16.1.1 CLINICAL RESEARCH PROTOCOL

DRUG:	SPH3127
STUDY NUMBER:	SPH3127-US-01
PROTOCOL TITLE:	A Double-Blind, Placebo-Controlled Trial to Investigate the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of SPH3127 in Patients with Mild-to-Moderate Ulcerative Colitis
IND NUMBER:	151940
SPONSOR:	Shanghai Pharma Biotherapeutics USA Inc. 3545 John Hopkins Ct., Suite 160 San Diego, CA 92121 USA Phone: (858) 775-5354 Email: info@sphbio.com
VERSION NUMBER:	V7
VERSION DATE:	April 8, 2021

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: **A Double-Blind, Placebo-Controlled Trial to Investigate the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of SPH3127 in Patients with Mild-to-Moderate Ulcerative Colitis**

Study No: **SPH3127-US-01**

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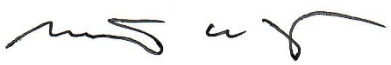
This study protocol was subject to critical review and has been approved by the appropriate protocol review committee of the sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational product.
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of GCP as described in 21 CFR parts 50, 54, 56 and 312 and according to applicable local requirements.

The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

Name and Title	**Approval**	**Signature**	**Date**
Author: Kenneth W. Locke, Ph.D. CSO [Name] [Title]	(Yes) No (circle one)		4/8/21
Clinical Operations: Li-Wei Jen Sr Director, Clinical Operations [Name] [Title]	(Yes) No (circle one)		4/8/21

SPH3127-US-01

A DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO INVESTIGATE THE PHARMACOKINETICS, PHARMACODYNAMICS, SAFETY, AND TOLERABILITY OF SPH3127 IN PATIENTS WITH MILD-TO-MODERATE ULCERATIVE COLITIS

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to SPH3127 are the confidential and proprietary information of Shanghai Pharma Biotherapeutics USA Inc. (SPHBio), and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of SPHBio.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practices and International Conference on Harmonization guidelines, and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by SPHBio or specified designees. I will discuss the material with them to ensure that they are fully informed about SPH3127 and the study.

Principal Investigator Name (printed) Signature

_____ _____

Date Site Number

STUDY SUMMARY

Title:	A Double-Blind, Placebo-Controlled Trial to Investigate the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of SPH3127 in Patients with Mild-to-Moderate Ulcerative Colitis
Rationale:	Recently, an association has been made between the renin-angiotensin system (RAS) and the development of colitis. The RAS is well known to regulate blood pressure and fluid and electrolyte balance, as well as systemic vascular resistance. Circumstantial evidence also suggests an involvement of the RAS in the pathogenesis of colitis. For example, increased colonic mucosal angiotensin I and II concentrations were reported in Crohn's disease (CD) patients with active inflammation, and in human biopsies, pro-inflammatory cytokines were suppressed in patients with inflammatory bowel disease who were on angiotensin receptor blocker (ARB) therapy compared to patients not receiving ARB therapy. In animal studies, renin inhibitors like SPH3127 have shown activity in rodent models of colitis. Consistent with an involvement of the RAS, SPH3127 improved physical measures of colitis (e.g., colon length, colon weight) and reduced colon levels of inflammatory cytokines (IL-1β, IL-6, IL-17A and TNF-α) in this model. This study seeks to establish the safety and tolerability SPH3127 in patients with mild-to-moderate ulcerative colitis and to provide initial indications of efficacy.
Target Population:	Mild-to-moderate ulcerative colitis patients
Number of Subjects:	30 subjects - 50 mg SPH3127 QD: 50 mg SPH3127 BID: Placebo, 1:1:1 randomization
Objectives:	To investigate the safety and tolerability of daily oral administration of SPH3127 or placebo for 8 weeks in patients with mild-to-moderate ulcerative colitis. To investigate the pharmacokinetics and pharmacodynamics of daily oral administration of SPH3127 or placebo for 8 weeks in patients with mild-to-moderate ulcerative colitis.
Study Design:	The SPH3127-US-01 is a multi-center, randomized, double-blind, placebo-controlled study to evaluate the safety and preliminary efficacy of SPH3127 for the treatment of mild-to-moderate ulcerative colitis. The study consists of five (5) visits: a Screening/confirmation of diagnosis visit, a study initiation visit (Day 1) and 2 subsequent treatment and assessment visits at 4-week intervals (Day 28; 56) and a single-day treatment and safety visit after the first 2 weeks of treatment (Day 14). All randomized subjects will have the opportunity to enter an active treatment

extension. The study blind (dose SPH3127) will be maintained through the extension period. Medication will be dispensed at 8-week intervals in eight 2-week blister packs for an additional 10 months in the active treatment extension. Safety information (adverse events) will be collected over this period. In addition, clinical laboratory tests and vital signs will be collected at 2-month intervals. Rectal bleeding and stool frequency will be collected daily using a subject diary. Flexible sigmoidoscopy will be performed at the final site visit (Day 336). The study design is presented in the STUDY SCHEMATIC (Figure 1).

The duration of subject participation in the primary study is approximately 13 weeks, including Screening and a follow-up call 1 week after the last dose (for those subjects who choose not to enter the extension). Subjects participating in the optional active treatment extension will participate for an additional 10 months.

