independent Ethics Committee or Institutional Review Board

Prior to initiation of the trial at any site, the trial, including the protocol, informed consent, and other trial documents must be approved by an appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC). The IRB/IEC must be constituted according to applicable regulatory requirements. As appropriate, amendments to the protocol must also be approved by the IRBs/IECs before implementation at the sites, unless warranted to eliminate an immediate hazard. The IRB/IEC approval should be obtained in writing, clearly identifying the trial, the documents reviewed (including informed consent), and the date of the review. The trial as described in the protocol (or amendment), informed consent, and other trial documentation may be implemented only after all the necessary approvals have been obtained and the sponsor has confirmed that it is acceptable for the investigator to do so.

In the event that the IRB/IEC requires changes in the protocol, the sponsor shall be advised and must approve the changes prior to implementation. The investigator shall not modify the trial described in the protocol once finalized and after approval by the IRB/IEC without the prior written approval of sponsor.

In countries where the investigator submits the trial protocol and statement of informed consent to the IRB/IEC, the investigator or qualified designee will forward the approvals to the sponsor.

9.1.2 Subject Information and Consent

The details of the protocol must be provided in written format and discussed with each potential subject, and written informed consent must be obtained for all subjects before any trial-related procedure is performed. In obtaining informed

consent, the information must be provided in language and terms understandable to the subject. The subject, or the subject's legal representative, must give their written consent to participate in the trial. The signed and dated consent form itself must be retained by the investigator as part of the trial records. A copy of the signed and dated consent form must be given to the subject. The consent form must include all of the required elements of informed consent in accordance with ICH Guidelines E6 and local laws. In addition, the sponsor specifically requests that the consent form identify it as the sponsor and state that use of the investigational product(s) is experimental and the side effects of the investigational product(s)are not completely known. The consent form must be approved by the appropriate IRB/IEC and sponsor before trial initiation at a trial site. Any subsequent changes to the approved informed consent form must be reviewed and approved by the appropriate IRB/IEC and sponsor before implementation.

9.1.3 Subject Identification Card

A Subject Identification Card is provided to each subject to carry on his or her person (e.g., in a wallet) at all times while the subject is participating in the trial. The Subject Identification Card must be provided to the subject no later than when IMP is dispensed. The card is to be shown to caregivers in the event of an emergency.

At a minimum, the card must contain the following information:

1. Protocol number;
2. The subject’s protocol identification number;
3. A statement identifying the card-carrier as a participant in a clinical trial (e.g., “This person is participating in a clinical research trial.”);
4. A statement indicating the person might be taking an investigational drug (e.g., “This person is taking an experimental drug which could have interactions with other medications, or placebo”); and
5. Contact information in the event of an emergency or hospitalization. The contact information on the card is to be the investigator or a designated site contact, rather than a contact from within the sponsor;

The cards may also include other trial-specific information to assist with treatment decisions in the event of an emergency, such as types of concomitant therapies that may, or may not be, permitted as part of emergency treatment. As with any other information provided to subjects, the Subject Identification Card must be approved by the IRB/IEC. Monitors will request that Investigators provide Subject Identification Cards to each subject. Investigators will be asked to request that subjects carry the cards with them while they are participating in the trial.

The Investigator/site should collect the cards at the end of the trial and retain them with other clinical trial documents.

9.1.4 Registration of the Trial

The trial will be registered by the sponsor on a publicly accessible database. The results will be disclosed by the sponsor on a publicly accessible database.

9.2 Reporting Trial Data to the Sponsor

9.2.1 Data Collection Forms

The Sponsor will provide the site with data collection forms, be they Case Report Forms (CRF), either in paper format or electronic Case Report Forms (eCRF); diaries; Electronic Data Capture (EDC) screens; or other appropriate data collection forms as the trial requires. The investigator is to provide subject data according to the Sponsor's instructions, in the designated data collection form, compliant with GCP practices. The Sponsor will also provide the site with instructions for assisting other parties - such as a central laboratory - to collect data. As instructed by the Sponsor, a designated central laboratory may collect data in a database and provide the completed database to sponsor. All data collection forms and the databases from the trial are the exclusive property of sponsor.

The investigator must maintain records and data during the trial in compliance with all applicable legal and regulatory requirements. Each data point must be supported by a source document at the trial site. Any records or documents used as the source of information (called the "subject source data") are to be retained for review by authorized representatives of the sponsor or a regulatory agency.

The investigator will ensure that there are sufficient time, staff, and facilities available for the duration of the trial to conduct and record the trial as described in the protocol and according to all applicable guidances, laws, and regulations.

All data collection forms (e.g., CRFs, diaries; EDC screens), electronic database entries, etc., should be completed as soon as possible after the evaluation has occurred. All dates appearing on the sponsor's subject data collection forms for laboratory tests, cultures, and other data collected, must be the dates on which the specimens were obtained, or the procedures performed.

9.2.2 Preparing Case Report Forms for All Subjects

A CRF must be completed for all subjects who have given informed consent. The Sponsor must not collect subject names, initials, or other personal information that is beyond the scope of the trial from any subject. Subjects are not to be identified by

name or initials on the CRF or any trial documents. The only acceptable identification for a subject who may appear on a CRF or trial document is the unique subject identification number. The investigator must maintain contact information for each participant so that all can be quickly contacted by the investigator, if necessary.

All entries into CRFs are the responsibility of the investigator and must be completed by the investigator or a qualified designee. The investigator will acknowledge in writing that he/she has verified the accuracy of the recorded data.

