A PHASE 2, RANDOMIZED, PLACEBO-CONTROLLED, MULTICENTER STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF GED-0507-34-LEVO (GED0507) FOR TREATMENT OF SUBJECTS WITH ACTIVE ULCERATIVE COLITIS

INVESTIGATIONAL PRODUCT:	**GED-0507-34-Levo**
PROTOCOL NUMBER:	**GED0507-UC-001 – FINAL**
PROTOCOL VERSION AND DATE:	
Original: Global	**Final Version 1.1 - 01-June-2016**
Amendment 1	**Final Version 2.0 - 24-Jan-2017**
EudraCT NUMBER:	**2016-001684-36**
IND NUMBER:	**126320**
SPONSOR NAME / ADDRESS:	PPM SERVICES SA Viale Serfontana 10 6834 MORBIO INFERIORE SWITZERLAND

SUMMARY OF AMENDMENT CHANGES

Revisions to Original Protocol Final Version 1.1 - 01-June-2016

Change	Rationale	Affected Protocol Sections
Inclusion Criteria 7: 'Subjects who have relapsed on maintenance therapy with doses of 5-ASA < 2.4 g/day' Exclusion Criteria 9: 'Subjects who have relapsed on maintenance therapy with doses of 5-ASA ≥ 2.4 g/day will be excluded from the study'	To better identify the study population, it has been decided to include in the trial, subject on 2.4g/day of 5-ASA treatment. The criteria to be satisfied are the following Inclusion Criteria 7: 'Subjects who have relapsed on maintenance therapy with doses of 5-ASA ≤ 2.4 g/day' Exclusion Criteria 9: 'Subjects who have relapsed on maintenance therapy with doses of 5-ASA > 2.4 g/day will be excluded from the study'	• Synopsis, Study Population • Section 10.2 • Section 10.3

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1 SIGNATURE PAGES

1.1 PPM SERVICES SA Therapeutic Area Head Signature Page

(See appended electronic signature page)

Signature of PPM SERVICES SA Therapeutic Area Head **dd mmm yyyy**

Printed Name of PPM SERVICES SA Therapeutic Area Head and Title

By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

1.2 Site Principal Investigator Signature Page

Signature of Site Principal Investigator **dd mmm yyyy**

Printed Name of Site Principal Investigator

Institution Name

By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from PPM SERVICES SA representatives, the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.

1.3 Coordinating Principal Investigator Signature Page

Signature of Coordinating Principal Investigator **dd mmm yyyy**

Printed Name of Coordinating Principal Investigator

Institution Name

By my signature, I agree the protocol has been written to comply with ICH Good Clinical Practices Guidelines and I agree to offer guidance throughout the study as needed.

2 SYNOPSIS

Study Title

A Phase 2, randomized, placebo-controlled, multicenter study to investigate the efficacy and safety of GED-0507-34-Levo (GED0507) for treatment of subjects with active ulcerative colitis.

Indication

Active ulcerative colitis (UC).

Objectives

Primary Objective:

To evaluate the clinical efficacy of GED-0507-34-Levo (80 mg twice daily [BID] and 160 mg BID), compared with placebo, in subjects with active UC.

Secondary Objective:

To evaluate the safety and tolerability of GED-0507-34-Levo (80 mg BID and 160 mg BID), compared with placebo, in subjects with active UC.

Exploratory Objective:

To evaluate the onset of clinical effect of GED-0507-34-Levo (80 mg BID and 160 mg BID), compared with placebo, in subjects with active UC.

Pharmacokinetic Objective:

- To characterize the pharmacokinetics (PK) of GED-0507-34-Levo in subjects with active UC.
- To evaluate the change in biomarkers such as C-reactive protein (CRP) and fecal calprotectin (FCP) in response to GED-0507-34-Levo (80 mg BID and 160 mg BID), compared with placebo, in subjects with active UC.
- To explore the histological effects of GED-0507-34-Levo (80 mg BID and 160 mg BID) such as inflammatory cell infiltration and tissue destruction in colonic mucosal biopsies from subjects with active UC (Geboes Index).

Study Design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of 2 doses of GED-0507-34-Levo in subjects with active, mild-to-moderate UC (defined as a Modified Mayo score [MMS] of ≥ 4 to ≤ 8, with a Stool Frequency sub-score [SFS] ≥ 1, a Rectal Bleeding sub-score [RBS] = 1 or 2 and an endoscopic sub-score > 1 and < 3).

Approximately 207 subjects will be treated with 80 mg BID, 160 mg BID, or identically appearing placebo BID for up to 8 weeks. Treatment will be assigned via an Interactive Web Response System (IWRS).

The study will consist of 3 parts:

- In Part 1, 24 subjects will be randomized with 8 subjects per treatment group. The Safety evaluation (clinical, hematological, and biochemistry) on these 24 subjects will be assessed by an Independent Safety Committee.
- After the 24th subject is enrolled in Part 1, then Part 2 will start in which new subjects will be randomized only in the 80 mg BID and placebo groups in a 1:1 ratio.

- Once the 24 subjects in Part 1 have completed 8 weeks of treatment and the Safety evaluation has been completed with no safety concerns, then Part 3 will continue to enroll subjects randomized into all 3 treatment groups. An unequal randomization will be used in Part 3 of the study in order to ensure approximately equal numbers of subjects randomized into each of the 3 treatment groups across the 3 study parts.

The study will consist of 3 phases:

- Screening Phase – up to 4 weeks
- Double-blind Placebo-controlled Phase – Weeks 0 to 8
- Follow-up Phase – Week 9

Double-blind Placebo-controlled Phase

Eligible subjects will enter the Double-blind Placebo-controlled Phase at the Baseline Visit (Week 0/Visit 2). Subjects will be randomly assigned to study treatment as described above. All subjects will receive high-density polyethylene (HDPE) bottles of identical appearance to maintain blinding.

Subjects will continue to receive the treatment assigned at baseline for 8 weeks.

Study Population

The study population consists of female and male subjects 18 years and older at the time of signing the informed consent form (ICF). The major eligibility criteria are:

- Diagnosis of UC with a duration of at least 3 months prior to the Screening Visit.
- MMS ≥ 4 to ≤ 8 prior to randomization in the study.
- SFS ≥ 1 and RBS = 1 or 2.
- Mayo endoscopic sub-score > 1 and < 3 prior to randomization in the study.
- Subjects with relapsing UC who have been in relapse for > 2 weeks will be excluded.
- Subjects who have relapsed on maintenance therapy with doses of 5-aminosalicylic acid (5-ASA) > 2.4 g/day will be excluded from the study. If a subject had a recent 5-ASA dose reduction from > 2.4 g/day to ≤ 2.4 g/day and relapsed within 2 weeks of that dose reduction, the subject will not be eligible.
- Subjects who have unsuccessfully treated their current relapse with steroids or a 5-ASA dose of > 2.4 g/day will be excluded from the study.
- Subjects with proctitis (extent of inflammation ≤ 15 cm), previous colonic surgery, Crohn's disease, immediate risk of toxic megacolon, or a stool culture positive for enteric pathogens (including *Salmonella, Shigella, Yersinia, Aeromonas, Plesiomonas,* or *Campylobacter*) will be excluded as well those with *Clostridium difficile* toxin present or with ova or parasites as detected by microscopy.
- The use of systemic or rectal steroids within the last 4 weeks, immunosuppressants within the last 6 weeks, antibiotic use within the last 7 days, or repeated use of any anti-inflammatory drugs within 7 days prior to the Baseline Visit will exclude subjects.
- The use of budesonide-multimatrix (MMx) within the last 8 weeks will exclude subjects.
- Subjects with hypersensitivity to salicylates and subjects with moderate/severe renal impairment are contra-indicated for treatment with 5-ASA compounds and will be excluded from the study.

- Subjects with previous treatment biologics (ie, adalimumab, infliximab, vedolizumab, and/or other monoclonal antibody) will be excluded from the study.

Length of Study

Subjects will spend up to 13 weeks in this study: up to 4 weeks in the Screening Phase; 8 weeks in the Double-blind Placebo-controlled Phase; and 1 week in the Follow-up Phase.

The End of Trial is defined as either the date of the last visit of the last subject to complete the study or the date of receipt of the last data point from the last subject that is required for primary, secondary, and/or exploratory analysis, as pre-specified in the protocol and/or the Statistical Analysis Plan, whichever is the later date.

Study Treatments

Subjects will receive 1 of 2 dose regimens of GED-0507-34-Levo in the Double-blind Placebo-controlled Phase (80 mg BID or 160 mg BID) or placebo BID. GED-0507-34-Levo will be provided in 60 mL HDPE bottles as 80 mg tablets. Matching placebo tablets will also be provided. Tablets will be taken by mouth BID, morning and evening, approximately 12 hours apart, on an empty stomach (ie, at least 3 hours after eating and at least 1 hour prior to eating breakfast or dinner).

Overview of Efficacy Assessments

- MMS at baseline, Week 8, or at the Early Termination Visit
- Endoscopy (flexible rectosigmoidoscopy) during the Screening Phase and at Week 8
- Histological Assessment of disease activity (Geboes Index), Nancy Index (Marchal-Bressenot et al, 2015), and Robarts Index (Mosli et al, 2015) at baseline and at Week 8
- Colonoscopy, as opposed to rectosigmoidoscopy, is required at screening only if one was not performed within 12 months prior to the Screening Visit

Images of all endoscopic procedures (flexible rectosigmoidoscopy/colonoscopy) will be captured and sent to blinded centralized readers for their assessment, which will be used for the calculation of the MMS.

Overview of Safety Assessments

- Adverse events (AEs)
- Physical examinations
- Vital signs
- Body weight
- Electrocardiograms (ECG) at screening/baseline, Week 4, and Week 8
- Clinical laboratory safety evaluation
- Pregnancy tests

Overview of Other Study Assessments

- Pharmacodynamic:
  - CRP at the Baseline Visit, Week 4, and Week 8
  - FCP at the Screening Visit, Week 0 (Baseline Visit), Week 4, and Week 8
  - Intestinal mucosal biopsy performed during the Screening Phase and at Week 8

Pharmacokinetics

- Sparse sampling PK at Visits 4 (Week 2), 5 (Week 4), 6 (Week 6), and 7 (Week 8) at predose and postdose at a random time between 2 to 4 hours postdose, > 4 to 6 hours postdose, and > 6 to 10 hours postdose.