Study Endpoints:

In this exploratory study, a variety of safety endpoints will be evaluated, including, but not limited to:

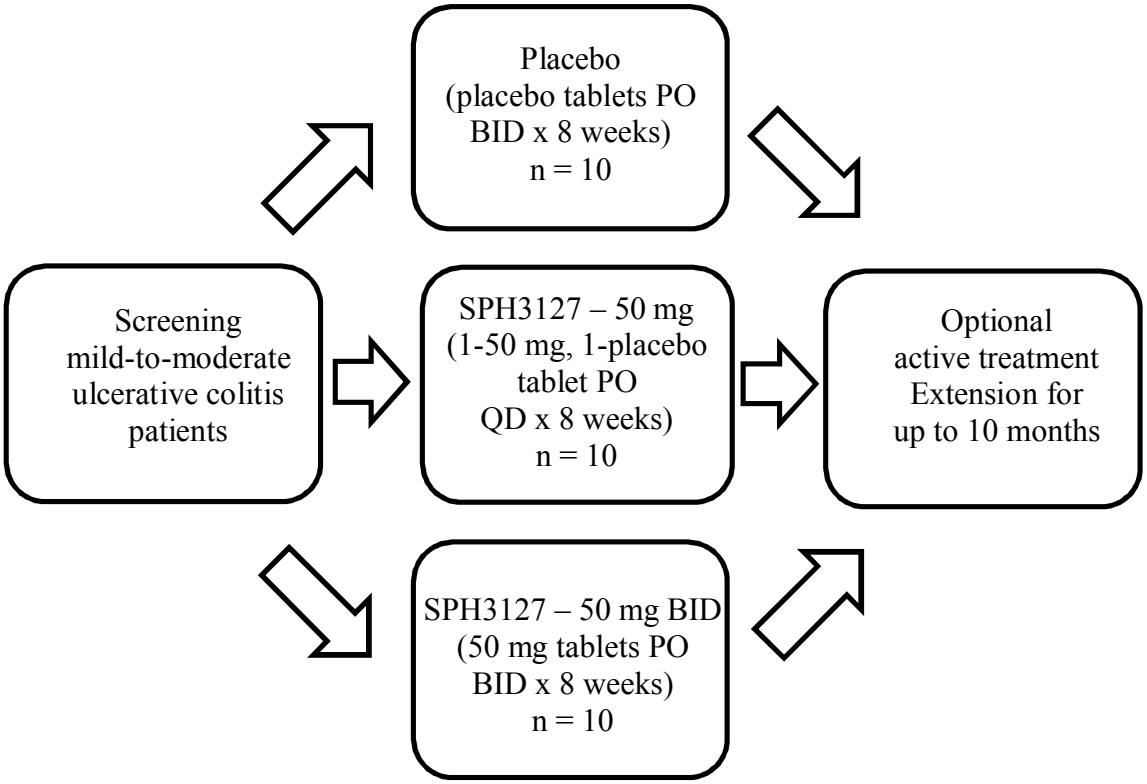
1. Vital signs (systolic and diastolic blood pressure (seated), temperature and pulse/heart rate);
2. Physical examination;
3. Clinical laboratory tests (hematology, serum chemistry, urinalysis); and,
4. Adverse events.

In this exploratory study, a variety of efficacy and translational endpoints will be evaluated, including, but not limited to:

1. Proportion of patients in clinical remission at week 8;
2. Endoscopic improvement (MCES ≤1) at week 8;
3. Endoscopic remission (MCES subscore of 0) at week 8;
4. Endoscopic response (>1-point reduction in MCES) at week 8;
5. Symptomatic remission at week 8;
6. Rectal bleeding subscore of 0 at week 8;
7. Clinical and endoscopic response at week 8;
8. Improvement in UC-100 score at week 8;
9. Change in fecal calprotectin concentration at week 8;
10. Change in Robarts Histopathology Index at week 8;
11. Change in tissue biomarkers (, angiotensin II, complement C3, IL-1β, IL-17A, TNF-α, IL-6, and IL-23) at week 8;

12. Plasma PK; and,
13. Correlation of change in tissue biomarkers with endoscopic and histology response.

Figure 1. STUDY SCHEMATIC



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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AII	Angiotensin II
API	Active Pharmaceutical Ingredient
ARB	Angiotensin Receptor Blocker
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
$AUC_{0-\infty}$	AUC from 0 to infinity
AUC_{0-t}	AUC from 0 hours to the time of the last measurable concentration
BID	Twice Daily
BP	Blood Pressure
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CI	Confidence Interval
C_{max}	Maximum Plasma Concentration
CONMED	Concomitant Medication
CRF	Case Report Form
CYP	Cytochrome P450 Enzyme
DBP	Diastolic Blood Pressure
DRI	Direct Renin Inhibitor
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
FDA	Food and Drug Administration

GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HED	Human Equivalent Dose
HR	Heart Rate
ICF	Informed Consent Form
IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medical Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
L	Liters
MCES	Mayo Clinic Endoscopic Subscale score
MMCS	Modified Mayo Clinic Score
mg	Milligram
min	Minute
mmHg	Millimeters Mercury
NOEL	No Observed Effect Level
NOAEL	No Observed Adverse Event Level
PK	Pharmacokinetic(s)

PO	Per Os, Orally
QD	Once Daily
RAS	Renin-Angiotensin System
RHI	Robarts Histopathology Index
SAE	Serious Adverse Event
SARs	Serious Adverse Reactions
SBP	Systolic Blood Pressure
SC	Subcutaneous(ly)
SD	Standard Deviation
SEM	Standard Error of the Mean
$t_{1/2}$	Half-life
T_{max}	Time to maximal plasma concentration
UC	Ulcerative Colitis
UC-100	Ulcerative Colitis rating scale (100-point)
ULN	Upper Limit of Normal
WHO	World Health Organization

1 INTRODUCTION AND RATIONALE

1.1 Background

Inflammatory bowel disease (IBD) is comprised of two major disorders, Crohn's disease (CD) and ulcerative colitis (UC). Both conditions are characterized by histologic chronic inflammation, periods of clinical relapse and remission, use of medication and risk of surgery, and impaired quality of life (Hazel and O'Connor, 2020). Despite some shared characteristics, these disorders can be distinguished by differences in genetic predisposition, risk factors, and clinical, endoscopic, and histological features. The precise cause of inflammatory bowel disease is unknown; however, genetically susceptible individuals seem to have a dysregulated mucosal immune response to commensal gut flora, which results in bowel inflammation (Schreiner et al., 2019).