9.2.3 Preparing Case Report Forms for Subjects Who Fail Screening

Data are to be collected from the time the informed consent form is signed until the subject is determined to have failed screening. A CRF with a minimum of the following information must be completed for subjects who fail screening: (1) demographics, (2) subject status, (3) reason for screen failure, and (4) serious adverse events.

9.3 Publications and Other Rights

9.3.1 Rights to Publish by the Investigator

The investigator has the right to publish or publicly present the results of the trial in accordance with this **Section 9.3** of the protocol. In the event that the protocol is a part of a multi-site trial, it is understood that it is the intent of the sponsor and the investigator to initially only publish or present the trial results together with the other sites, unless specific written permission is obtained in advance from the sponsor to publish separate results. The sponsor shall advise as to the implications of timing of any publication in the event clinical trials are still in progress at sites other than the investigator's site.

The investigator agrees not to publish or publicly present any interim results of the trial without the prior written consent of the sponsor. The investigator further agrees to provide to the sponsor 45 days prior to submission for publication or presentation, review copies of abstracts or manuscripts for publication (including, without limitation, slides and texts of oral or other public presentations and texts of any transmission through any electronic media, eg, any computer access system such as the Internet, World Wide Web, etc) that report any results of the trial. The sponsor shall have the right to review and comment with respect to publications, abstracts, slides, and manuscripts and the right to review and comment on the data analysis and presentation with regard to the following concerns:

1. Proprietary information that is protected by the provisions contained in **Section 9.3.2**;

The accuracy of the information contained in the publication; and

To ensure that the presentation is fairly balanced and in compliance with FDA regulations.

If the parties disagree concerning the appropriateness of the data analysis and presentation, and/or confidentiality of the sponsor's confidential information, investigator agrees to meet with the sponsor's representatives at the clinical trial site or as otherwise agreed, prior to submission for publication, for the purpose of making good faith efforts to discuss and resolve any such issues or disagreement.

9.3.2 Use of Proprietary or Confidential Information in a Publication

No publication or manuscript shall contain any trade secret information of the sponsor or any proprietary or confidential information of the sponsor and shall be confined to new discoveries and interpretations of scientific fact. If the sponsor believes there is patentable subject matter contained in any publication or manuscript submitted for review, the sponsor shall promptly identify such subject matter to investigator. If sponsor requests and at sponsor's expense, investigator shall use its best efforts to assist sponsor to file a patent application covering such subject matter with the USA Patent and Trademark Office or through the Patent Cooperation Treaty prior to any publication.

9.3.3 Use of Trial Information in a Publication

Investigator is granted the right subject to the provisions of this protocol to use the results of all work provided by investigator under this protocol, including but not limited to, the results of tests and any raw data and statistical data generated for investigator's own teaching, research, and publication purposes only. Investigator/Institution agrees, on behalf of itself and its employees, officers, trustees, and agents, not to cause said results to be knowingly used for any commercial purpose whatsoever except as authorized by the sponsor in writing.

9.3.4 Authorship of Publications

Authors of publications must meet the International Committee of Medical Journal Editors (ICMJE) guidelines for authorship and must satisfy the 3 criteria that follow:

1. Authors must make substantial contributions to the conception and design of the trial, acquisition of data, or analysis of data and interpretation of results;
2. Authors must draft the publication or, during draft review, provide contributions (data analysis, interpretation, or other important intellectual content) leading to significant revision of the manuscript with agreement by the other authors;
3. Authors must provide written approval of the final draft version of the publication prior to submission.

All contributors who do not meet the 3 criteria for authorship should be listed in an acknowledgments section within the publication, if allowed by the journal, per the ICMJE guidelines for acknowledgment.

Appearance of the name of authors in the publications will follow the order stated below, in accordance with International Committee of Medical Journal Editors (ICMJE) guidelines criteria for authorship of Publications or the scientific journal specific rules: the first author is the national study coordinator, followed by the list of names of the principal investigators and co-investigators of the centers according to their contribution to the trial, and the last author is the investigator responsible for the analysis and interpretation of histologic data.

9.4 Trial Documents and Records Retention

During the trial and after termination of the trial – including after early termination of the trial – the investigator must maintain copies of all documents and records relating to the conduct of the trial. This documentation includes, but is not limited to, protocols, CRFs and other data collection forms, advertising for subject participation, adverse event reports, subject source data, correspondence with health authorities and IRBs/IECs, consent forms, investigator's curricula vitae/biosketch, monitor visit logs, laboratory reference ranges, and laboratory certification or quality control procedures and laboratory director curriculum vitae. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, or as specified below. The sponsor must be consulted if the investigator wishes to assign the files to someone else, remove them to another location, or is unable to retain them for the specified period.

The investigator must retain trial records for the amount of time specified by applicable laws and regulations. At a minimum, trial records must be retained for the amount of time specified by ICH Guidelines, the EU Good Clinical Practices Directive, or applicable local laws, whichever is longer:

1. The ICH Guidelines specify that records must be retained for a minimum of 2 years after a marketing application for the indication is approved (or not approved) or 2 years after notifying the appropriate regulatory agency that an investigation is discontinued.

The European Union (EU) Commission Directive 2003/63/EC which requires that Essential Documents (including Case Report Forms) other than subjects' medical files, are retained for at least fifteen (15) years after completion or discontinuation of the trial, as defined in the protocol.

All trial documents shall be made available if required by relevant health authorities. The investigator should consult with the sponsor prior to discarding trial and/or subject files.