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4 LIST OF ABBREVIATIONS

Abbreviation	Definition
5-ASA	5-Aminosalicylic acid
6-MP	6-mercaptopurine
ADL	Activities of Daily Life
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{0-24}	area under the curve from time 0 to 24 hours
AZA	azathioprine
BID	twice daily
BMI	body mass index
BUN	blood urea nitrogen
CD-ROM	compact discs read-only memory
CFR	Code of Federal Regulations
CIN	cervical intraepithelial neoplasia
CIOMS-VI	Council for International Organizations of Medical Sciences Form VI
C_{max}	maximum plasma concentration
CPK	creatine phosphokinase
CRO	contract research organization
CRP	C-reactive protein
DMC	data monitoring committee
DSMB	data safety monitoring board
EC	Ethics Committee
ECCO	European Crohn and Colitis Organisation
ECG	electrocardiogram
eCRF	electronic case report form
EEA	European Economic Area
EMA	European Medicines Agency
FCBP	females of childbearing potential
FCP	fecal calprotectin
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
H&E	Haematoxylin Eosin (staining)
HDL	high-density lipoprotein
HDPE	high-density polyethylene
hERG	human ether-a-go-go-related gene
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Council for Harmonisation
IFN	interferon

IgG	immunoglobulin G
IgM	immunoglobulin M
IL	interleukin
IP	investigational product
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LC-MS/MS	liquid chromatography-mass spectroscopy/mass spectroscopy
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LLN	lower limit of normal
LOCF	last-observation-carried-forward
MCS	Mayo Clinic Score or Mental Component Subscore
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMP	matrix metalloproteinases
MMS	Modified Mayo score
mRNA	messenger ribonucleic acid
MTX	methotrexate
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
NSAID	nonsteroidal anti-inflammatory drug
PCS	Physical Component Score
PD	pharmacodynamics
PGA	Physician's Global Assessment
PIN	personal identification number
PIND	pre-IND meeting
PK	pharmacokinetic
PO	per os (by mouth)
PP	per-protocol
PPAR	peroxisome proliferator-activated receptor
QTc	corrected QT
RBC	red blood cell
RBS	Rectal Bleeding sub-score
SAE	serious adverse event
SAP	Statistical Analysis Plan
SF	stool frequency
SFS	Stool Frequency sub-score
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SMT	Safety Management Team
SOP	standard operating procedure
SSZ	Sulfasalazine

SUSAR	suspected unexpected serious adverse reaction
TMS	Total Mayo Score
TNFα	tumor necrosis factor-alpha
UC	Ulcerative Colitis
UC-DAI	Ulcerative Colitis Disease Activity Index
UCEIS	Ulcerative Colitis Endoscopic Index of Severity
ULN	upper limit of normal
WBC	white blood cell

5 INTRODUCTION

5.1 Ulcerative Colitis

Ulcerative colitis (UC) is a chronic, relapsing inflammatory disease of the large intestine characterized by inflammation and ulceration of the mucosal and submucosal intestinal layers. It is one of the most common forms of inflammatory bowel disease (IBD). The worldwide incidence of UC is 1.2 to 20.3 cases per 100,000 persons per year, and its prevalence is 7.6 to 246.0 cases per 100,000 persons per year (Danese et al, 2011). Clinical characteristics include rectal bleeding, diarrhea, and abdominal pain, as well as extraintestinal manifestations involving the skin, liver, and other sites (Danese et al, 2011). Patients with UC often have a poor quality of life and are at risk for disease flares leading to hospitalizations and/or surgeries.

The main objectives of treatment in patients with UC are to induce and maintain the remission of symptoms and mucosal inflammation in order to improve patients' quality of life. Treatment of UC currently involves pharmacological therapy and surgery, which is indicated when pharmacological treatment fails or when a surgical emergency (eg, perforation of the colon) occurs. Pharmacological treatment usually involves aminosalicylates and glucocorticoids as an initial approach. Various immunosuppressants, as well as biological tumor necrosis factor (TNF) blockers and the more recently approved biologics (ie, vedolizumab and etrolizumab), are used in refractory or severe disease. Although these drugs can provide clinical benefit, they have important limitations. Aminosalicylates are only modestly effective. Glucocorticoids can cause unacceptable adverse events (AEs) and do not provide a benefit as maintenance therapy. Additionally, immunosuppressant use has been restricted to maintenance therapy and is also associated with significant potential toxicities. The TNF blockers, although efficacious, predispose patients to serious infections (including opportunistic infections) and possibly malignancies (Kornbluth et al, 2010; Mariette et al, 2011).

5-Aminosalicylic acid (5-ASA) is the standard treatment for induction of remission in patients with mild-to-moderate UC. Despite the development of oral advanced formulations, the use of high dosages of 5-ASA required for the treatment of UC results in intakeof multiple large-size tablets per day.

Thus, there is a medical need to develop a new anti-inflammatory agent able to induce remission in active, mild-to-moderate UC and to maintain the remission, with at least a comparable rate of success but at significantly lower doses of active product than 5-ASA. A new anti-inflammatory agent, at lower doses and with smaller tablets, which may improve the patient's compliance, could increase the rate of anti-inflammatory treatment responders, thus avoiding the use of corticosteroids and immunosuppressive drugs in UC.

5.2 Results of Non-clinical Studies

GED-0507-34-Levo is a small molecule designed to selectively target inflammatory pathways. GED-0507-34-Levo anti-inflammatory activity has been demonstrated in vitro in several cell lines and in vivo in mouse models of induced colitis. Non-clinical pharmacology studies have shown that GED-0507-34-Levo exerts its anti-inflammatory properties in intestinal epithelial cells through inhibition of production of pro-inflammatory mediators such as TNFα and

interleukin-8 (IL-8), in a peroxisome proliferator-activated receptor gamma (PPARγ)-dependent manner. In vivo, the administration of GED-0507-34-Levo to murine models of induced colitis markedly reduced the severity of inflammation both at a macroscopic and histologic level.

In safety pharmacology studies, GED-0507-34-Levo did not show any effect on the central nervous system (Irwin's test) and on the respiratory function in rats up to the dose of 2000 mg/kg, which was the no-observed-effect-level (NOEL). In the human ether-a-go-go-related gene (hERG) assay, no effect on the IKr channel was observed up to the concentration of 1000 µM. GED-0507-34-Levo did not show any effect on cardiovascular parameters and body temperature in a telemetry study in dogs up to the single dose of 2000 mg/kg, which was therefore the NOEL. Furthermore, no changes in electrocardiogram (ECG) parameters (including QT and QTc [corrected QT interval]) were seen after 14-day repeated administrations in dogs up to the dose of 2000 mg/kg/day.

Across the animal species investigated (rats and dogs), GED-0507-34-Levo showed a low clearance accounting for about 34% and 14% of the hepatic blood flow in rats and dogs, respectively. The volume of distribution was limited in the rat (about one-half of the total body water), while in the dog it was about 5 times higher than the total body water. Terminal half-lives of about 0.23 and 8 hours were estimated in rats and dogs, respectively.

Following single oral administration in male rats, the compound showed a limited oral bioavailability (11.5%), whilst in dogs it resulted much higher either formulated with gelatin capsules (56%) or Methocel/Tween 80 (92%), with terminal half-life of about 4-5 hours.

Systemic exposure was assessed in all toxicity studies. Either in rats or in dogs, negligible accumulation of both maximum plasma concentration (C_{max}) and area under the curve from time 0 to 24 hours (AUC_{0-24}) values was observed after 14-day or 3-month repeated oral administrations. In both animal species, either on Day 1 or on the day of the last administration, C_{max} and $AUC_{0-24}/AUC_{0-t(last)}$ increased with the dose. No major gender differences were observed in both species after repeated administration.

No significant chiral inversion was observed in rats and dogs following 13-week administration of GED-0507-34-Levo. Plasma protein binding was low (less than 13%) and concentration independent.

In vivo, the only metabolite detected in plasma and urine of rats was the N-acetyl derivative of GED-0507-34-Levo (N-Acetyl-GED-0507-34-Levo).

In the Good Laboratory Practice (GLP) 14-day toxicity study in rats, GED-0507-34-Levo was well tolerated up to the highest dose of 2000 mg/kg/day. In the GLP 13-week toxicity study in rats, GED-0507-34-Levo did not cause any mortality or clinical signs up to the highest dose of 2000 mg/kg/day with a no-observed-adverse-effect level (NOAEL) of 250 mg/kg/day. In the GLP 14-day toxicity study in dogs, no mortality occurred up to the highest tested dose of 2000 mg/kg/day. No treatment-related effects were noted at the dose of 30 mg/kg/day (that was therefore the NOAEL in the 14-day toxicity study in dogs). In the GLP 13-week toxicity study in the dog, GED-0507-34-Levo was well tolerated up to the dose of 45 mg/kg/day that was the NOAEL.

In both rats and dogs, treatment-related changes were observed in the thyroid of animals only when high systemic exposure levels were achieved. The 13-week repeat-dose toxicity studies, which included a 2-week recovery period, demonstrated that thyroid changes are transitory during the dosing period and recover during the dose-free phase.

The main oral embryofetal developmental toxicity study was performed in rats and rabbits. The NOEL for the mother and for embryofetal development and teratogenicity was 2000 mg/kg/day in the rat. In the rabbit, 500 mg/kg/day was the NOEL for maternal toxicity and teratogenicity, and the same dose was the NOAEL for embryofetal development.

GED-0507-34-Levo and its N-acetyl metabolite were not genotoxic in the Ames test. In addition, GED-0507-34-Levo did not induce chromosome aberrations in human peripheral blood lymphocytes in vitro or micronuclei in rat bone marrow cells in vivo.

5.3 Results of Clinical Studies in Humans

The clinical formulation of GED-0507-34-Levo is a solid dosage oral form, a gastro-resistant, pH-dependent release tablet designed for colonic release of the drug substance.

To date, the GED-0507-34-Levo clinical development program for the treatment of UC consists of 2 studies: Study GED-0507-01-09, a Phase 1 first-in-human, double-blind, placebo-controlled study of a single dose of GED-0507-34-Levo gastro-resistant prolonged release tablets, administered at rising doses in healthy volunteers to evaluate safety and pharmacokinetics (PK); and Study GED-0507-01-11, a Phase 2a multicenter, single-arm, single-stage, open-label, Fleming's design, early-escape design, proof-of-concept clinical study on the efficacy and safety of GED-0507-34-Levo, in patients with active UC. Treatment duration in the Phase 2a study was 8 weeks; one 80 mg tablet twice per day (BID) was administered, for a total daily dose of 160 mg per day.

In the Phase 1 study, no serious adverse events (SAEs) or suspected-unexpected serious adverse reactions (SUSARs) were reported during the study. Only 2 AEs were considered possibly related to study treatment: transient amylase value increase (shown to be salivary and not pancreatic) and headache. In the Phase 2a study, 5 AEs were considered possibly or probably related to study medication (possibly related: worsening of UC, stomach ache, nausea, increase of creatine phosphokinase [CPK]; probably related: worsening of abdominal symptoms); 3 AEs led to permanent discontinuation that were considered by the Investigator to be possibly related (worsening of underlying disease, nausea, and stomach ache) and 1 AE that was considered probably related (abdominal symptom) led to permanent discontinuation. The clinical safety results show that GED-0507-34-Levo is well tolerated, and there were no safety concerns in either of the 2 studies.

In a different therapeutic area, a Phase 1 clinical study was also performed in patients affected by psoriasis with GED-0507-34-Levo formulated as cream for topical administration (Study GED-0507-PSO-01-12). No SAE occurred during the study. GED-0507-34-Levo was well tolerated; no patient dropped out during the study and no safety concern was raised. Only one event ("redness and itch in both treated areas" in a subject of GED-0507-34-Levo 0.5% group) was defined as "probably related" to study drug.

Additional details of the non-clinical and clinical studies of GED-0507-34-Levo are provided in the Investigator's Brochure (IB).

5.4 Rationale for the Current Study GED0507-UC-001

At the time the Phase 2a study was designed, a 40% remission rate with the active treatment was used as assumption, based on the available 5-ASA clinical data in mild-to-moderate UC that showed a primary therapeutic success rate up to 70%. The therapeutic success, however, was based mainly on evaluation of clinical symptoms only. A consensus of European Crohn and Colitis Organization (ECCO) reported that over the years a variety of scoring systems have been developed to assess disease activity in UC patients, based both on clinical symptoms and on endoscopic findings, making it difficult to compare the results of clinical trials (Travis et al, 2011). Therefore, the reported remission rates for 5-ASA can vary by as much as 2-fold depending on the definition of remission used in the trials.

In 2012, Romkens reported in a review an analysis of published data, taking into consideration 5-ASA therapeutic success based on both clinical and endoscopic scores (Romkens et al, 2012). Noteworthy, if we take into considerations the results of the trials in which remission is defined based on both clinical and endoscopic sub-scores as the Ulcerative Colitis Disease Activity Index (UC-DAI) ≤ 1, the 5-ASA mean remission rate in mild-to-moderate UC patients drops down to 23.37% (range 0%-39%).

Furthermore, a recent well-designed randomized clinical trial (Sandborn et al, 2012) recruiting active mild-to-moderate UC patients (n=509) and using the same definition of primary efficacy endpoint as the one used in our GED-0507-01-11 trial reported a placebo response rate of 7.4% and a response to active medications (budesonide-MMX® or mesalamine) in a range between 17.9% (p=0.014) and 12.1% (not statistically significant). These figures are both quite different from the remission rates assumed in the Fleming's design of our study (20% for placebo and 40% for treatment arms).

These results suggest that the 14.7% of remission rate in our study might not be far from the percentages observed in the study published by Sandborn, despite the higher clinical severity of the population included in our trial.