Ulcerative colitis is a chronic, idiopathic inflammatory disease characterized by relapsing and remitting mucosal inflammation, starting in the rectum and extending to proximal segments of the colon. Disruption of tight junctions and the mucus film covering the epithelial layer causes increased permeability of the intestinal epithelium, resulting in increased uptake of luminal antigens. Macrophages and dendritic cells (innate immune cells), on recognition of non-pathogenic bacteria (commensal microbiota) through molecular pattern recognition receptors (toll-like receptors), change their functional status from tolerogenic to an activated phenotype. Activation of nuclear factor-κB (NF-kB) pathways stimulates the transcription of proinflammatory genes, resulting in increased production of proinflammatory cytokines (TNF-α, interleukins 12, 23, 6, and 1β). After processing of antigens, macrophages and dendritic cells present them to naive CD4 T-cells, promoting differentiation into Th2 effector cells, characterized by production of interleukin 4. Natural-killer T cells are the main source of interleukin 13, which has been associated with disruption of the epithelial cell barrier. Circulating T cells bearing integrin-α4β7 bind to colonic endothelial cells of the microvasculature through the mucosal vascular addressin-cell adhesion molecule 1, whose expression is enhanced in the inflamed intestine, leading to increased entry of gut-specific T cells into the lamina propria. Upregulation of inflammatory chemokines, such CXCL1, CXCL3, and CXCL8, leads to recruitment of circulating leucocytes which perpetuates the cycle of inflammation (see Ordas et al., 2012).

Historically, the mainstay of treatment for UC has been aminosalicylates, with short courses of steroids for severe flares, and escalation to immunomodulators and anti-tumor necrosis factor alpha (anti-TNFα) inhibitors should remission not be maintained. Anti-TNFα inhibitors have become the cornerstone of treatment for moderate-to-severe UC and CD, resulting in improved health outcomes and a decreased need for surgical intervention (Chudy-Onwugaje et al., 2019). Despite the tremendous advances made in recent years in IBD therapeutics, approximately 30% of patients are unresponsive to anti-TNFα inhibitors and even among responders, up to 10% will lose their response to the drug every year (Hazel and O'Connor, 2020). In addition, anti-TNFα inhibitors are associated with an increased risk of serious infection, paradoxical autoimmune reactions, and a small, but increased risk of malignancy (Chudy-Onwugaje et al., 2019). Therefore, it is clear that the development of highly effective drugs or drug combinations with favorable side effect profiles for patients with UC is an important, unmet need.

Recently, an association has been made between the renin-angiotensin system (RAS) and the development of colitis (Shi et al., 2016). The RAS is well known to regulate blood pressure and fluid and electrolyte balance, as well as systemic vascular resistance. Circumstantial evidence suggests an involvement of the RAS in the pathogenesis of colitis. For example, increased colonic mucosal angiotensin I and II concentrations were reported in Crohn's disease (CD) patients with active inflammation (Jaszewski et al., 1990). Genetically mutant mice with deletion in the angiotensin 1 (AT1) receptor or the angiotensinogen gene developed less severe colitis than wild-type mice in experimental colitis models (Katada et al., 2008; Mizushima et al., 2010; Inokuchi et al., 2005). Shi et al. (2016) showed that RenTgMK mice that overexpress active renin from the liver developed more severe colitis than wild-type controls. More than 50% RenTgMK mice died, whereas all wild-type mice recovered. Treatment with aliskiren (a renin inhibitor), but not hydralazine (a smooth muscle relaxant), ameliorated colitis in RenTgMK mice, although both drugs normalized blood pressure. Chronic infusion of angiotensin II into wild-type mice mimicked the severe colitic phenotype of RenTgMK mice and treatment with losartan, an AT1 receptor blocker (ARB), ameliorated colitis in wild-type mice, confirming a colitogenic role for the endogenous RAS. In human biopsies, pro-inflammatory cytokines were suppressed in patients with inflammatory bowel disease who were on ARB therapy compared to patients not receiving ARB therapy. These observations suggest that activation of the RAS promotes colitis in a blood pressure independent manner and that blockade of the RAS has the potential to reduce the severity of colitis.

As a potent and selective direct renin inhibitor, SPH3127 is anticipated to block the RAS pathway to ameliorate the symptoms and pathologic changes in ulcerative colitis. The clinical dose of SPH3127 for this Phase 2a proof-of-concept study was selected based on safety and suppression of plasma renin activity in the initial clinical studies. Daily multiple oral doses of 50 mg SPH3127 reduced median plasma renin activity by approximately 70-90% for 24 hours and was well tolerated by both volunteers and hypertensive patients.

1.2 Nonclinical Studies

1.2.1 Nonclinical Pharmacology

SPH3127 downregulates the RAS by directly inhibiting the enzyme renin and the conversion of angiotensinogen to angiotensin I. *In vitro* studies confirmed the direct inhibitory effects of SPH3127 on renin. SPH3127 (or its free base 3002470) had strong inhibitory activity against recombinant human renin or human plasma renin with *in vitro* IC_{50} values of 0.51 ± 0.08 and 0.28 nM (95% CI, 0.23–0.34), respectively, while the data for aliskiren, another renin inhibitor (formerly marketed by Novartis) were 1.52 ± 0.14 and 1.34 nM (95% CI, 1.24–1.46), respectively.

SPH3127 was also evaluated for activity in an animal model of IBD. Colitis was induced in Wistar rats by intracolonic administration of 0.5 mL 2,4-dinitrobenzenesulfonic acid (DNBS) solution (50 mg/mL DNBS in 30% ethanol). Groups of rats were then treated for 7 days with 30 or 100 mg/kg SPH3127 po QD, 30 mg/kg tofacitinib (XELJANZ®) po BID, or the combination of 100 mg/kg SPH3127 and tofacitinib. SPH3127 improved

several physical measures of colitis (e.g., colon weight, colon length). SPH3127, in contrast to tofacitinib, also reduced colon tissue levels of the inflammatory cytokines IL-1β, IL-6, IL-17A and TNF-α.