Sponsor will retain all sponsor-required documentation pertaining to the trial for the lifetime of the investigational product. Archived data may be held on microfiche or electronic record, provided that a back-up exists and that a paper copy can be obtained from it, if required.

10.0 INVESTIGATORS AND TRIAL ADMINISTRATIVE STRUCTURE

10.1 Sponsor

The sponsor of this trial is indicated in **Section 1.0**, Title Page.

10.2 Investigators

10.2.1 Selecting Investigators

Only investigators qualified by training and experience to perform a clinical investigation with golimumab are selected. The sponsor will contact and select all investigators (i.e., the legally responsible party(ies) at each trial site), who, in turn, will select their staff.

10.2.2 Financial Disclosure Requirement

In connection with the clinical trial described in the protocol, the investigator certifies that, if asked, the investigator will read and answer the Certification/Disclosure Form or equivalent document truthfully and to the best of investigator's ability. Investigator

also certifies that, if asked, the investigator will have any other applicable party(ies) (eg, subinvestigators) read and answer the Certification/Disclosure Form as a condition of their participation in the trial.

If the financial interests reported on the Certification/Disclosure Form change during the course of the trial or within 1 year after the last subject has completed the trial as specified in the protocol, the investigator and the other applicable party(ies) are obligated to inform the sponsor of such financial change.

10.2.3 Clinical Study Report Coordinator Investigator

A Clinical Study Report (CSR) will be prepared by the sponsor or its qualified designee to describe the results of the trial. One of the investigators shall be selected by the sponsor to review the CSR and provide approval of the final CSR in writing. The investigator chosen to review and approve the CSR is to be called the CSR Coordinating Investigator. A second investigator shall be selected as the Alternate CSR Coordinating Investigator. The Alternate CSR Coordinating Investigator is to review and approve the CSR should the first CSR Coordinating Investigator be unable to do so. The sponsor is to select the CSR Coordinating Investigator and Alternate CSR Coordinating Investigator from the investigators using the following criteria:

1. Must be the Principal Investigator at a trial site actively enrolling subjects and participating in the trial;
2. Must be willing and capable of completing the necessary reviews and providing approval of the CSR in writing;

10.3 Central Organizations

Central organizations to be used in the conduct, monitoring, and/or evaluation or other activities as appropriate of this trial are provided on the Contact List.

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Appendix 1 Code of Conduct for Clinical Trials

Merck*

Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these studies in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical studies will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (eg, contract research organizations, collaborative research efforts). This Code is not intended to apply to studies which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated studies (eg, Medical School Grant Program), which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation studies, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, studies to assess or validate various endpoint measures, or studies to determine patient preferences, etc.

The design (ie, subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate patients, adequacy of facilities and staff, previous performance in Merck studies, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

D. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of studies it conducts. Some early phase or pilot studies are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC Review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck's Consent Form Review department (U.S. studies) or Clinical Research Director (non-U.S. studies) will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. DNA Research

DNA sequence analyses, including use of archival specimens collected as part of a clinical trial, will only be performed with the specific informed consent of the subject. With IRB approval, an exception to this restriction on use of archival specimens may be possible (for instance, if specimens are de-identified and are not referable to a specific subject).

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck studies. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck studies will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (eg, to scientific meetings, investigator meetings, etc) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an attachment to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp, which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

Appendix 2 Specimen Handling and Shipping Instructions

Detailed instructions for storage, labelling and shipment of all samples will be provided in the Laboratory Manual.

Appendix 3 Mayo scoring system for assessment of ulcerative colitis activity

Stool frequency[a]

0 = Normal number of stools for this patient
1 = 1-2 stools more than normal
2 = 3-4 stools more than normal
3 = 5 or more stools more than normal

Rectal bleeding[b]

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 passed

Findings of endoscopy

0 = Normal or inactive disease
1 = Mild disease (erythema, decreased vascular pattern, mild friability)
2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3 = Severe disease (spontaneous bleeding, ulceration)

Physician's global assessment[c]

0 = Normal
1 = Mild disease
2 = Moderate disease
3 = Severe disease

[a] Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency.

[b] The daily bleeding score represents the most severe bleeding of the day.

[c] The physician's global assessment acknowledges the 3 other criteria, the patient's recall of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.

Appendix 4 Ulcerative Colitis Endoscopic Index Of Severity (UCEIS©)

Descriptors and definitions: UCEIS = sum of scores, which accounts for 91% of the variance between observers in the overall assessment of endoscopic severity

Descriptor (Score most severe lesions)	Likert Scale anchor points	Definition
Vascular pattern	Normal (1)	Normal vascular pattern with arborisation of capillaries clearly defined, or with blurring or patchy loss of capillary margins
	Patchy obliteration (2)	Patchy obliteration of vascular pattern
	Obliterated (3)	Complete obliteration of vascular pattern
Bleeding	None (1)	No visible blood
	Mucosal (2)	Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope, which can be washed away
	Luminal mild (3)	Some free liquid blood in the lumen
	Luminal moderate or severe (4)	Frank blood in the lumen ahead of endoscope or visible oozing from mucosa after washing intra-luminal blood, or visible oozing from a haemorrhagic mucosa
Erosions & Ulcers	None (1)	Normal mucosa, no visible erosions or ulcers
	Erosions (2)	Tiny (< 5mm) defects in the mucosa, of a white or yellow colour with a flat edge
	Superficial ulcer (3)	Larger (>5mm) defects in the mucosa, which are discrete fibrin-covered ulcers when compared to erosions, but remain superficial
	Deep ulcer (4)	Deeper excavated defects in the mucosa, with a slightly raised edge

For the UCEIS© Working Group 2011 (Travis SPL, Schnell D, Krzeski P, Abreu MT, Altman DG, Colombel JF, Feagan BG, Hanauer SB, Lémann M, Lichtenstein GR, Marteau PR, Reinisch W, Sands BE, Yacyshyn BR, Bernhardt CA, Mary JY, Sandborn WJ). The trademark is registered to Warner Chilcott Pharmaceuticals.