If a post-hoc revision of the Fleming's design and assumptions is performed based on the recently published figures, ie, considering the remission rates of 20% (Active Treatment) and 5% (Placebo), with a one-sided α of 5% and 90% power ($1-\beta$), then the revised protocol Fleming's design would recommend a sample size of 34 with a best cut-off of ≥ 5 successes, that is the primary endpoint result of the intent-to-treat (ITT) population.

Moreover, analysis of the per-protocol (PP) population (remission rate 33.3%, clinical improvement rate 53.3% with UC-DAI total scores 6.9 [±1.2, median 7] and 4.1 [±3.1, median 4] at baseline and Week 8) suggests that GED-0507-34-Levo might be able to induce a clinically significant rate of remission of active UC and to improve general conditions as also suggested by the score of the physician's assessment of patient's condition (PP) that mirrors the improvements observed for the secondary endpoints: from 1.8 at baseline to 1.0 at Week 8 (-0.8).

Therefore, the current study GED0507-UC-001 was designed to evaluate the clinical efficacy of GED-0507-34-Levo (80 mg BID and 160 mg BID), compared with placebo, in subjects with active UC.

This study will be performed in compliance with the protocol, International Conference on Harmonisation (ICH} Good Clinical Practice (GCP), and applicable regulatory requirements.

5.5 Benefit / Risk Assessment

GED-0507-34-Levo is a novel therapeutic product in clinical development for the treatment of patients with UC.

GED-0507-34-Levo is small molecule new chemical entity designed to selectively target inflammatory pathways. GED-0507-34-Levo anti-inflammatory activities have been demonstrated in vitro in several cell lines and in vivo in mouse models of induced colitis and compared to the activity mediated by 5-ASA, the standard treatment for mild-to-moderate UC. Both in vitro and in vivo GED-0507-34-Levo shows a higher anti-inflammatory activity as compared to 5-ASA in the non-clinical pharmacology studies. Non-clinical pharmacology studies have shown that GED-0507-34-Levo exerts its anti-inflammatory properties in intestinal epithelial cells through inhibition of production of pro-inflammatory mediators such as TNF-α and IL-8. This occurs via up-regulation of IkBα expression and consequent inhibition of NF-κB activation in a PPARγ-dependent manner.

Clinical safety data are available from the subjects enrolled in the completed Phase 1 and Phase 2a clinical studies. The clinical data collected so far were obtained with a gastro-resistant 80 mg tablet whose release was prolonged during time. Single doses up to 320 mg/day were tested in healthy volunteers in the Phase 1 study, and 8-week administration of 160 mg/day dose was tested in UC subjects in the Phase 2a trial. Adverse events considered possibly or probably related to GED-0507-34-Levo included transient amylase value increase (shown to be salivary and not pancreatic), headache, worsening of UC, stomach ache, nausea, increase of CPK, and worsening of abdominal symptoms. All related AEs were mild in intensity except the high amylase value, which was considered severe. Otherwise, GED-0507-34-Levo appeared to be safe and well tolerated.

The present Phase 2 clinical study GED-0507-UC-001 will explore the efficacy and safety of 2 dose levels of GED-0507-34-Levo (80 mg BID and 160 mg BID), compared with placebo, in subjects with active UC. The doses have been selected mainly based on the results obtained in the completed Phase 2a Fleming design study. In the Phase 2a study GED-0507-34-Levo was well tolerated and, when the population of subjects who completed the 8-week treatment is taken into consideration, a 33% induction of remission rate is observed. However, many subjects either dropped out or withdrew early from the study, due to no effect or to worsening of the disease within the first 4 weeks of treatment. In the upcoming Phase 2 dose-finding study, in which a mild-to-moderate population will be included, the same dose of 160 mg/day used in the Phase 2a study (where a population with a higher severity grading was enrolled) and a higher (double) dose (320 mg/day) have been selected.

In the upcoming Phase 2 clinical trial, a slightly different oral formulation of GED-0507-34-Levo will be employed. The new formulation is a gastro-resistant delayed-release 80 mg tablet, designed as the previous one for the local delivery of the drug substance in the colon by making use of pH-dependent coating polymers. Based on the composition of the tablet, taking into consideration the PK profile of these colon release formulations with limited systemic exposure, and in analogy with 5-ASA formulations on the market (ie, 5-ASA-MMx and Asacol), no significant difference in the PK parameters with the GED-0507-34-Levo new formulation having an impact on safety are expected. However, to account both for the use of the new formulation and for the administration of a 320 mg/day dose (160 mg BID) for 8 weeks, as agreed during the pre-IND meeting (PIND) 126320, an Independent Safety Evaluation will be performed in an initial cohort of subjects before enrolling more subjects in the 320 mg/day (160 mg BID) high dose.

Based on the incidence of UC, on the limited percentage of subjects who respond clinically and endoscopically to the available anti-inflammatory therapies, and on the side effects that may be elicited by immunosuppressants, immunomodulators, and anti-TNF therapies, there is clearly a medical need for new treatments for (mild-to-moderate) UC subjects. Moreover, currently available anti-inflammatory therapies for UC are formulated as large tablets that negatively impact subject compliance. Therefore, a new anti-inflammatory agent for the treatment of mild-to-moderate UC, to be administered in the form of small gastro-resistant delayed-release tablets for the delivery of the drug substance in the colon, would represent an important achievement in the treatment of this pathology.

Overall, based on the medical need and on the available GED-0507-34-Levo safety, tolerability, and efficacy data, the proposed Phase 2 clinical trial design is considered appropriate and potential benefits of evaluating GED-0507-34-Levo in the Phase 2 study outweigh the perceived risks.

6 STUDY OBJECTIVES

6.1 Primary Objective

The primary objective of the study is to evaluate the clinical efficacy of GED-0507-34-Levo (80 mg BID and 160 mg BID), compared with placebo, in subjects with active UC.

6.2 Secondary Objective

The secondary objective of the study is to evaluate the safety and tolerability of GED-0507-34-Levo (80 mg BID and 160 mg BID), compared with placebo, in subjects with active UC.

6.3 Exploratory Objective

The exploratory objective of the study is to evaluate the onset of clinical effect of GED-0507-34-Levo (80 mg BID and 160 mg BID), compared with placebo, in subjects with active UC.

6.4 Pharmacokinetic and Pharmacodynamic

The PK and pharmacodynamic (PD) objectives are:

- To characterize the PK of GED-0507-34-Levo in subjects with active UC
- To evaluate the change in biomarkers such as C-reactive protein (CRP) and fecal calprotectin (FCP) in response to GED-0507-34-Levo (80 mg BID and 160 mg BID), compared with placebo, in subjects with active UC
- To explore the histological effects of GED-0507-34-Levo (80 mg BID and 160 mg BID) such as inflammatory cell infiltration and tissue destruction in colonic mucosal biopsies from subjects with active UC (Geboes Index, Robarts Index, and Nancy Index)

7 STUDY ENDPOINTS

7.1 Primary Endpoint

The primary endpoint of this study is the proportion of subjects achieving a clinical remission in the Modified Mayo score (MMS) at Week 8, defined as an MMS of ≤ 2, with individual sub-scores (stool frequency [SF] and Endoscopy) ≤ 1 and Rectal Bleeding sub-score (RBS) = 0

7.2 Secondary Endpoints

7.2.1 Secondary Efficacy Endpoints

The secondary efficacy endpoints are the following:

- The proportion of subjects achieving clinical response at Week 8, defined as a decrease from baseline in the MMS of at least 2 points and at least 25%, along with a reduction in the RBS of at least 1 point or an absolute RBS of ≤ 1
- The proportion of subjects achieving endoscopic remission at Week 8, defined as a Mayo endoscopic sub-score = 0
- The proportion of subjects achieving endoscopic response at Week 8, defined as a decrease from baseline of at least 1 point in the Mayo endoscopic sub-score
- The proportion of subjects achieving an RBS ≤ 1 at Week 8

7.2.2 Secondary Safety Endpoints

The following safety parameters will be evaluated for the duration of the study:

- Type, frequency, severity, and relationship of AEs to investigational product (IP)
- Number of subjects who discontinue IP due to any AE
- Frequency of clinically significant changes in vital signs and/or laboratory findings

7.3 Exploratory Endpoints (Efficacy)

Exploratory efficacy endpoints

- The proportion of subjects who are in clinical remission per the MMS, as applicable, over time
- The proportion of subjects who are in clinical response per the MMS, as applicable, over time
- The proportion of subjects achieving an RBS ≤ 1 over time, except at Week 8
- The proportion of subjects achieving Stool Frequency sub-score [SFS] ≤ 1 over time
- The change from baseline in the MMS at Week 2, at Week 4, and at Week 8

- Change from baseline in the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) endoscopic score
- The change from baseline in the Geboes Index, Robarts Index, and Nancy Index at Week 8

7.4 Exploratory Endpoints (Other)

PK Endpoint:

- The population-based PK estimates of GED-0507-34-Levo

PD/Biomarker Endpoints:

- The change from baseline in CRP concentration over time
- The change from baseline in FCP concentration over time
- The correlation between FCP/CRP and clinical outcomes over time

8 OVERALL STUDY DESIGN

8.1 Study Design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of 2 doses of GED-0507-34-Levo in subjects with active, mild-to-moderate UC (defined as an MMS of ≥ 4 to ≤ 8, with a Stool Frequency sub-score ≥ 1, an RBS = 1 or 2, and an endoscopic sub-score > 1 and < 3).

Approximately 207 subjects (69 subjects per arm) will be randomized in a 1:1:1 ratio using an Interactive Web Response System (IWRS) to receive oral GED-0507-34-Levo (80 mg BID or 160 mg BID) or identically appearing placebo BID for up to 8 weeks. Treatment will be assigned via IWRS.

The study will consist of 3 parts:

- In Part 1, 24 subjects will be randomized with 8 subjects per treatment group. The Safety evaluation (clinical, hematological, and biochemistry) on these 24 subjects will be assessed by an Independent Safety Committee.
- After the 24th subject is enrolled in Part 1, then Part 2 will start in which new subjects will be randomized only in the 80 mg BID and placebo groups in a 1:1 ratio.
- Once the 24 subjects in Part 1 have completed 8 weeks of treatment and the Safety evaluation has been completed with no safety concerns, then Part 3 will continue to enroll subjects randomized into all 3 treatment groups. An unequal randomization will be used in Part 3 of the study in order to ensure approximately equal numbers of subjects randomized into each of the 3 treatment groups across the 3 study parts.

The study will consist of 3 phases:

- Screening Phase – up to 4 weeks
- Double-blind Placebo-controlled Phase – Week 0 to Week 8
- Follow-up Phase – Week 9

8.1.1 Safety/PK Sub-studies

Safety will be assessed on the first 24 randomized subjects (8 in 160 mg/day, 8 in 320 mg/day, and 8 in Placebo group) by an Independent Safety Committee before more subjects in the high dose group are enrolled in the study.

After enrollment of subject number 24, and until the Independent Safety Evaluation is complete, enrollment will continue and subjects will be randomized in the placebo and 80 mg BID (160 mg/day) dose groups.

Upon completion of the Independent Safety Evaluation and provided a positive safety outcome is obtained, enrollment of subjects in the 3 dose groups will be performed until end of study.

A PK sub-study will be conducted at selected sites. The target for the PK sub-study is to achieve participation of approximately 50% of the randomized subjects

8.1.2 Double-blind Placebo-controlled Phase

Eligible subjects will enter the Double-blind Placebo-controlled Phase for 8 weeks, at the Baseline Visit (Week 0, Visit 2). Subjects will be randomly assigned to study treatment as described above. All subjects will receive high-density polyethylene (HDPE) bottles of identical appearance to maintain blinding. Subjects will continue to receive the treatment assigned at baseline for 8 weeks.