1.2.2 Nonclinical Absorption, Distribution, Metabolism, and Excretion

After a single intravenous administration of SPH3127 in rats and monkeys, high clearance and volume of distribution and a short terminal elimination half-life were seen for both species. The oral bioavailability of SPH3127 in rats and monkeys ranged from 11.5–24.5% and 3.3–11.3% depending on dose, respectively, with a short time to peak plasma concentration (t_{max}) of 0.25 to 1.3 h. After administration of multiple oral doses of 3 mg/kg SPH3127 to monkeys once daily, plasma concentrations reached steady state on the fifth day with no apparent accumulation by Day 7.

SPH3127 shows low permeability across Caco-2 cell membranes and is widely distributed in tissues. Peak concentrations in most tissues and organs were reached 0.25 h after dosing and rapidly eliminated. Phenotyping data revealed that CYP3A4 was the most active enzyme catalyzing the metabolism of SPH3127. However, *in vitro* CYP inhibition studies found only very weak action for CYP3A4 (midazolam 1′-hydroxylation) and CYP3A4 (midazolam 6β-hydroxylation) with IC_{50} values of 56.8 μM and 41.1 μM, respectively, which were much higher than the human plasma C_{max} for the highest single oral dose of 800 mg SPH3127 tested to date. The predicted IC_{50} values of SPH3127 for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 were greater than 100 μM, and thus unlikely to be involved in the metabolism of SPH3127. In addition, an *in vitro* CYP induction study did not indicate any induction potential for human CYP1A2 and CYP3A4. Excretion studies in rats suggest that fecal, urine and bile excretion represent about 15% of the intake dose, indicating that SPH3127 undergoes extensive metabolism after oral dosing.

1.2.3 Nonclinical Toxicity

SPH3127 has been evaluated in an extensive set of GLP nonclinical safety studies, including long-term general safety studies in rats and monkeys, reproductive toxicity testing and an evaluation of mutagenic potential. The general toxicity program conducted in rats and cynomolgus monkeys demonstrated that SPH3127 was well-tolerated following oral administration and that SPH3127-related findings were minimal and reversible. Measurable, dose-related systemic exposure to orally administered SPH3127 was achieved in these studies. In general, no adverse effects of SPH3127 were observed in reproductive toxicity evaluations up to the highest doses tested. SPH3127 showed no mutagenic potential in a battery of *in vitro* and *in vivo* assays. Safety margins (based on body surface area scaling) of approximately 4.5-fold to 226-fold over the human dose of 50 mg SPH3127 were established in these nonclinical studies.

In a safety pharmacology study in monkeys, SPH3127 produced dose-related reductions in blood pressure that were reversible within 24 hours. These changes in blood pressure were an expected pharmacologic consequence of the mechanism of action of SPH3127 (renin inhibition) and were not considered adverse reactions.

1.3 Effects in Humans

Three Phase 1 studies SPH3127 have been completed in healthy volunteers – a single ascending dose tolerance study, a dose-ranging multiple dose study and a fed/fasted study. A dose-ranging, multiple dose Phase 2 study in patients with mild-to-moderate essential hypertension has also been completed.

1.3.1 Safety in Humans

Across all clinical studies, the oral administration of SPH3127 was well-tolerated. No dose-limiting toxicity (DLT) was observed at any dose of SPH3127. Across all studies, the oral administration of SPH3127 was well-tolerated. No dose-limiting toxicity (DLT) was observed at any dose of SPH3127. Known and well-characterized pharmacology of direct renin inhibitors is a reduction in blood pressure. It is the desired therapeutic effect for the treatment of hypertension. Aliskiren (Tekturna), another direct renin inhibitor, is marketed for this purpose and a daily oral dose of 100 mg SPH3127 has been selected for further clinical development as a treatment for hypertension. A dose of 50 mg QD or BID SPH3127 has been selected for the proposed POC trial in ulcerative colitis patients. These doses were selected to evaluate the influence of dose and half-life on therapeutic activity, while minimizing the potential effects of SPH3127 on blood pressure in normotensive ulcerative colitis patients.

AEs from single oral doses of SPH3127 from 25 to 800 mg were mild in severity and self-limiting. AEs were hypotension, dizziness, and neutropenia, among which hypotension and dizziness of the subjects may be related to the pharmacologic mechanism of action of SPH3127. Dizziness, likely as a consequence of hypotension, occurred only at the higher doses of SPH3127. Similarly, oral doses of 100 – 400 mg SPH3127 daily for 7 days produced AEs of mild, reversible hypotension, neutropenia, and ALT increases. No SPH3127-related AEs were observed following oral doses of 200 mg in a fed or fasted state in a crossover biopharmaceutics study. SPH3127 (50 – 200 mg) was well-tolerated in a study of daily oral administration for 8 weeks to patients with mild-to-moderate hypertension. There were 2 serious adverse events (adenomyosis, infiltrating ductal breast cancer) in a single patient that were unrelated to treatment in the Phase 2 trial. There were also 5 significant adverse events in the Phase 2 trial, including: triglyceride elevation in a placebo patient; a moderate increase in liver function tests (ALT, AST, γ-GT) that resolved without sequelae on study drug discontinuation; a moderate elevation of AST in a patient who was not discontinued, but lost to follow-up; and, 2 patients with an exacerbation of hypertension, one of whom was discontinued from treatment. Although generally mild and transient, as a group across studies, elevations in liver function tests (e.g., ALT, AST, γGT, ALP, DBIL, TBIL) showed an increase in frequency compared to placebo; these liver function test elevations do not appear to be dose-related.

1.3.2 Pharmacokinetics in Humans

Pharmacokinetic analyses showed that the C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of SPH3127 increased linearly with single oral doses over the dose range of 25 to 800 mg. T_{max} was reached in approximately 30 minutes after oral administration. The $t_{1/2}$ of SPH3127 ranged from 3 to 6 hours. In multiple oral doses, the C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of

SPH3127 increased linearly over the dose range of 100 to 400 mg. T_{max} was reached in approximately 30 - 60 minutes after oral administration and the $t_{1/2}$ of SPH3127 was approximately 4 hours. There was essentially no accumulation after daily oral dosing for 7 days. Dosing with SPH3127 after a high calorie, high fat meal reduced C_{max}, but had no effect on total exposure (AUC) compared to dosing after fasting.