Appendix 5 Geboes score for assessment of ulcerative colitis histologic disease activity

Grade 0	**Structural (architectural changes)**
Subgrades	
0.0	No abnormality
0.1	Mild abnormality
0.2	Mild or moderate diffuse or multifocal abnormalities
0.3	Severe diffuse or multifocal abnormalities
Grade 1	**Chronic inflammatory infiltrate**
Subgrades	
1.0	No increase
1.1	Mild but unequivocal increase
1.2	Moderate increase
1.3	Marked increase
Grade 2	**Lamina propria neutrophils and eosinophils**
2A *Eosinophils*	
2A.0	No increase
2A.1	Mild but unequivocal increase
2A.2	Moderate increase
2A.3	Marked increase
2B Neutrophils	
2B.0	No increase
2B.1	Mild but unequivocal increase
2B.2	Moderate increase
2B.3	Marked increase
Grade 3	**Neutrophils in epithelium**
Subgrades	
3.0	None
3.1	< 5 % Crypts involved
3.2	< 50 % Crypts involved
3.3	> 50 % Crypts involved
Grade 4	**Crypt destruction**
Subgrades	
4.0	None
4.1	Probable - local excess of neutrophils in part of crypt
4.2	Probable - marked attenuation
4.3	Unequivocal crypt destruction
Grade 5	**Erosion or ulceration**
Subgrades	
5.0	No erosion, ulceration, or granulation tissue
5.1	Recovering epithelium + adjacent inflammation
5.2	Probable erosion focally stripped
5.3	Unequivocal erosion
5.4	Ulcer or granulation tissue

Appendix 6 Collection and Management of Specimens for Future Biomedical Research

6.1 Scope of Future Biomedical Research

The plasma specimen(s) will be stored to provide a resource for future studies conducted by Merck focused on the study of biomarkers responsible for how a drug enters and is removed by the body, how a drug works, other pathways a drug may interact with, or other aspects of disease.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by Merck or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

6.2 Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[a]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug response.[b]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug response.[b]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

6.3 Summary of Procedures for Future Biomedical Research

a. Subjects for Enrolment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-study.

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[a] National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker

[b] International Conference on Harmonization: Definitions For Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc) will be obtained during screening for protocol enrolment from all subjects or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens.

Subjects are not required to participate in the Future Biomedical Research sub-study in order to participate in the main trial.

Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons. Information contained on the consent form alone cannot be traced to any specimens, test results, or medical information once the specimens have been rendered de-identified. Subjects who decline to sign the Future Biomedical Research informed consent will not have the specimen collected nor will they be discontinued from the main study.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

Each informed consent approved by an ethics committee is assigned a unique tracking number. The tracking number on this document will be used to assign specimen permissions for each specimen into the Entrusted Keyholder's Specimen Database.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of both consent and acquisition of Future Biomedical Research specimens will be captured in the electronic Case Report Forms (eCRFs). Reconciliation of both forms will be performed to assure that only appropriately-consented specimens are used for this sub-study's research purposes. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Blood specimens will usually be obtained at a time when the subject is having blood drawn for other study purposes. Specimens like tissue and bone marrow will usually be obtained at a time when the subject is having such a procedure for clinical purposes.

Specimens will be collected and sent to the laboratory designated for the trial where they will be processed following the Merck approved policies and procedures for specimen handling and preparation.

6.4 Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, Merck has developed secure policies and procedures. All specimens will be de-identified as described below.

At the clinical site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

This first code will be replaced with a second code at a Merck designated storage/lab facility. The second code is linked to the first code via a second key. The specimen is now double coded. Specimens with the second code are sometimes referred to as de-identified specimens. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code. Access to both keys would be needed to link any data or specimens back to the subject's identification.

The second code is stored separately from the first code and all associated personal specimen identifiers. A secure link, the second key, will be utilized to match the second code to the first code to allow clinical information collected during the course of the study to be associated with the specimen. This second key will be transferred under secure procedures by the Merck designated facility to an Entrusted Keyholder at Merck. The second code will be logged into the primary biorepository database at Merck and, in this database, this identifier will not have identifying demographic data or identifying clinical information (i.e., race, sex, age, diagnosis, lab values) associated with it. The specimen will be stored in a designated biorepository site with secure policies and procedures for specimen storage and usage.

The second key can be utilized to reconstruct the link between the results of future biomedical research and the clinical information, at the time of analysis. This linkage would not be possible for the scientist conducting the analysis, but can only be done by the Merck Entrusted Keyholder under strict security policies and procedures. The Merck Entrusted Keyholder will link the information and then issue a de-identified

data set for analysis. The only other circumstance by which future biomedical research data would be directly linked to the full clinical data set would be those situations mandated by health authorities (e.g., EMEA, FDA), whereby this information would be directly transferred to the health authority.