8.2 Internal PPM SERVICES SA Safety Monitoring During the GED-0507-34-Levo Program

In addition to ongoing safety monitoring conducted by Investigators and individual study personnel, cumulative and interval blinded AEs, SAEs, discontinuations due to AEs, and abnormal laboratory findings will be reviewed internally by the Safety Management Team (SMT). The review follows the Council for International Organizations for Medical Sciences, Working Group VI (CIOMS VI) recommendations. The SMT is comprised of lead representatives from multiple PPM SERVICES SA functions engaged in the GED-0507-34-Levo development program. The scope, conduct, processes, and accountabilities of the SMT are specified in the SMT charter.

8.3 Internal Data Safety Monitoring Board During the Study

Unblinded safety data will be reviewed periodically by an internal data safety monitoring board (DSMB) at PPM SERVICES SA that is independent of the study team. The external data monitoring committee (DMC; Section 8.4) may be convened ad hoc at the request of the DSMB.

8.4 External Safety and Efficacy Monitoring During GED-0507-34-Levo Program

Monitoring will also be performed by an independent, external DMC that will assess safety as outlined in the DMC charter (available upon request) after 24 randomized subjects: 8 treated with 160 mg/day (80 mg BID), 8 with 320 mg/day (160 mg BID), and 8 with placebo. The DMC is comprised of 3 independent external trialists and an independent, external statistician, for whom there is no identified conflict of interest. The DMC will be convened approximately every 12 months or ad hoc at the request of the DSMB or SMT. The DMC scope, conduct, processes, and accountabilities are pre-specified in its charter. Recommendations of the DMC based on the overall benefit/risk evaluation may include proceeding with the study per protocol, proceeding with the study with modification, or study suspension.

8.5 Study Design Rationale

This study represents the second investigation of GED-0507-34-Levo in subjects with UC. This study will provide information on the safety and clinical efficacy in the UC population prior to advancing to larger clinical trials, as well as provide critical information for the design of future studies in this population.

The purpose of this study is to determine whether GED-0507-34-Levo is effective and safe in the treatment of subjects with active UC. The primary measure of efficacy will be clinical remission determined by the MMS in a double-blind, placebo-controlled study at Week 8. Clinical remission is defined as an MMS ≤ 2, with no individual sub-score > 1, at Week 8. The laboratory results, AEs, vital signs, ECGs, pregnancy tests, and physical examinations will be monitored to evaluate safety.

A schematic diagram illustrating the study design is shown in Figure 1.

8.6 Study Duration

Subjects will spend up to 13 weeks in this study: up to 4 weeks in the Screening Phase; 8 weeks in the Double-blind Placebo-controlled Phase; and 1 week in the Follow-up Phase.

8.7 End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the study or the date of receipt of the last data point from the last subject that is required for primary, secondary, and/or exploratory analysis, as pre-specified in the protocol and/or the Statistical Analysis Plan (SAP), whichever is the later date.

Figure 1: Overall Study Design

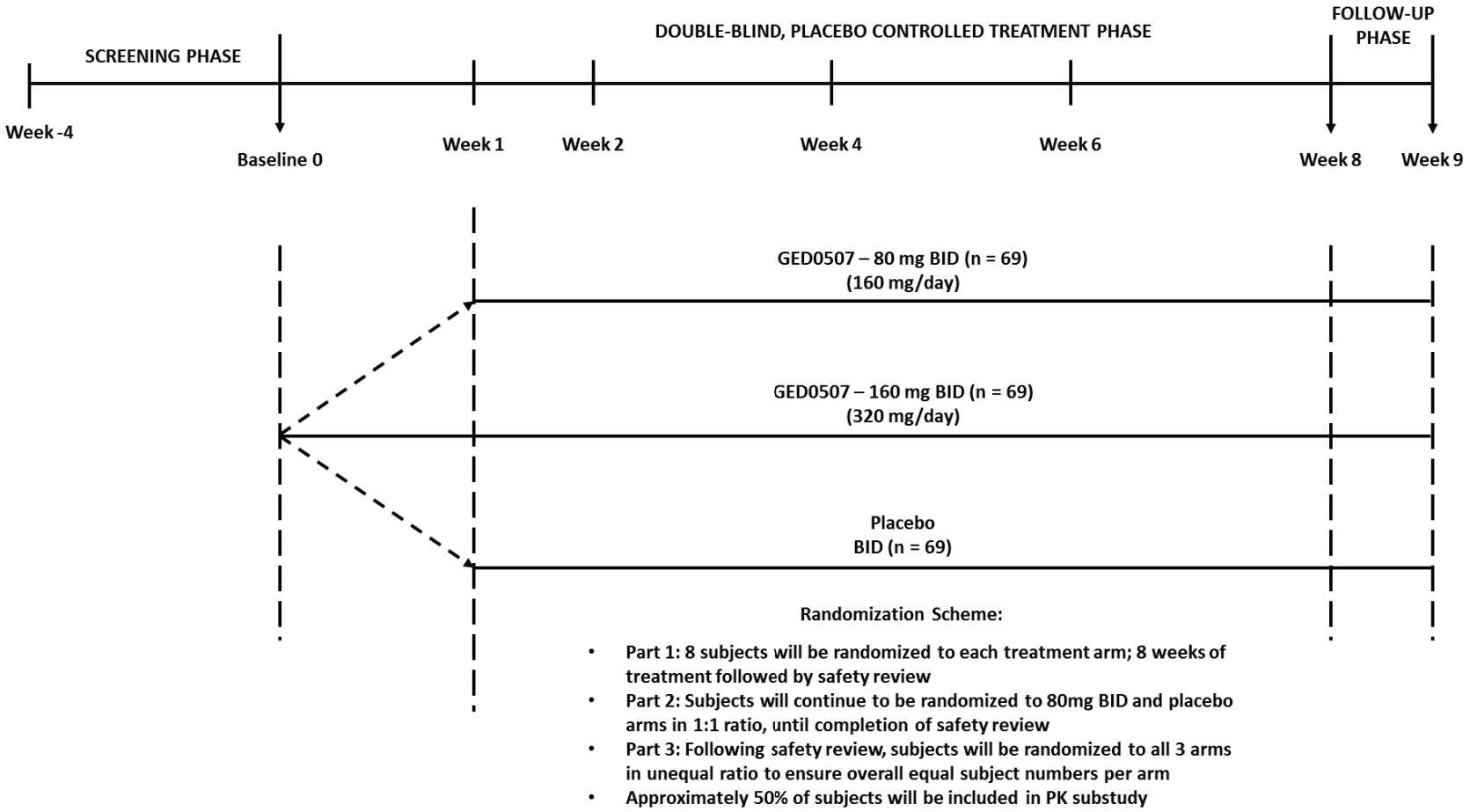

Table 1 Schedule of Events

	Screening Phase	Double-blind Placebo-controlled Phase						Follow-up Phase
Visit Number	**1**	**2 Baseline Visit**	**3**	**4**	**5**	**6**	**7 End of Treatment/ Early Termination Visit[a]**	**8**
Week	**-4 to -1**	**0 (Day 1)**	**1 (Day 7)**	**2 (± 3 days)**	**4 (± 3 days)**	**6 (± 3 days)**	**8 (± 3 days)**	**9 (± 3 days)**
Informed Consent	X							
Inclusion / Exclusion Criteria	X	X						
Medical History	X							
Prior / Concomitant Medications	X	X	X	X	X	X	X	X
Pregnancy Test and Contraception Education [b]	X	X	X	X	X	X	X	X
Hepatitis B and C Tests	X							
Clinical Lab Evaluations	X	X			X		X	X
Stool Culture / Microscopy	X							
Height	X							
Vital Signs / Weight	X	X			X	X	X	X
Physical Exam	X	X					X	X
Adverse Events	X	X	X	X	X	X	X	X
12-lead ECG	X		X	X			X	
PK Draw at Selected Sites[c]				X	X	X	X	
Subject Diary for UC Disease Activity	X	X	X	X	X	X	X	
MMS	X	X	X	X	X	X	X	
Endoscopy [d,e]	X						X	
PGA	X						X	
TMS	X						X	
Intestinal Mucosal Biopsies [f]	X						X	

	Screening Phase	Double-blind Placebo-controlled Phase						Follow-up Phase
Visit Number	**1**	**2 Baseline Visit**	**3**	**4**	**5**	**6**	**7 End of Treatment/ Early Termination Visit[a]**	**8**
Week	**-4 to -1**	**0 (Day 1)**	**1 (Day 7)**	**2 (± 3 days)**	**4 (± 3 days)**	**6 (± 3 days)**	**8 (± 3 days)**	**9 (± 3 days)**
Fecal Calprotectin	X	X	X		X	X	X	
CRP	X	X	X		X	X	X	
Dispense IP		X			X			
Return and Count IP		X	X	X	X	X	X	

CRP = high sensitivity C-reactive protein; ECG=electrocardiogram; ET= Early Termination Visit; IP = Investigational Product; MMS = Modifed Mayo score; PK = pharmacokinetics; PGA= Physician's Global Assessment; TMS = Total Mayo Score; UC = ulcerative colitis.

a. Subjects who discontinue from the study prior to the Week 8 Visit will have an Early Termination Visit.
b. The female subject's chosen form of contraception must be effective by the time the female subject is randomized into the study (for example, hormonal contraception should be initiated at least 28 days before randomization). Serum pregnancy tests will be performed at screening, and urine pregnancy testing will be done at all remaining visits, including an Early Termination Visit. Urine pregnancy test kits will be provided to the site. A pregnancy test(s) should be administered if the subject misses a menstrual period during the study treatment period.
c. Sparse PK samples as described in Section 9.9.1.
d. The screening endoscopy will consist of a colonoscopy or flexible rectosigmoidoscopy. Colonoscopy is required at screening only for those subjects who have not had a colonoscopy within 12 months prior to the Screening Visit. Rectosigmoidoscopies will be repeated at Week 8 or at the Early Termination Visit.
e. Rectosigmoidoscopy will not be repeated if within 4 weeks of the previous endoscopy.
f. Two intestinal mucosal biopsies will be performed with the endoscopy during the Screening Phase and also at the Week 8 Visit or the Early Termination Visit if the subject discontinues prior to Week 8. Biopsies should be taken from the most inflamed area of the rectum or rectosigmoid junction, while avoiding ulcerated mucosa. Week 8 biopsies should be taken from the same location as the baseline biopsy.

9 PROCEDURES

The following procedures/assessments will be conducted according to the schedule indicated in Table 1 Schedule of Events.

9.1 Informed Consent

An informed consent form (ICF) must be signed by the subject before any study-related assessments are performed. In addition, the randomized subjects must consent specifically for the PK sub-study. Details of the informed consent process may be found in Section 17.3.

9.2 Contraception Education

The risks to a fetus or to a nursing child from GED-0507-34-Levo are not known at this time.

A female of childbearing potential (FCBP) is a sexually mature female who 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been postmenopausal for at least 24 consecutive months (that is, has had menses at any time during the preceding 24 consecutive months).

All FCBP must use one of the approved contraceptive options as described in Section 10.2 while on IP and for at least 28 days after administration of the last dose of the IP.

At the time of study entry, and at any time during the study when an FCBP's contraceptive measures or ability to become pregnant changes, the Investigator will educate the subject regarding contraception options and correct and consistent use of effective contraceptive methods in order to successfully prevent pregnancy.

9.3 Medical and Disease History

Relevant medical history should be recorded, including caffeine consumption, smoking and alcohol history, as well as previous relevant surgeries. Disease history includes history of UC (i.e, the disease under study).

9.4 Inclusion/Exclusion Criteria

Subjects must meet all inclusion criteria (Section 10.2) and must not have any of the conditions specified in the exclusion criteria (Section 10.3) to qualify for participation in the study. The subject's source documents must support his/her qualifications for the study (eg, if a female subject does not require pregnancy testing and birth control because of a hysterectomy, the date of the hysterectomy must be included in the medical history).

9.5 Prior/Concomitant Medications and Therapies

All medications (prescription and nonprescription, including vitamins) taken by the subject up to 30 days prior to the Screening Visit (Visit 1) should be recorded, including the stop dates for medications prohibited in the study. All medications taken by the subject at any time during the

study must also be recorded. Other key medications and therapies, such as previous treatment for tuberculosis or relevant diseases, should also be recorded.