Metabolite studies revealed a total of 28 metabolites in human plasma, mainly the lactam metabolite M7-4 formed by monooxidation and dehydrogenation of the morpholine ring, followed by M8-7 and M24-1. A total of 39 metabolites were detected in human urine, mainly lactam metabolites M7-4 and M8-7, followed by M24-1 and M24-2. A total of 34 metabolites were detected in human feces, mainly sulfate conjugate M12, monooxidative metabolites M8-2 and M8-3, followed by M7-4.

1.3.3 Efficacy and Pharmacodynamics in Humans

SPH3127 has a significantly longer pharmacodynamic than pharmacokinetic $t_{1/2}$ with significantly reduced plasma renin activity (PRA) with near complete inhibition within ~30 min of administration and full recovery at 48 hours with only the lowest doses. With repeated doses, PRA suppression is maintained at 70-90%.

As expected from its mechanism of action, SPH3127 produced reductions in both systolic and diastolic blood pressure in all clinical trials. Based on the results of a Phase 2a study in essential hypertension patients, a daily oral dose of 100 mg SPH3127 will be evaluated in future trials of its safety and effectiveness in essential hypertension. A dose of 50 mg QD or BID will be investigated for safety and efficacy in this trial (i.e., ulcerative colitis) to minimize the effects of SPH3127 on blood pressure and to evaluate the relative importance of dose and half-life on therapeutic activity.

2 STUDY OBJECTIVES

2.1 Primary

To investigate the safety and tolerability of daily oral administration of SPH3127 given as one 50 mg tablet in the morning and one placebo tablet in the evening, or given as one 50 mg tablet in the morning and one 50 mg tablet in the evening (100 mg total daily dose) or placebo (one placebo tablet in the morning and evening) for 8 weeks in patients with mild-to-moderate ulcerative colitis.

2.2 Secondary

To investigate the pharmacokinetics and pharmacodynamics of daily oral administration of SPH3127 (50 or 100 mg total daily dose) or placebo for 8 weeks in patients with mild-to-moderate ulcerative colitis.

3 STUDY ENDPOINTS

In this exploratory study, a variety of safety endpoints will be evaluated, including, but not limited to:

1. Vital signs (systolic and diastolic blood pressure (seated) and pulse/heart rate, temperature);

2. Physical examination;
3. Clinical laboratory tests (hematology, serum chemistry, urinalysis); and,
4. Adverse events.

In this exploratory study, a variety of efficacy and translational endpoints will be evaluated, including, but not limited to:

5. Proportion of patients in clinical remission at week 8;
6. Endoscopic improvement (MCES subscore ≤1) at week 8;
7. Endoscopic remission (Mayo Clinic Endoscopic Subscore (MCES) subscore of 0) at week 8;
8. Endoscopic response (>1-point reduction in MCES) at week 8;
9. Symptomatic remission at week 8;
10. Reduction in rectal bleeding subscore of 0 at week 8;
11. UC-100 score improvement at week 8;
12. Improvement in clinical response at week 8;
13. Change in fecal calprotectin concentration at week 8;
14. Improvement in Robarts Histology Index;
15. Change in tissue biomarkers (e.g., angiotensin II, complement C3, IL-1β, IL-17A, TNF-α, IL-6, and IL-23);
16. Change in plasma and tissue PK; and,
17. Correlation of change in tissue biomarkers with endoscopic and histology response.

4 STUDY PLAN

4.1 Study Design

In this double-blind, placebo-controlled, multi-center trial, patients ≥ 18 to ≤ 70 years of age with mild-to-moderate ulcerative colitis (UC) will be randomly assigned to daily oral treatment with SPH3127 (given as one 50 mg tablet in the morning and one placebo tablet in the evening, or given as one 50 mg tablet in the morning and one 50 mg tablet in the evening (100 mg total daily dose) or matching placebo tablets (one placebo tablet in the morning and evening) for 8 weeks. The objective of this study is to assess the safety and tolerability of SPH3127. In addition, the PK and PD effects of SPH3127 will be

assessed; PD effects will be assessed through plasma and colitis lesion biomarkers and validated measures of disease activity (e.g., modified Mayo Score (MMS), UC-100, Robarts Histology Index (RHI) and fecal calprotectin).

A total of 30 eligible patients will be randomly assigned to one of three treatment arms (10 subjects per treatment group):

- Treatment A: 50 mg SPH3127 (given as one 50 mg tablet in the morning and one placebo tablet in the evening) PO daily for 8 weeks
- Treatment B: 100 mg SPH3127 (given as one 50 mg tablet in the morning and one 50 mg tablet in the evening) PO daily for 8 weeks
- Treatment C: Matching placebo tablets PO daily (given as one tablet in the morning and one tablet in the evening) for 8 weeks

A patient will be considered enrolled in the trial once they have provided signed informed consent, met all inclusion/exclusion criteria, been randomized to treatment and received at least one dose of study drug. Baseline measurements will be taken at screening or on Day 1 prior to the first treatment.

After the 12-week trial period (including screening), all randomized subjects will have the opportunity to enter an optional active treatment extension for an additional 10 months. Those subjects receiving Treatment A and who choose to enter the extension will continue on Treatment A in a blinded manner (will not know SPH3127 dose). Those subjects receiving Treatment B and who choose to enter the extension will continue on Treatment B in a blinded manner (will not know SPH3127 dose). Those subjects receiving Treatment C (placebo) and who choose to enter the extension will be randomized to receive Treatment A or Treatment B in a blinded manner (will not know SPH3127 dose). Those subjects who choose not to enter the optional active treatment extension will receive a follow-up safety call one week after the last treatment (D63). The STUDY SCHEMATIC is presented in Figure 1.