6.5 Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. However, exploratory analyses will not be conducted under the highly validated conditions usually associated with regulatory approval of diagnostics. The scope of research performed on these specimens is limited to the investigation of the variability in biomarkers that may correlate with a clinical phenotype in subjects.

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens. Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-study. Future Biomedical Research specimens remaining with the third party after the specific analysis is performed will be returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

6.6 Withdrawal from Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by writing to the principal investigator for the main study. If medical records for the main study are still available, the Investigator will contact MERCK using the designated mailbox PPD and a form will be provided by MERCK to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from MERCK to the investigator confirming the destruction. It is the responsibility of the Investigator to inform the patient of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (e.g., if the investigator is no longer required by regulatory agencies to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the patient’s personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

6.7 Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from acquisition. Specimens may be stored for longer if a regulatory or governmental agency has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the site will be shipped to a central laboratory and then shipped to the Merck designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Merck policies and procedures and this destruction will be documented in the biorepository database.

6.8 Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-study will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized sponsor and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based in international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These data are collected for future biomedical research purposes only as specified in this sub-study will not be used for any other purpose.

6.9 Reporting of Future Biomedical Research Data to Subjects

There is no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations globally that research results have to be, in all circumstances, returned to study participant. Some guidelines advocate a proactive return of data in certain instances. No information obtained from exploratory laboratory studies will be reported to the subject or family, and this information will not be entered into the clinical database maintained by Merck on subjects. Principle reasons not to inform or return results to the subject include: lack of relevance to subject health, limitations of predictive capability, concerns of misinterpretation, and absence of good clinical practices standards in exploratory research typically used for diagnostic testing.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information as to how to offer clinical diagnostic testing (paid for by Merck) to

subjects enrolled and will be advised that counselling should be made available for all who choose to participate in this diagnostic testing.

If any exploratory results are definitively associated with clinical significance after completion of a clinical trial, Merck will publish the results without revealing specific subject information, inform all sites who participated in the Merck clinical trial, and post anonymized results on our website or other accredited website(s) that allow for public access (e.g., Disease societies who have primary interest in the results) in order that physicians and patients may pursue clinical diagnostic testing if they wish to do so.

6.10 Gender, Ethnicity and Minorities

Although many diagnoses differ in terms of frequency by ethnic population and gender, every effort will be made to recruit all subjects diagnosed and treated on Merck clinical trials for future biomedical research. When studies with specimens are conducted and subjects identified to serve as controls, every effort will be made to group specimens from subjects and controls to represent the ethnic and gender population representative of the disease under current investigation.

6.11 Risks versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. Risks include those associated with venipuncture to obtain the whole blood specimen. This specimen will be obtained at the time of routine blood specimens drawn in the main study.

Merck has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

It is necessary for subject-related data (i.e., ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc.) to be reassociated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure Merck database, and all specimens will be stripped of subject identifiers. No information concerning results obtained from future biomedical research will be entered into clinical records, nor will it be released to outside persons or agencies, in any way that could be tied to an individual subject.