9.6 Safety Assessments

9.6.1 Serum and Urine Pregnancy Tests for Females of Childbearing Potential

A urine pregnancy test will be performed on all FCBP at the Baseline Visit, all onsite visits, and at Follow-up or at the Early Termination Visit. A urine pregnancy test kit will be provided by the central laboratory. Pregnancy tests should be performed if the FCBP has missed a menstrual period or the contraception method has changed.

9.6.2 Hepatitis B and C

The hepatitis screen includes testing for hepatitis B surface antigen and antibody, hepatitis B core antibodies (immunoglobulin G [IgG]/immunoglobulin M [IgM]), and antibodies to hepatitis C.

9.6.3 Vital Signs, Height, and Weight

Vital signs, including temperature, pulse, and seated blood pressure, will be taken during the visits indicated in Table 1 Schedule of Events. Height will be measured and recorded at screening; weight will also be measured and recorded at screening and then as indicated in Table 1 Schedule of Events. Body mass index (BMI) will be calculated at screening.

9.6.4 Physical Examinations

Complete physical examinations will include evaluation of the skin, respiratory, cardiovascular, abdominal, neurological, lymphatic, and musculoskeletal systems. Results of the physical examinations will be recorded only in the source documents.

Clinically significant abnormal findings (with the exception of the disease under study [UC]) identified prior to first dose of IP will be recorded on the electronic case report form (eCRF) as medical history; clinically significant findings after the first dose of IP will be recorded as AEs.

Note: Gynecological and urogenital examinations will not be performed unless for cause.

9.6.5 Stool Culture / Microbiology

Stool culture analysis and assessment of *Clostridium difficile* toxin will be performed at the Screening Visit, as well as *Salmonella, Shigella, Yersinia, Aeromonas, Plesiomonas*, or *Campylobacter*. Subjects who are initially positive for *C. difficile* may re-screen for the study after they have successfully completed therapy and had 2 months of consecutive negative tests for C. *difficile*.

9.6.6 12-lead Electrocardiogram

The 12-lead ECG will be performed after the subject has been supine for approximately 3 minutes. Sites are to utilize their own local ECG machines for the study, and the automated ECG readings will be further interpreted by the Investigator by clinically correlating them with the subject's condition. The Investigator's clinical interpretation will be recorded in the eCRF as one of the following: "normal", "abnormal, not clinically significant", or "abnormal, clinically significant". "Abnormal, clinically significant" results should be recorded in the Medical History eCRF if found prior to the first dose of IP or in the AE eCRF if found after the first dose of IP.

9.6.7 Clinical Laboratory Evaluations

A central laboratory will be used for this study. Clinical laboratory evaluations will include the following:

- Hematology: complete blood count (red blood cell [RBC] count, hemoglobin, hematocrit, white blood cell [WBC] count and differential, absolute WBC counts, platelet count)
- Serum chemistries: total protein, albumin, calcium, phosphorous, glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, uric acid, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST)/ serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/ serum glutamic pyruvic transaminase (SGPT), sodium, potassium, chloride, carbon dioxide, blood urea nitrogen (BUN), creatinine, lactate dehydrongenase (LDH), magnesium, amylase (pancreatic)
- Urinalysis: dipstick urinalysis (specific gravity, pH, glucose, ketones, protein, blood, bilirubin, leukocyte esterase, nitrite, and urobilinogen)
    - Microscopic urinalysis (epithelial cells, RBC, WBC, and casts) will be performed only if the dipstick urinalysis is abnormal

Note: Clinical laboratory evaluations are not required to be fasting. However, the site will record whether a clinical laboratory evaluation was fasting or nonfasting on the lab requisition form.

9.6.8 Adverse Events

Adverse events (Section 14.1) will be recorded by the Investigator from the time the subject signs informed consent to 28 days after the last dose of IP. The AEs, including SAEs, will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs must be reported to PPM SERVICES SA Drug Safety within 24 hours of the Investigator's knowledge of the event (see Section 14.5). Worsening of a subject's UC, including UC flare, should be considered as worsening of disease under study, and should not be captured as an AE. Worsening or exacerbation of UC, including UC flare, meeting the definition of an SAE should be reported as an SAE.

9.7 Efficacy Assessments

9.7.1 Subject Diary for Ulcerative Colitis Disease Activity

Subjects will be provided with the Subject Diary for UC Disease Activity at study visits in order to record the following information:

(1) Frequency of bowel movements:

As usual
1-2 times a day more than usual
3-4 times a day more than usual
More than 5 times a day more than usual

(2) Blood in stools

Absent
Traces of blood in stools
A lot of blood in stools
Blood only

(3) General Well-Being

Generally Well
Fair
Poor
Terrible

Diaries will be completed throughout the study and assessed at the clinic, at each study visit, from screening until the Week 8 Visit or Early Termination Visit. The information extracted will be used for calculation of the Mayo score. In order to encourage consistent diary recording, subjects are required to enter diary data continuously throughout the study. The method of diary data collection will be electronic data capture and may include paper.

9.7.2 Endoscopy

The screening endoscopy may consist of either a flexible rectosigmoidoscopy or a colonoscopy. A colonoscopy is required during the Screening Phase only for those subjects who have not had a colonoscopy within 12 months prior to the Screening Visit. Subsequent endoscopies (rectosigmoidoscopies) will be performed at Week 8 or at the Early Termination Visit. The flexible rectosigmoidoscopy will not be repeated within 4 weeks of the previous rectosigmoidoscopy.

Images/Videos of all endoscopic procedures (flexible rectosigmoidoscopy/colonoscopy) will be captured and sent to a centralized reader for their assessment, which will be used for the calculation of the MMS. The endoscopy assessment performed by the Investigator will be used

to calculate the MMS for the determination of subjects who do not achieve at least a 20% decrease from baseline in the MMS at Week 8.

Mucosal biopsies, collected for assessment of histological disease activity (Section 9.8), will be performed during the Screening Phase and at the Week 8 Visit when the endoscopies are done. Biopsies should be taken from the most inflamed area of the rectum or rectosigmoid junction, while avoiding ulcerated mucosa. Week 8 biopsies should be taken from the same location as the baseline biopsy. Subjects who discontinue study prior to the Week 8 Visit will have the biopsies performed at the Early Termination Visit with the endoscopy.

Central reading of endoscopies will be performed throughout this study, and a detailed charter will address the standardization of endoscopic procedures, video recordings, and equipment, as well as the criteria for endoscopic assessment. For each subject, video recording of the entire endoscopic procedure will be performed. Annotation of the rectum, sigmoid and descending colon will be performed by the site endoscopist on withdrawal, using the equipment provided.

All video recordings will be quality checked by the central read vendor to produce a video clip visualized up to the splenic flexure only (rectum, sigmoid, and descending colon). The video clips will be read centrally for mucosal lesions and endoscopic severity by an independent gastroenterologist experienced in IBD who is blind to the subject's clinical activity and treatment allocation. The Mayo Clinic Score (MCS) endoscopic sub-score is to be determined both locally (at the investigator site) and centrally as described above. Each segment of the colon up to the splenic flexure (rectum, sigmoid, and descending colon) will be assigned an endoscopic sub-score, and the score from the worst affected segment up to the splenic flexure is to be used for the MCS calculation. In the event that there is a discrepancy between the endoscopic sub-score obtained by the local versus the central readers, a third adjudication read is to be conducted by a different central reader.

Training of the site and central readers, and the adjudication process in the event of a discrepancy between site and central reader; will be described in detail in the Endoscopy charter

9.7.3 Modified Mayo Score

The Mayo Score is an instrument designed to measure disease activity of UC. The Mayo Score ranges from 0 to 12 points. It consists of 4 sub-scores, each graded from 0 to 3 with higher scores indicating more severe disease (Appendix C).

A modification to the Total Mayo Score (TMS) will be implemented in this study. This MMS will be based on the stool frequency, rectal bleeding, and endoscopy sub-scores of the TMS and will exclude the Physician's Global Assessment (PGA) sub-score, since this is a global measure that is subjective in nature. The MMS ranges from 0 to 9 points. Clinical response is defined as a decrease from baseline in modified Mayo Score of at least 2 points and at least 25%, with an accompanying decrease in the RBS of at least 1 point or an absolute RBS of 0 or 1. Clinical remission is defined as an MMS of 2 points or lower, with no individual sub-score exceeding 1 point.

- SFS

- RBS
- Endoscopy Sub-score

The frequency of the TMS assessment is described in Table 1 Schedule of Events.

9.7.4 Physician Global Assessment

The PGA is done as part of the Mayo score. It acknowledges 3 other criteria: the subject's daily recollection of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the subject's performance status.

9.8 Pharmacodynamic/Biological Markers

Peripheral blood will be analyzed for CRP, which is a protein that provides an objective criterion of inflammatory activity. C-reactive protein enables identification of subjects with UC symptoms who have objective evidence of active inflammatory disease (Sands 2015). Fecal calprotectin, a biomarker of intraluminal intestinal inflammation, will be assessed by a central reader. Fecal calprotectin is a directly proportional measurement of neutrophil migration to the gastrointestinal (GI) tract. The schedule and frequency of PD/biological markers are discussed in Table 1 Schedule of Events.

Intestinal mucosal biopsies will be performed during endoscopy as indicated in Table 1 Schedule of Events in order to assess inflammatory cell infiltration and tissue destruction in the colonic mucosa. One biopsy will be stained with Haematoxylin Eosin (H&E), and the degree of cellular inflammatory infiltrate and of tissue destruction present in the colonic mucosa will be measured using a microscopic tissue grading score.

9.9 Pharmacokinetics

A PK sub-study will be conducted at selected sites to evaluate the PK profile of GED-0507-34-Levo (parent compound) and N-Acetyl-GED-0507-34-Levo (metabolite) in subjects with active UC and to explore the relationship between GED-0507-34-Levo PK exposures and key efficacy endpoints. The target for the PK sub-study is to achieve participation of approximately 50% of the randomized subjects. A separate consent will be signed for this assessment at the Screening Visit.

Pharmacokinetic measurements will be carried out by Accelera Srl (Viale Pasteur 10, 20014 Nerviano, Milano, Italy) using a validated method for the detection of GED-0507-34-Levo and its metabolite N-Acetyl-GED-0507-34-Levo in Human Plasma by liquid chromatography – tandem mass spectroscopy (LC-MS/MS).

9.9.1 Pharmacokinetics Blood Draw

For each subject participating in the PK sub-study, the date and time of his/her first dose will be recorded in the source documents and eCRF.

The subjects participating in the PK sub-study will have 4 blood specimens drawn (1 predose during the treatment and 3 postdose). For the predose blood draw, the subject must be reminded to provide the date and time of his/her last evening dose from the day before the visit, which will be recorded in the source documents and eCRF together with the blood draws prior to the morning intake of the compound.

Postdose plasma population PK samples should be taken at a random time between 2 to 4 hours postdose, > 4 to 6 hours postdose, and > 6 to 10 hours postdose. The date and time of his/her dose prior to the blood draws and the date and time of blood draws will be recorded in the source documents and eCRF.

PK blood draws are to take place in the clinic at Visits 4 (Week 2), 5 (Week 4), 6 (Week 6), and 7 (Week 8). It is recommended that subjects have 1 blood specimen collected from each of these time windows over the course of the PK sub-study.

Specific details regarding collection, handling, processing, storage, and shipment of PK samples will be presented separately.

9.10 Dosing

9.10.1 Investigational Product Dispensing and Counting

After the subject has satisfied all inclusion and exclusion criteria, IP will be dispensed as specified by the IWRS. Subjects must be instructed to return all previously issued empty HDPE bottles and/or unused IP at the time that new IP is issued. A detailed record of tablets issued and returned at each visit must be maintained in the subject's record.