4.2 Schedule of Assessments

	Main Study								Active Treatment Extension				
Event	**D-28 ± 2**	**D-5 ± 2**	**D1**	**D14 ± 2**	**D28 ± 2**	**D46 ± 2**	**D56 ± 2**	**D63[d] ± 4**	**D112 ± 4**	**D168 ± 4**	**D224 ± 4**	**D280 ± 4**	**D336 ± 4**
Informed Consent	X												
Screening	X												
Medical History/ Demographics	X												
Physical exam	X		X	X	X		X						X
Vital Signs (BP, HR, Temp)	X		X	X	X		X		X	X	X	X	X
ECG	X		X				X						
Stool sample[e]	X												
Labs	X		X	X	X		X		X	X	X	X	X
Urine drug screen, alcohol breathalyzer	X												
Urine pregnancy test	X		X										
Con Meds	X		X	X	X		X		X	X	X	X	X
AEs	X		X	X	X		X	X	X	X	X	X	X

	Main Study								Active Treatment Extension				
Event	**D-28 ± 2**	**D-5 ± 2**	**D1**	**D14 ± 2**	**D28 ± 2**	**D46 ± 2**	**D56 ± 2**	**D63[d] ± 4**	**D112 ± 4**	**D168 ± 4**	**D224 ± 4**	**D280 ± 4**	**D336 ± 4**
Modified Mayo Clinical Score													
Stool Frequency[a]	X		X	X	X		X		X	X	X	X	X
Rectal Bleeding[a]	X		X	X	X		X		X	X	X	X	X
Flexible Sigmoidoscopy[b]	X						X						X
UC-100 Score	X						X						X
UC Lesion Samples[c]													
Robarts Histopathology Index[b]	X						X						X
Biomarkers	X						X						
I/E Confirmation (phone call to patient)		X											
Plasma Biomarkers (-10", 1', 2', 4', 8')			X		X		X						
PK (-10", 15", 30", 1', 2', 4', 8')			X		X		X						
Fecal Calprotectin	X[e]				X		X						

	Main Study								Active Treatment Extension				
Event	**D-28 ± 2**	**D-5 ± 2**	**D1**	**D14 ± 2**	**D28 ± 2**	**D46 ± 2**	**D56 ± 2**	**D63[d] ± 4**	**D112 ± 4**	**D168 ± 4**	**D224 ± 4**	**D280 ± 4**	**D336 ± 4**
Dispense Medication and Perform Accountability			X	X	X		X		X	X	X	X	
Take Medication on Site			X	X	X		X						
Participation in extension? (phone call to patient)													
Post-Study Follow-Up[d]								X					

[a]Via patient report at D-28. Via electronic diary starting at D-5.

[b]Within 2 weeks after D-28 (screening) and within 2 days after D56 and D336

[c]Samples collected during sigmoidoscopy

[d]Patients who don't enter the active treatment extension will receive a post-study phone call to query for adverse events.

[e]Within 2 weeks after D-28 (screening). If possible, the first stool of the day should be collected. Sample should not be collected on the day of sigmoidoscopy or bowel preparation.

5 POPULATION

5.1 Number of Subjects

30 mild-to-moderate ulcerative colitis patients

5.2 Number of Study Sites

~20 sites in the U.S.

5.3 Inclusion Criteria

1. Signed Informed Consent Form (ICF);
2. Adult males and females ≥ 18 to ≤ 70 years of age on the day of signing the ICF.
3. A diagnosis of UC (documented or confirmed at screening) will be eligible provided they have mild-to-moderate active UC extending ≥ 15 cm from the anal verge.
4. At screening/baseline, a Modified Mayo Clinic Score (MMCS) from 4-9, a rectal bleeding subscore ≥ 1, and a Mayo Clinic Endoscopic Subscale (MCES) score ≥ 2 determined by central reading.
5. Patient has a negative urine drug screen (e.g., amphetamines, barbiturates, benzodiazepines, cannabis, cocaine, opiates, methadone) at Screening.
6. Patient has a negative alcohol breath test at Screening.
7. Female patients who have a negative pregnancy test at Screening and who agree to use adequate birth control methods throughout the entire study (and extension, if applicable) or who is post-menopausal (i.e., amenorrhea ≥ 1 year) or who have been surgically sterilized.
8. Male patients with partners of child-bearing potential who agree to use adequate birth control methods throughout the entire study (and extension, if applicable) or who have been surgically sterilized.

5.4 Exclusion Criteria

An eligible subject will not be enrolled in the trial if any of the following exclusion criteria are met:

1. Diagnosis of severe UC, defined as the presence of ≥ 6 bloody stools daily with one or more of the following: (1) oral temperature > 37.8°C or > 100.0°F; (2) pulse > 90 beats/min; (3) hemoglobin concentration < 10.5 g/dL; or erythrocyte sedimentation ratio (ESR) > 30.
2. Patients treated with oral mesalamine >2.4 g/d, systemic steroids or rectal steroids within 4 weeks prior to randomization, rectal mesalamine (within 2 weeks), immunomodulators or immunosuppressant drugs, including, but not limited to, IL-6 inhibitors, TNF inhibitors, anti-IL-1 agents and JAK inhibitors within 5 half-lives prior to randomization, antibiotics, anti-diarrheals (within 2 weeks), drugs blocking the renin-angiotensin system (e.g., direct renin inhibitors, angiotensin converting enzyme inhibitors, or angiotensin II receptor blockers) (within 4 weeks) or

administration of any investigational drug (within 4 weeks). Because SPH3127 is a direct renin inhibitor with the potential to reduce blood pressure, other classes of antihypertensives (e.g., calcium channel blockers, beta blockers, diuretics, direct vasodilators, alpha blockers, central α2 antagonists) (within 4 weeks) will also be excluded. Drugs, herbal medicines and substances that inhibit or induce CYP3A4 (e.g., ritonavir, itraconazole, grapefruit juice) (within 2 weeks or 5 half-lives, whichever is longer) will be excluded.