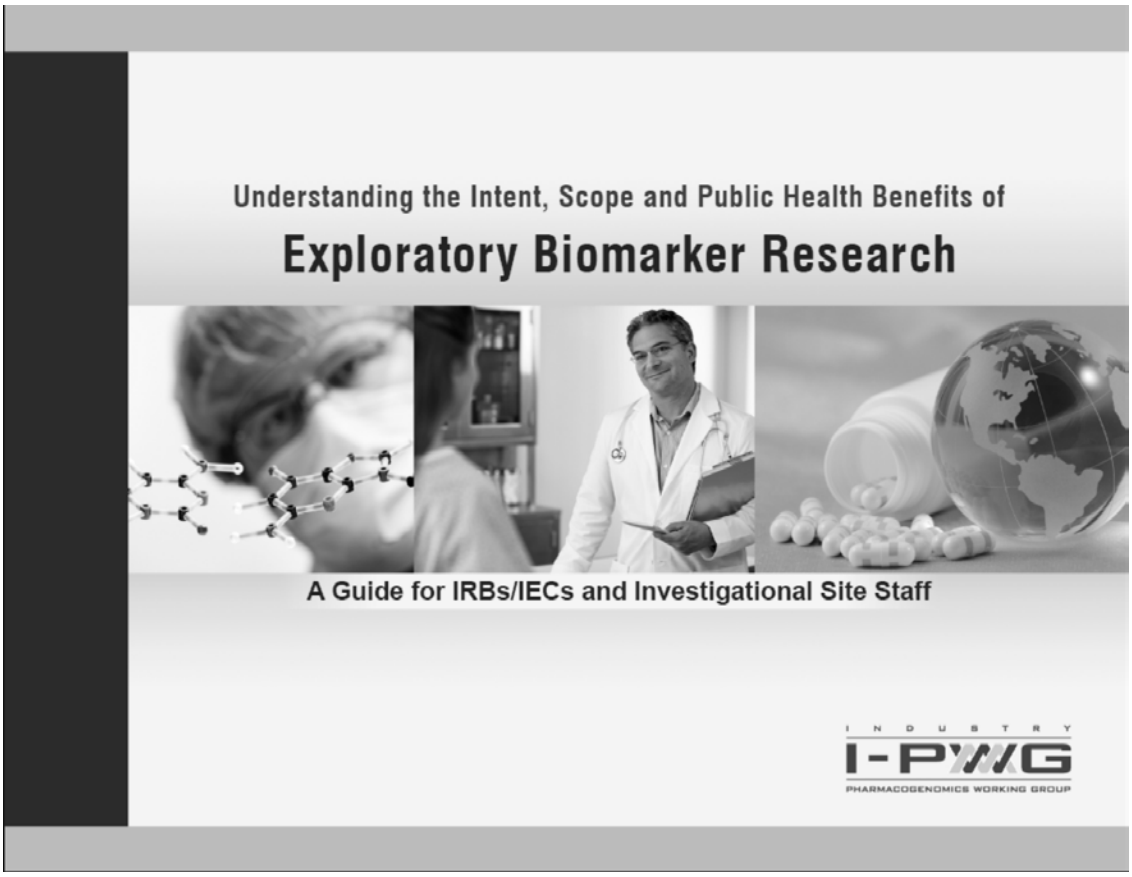
6.12 Self-Reported Ethnicity

Subjects who participate in future biomedical research will be asked to provide self reported ethnicity. Subjects who do not wish to provide this data may still participate in future biomedical research.

6.13 Questions

Any questions related to the future biomedical research should be e-mailed directly to PPD

Appendix 7 Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff



This informational brochure is intended for IRBs/IECs and Investigational Site Staff. The brochure addresses issues relevant to specimen collection for biomarker research in the context of pharmaceutical drug and vaccine development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

1. What is a Biomarker and What is Biomarker Research?

A biomarker is a *"characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".* [1]

Biomarker research, including research on pharmacogenomic biomarkers, is a tool used to improve the development of pharmaceuticals and understanding of disease. It involves the analysis of biomolecules (such as DNA, RNA, proteins, and lipids), or other measurements (such as blood pressure or brain images) in relation to clinical endpoints of interest. Biomarker research can be influential across all phases of drug development, from drug discovery and preclinical evaluations to clinical development and post-marketing studies. This brochure focuses on biomarker research involving analysis of biomolecules from biological samples collected in clinical trials. Please refer to I-PWG Pharmacogenomic Informational Brochure[2] and ICH Guidance E15[3] for additional information specific to pharmacogenomic biomarkers.

2. Why is Biomarker Research Important?

Importance to Patients and Public Health
Biomarker research is helping to improve our ability to predict, detect, and monitor diseases and improve our understanding of how individuals respond to drugs. This research underlies personalized medicine: a tailored approach to patient treatment based on the molecular analysis of genes, proteins, and metabolites.[4] The goal of biomarker research is to aid clinical decision-making toward safer and more efficacious courses of treatment, improved patient outcomes, and overall cost-savings. It also allows for the continued development and availability of drugs that are effective in certain sub-populations when they otherwise might not have been developed due to insufficient efficacy in the broader population.

Recent advances in biomedical technology, including genetic and molecular medicine, have greatly increased the power and precision of analytical tools used in health research and have accelerated the drive toward personalized medicine. In some countries, highly focused initiatives have been created to promote biomarker research (e.g., in the US: www.fda.gov/oc/initiatives/criticalpath/ ; in the EU: www.imi.europa.eu/index_en.html).

Importance to Drug Development
Biomarker research is being used by the pharmaceutical industry to streamline the drug development process. Some biomarkers are used as substitutes or "surrogates" for safety or efficacy endpoints in clinical trials particularly where clinical outcomes or events cannot practically or ethically be measured (e.g., cholesterol as a surrogate for cardiovascular disease).[5] By using biomarkers to assess patient response, ineffective drug candidates may be terminated earlier in the development process in favor of more promising drug candidates. Biomarkers are being used to optimize clinical trial designs and outcomes by identifying patient populations that are more likely to respond to a drug therapy or to avoid specific adverse events.

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Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.

3. Importance of Biomarkers to Regulatory Authorities

Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of *CYP2C9* and *VKORC1* genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3, 6-24]

4. How are Biomarkers Being Used in Drug/Vaccine Development?

Biomarker research is currently being used in drug/vaccine development to:

- Explain variability in response among participants in clinical trials
- Better understand the mechanism of action or metabolism of investigational drugs
- Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
- Address emerging clinical issues such as unexpected adverse events
- Determine eligibility for clinical trials to optimize trial design
- Optimize dosing regimens to minimize adverse reactions and maximize efficacy
- Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of experiencing adverse events
- Provide better understanding of mechanisms of disease
- Monitor clinical trial participant response to medical interventions

Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.[7] Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.

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5. Biomarkers are Already a Reality in Health Care

A number of drugs now have biomarker information included in their labels.[25] Biomarker tests are already being used in clinical practice to serve various purposes:

Predictive biomarkers (efficacy) – In clinical practice, predictive efficacy biomarkers are used to predict which patients are most likely to respond, or not respond, to a particular drug. Examples include: i) *Her2/neu* overexpression analysis required for prescribing trastuzumab (Herceptin®) to breast cancer patients, ii) *c-kit* expression analysis prior to prescribing imatinib mesylate (Gleevec®) to gastrointestinal stromal tumor patients, and iii) *KRAS* mutational status testing prior to prescribing panitumumab (Vectibix®) or cetuximab (Erbitux®) to metastatic colorectal cancer patients.

Predictive biomarkers (safety) – In clinical practice, predictive safety biomarkers are used to select the proper drug dose or to evaluate the appropriateness of continued therapy in the event of a safety concern. Examples include: i) monitoring of blood potassium levels in patients receiving drospirenone and ethinyl estradiol (Yasmin®) together with daily long-term drug regimens that may increase serum potassium, and ii) prospective *HLA-B*5701* screening to identify those at increased risk for hypersensitivity to abacavir (Ziagen®).