9.11 Early Termination Visit

The Early Termination Visit is based on the subject's withdrawal from the study prior to Week 8. Participation in the study is completely voluntary. Subjects are also free to withdraw from the study at any time if they feel they are not benefiting from the study in order to receive rescue therapy and/or receive treatment with standard medical care. In addition, the Investigator may discontinue the subject from the study at any time based on his/her assessment of clinical efficacy and/or safety. The decision to discontinue a subject remains the responsibility of the treating physician, which will not be delayed or refused by the sponsor. When a subject withdraws or is discontinued from the study, every effort should be made to complete as many safety and efficacy assessments as reasonably appropriate. Refer to Table 1 for the assessments to be performed at the Early Termination Visit.

9.11.1 Lost to Follow-up

Subjects will be considered lost to follow-up when they fail to attend study visits without stating an intention to withdraw from the study. The Investigator should show due diligence by documenting in the source documents the steps taken to contact the subject through at least 2 telephone calls and/or emails and 1 registered letter. After all reasonable attempts have been made to contact the subject, the subject should be recorded as "lost to follow-up" in the eCRF.

9.12 Study Completion

The End of Trial is defined as either the date of the last visit of the last subject to complete the study or the date of receipt of the last data point from the last subject that is required for primary, secondary, and/or exploratory analysis, as pre-specified in the protocol and/or the SAP, whichever is the later date.

Study completion for an individual subject is defined as reaching the Week 9 Follow-up Visit. Subjects not meeting this definition will be considered early termination subjects.

10 STUDY POPULATION

10.1 Number of Subjects and Sites

Approximately 207 subjects will be enrolled in this study at approximately 85 sites.

10.2 Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Male or female aged 18 and over at the time of signing the informed consent.
2. Must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
3. Must be able to adhere to the study visit schedule and other protocol requirements.
4. Diagnosis of UC with a duration of at least 3 months prior to the Screening Visit.
5. MMS ≥ 4 to ≤ 8 (range: 0 - 9) prior to randomization in the study
   - SFS ≥ 1 and RBS = 1 or 2
   - Mayo endoscopic sub-score > 1 and < 3 prior to randomization in the study
6. Subjects are required to have a colonoscopy if one has not been performed within 12 months prior to the Screening Visit.
7. Subjects who have relapsed on maintenance therapy with doses of 5-ASA ≤ 2.4 g/day.
8. Must meet the following laboratory criteria:
   - WBC count ≥ 3000/mm^3 (≥ 3.0 × 10^9/L) and < 14,000/mm^3 (< 14 × 10^9/L)
   - Platelet count ≥ 100,000/mm^3 (≥ 100 × 10^9/L)
   - Serum creatinine ≤ 1.5 mg/dL (≤ 132.6 μmol/L)
   - AST (SGOT) and ALT (SGPT) ≤ 2 upper limit of normal (ULN). If initial test shows ALT or AST > 2 ULN, 1 repeat test is allowed during the screening period
   - Total bilirubin ≤ 2 mg/dL (≤ 34 mol/L) and albumin > lower limit of normal (LLN). If initial albumin test result is < 2 g/dL, 1 repeat test is allowed during the screening period
   - Hemoglobin ≥ 9 g/dL (≥ 5.6 mmol/L)
9. FCBP must have a negative pregnancy test at screening and the Baseline Visit. While on IP and for at least 28 days after taking the last dose of IP, FCBP who engage in activity in which conception is possible must use one of the approved contraceptive options[2] described below:

   Option 1: Any one of the following highly effective methods: hormonal contraception (oral, injection, implant, transdermal patch, vaginal ring); intrauterine device (IUD); tubal ligation; or partner's vasectomy

   OR

Option 2: Male or female condom (latex condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane]); PLUS one additional barrier method: (a) diaphragm with spermicide; (b) cervical cap with spermicide; or (c) contraceptive sponge with spermicide

10. Male subjects (including those who have had a vasectomy) who engage in activity in which conception is possible must use barrier contraception (male latex condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane]) while on investigational product and for at least 28 days after the last dose of investigational product.

10.3 Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Diagnosis of Crohn's disease, indeterminate colitis, ischemic colitis, microscopic colitis, radiation colitis, or diverticular disease-associated colitis.
2. UC restricted to the distal 15 cm or less (eg, ulcerative proctitis).
3. Subjects who have had surgery as a treatment for UC or who, in the opinion of the Investigator, are likely to require surgery for UC during the study.
4. Clinical signs suggestive of fulminant colitis or toxic megacolon.
5. Evidence of pathogenic enteric infection.
6. History of colorectal cancer or colorectal dysplasia.
7. Prior use of any TNF inhibitor (or any biologic agent).
8. Prior use of mycophenolic acid, tacrolimus, sirolimus, cyclosporine, or thalidomide.
9. Subjects who have relapsed on maintenance therapy with doses of 5-ASA > 2.4 g/day will be excluded from the study. If a subject had a recent 5-ASA dose reduction from > 2.4g/day to ≤ 2.4 g/day and relapsed within 2 weeks of that dose reduction.
10. Oral aminosalicylates are not permitted during the study.
11. Use of budesonide-MMx within the last 8 weeks.
12. Use of oral and/or IV corticosteroids within 2 weeks of the Screening Visit.
13. Use of immunosuppressants (azathioprene [AZA], 6-mercaptopurine [6-MP] or methotrexate [MTX]) within 8 weeks of the Screening Visit.
14. Use of topical treatment with 5-ASA or corticosteroid enemas or suppositories within 2 weeks of the Screening Visit.
15. History of any clinically significant neurological, renal, hepatic, GI, pulmonary, metabolic, cardiovascular, psychiatric, endocrine, hematological disorder or disease or any other medical condition that, in the Investigator's opinion, would preclude participation in the study.

16. Prior history of suicide attempt at any time in the subject's lifetime prior to randomization in the study or major psychiatric illness requiring hospitalization within 3 years of study randomization.
17. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she was to participate in the study or confounds the ability to interpret data from the study.
18. Pregnant or breast feeding.
19. History of any of the following cardiac conditions within 6 months of screening: myocardial infarction, acute coronary syndrome, unstable angina, new onset atrial fibrillation, new onset atrial flutter, second- or third-degree atrioventricular block, ventricular fibrillation, ventricular tachycardia, heart failure, cardiac surgery, interventional cardiac catheterization (with or without a stent placement), interventional electrophysiology procedure, or presence of implanted defibrillator.
20. Known active current or history of recurrent bacterial, viral, fungal, mycobacterial, or other infections (including but not limited to tuberculosis, atypical mycobacterial disease, and herpes zoster), human immunodeficiency virus (HIV), or any major episode of infection requiring hospitalization or treatment with IV or oral antibiotics within 4 weeks of screening.
21. Subjects with active hepatitis B infection, as described in Appendix D, are ineligible for the study. Subjects without current hepatitis B infection, as described in Appendix E, may participate in the study.
22. Subjects who are positive for the hepatitis C antibody are not eligible for the study.
23. History of congenital or acquired immunodeficiency (eg, Common Variable Immunodeficiency Disease).
24. History of malignancy, except for:
    a. Treated (ie, cured) basal cell or squamous cell in situ skin carcinomas
    b. Treated (ie, cured) cervical intraepithelial neoplasia (CIN) or carcinoma in situ of the cervix with no evidence of recurrence within the previous 5 years
25. Any condition that could affect oral drug absorption, including gastric resections, gastroparesis, or bariatric surgery, such as gastric bypass.
26. Subjects who have received any investigational drug or device within 3 months of study randomization.
27. History of alcohol, drug, or chemical abuse within the 6 months prior to screening.
28. Known hypersensitivity to GED-0507-34-Levo or any excipients in the formulation.

11 DESCRIPTION OF STUDY TREATMENTS

11.1 Description of Investigational Product(s)

The chemical name of GED-0507-34-Levo (GED0507) is (S)-(-)-3-(4-aminophenyl))-2-methoxypropionic acid.

GED-0507-34-Levo will be provided as 80 mg tablets. Placebo will be provided as identically appearing tablets.

11.2 Treatment Administration and Schedule

Tablets will be taken by mouth BID, in the morning (AM) and in the evening (PM), approximately 12 hours apart, on an empty stomach (ie, at least 3 hours after eating and at least 1 hour prior to eating breakfast or dinner).

80 mg BID group: 2 tablets AM (1 placebo + 1 active 80 mg) and 2 tablets PM (1 placebo + 1 active 80 mg).

160 mg BID group: 2 tablets AM (2 active 80 mg) and 2 tablets PM (2 active 80 mg).

Placebo Group: 2 tablets AM and 2 tablets PM.

11.3 Method of Treatment Assignment

After the ICF is signed, subjects will be assigned a subject identification number using a centralized IVRS/IWRS. At the Baseline Visit, a centralized schema will be applied to assign subjects who meet the inclusion/exclusion criteria in a 1:1:1 ratio to receive GED-0507-34-Levo 80 mg by mouth (PO) BID, 160 mg PO BID, or placebo.

Designated study personnel at the investigational sites will be assigned password-protected, coded identification numbers that give them authorization to connect to IWRS to randomize subjects. The system will present a menu of questions by which the study personnel will identify the subject and confirm eligibility. When all questions have been answered, the IWRS will assign a randomization identification number.

During the study visits, the pharmacy or authorized study personnel at the investigational site will dispense coded IP kits in accordance with the randomization number assigned by the IWRS.

11.4 Packaging and Labeling

All IP, including placebo and GED-0507-34-Levo tablets, will be supplied by PPM SERVICES SA (or designee) to the principal Investigator as HDPE bottles during the Double-blind Placebo-controlled Phase.

GED-0507-34-Levo will be provided in HDPE bottles as 80 mg tablets.. Tablets will be taken by mouth BID, morning and evening, approximately 12 hours apart, on an empty stomach (ie, at least 3 hours after eating and at least 1 hour prior to eating breakfast or dinner).

The label(s) for IP will include the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

11.5 Investigational Product Accountability and Disposal

The Investigator, or designee, is responsible for taking an inventory of each shipment of IP received and comparing it with the accompanying IP shipping order/packing list.

The Investigator, or designee, will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to PPM SERVICES SA.

The IP will be stored according to the storage conditions identified on the drug label. At the study site, all IP will be stored in a locked, safe area to prevent unauthorized access.

PPM SERVICES SA (or designee) will review with the Investigator and relevant site personnel the process for IP return, disposal, and/or destruction, including responsibilities for the site versus PPM SERVICES SA (or designee).

11.6 Investigational Product Compliance

Study personnel will review the instructions printed on the package with the study subjects prior to dispensing the IP. Investigational Product will be dispensed as noted in Table 1 Schedule of Events. The subjects will be instructed to return the IP containers, including any unused medication, to the study site at each visit for tablet counts and reconciliation. Subjects will be asked whether they have taken their IP as instructed at each study visit. Any problems with IP compliance will be reviewed with the subject. If a subject misses 4 or more consecutive days of dosing, PPM SERVICES SA must be contacted to decide whether dosing should resume or whether the subject should be terminated from the study.

Gross compliance problems (eg, missing 4 or more consecutive days of dosing or taking less than 75% of the doses between study visits) should be discussed with PPM SERVICES SA. Compliance is defined as taking between 80% and 120% of dispensed IP.

12 CONCOMITANT MEDICATIONS AND PROCEDURES

All medications (prescription and non-prescription), treatments, and therapies taken by the subject from screening throughout their entire participation in the study, including those initiated prior to the start of the study, must be recorded on the subject's source document and on the appropriate page of the eCRF. The dose, unit, frequency, route, indication, date the medication was started, and date the medication was stopped (if not ongoing) must be recorded.

12.1 Prohibited Concomitant Medications and Procedures

The following concomitant medications are prohibited during the treatment portion of the study, Week 0 Visit (Day 1) to the Week 8 Visit, or the Early Termination Visit for subjects who discontinue prematurely during the study:

- Use of any biologic agents, including TNF blockers
- Use of oral aminosalicylates (sulfasalazine [SSZ] or 5-ASA compounds)
- Use of mycophenolic acid, tacrolimus, sirolimus, cyclosporine, or thalidomide
- Use of topical treatment with 5-ASA or corticosteroid enemas or suppositories is prohibited during the study and must be discontinued 2 weeks prior to the Screening Visit
- Use of oral and/or IV corticosteroids is prohibited during the study and must be discontinued 2 weeks prior to the Screening Visit
- Use of AZA, 6-MP, or MTX is prohibited during the study and must be discontinued 8 weeks prior to the Screening Visit
- Chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs).