3. History of colectomy or partial colectomy, colorectal dysplasia, Crohn's disease, toxic megacolon, or bleeding disorders.
4. A stool sample positive for enteric pathogens, including *Clostridium difficile*.
5. Patients with an estimated glomerular filtration rate (eGFR) $\leq$ 60.
6. Patients with hepatic impairment or history of liver cirrhosis.
7. Serum creatinine > 1.5 times the upper limit of normal, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBIL) or alkaline phosphatase (ALP) > 2 times the upper limit of normal.
8. Serious underlying disease other than UC.
9. Previous participation in clinical trials with SPH3127
10. Known hypersensitivity to tablet ingredients or history of a significant allergic reaction to any drug as determined by the investigator.
11. Known seropositivity or positive test at screening for an active viral/bacterial infection with:
    - Hepatitis B virus (HBV) (except seropositivity due to HBV vaccination)
    - Hepatitis C virus
    - Human immunodeficiency virus
    - COVID-19 (only active infection excluded)
    - Tuberculosis
12. Known clinically relevant immunological disorders.
13. History of severe allergic or anaphylactic reactions.
14. History of malignancy, unless deemed cured by adequate treatment with no evidence of recurrence for a minimum 3 years before screening; completely eradicated non-melanoma skin cancer (such as basal cell carcinoma or squamous cell carcinoma) is not exclusionary.
15. Clinically relevant abnormalities detected on ECG regarding either rhythm or conduction (e.g., QTcF > 450 ms or a known long QT syndrome). A first-degree heart block or sinus arrhythmia will not be considered a significant abnormality.
16. Low blood pressure at screening (i.e., SBP < 90 mmHg or DBP < 60 mmHg).
17. Clinically relevant abnormalities detected on vital signs prior to dosing.

18. Significant blood loss (including blood donation > 500 mL) or transfusion of any blood product within 12 weeks prior to the IP administration or scheduled transfusion within 4 weeks after the end of the trial.
19. Treatment with any drug known to have a well-defined potential for toxicity to a major organ in the last 3 months preceding the initial investigational product (IP) administration.
20. Concurrent participation, or participation within 30 days prior to the IP administration or 5 half-lives of the investigational drug (whichever is longer), in any drug/device or biologic investigational research trial.
21. Women who are breastfeeding.
22. Vaccination (including influenza and COVID-19) within the last 4 weeks prior to randomization.
23. History of drug or alcohol abuse.
24. Is an investigator, sub-investigator, research assistant, pharmacist, trial coordinator, or other staff of a relative who is directly involved in the conduct of the trial.
25. Any condition or circumstances that in the opinion of the investigator may make a subject unlikely or unable to complete the trial or comply with trial procedures and requirements.

6 STUDY CONDUCT

6.1 General Instructions

Trial procedures will be conducted as specified as below and in the Schedule of Assessments.

6.2 Study Procedures by Time Point

6.2.1 Screening (Day -28 ± 2 days)

Signing of Informed Consent will precede screening to establish/confirm a diagnosis of mild-to-moderate UC and to determine trial suitability (inclusion/exclusion criteria) approximately 4 weeks prior to Day 1.

The following procedures will be performed at Screening:

- Medical history (including drug allergies) and demographic information;
- Physical exam;
- Vital signs assessment (systolic and diastolic blood pressure (seated), heart rate, temperature);
- ECG;
- Stool sample within 2 weeks of Informed Consent (split stool sample for enteric pathogens (e.g., *Clostridium Difficile*) and fecal calprotectin);

- Clinical laboratory assessments;
- Urine drug screen, breathalyzer;
- Urine pregnancy test;
- Viral/bacterial infection (hepatitis B, hepatitis C, HIV, COVID-19, TB) tests
- Concomitant medications;
- Adverse events;
- Modified Mayo Clinical Score:
  - Stool frequency (patient report (rather than diary))
  - Rectal bleeding (patient report (rather than diary))
  - Flexible sigmoidoscopy (within 2 weeks of Informed Consent)
- UC lesion tissue collection (during sigmoidoscopy) for Robarts Histology Index (RHI) and biomarkers.

Patients who meet all inclusion/exclusion criteria will receive phone confirmation at least 5 days before the Day 1 study visit (Day -5).

6.2.2 Baseline and Randomization Visit (Day 1)

On Day 1, all Events will be completed, except PK and plasma biomarkers, prior to oral dosing. PK and plasma biomarker samples will be collected at the defined intervals ± 5 min.

The following procedures will be performed on **Day 1 (pre-dose)**:

- Randomization to treatment (can be performed up to 2 days prior to Day 1);
- Physical examination;
- Vital signs assessment (systolic and diastolic blood pressure (seated), heart rate, temperature (-10" pre-dose);
- ECG;
- Clinical laboratory assessments;
- Urine pregnancy test;
- Concomitant medications;
- Stool frequency (from diary);
- Rectal bleeding (from diary);
- PK (-10" pre-dose);
- Plasma biomarkers (-10" pre-dose);
- Dispense medication (2-week blister packs) and drug accountability – Take first morning oral dose on-site.

The following procedures will be performed on **Day 1 (post-dose)**:

- Vital signs assessment (systolic and diastolic blood pressure (seated), heart rate, temperature (30", 2', 4', 8');
- PK (15", 30", 1', 2', 4', 8');
- Plasma biomarkers (1', 2', 4', 8').

6.2.3 Visit Day 14 (± 2 days)

Day 14 is primarily a safety and compliance check.

The following procedures will be performed on **Day 14 (pre-dose)**:

- Physical examination;
- Vital signs assessment (systolic and diastolic blood pressure (seated), heart rate, temperature);
- Concomitant medications;
- Adverse events;
- Stool frequency (from diary);
- Rectal bleeding (from diary);
- Dispense medication (2-week blister packs) and drug accountability – Take morning oral dose on-site.

6.2.4 Visit Day 28 (± 2 days)

The events at the site visit on Day 28 are similar to the Events on Day 1.