Surrogate biomarkers – In clinical practice, surrogate biomarkers may be used as alternatives to measures such as survival or irreversible morbidity. Surrogate biomarkers are measures that are reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. Examples include: i) LDL level as a surrogate for risk of cardiovascular diseases in patients taking lipid-lowering agents such as atorvastatin calcium (Lipitor®), ii) blood glucose as a surrogate for clinical outcomes in patients taking anti-diabetic agents, and iii) HIV plasma viral load and CD4 cell counts as surrogates for time-to-clinical-events and overall survival in patients receiving antiretroviral therapy for HIV disease.

Prognostic biomarkers – Biomarkers can also help predict clinical outcomes independent of any treatment modality. Examples of prognostic biomarkers used in clinical practice include: i) CellSearch™ to predict progression-free survival in breast cancer, ii) anti-CCP (cyclic citrullinated protein) for the severity of rheumatoid arthritis, iii) estrogen receptor status for breast cancer, and iv) anti-dsDNA for the severity of systemic lupus erythematosus.

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

Adequate sample sizes and high-quality data from controlled clinical trials are key to advancements in biomarker research. Samples collected in clinical trials create the opportunity for investigation of biomarkers related to specific drugs, drug classes, and disease areas. Clinical drug development programs are therefore an invaluable resource and a unique opportunity for highly productive biomarker research. In addition to conducting independent research, pharmaceutical companies are increasingly contributing to consortia efforts by pooling samples, data, and expertise in an effort to conduct rigorous and efficient biomarker research and to maximize the probability of success.[26-27]

7. Informed Consent for Collection & Banking of Biomarker Samples

Collection of biological samples in clinical trials must be undertaken with voluntary informed consent of the participant (or legally-acceptable representative). Policies

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and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[28-31]

Optional vs. Required Subject Participation

Depending on the relevance of biomarker research to a clinical development program at the time of protocol development, the biomarker research may be a core required component of a trial (e.g., key to elucidating the drug mechanism of action or confirming that the drug is interacting with the target) or may be optional (e.g., to gain valuable knowledge that enhances the understanding of diseases and drugs). Informed consent for the collection of biomarker samples may be presented either in the main clinical informed consent form or as a separate informed consent form, with approaches varying somewhat across pharmaceutical companies. The relevance of biomarker research to a clinical development program may change over time as the science evolves. The samples may therefore increase in value after a protocol is developed.

Consent for Future Research Use

While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants are informed of the scope of the intended future research, even if this is broadly defined (see potential uses in Section 4 above), iii) autonomy is respected by providing the option to consent separately to future use of samples or by providing the option to terminate further use of samples upon request (consent withdrawal / sample destruction), and iv) industry standards for confidentiality protection per Good Clinical Practice guidelines are met.[3, 31] Importantly, any research using banked samples should be consistent with the original informed consent, except where otherwise permitted by local law or regulation.

Important elements of informed consent for **future use** of samples include, but are not limited to:[35]

The scope of research – Where the scope of the potential future research is broad, participants should be informed of the boundaries of the research. While it may not be possible to describe the exact analytical techniques that will be used, or specific molecules that will be analyzed, it is possible to clearly articulate in reasonable detail the type of research to be conducted and its purpose. Information regarding whether stored samples may be shared with other parties or utilized for commercialization purposes should also be addressed.

Withdrawal of consent / sample destruction – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants should be informed that it is not possible to destroy samples that have been anonymized.[3] In addition, according to industry standards and regulatory guidance, participants should be informed that data already generated prior to a consent withdrawal request are to be maintained as part of the study data.[36]

The duration of storage – The permissible duration of storage may vary according to the nature and uses of the samples and may also vary on national, state, and local levels. The intended duration of storage, including indefinite storage, should be specified.

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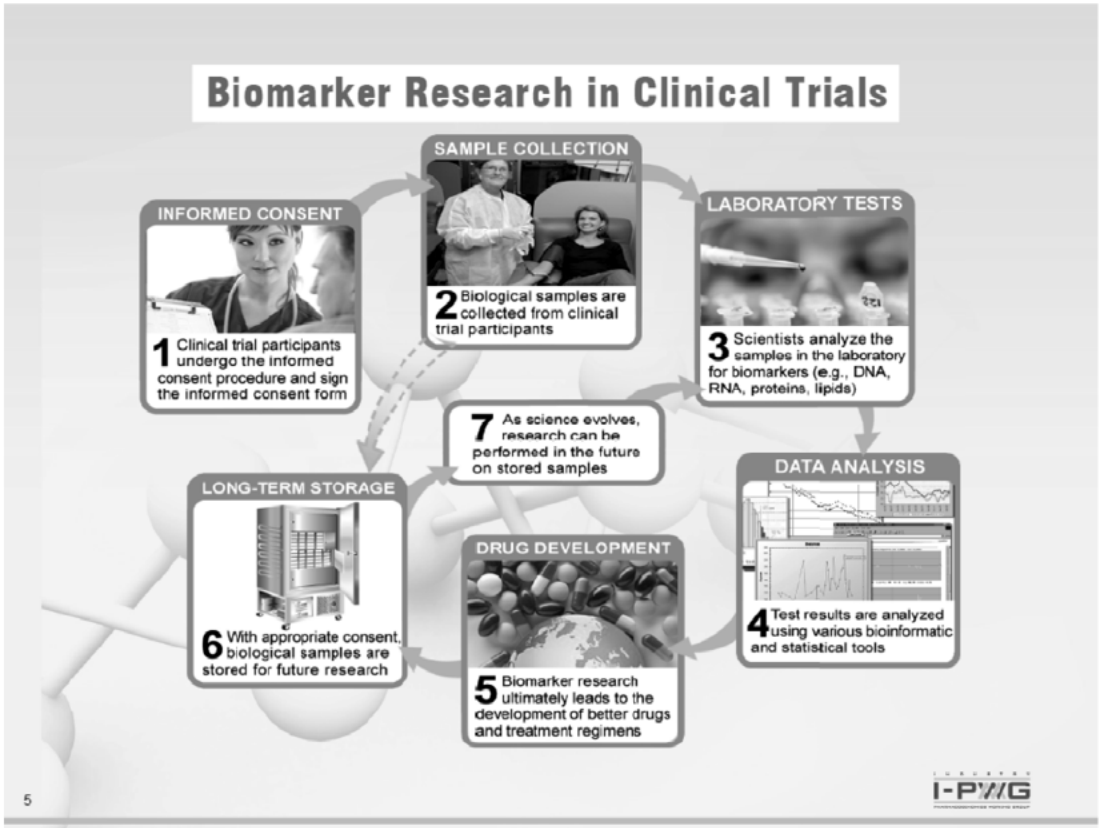