13 STATISTICAL ANALYSES

13.1 Overview

Key elements of the SAP are outlined in this section. The comprehensive plan will be documented in a separate SAP.

13.2 Study Population Definitions

Safety analyses will be based on the safety population, which will include all subjects who are randomized and receive at least 1 dose of IP. Subjects will be included in the treatment group corresponding to the IP they actually received for the analyses using the safety population.

The ITT population will consist of all subjects who are randomized as specified in the protocol and receive at least 1 dose of IP. Subjects will be included in the treatment group to which they were randomized, irrespective of the treatment actually received, for the analyses using the ITT population.

The modified intent-to treat (mITT) population is defined as the ITT population with the exclusion of the subjects who: a) withdraw from the study due to a reason clearly documented as independent of either the study treatment or the UC; or b) remained on study for less than 7 days. The mITT population will be the primary population for efficacy analyses.

The PP population will consist of all subjects included in the mITT population who have at least 1 post-baseline efficacy evaluation and no protocol violations that may substantially affect the efficacy results. The final determination on these protocol violations, and thereby the composition of the PP population, will be made prior to the Placebo-controlled Phase analysis and will be separately documented.

The PK population will consist of all subjects in the safety population who have at least one analyzable PK sample. It is expected that the PK population will consist of approximately 50% of the overall study population.

13.3 Sample Size and Power Considerations

Given that the purpose of this Phase 2a trial is to determine whether the drug is efficacious and therefore whether to proceed with further development, there is only 1 outcome of interest: superiority of 1 or more experimental arms to the control. In this scenario, a one-sided testing framework is appropriate.

Moreover, given the need for the trial to be small (one or more Phase 3 trials will be required to confirm the efficacy), standard type I error rate control at the 2.5% level is not strictly necessary. For decisions concerning the future of the project, the sponsor will consider a more relaxed approach to false positive rate, allowing a 5% type I error for the one-sided test of the null hypothesis (ie, the primary outcome is no different between each treatment group and control) rather than the usual 2.5% required for a pivotal trial. The use of this higher type I error and of a low type II error of 15% give to the trial a high statistical power to detect the clinically meaningful effects while maintaining an acceptable and feasible size. Finally, because this trial is

a multiple-experimental arm randomized trial with a control, sample size is increased in order to maintain an overall type I error rate as close as possible to the nominal value of 5%. Assuming the following:

- A 6% Clinical Remission rate for the placebo, which after allowing for a 15% dropout rate being interpreted as treatment failure, equates to a 5.1% Clinical Remission rate.
- A 26% Clinical Remission rate for the highest dose of GED-0507-34-Levo (20% more than placebo group), which after allowing for a 15% dropout rate being interpreted as treatment failure, equates to a 22.1% Clinical Remission rate.
- A type I (α) error of 0.05.
- A power of 85%, type II (β) error = 0.15, to detect, if it exists, the above stated difference between GED-0507-34-Levo and placebo.
- A one-tailed test for proportions.
- A drop-out rate of 15%.

Fifty five (55) subjects per group are needed.

However, in order to take into account the multiplicity of the tests and the need of maintaining the experiment-wise error at the nominal alpha level, the number of subjects per group is increased to 69, for a total of 207 subjects. With this number of subjects, the alpha level actually considered is 2.5%, as the Bonferroni-Holm method will require for the significance testing of the lower p-value.

Table 2 shows how the statistical power would change if the Clinical Remission rate in the placebo group was different from the estimated 6% (maintaining a 20% greater effect in the treatment group before adjustment for dropouts).

Table 2 Change in Statistical Power Based on Clinical Remission Rate

# of Subjects per Group	# of Estimated Subjects per Group Who Will Complete Study [a]	Clinical Remission Rate		Type I Error	Statistical Power
		Placebo Group	Treatment Group		
69	59	4%	24%	2.5%	89%
69	59	5%	25%	2.5%	87%
69	59	6%	26%	2.5%	85%
69	59	7%	27%	2.5%	83%
69	59	8%	28%	2.5%	81%
69	59	9%	29%	2.5%	80%
69	59	10%	30%	2.5%	78%

a. assuming a drop-out rate of 15%

Computations for sample size and power estimation are performed using the formula of Chow (Chow et al, 2007).

13.4 Statistical Methods

The primary efficacy variable is the proportion of subjects who are in Clinical Remission at Week 8, as defined by an MMS of ≤ 2, with individual sub-scores (SF and Endoscopy) ≤ 1, and RBS = 0.

GED-0507-34-Levo treatment arms will be compared with placebo using the chi-squared test and using the Bonferroni-Holm method to control the false positive error rate. Corresponding confidence intervals for the risk ratios of GED-0507-34-Levo against placebo will be presented. Subjects who withdraw will be assumed not to be in remission at Week 8. The last-observation-carried-forward (LOCF) method will be used to impute MMS in the case of missing values in subjects completing the study. The above primary analysis does not adjust for the effects of center under the assumption that there will be many centers who do not recruit at least 1 subject on every treatment. Should this assumption not appear to be the case, the primary analysis methodology will be updated in the SAP prior to breaking the blind for the study.

The primary analysis of the primary efficacy variable will be on the mITT population and will be the comparison of each of the GED-0507-34-Levo doses against placebo as described above.

Additional supportive analysis of the primary efficacy variable will be performed on the ITT and PP populations. A further exploratory log-binomial regression analysis will be performed to investigate the association of prognostic factors with proportion of subjects in Clinical Remission at Week 8.

Summary statistics will be presented for efficacy variables and their changes from baseline at each time point on the mITT, ITT, and PP populations.

13.5 Background and Demographic Characteristics

Subjects' age, height, weight, and other continuous demographic and baseline characteristics will be summarized using descriptive statistics, while gender, race, and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by system organ class and preferred term.

13.5.1 Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued along with primary reason for discontinuation, completed) will be summarized using frequency and percentage. Time to withdrawal from the start of study medication will be compared between the three treatment groups using Kaplan-Meier curves.

A summary of subjects enrolled by site will be provided.

Protocol violations/deviations will be summarized using frequency tabulations.

13.6 Efficacy Analysis

The mITT population (Section 13.2) will be the primary population for efficacy analyses. Supportive analyses using the ITT and PP populations will also be performed for the primary efficacy endpoint.

The primary efficacy variable is the proportion of subjects achieving a clinical remission in the MMS at Week 8, defined as a MMS of ≤ 2 with individual sub-scores (SF and Endoscopy) ≤ 1, and RBS = 0.

The methodology for the primary efficacy analysis is described in Section 13.4. The following secondary and exploratory efficacy endpoints will be analyzed using similar methodology.

- The proportion of subjects achieving clinical response at Week 8, defined as a decrease from baseline in the MMS of at least 2 points and at least 25 %, along with a reduction in the RBS of at least 1 point or an absolute RBS of ≤ 1
- The proportion of subjects achieving endoscopic remission at Week 8, defined as a Mayo endoscopic sub-score of 0
- The proportion of subjects achieving endoscopic response at Week 8, defined as a decrease from baseline of at least 1 point in the Mayo endoscopic sub-score
- The proportion of subjects achieving a RBS ≤ 1 at Week 8

Additional endpoints may be added to the hierarchy and specified in the SAP.

Summary of all efficacy endpoints over time will be provided using frequency and percentage for categorical endpoints and descriptive statistics for continuous endpoints.

The MMS consists of the SFS, RBS, and endoscopy sub-scores of the TMS and excludes the PGA sub-score, since this is a global measure that is subjective in nature. Each of these parameters will be assessed on a scale of 0 to 3. The sum of scores for all 3 parameters will determine the MMS. The MMS ranges from 0 to 9 points.

Clinical response is defined as a decrease from baseline in MMS of at least 2 points and at least 25%, with an accompanying decrease in the RBS of at least 1 point or an absolute RBS of 0 or 1. Assessment of sigmoidoscopic appearance will be performed in the worst inflamed area in the rectum or in the sigmoid if the rectum is not inflamed. The same area should be evaluated at baseline and at the End of Study/Early Withdrawal Visit.

Images of all endoscopic procedures will be captured and sent to a centralized reader for their assessment.

Improvement of symptoms at Weeks 2, 4, 6, and 8 will be assessed by using 2 individual parameters of the MMS: rectal bleeding and stool frequency. Subjects will report details regarding rectal bleeding and stool frequency to the electronic diary system every day during the study. Assessment of rectal bleeding and stool frequency will be done by the subject. The Investigator will calculate the average score of each parameter for the last 3 available days in the

5-day period immediately prior to each clinic visit and record the score in the CRF. No data older than 5 days will be used.

13.7 Safety Analysis

Safety and tolerability will be assessed by AEs, laboratory testing (haematology, biochemistry, and urinalysis), and vital signs.

The safety analyses will be performed using the safety population (Section 13.2). Treatment-emergent AEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. All AEs will be summarized by system organ class, preferred term, severity, and relationship to IP. Adverse events leading to death or to discontinuation from treatment and SAEs will also be tabulated. In the by-subject analysis, a subject having the same event more than once will be counted only once and by greatest severity.

Laboratory data will be summarized descriptively by visit. In addition, shift tables showing the number of subjects with values low, normal, and high compared to the normal ranges pretreatment versus post-treatment will be provided.

Vital sign measurements, including weight, will be summarized descriptively by visit and presented as shift tables.

13.8 Pharmacokinetic Assessments

Nonlinear mixed effect models will be used for the evaluation of the population PK profile. The population PK analysis will be performed using NONMEM® software. The evaluation will be performed for describing the PK in the subject population and for identifying the relevant demographic and pathophysiological covariates.

The approach will be based on the development of the following 3 models:

- Identification of the structural model that best describe the pharmacokinetic data in absence of covariates.
- Random Effect Models: defining the inter-individual variability and the residual error. Different forms of residual error (additive, multiplicative or both) will be explored.
- Covariate Model: identifying the relevant demographic and pathophysiological covariates affecting the PK profile of the compound. The selection of the covariates will be performed using an appropriate statistical methodology.

13.9 Pharmacodynamic Assessments

The relationship between CRP and UC-DAI score will be assessed using scatter plots and correlations.

13.10 Interim Analysis

An interim safety review will be performed by an independent safety committee on data from the 24 subjects randomized into Part 1 of the study. The scope of this analysis will be documented prior to analysis in a safety committee charter. Initiation of Part 3 of the study will follow completion of this review.

14 ADVERSE EVENTS

14.1 Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 14.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity, or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE, should be reported on the drug exposure eCRF page. Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE eCRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE eCRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and eCRF but should not be reported as an SAE itself.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms; weight loss; diarrhea; laboratory; pathological; radiological or surgical findings; physical examination findings; or findings from other tests and/or procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent until 28 days after the last dose of IP, and those SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP. Adverse events and SAEs will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs must be reported to PPM SERVICES SA Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

14.2 Evaluation of Adverse Events

A qualified Investigator will evaluate all AEs as to:

14.2.1 Seriousness

An SAE is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);

- Results in persistent or significant incapacity/disability (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect; and/or
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- A procedure for protocol/disease-related investigations (eg, scans, endoscopy, sampling for laboratory tests). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (ie, planned prior to starting of treatment on study) must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to IP, action taken regarding IP, and outcome.

14.2.2 Severity/Intensity

For both AEs and SAEs, the Investigator must assess the severity/intensity of the event.

Mild

- Asymptomatic or mild symptoms; clinical or diagnostic observations only
- Intervention not indicated
- Activities of Daily Life (ADLs) minimally or not affected
- No or minimal intervention/therapy may be required

Moderate

- Symptom(s) cause moderate discomfort

- Local or noninvasive intervention indicated
- More than minimal interference with ADLs but able to carry out daily social and functional activities.
- Drug therapy may be required

Severe (could be nonserious or serious)

- Symptoms causing severe discomfort/pain
- Symptoms requiring medical/surgical attention/intervention
- Interference with ADLs, including inability to perform daily social and functional activities (eg, absenteeism and/or bed rest)
- Drug therapy is required.

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as "serious," which is based on subject/event outcome or action criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

14.2.3 Causality

The Investigator must determine the relationship between the administration of IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not Suspected: Means a causal relationship of the AE to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

Suspected: Means there is a **reasonable possibility** that the administration of IP caused the AE. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the AE.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary, or additional IP that has not been manufactured or provided by PPM SERVICES SA, the name of the manufacturer when reporting the event will be provided.

14.2.4 Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

14.2.5 Action Taken

The Investigator will report the action taken with IP as a result of an AE or SAE, as applicable (eg, discontinuation, interruption, or reduction of IP, as appropriate), and report if concomitant and/or additional treatments were given for the event.

14.2.6 Outcome

The Investigator will report the outcome of the event for both AEs and SAEs. All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered, or death (due to the SAE).

14.3 Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as an SAE.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the eCRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

14.4 Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject or partner of a male subject are immediately reportable events.

14.4.1 Females of Childbearing Potential

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 28 days of the subject's last dose of IP, are considered immediately reportable events. Investigational product is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to PPM SERVICES SA Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject may be referred to an obstetrician-gynecologist or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy and must notify PPM SERVICES SA Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to PPM SERVICES SA Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to PPM SERVICES SA Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

14.4.2 Male Subjects

If a female partner of a male subject taking IP becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

14.5 Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE is required to be recorded via completion of the AE/ SAE screens of the eCRF. SAEs must be reported in the eCRF within 24 hours of the Investigator's knowledge of the event. This timeline pertains to initial SAE reports as well as any follow-up information. If the eCRF is unavailable at the time of reporting, the Investigator must report the event using the appropriate paper reporting forms to comply with required timelines. All SAEs reported using paper forms must be entered into the eCRF as soon as the system becomes available.

The Investigator is required to ensure that the data on these forms is accurate and consistent.

This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until 28 days after the last dose of IP) or any SAE made known to the Investigator at any time thereafter that is suspected of being related to IP. Serious AEs occurring prior to treatment (after signing the ICF) will be captured.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to PPM SERVICES SA Drug Safety as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to PPM SERVICES SA Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file, including correspondence with PPM SERVICES SA and the IRB/EC.

14.5.1 Safety Queries

Queries pertaining to SAEs will be communicated from PPM SERVICES SA Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, PPM SERVICES SA Drug Safety will determine the expectedness of events suspected of being related to GED-0507-34-Levo based on the Investigator's Brochure (IB).

In the United States, all SUSARs will be reported in an expedited manner in accordance with the Code of Federal Regulations Title 21 (21 CFR) Section 312.32.

For countries within the European Economic Area (EEA), PPM SERVICES SA or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, SUSARs in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification, and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

PPM SERVICES SA or its authorized representative shall notify the Investigator of the following information:

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with PPM SERVICES SA and the IRB/EC (see Section 18.3 for record retention information).

14.6 PPM SERVICES SA Drug Safety Contact Information

For PPM SERVICES SA Drug Safety contact information, refer to the Serious Adverse Event Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.

15 DISCONTINUATIONS

The following events are considered sufficient reasons for discontinuing a subject from the IP and/or from the study:

- Lack of therapeutic effect after at least 4 weeks
- Withdrawal of consent
- Death
- Lost to follow up
- Protocol violation
- Study terminated by sponsor
- Pregnancy
- Unexplained weight loss ≥ 7.5% from baseline

The decision to discontinue a subject remains the responsibility of the treating physician, which will not be delayed or refused by the sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion. The reason for discontinuation should be recorded in the eCRF and in the source documents.

16 EMERGENCY PROCEDURES

16.1 Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call PPM SERVICES SA/CRO Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

16.2 Emergency Identification of Investigational Products

The blind must not be broken during the course of the study unless, in the opinion of the Investigator, it is absolutely necessary to safely treat the subject. If it is medically imperative to know what IP the subject is receiving, IP should be temporarily discontinued if, in the opinion of the Investigator, continuing IP can negatively affect the outcome of the subject's treatment.

The decision to break the blind in emergency situations remains the responsibility of the treating physician, which will not be delayed or refused by the sponsor. However, the Investigator may contact the Medical Monitor prior to breaking the blind to discuss unblinding, mainly in the interest of the subject.

The Investigator should ensure that the code is broken only in accordance with the protocol. The Investigator should promptly notify the Medical Monitor of the emergency unblinding and the reason for breaking the blind, which should be clearly documented by the Investigator in the subject's source documentation.

Emergency unblinding should only be performed by the Investigator thorough the IVRS/IWRS by using an emergency unblinding personal identification number (PIN), and the Investigator should call IVRS/IWRS for unblinded dose information.

17 REGULATORY CONSIDERATIONS

17.1 Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that PPM SERVICES SA, its authorized representative, and Investigator abide by GCP, as described in ICH Guideline E6, and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

17.2 Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for GCP and in the local regulations. PPM SERVICES SA staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, and study-related duties and functions. The Investigator should maintain a list of sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an ICF and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries, and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of eCRFs and queries.

17.3 Subject Information and Informed Consent

The Investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study-related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents, including the date. The original ICF signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts the content of the ICF, the ICF must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF. The revised ICF signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

17.4 Confidentiality

PPM SERVICES SA affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). PPM SERVICES SA requires the Investigator to permit PPM SERVICES SA's representatives and, when necessary, representatives from regulatory authorities to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

17.5 Protocol Amendments

Any amendment to this protocol must be approved by the PPM SERVICES SA Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title, and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/EC approval but will be submitted to the IRB/EC for information purposes.

17.6 Institutional Review Board/Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

Investigational product can only be supplied to an Investigator by PPM SERVICES SA or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by PPM SERVICES SA or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations, and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by PPM SERVICES SA and the IRB/EC prior to use.

17.7 Ongoing Information for Institutional Review Board/Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected AEs as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

17.8 Closure of the Study

PPM SERVICES SA reserves the right to terminate this study at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc).

In addition, the Investigator or PPM SERVICES SA has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

18 DATA HANDLING AND RECORDKEEPING

18.1 Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed, and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy and the laboratories, as well as copies of eCRFs or compact discs random-only memory (CD-ROM).

18.2 Data Management

Data will be collected via eCRF and entered into the clinical database per PPM SERVICES SA standard operating procedures (SOPs). This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

18.3 Record Retention

Essential documents must be retained by the Investigator for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include but are not limited to the following:

- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, PPM SERVICES SA, and their authorized representative(s);
- List of sub-Investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc);

- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify PPM SERVICES SA if he/she wishes to assign the essential documents to someone else, remove them to another location, or is unable to retain them for a specified period. The Investigator must obtain approval in writing from PPM SERVICES SA prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask PPM SERVICES SA for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

19 QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by PPM SERVICES SA or its authorized representative for compliance with applicable government regulations with respect to current GCP and SOPs.

19.1 Study Monitoring and Source Data Verification

PPM SERVICES SA ensures that appropriate monitoring procedures are performed before, during, and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigator meeting. Prior to enrolling subjects into the study, a PPM SERVICES SA representative will review the protocol, eCRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, eCRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the PPM SERVICES SA representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the eCRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria, and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

19.2 Audits and Inspections

In addition to the routine monitoring procedures, a GCP Quality Assurance unit exists within PPM SERVICES SA. Representatives of this unit will conduct audits of clinical research activities in accordance with PPM SERVICES SA SOPs to evaluate compliance with GCP guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs, and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, Food and Drug Administration [FDA], European Medicines Agency [EMA], Health Canada), and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact PPM SERVICES SA immediately.

20 PUBLICATIONS

Study results will be communicated in full to the competent Health Authorities by the submission of a complete clinical study report.

The sponsor agrees that the study results (including negative and inconclusive as well as positive results) can be made publicly available by the investigator publishing in peer reviewed journals, presenting results at scientific congresses and posting information and results on internet-based public registers and databases. As the sponsor agrees that the study results can be published by the investigators, the investigator agrees to submit any manuscript (abstract, publication, paper, etc.) to the sponsor before any public disclosure. This will be done in order to ensure that clinical study results are reported in an objective, accurate and balanced manner. The sponsor reviews the proposed manuscripts, before submission, within a reasonable period of time (30-90 days in relation with the complexity of the work).

Selection of first authorship will be based on several considerations, including but not limited to study participation, contribution to the protocol development, and analysis and input into the manuscript, related abstracts, and presentations in a study.

21 REFERENCES

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22 APPENDICES

Appendix A Subject Diary for Ulcerative Colitis Disease Activity

Based on Ulcerative Colitis Disease Activity Index (Schroeder 1987)

Please tick the appropriate box		
(1)Frequency of bowel movements:		
As usual	**0**	☐
1-2 times a day more than usual	**1**	☐
3-4 times a day more than usual	**2**	☐
More than 5 times a day more than usual	**3**	☐
(2)Blood in stools		
Absent	**0**	☐
Traces of blood in stools	**1**	☐
A lot of blood in stools	**2**	☐
Blood only	**3**	☐
(3)General Well-Being		
Generally Well	**0**	☐
Fair	**1**	☐
Poor	**2**	☐
Terrible	**3**	☐

Appendix B Mayo Scoring System

Stool Frequency Sub-score (SFS)*

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

* Each patient serves as his or her own control to establish normal stool frequency and the degree of abnormal stool frequency.

Rectal Bleeding Sub-score (RBS)**

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

** The daily bleeding score represents the most severe bleeding of the day.

Endoscopy Sub-score: Findings of Flexible Sigmoidoscopy

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 Sub-score (PGA)

0 = Normal

1 = Mild disease

2 = Moderate disease

3 = Severe disease

Source: Schroeder 1987.

Appendix C Modified Mayo Scoring System

Stool Frequency Sub-score (SFS)*

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

* Each patient serves as his or her own control to establish normal stool frequency and the degree of abnormal stool frequency.

Rectal Bleeding Sub-score (RBS)**

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

** The daily bleeding score represents the most severe bleeding of the day.

Endoscopy sub-score: Findings of flexible sigmoidoscopy

0 = Normal or inactive disease

1 = Mild disease (erythema, decreased vascular pattern)

2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)

3 = Severe disease (spontaneous bleeding, ulceration)

Appendix D Hepatitis B Criteria Indicating Current Infection or Risk of Current Infection

Criteria	Result	Interpretation
HBsAg	Positive	Acutely infected
anti-HBc	Positive	
IgM anti-HBC	Positive	
anti-HBs	Negative	
HBsAg	Positive	Chronically infected
anti-HBc	Positive	
IgM anti-HBC	Negative	
anti-HBs	Negative	
HBsAg	Negative	Interpretation unclear; 4 possibilities: • Resolved infection (most common) • False-positive anti-HBc, thus susceptible • "Low level" chronic infection • Resolving acute infection
anti-HBc	Positive	
anti-HBs	Negative	

HBsAg = hepatitis B surface antigen; anti-HBc = antibody to the hepatitis B core antigen; anti-HBs = antibody to hepatitis B surface antigen; IgM anti-HBC = IgM antibody to hepatitis B core antigen
Source: Mast 2005.

Appendix E Hepatitis B Criteria Indicating the Absence of Current Infection

Criteria	Result	Interpretation
HBsAg	Negative	Susceptible to hepatitis B infection
anti-HBc	Negative	
anti-HBs	Negative	
HBsAg	Negative	Immune due to natural infection
anti-HBc	Positive	
anti-HBs	Positive	
HBsAg	Negative	Immune due to hepatitis B vaccination
anti-HBc	Negative	
anti-HBs	Positive	

HBsAg= hepatitis B surface antigen; anti- HBc= antibody to the hepatitis B core antigen;
anti- HBs= antibody to hepatitis B surface antigen; IgM anti-HBC= IgM antibody to hepatitis B core antigen
Source: Mast 2005.