8. Biomarker Sample Collection in Different Countries

Collection of biological samples for biomarker research is straightforward in most jurisdictions. Some countries have specific laws and regulations regarding collection, labeling, storage, export, and/or use of exploratory samples. In addition, some regulations distinguish between DNA and non-DNA samples or between samples used for diagnostic purposes and samples collected for scientific research. Processes for the collection, labeling, storage, export, and/or use of biomarker samples should always adhere to the laws and regulations of the country/region in which those samples are collected.

9. Return of Research Results to Study Participants

Policies for the return of biomarker research results to study participants who request them vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of biomarker research results to study participants. These include:

i) the conditions under which biomarker research results were generated (i.e., exploratory research laboratory versus accredited diagnostic laboratory)

ii) whether the results will have an impact on the medical care of the participant or on a related person, if applicable

iii) whether genetic counseling is recommended (for genetic results)

iv) the ability to accurately link the result to the individual from whom the sample was collected

v) international, national, and local guidelines, policies, legislation, and regulations regarding participants' rights to access data generated on them

Renegar *et al*. 2006 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-35]

10. Benefits and Risks Associated with Biomarker Research

Benefits

While it may not always directly benefit the study participant who is providing the samples, biomarker research can improve overall understanding of disease and treatment of future patients receiving therapies developed from such research. Patients are now benefiting from retrospective biomarker research conducted on samples collected from clinical trials and stored for exploratory research. One example is the recent label update to the EGFR antibody drugs cetuximab (Erbitux®) and panitumumab (Vectibix®) which highlights the value of *KRAS* status as a predictive biomarker for treatment of metastatic colorectal cancer with this class of drug.

The humanitarian benefit of human research is recognized by the Nuremberg Code.[28,33] Provided that the degree of risk does not exceed that determined by the humanitarian importance of the problem to be solved, research participants should not be denied the right to contribute to the greater common good.[28,32]

Risks

Risks associated with biomarker research are primarily related to the physical aspects of obtaining the sample and to patient privacy concerns.

Physical risks associated with biomarker sample collection in clinical trials can be characterized in two ways: i) negligible additional risk when the biomarker sample is collected as part of a procedure conducted to support

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other core trial objectives, and ii) some added risk where the sampling procedure would otherwise have not been performed as a core component of a trial. Risks are also determined by the invasiveness of the sample collection procedure.

Privacy risks are generally those associated with the inappropriate disclosure and misuse of data. Pharmaceutical companies have policies and procedures for confidentiality protection to minimize this risk for all data collected and generated in clinical trials. These may vary across companies, but are based on industry standards of confidentiality and privacy protection highlighted in the following section. Importantly, privacy risks inherent to biomarker data are no greater than other data collected in a clinical trial.

11. Privacy, Confidentiality, and Patient Rights

Maintaining the privacy of study participants and the confidentiality of information relating to them is of paramount concern to industry researchers, regulators, and patients. Good Clinical Practice (GCP), the standard adhered to in pharmaceutical clinical research, is a standard that

"...provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected",

where confidentiality is defined as, *"The prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity."*

This standard dictates that *"the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements."* [31]

Exploratory biomarker research in pharmaceutical development is commonly conducted in research laboratories that are not accredited to perform diagnostic tests used for healthcare decision-making. Therefore, results from exploratory biomarker research usually are not appropriate for use in making decisions about a trial participant's health. In addition, exploratory research data should not be included as part of a participant's medical record accessible for use by insurance companies. Legislation and policies to protect individuals against discrimination based on genetic information continually evolve based on social, ethical, and legal considerations. Examples of such legislation include the Human Tissue Act 2004 (UK) and the Genetic Information Nondiscrimination Act (GINA) 2008 (USA).[36-37]

12.Where to Get More Information?

Educational resources related to biomarker and pharmacogenomic research that caters to health care professionals, IRBs/IECs, scientists, and patients are continually being created and are publicly available. Links to many of these resources are available through the I-PWG website: www.i-pwg.org.

13. What is I-PWG?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in pharmacogenomic research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of pharmacogenomic and other biomarker research for key stakeholders. The I-PWG interacts with regulatory authorities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

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14. Contributing authors

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