The following procedures will be performed on **Day 28 (pre-dose)**:

- Physical examination;
- Vital signs assessment (systolic and diastolic blood pressure (seated), heart rate, temperature (-10" pre-dose));
- Clinical laboratory assessments;
- Concomitant medications;
- Adverse events;
- Fecal calprotectin (stool collection);
- Stool frequency (from diary);
- Rectal bleeding (from diary);
- PK (-10" pre-dose);
- Plasma biomarkers (-10" pre-dose);

- Dispense medication (2-week blister pack x 2) and drug accountability – Take morning oral dose on-site.

The following procedures will be performed on **Day 28 (post-dose)**:

- Vital signs assessment (systolic and diastolic blood pressure (seated), temperature (30", 2', 4', 8');
- PK (15", 30", 1', 2', 4', 8');
- Plasma biomarkers (1', 2', 4', 8').

6.2.5 Visit Day 56 (± 2 days)

The following procedures will be performed on **Day 56 (pre-dose)**:

- Physical examination
- ECG;
- Clinical laboratory assessments;
- Concomitant medications;
- Adverse events;
- Vital signs assessment (systolic and diastolic blood pressure (seated), heart rate, temperature (-10" pre-dose);
- PK (-10" pre-dose);
- Plasma biomarkers (-10" pre-dose);
- Fecal calprotectin (stool collection);
- Take morning oral dose on-site and drug accountability.

The following procedures will be performed on **Day 56 (post-dose)**:

- Vital signs assessment (systolic and diastolic blood pressure (seated), temperature (30", 2', 4', 8');
- PK (15", 30", 1', 2', 4', 8');
- Plasma biomarkers (1', 2', 4', 8')
- Dispense medication (for those participating in the active extension).
- Modified Mayo Clinical Score
  - Stool frequency (from diary)
  - Rectal bleeding (from diary)
  - Flexible sigmoidoscopy within 2 days of visit to allow for bowel prep/cleansing)
- UC lesion tissue collection (during sigmoidoscopy) for Robarts Histology Index (RHI) and biomarkers (within 2 days of visit).

6.2.6 Day 63 (± 2 days) Follow-Up (phone)

- Query for adverse events (phone call only for subjects not entering the active treatment extension)

6.2.7 Active Treatment Extension

All randomized subjects will have the opportunity to enter an active treatment extension after the last main study visit (Day 56). A phone call will be made to each subject to confirm interest in participating on Day 46 ± 2. Medication will be dispensed at 8-week intervals in the same 2-week blister packs as the main study for an additional 10 months in the active treatment extension. Those subjects receiving Treatment A (50 mg SPH3127 total daily dose) and who choose to enter the extension will continue on Treatment A in a blinded manner (will not know SPH3127 dose). Those subjects receiving Treatment B (100 mg SPH3127 total daily dose) and who choose to enter the extension will continue on Treatment B in a blinded manner (will not know SPH3127 dose). Those subjects receiving Treatment C (placebo) and who choose to enter the extension will be randomized to receive Treatment A or Treatment B in a blinded manner (will not know SPH3127 dose). Safety information (i.e., adverse events, clinical laboratory tests, vital signs, concomitant medications) will be collected at the designated intervals (every 8-weeks) in the Schedule of Assessments. Rectal bleeding and stool frequency will be collected daily using a subject diary. At the final site visit (D336), a physical examination and flexible sigmoidoscopy (within 2 days of visit) will also be performed.

6.3 Premature Discontinuation

An enrolled subject is defined as having signed an informed consent, met all inclusion/exclusion criteria, been randomized to treatment and having received at least one dose of study drug.

A subject has the right to withdraw from the study at any time for any reason without prejudice or without jeopardizing their medical care. The Investigator must withdraw the subject from the study if the subject requests to be withdrawn.

The Investigator may discontinue a subject from the study when, in his/her judgment it is necessary for any reason, including any of the following:

- Adverse event (serious or non-serious);
- Failure to comply with the protocol;
- Requires a medication that is specifically prohibited by the protocol; or,
- It is in the subject's best interest.

The Investigator may also withdraw a subject upon the request of the Sponsor, or if the Sponsor terminates the study for clinical or administrative reasons.

If a subject is withdrawn from participation in the study, the reason(s) for discontinuation shall be documented. A subject who discontinues the study early (regardless of cause) will be requested to return to the clinic and have all the early termination assessments

performed. If a subject is discontinued from study due to an adverse event, the subject will be followed until the event is resolved or deemed clinically stable.

A subject that has been met all the eligibility criteria at Screening, but not at baseline (Day 1), will be replaced. A subject that has enrolled in the study (signed informed consent, met all inclusion/exclusion criteria, has been randomized and received at least one dose of study drug) that discontinues from the study (for any reason) will not be replaced.

7 DESCRIPTION OF STUDY PROCEDURES

Patients will be assigned a unique study subject identification number at the Screening Visit. Once this number has been assigned to a study subject, it cannot be reassigned.

7.1 Informed Consent

Written informed consent will be obtained for each patient prior to any screening or study-related procedures being performed. The Investigator or trained designee must explain to each patient the nature of the treatment, its purpose, procedures, expected duration and the potential risks and benefits associated with the clinical research study. Each patient will be given the opportunity to discuss questions related to study participation with the Investigator or trained designee and/or with friends and relatives, prior to signing the informed consent form (ICF). Each patient will also be provided with a printed copy of the study ICF detailing the relevant study information. The original ICF will be kept in the Investigator Site File. A notation that written informed consent has been obtained will be made in the subject's medical record.

7.2 Medical History/Demographics

Demographic information and a complete medical history, including any clinically significant pre-existing conditions, concomitant medications and drug allergies, will be collected and recorded at Screening.

7.3 Physical Examinations

Physical examinations will include the examination of the following organ systems - dermatological, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, cardiovascular, respiratory, gastrointestinal and neurological.

Physical examinations will be performed at Screening, Days 1, 14, 28 and at the End-of-Study Visit (Day 56; or the Early Termination Visit). In addition, a physical examination will be conducted at the end of the active treatment extension period (Day 336) for those that participate in this portion of the trial. During the physical examination at the End-of-Study Visit (or Early Termination Visit), the subject will be queried regarding any changes in health status since the previous examination.

7.4 ECG

A conventional 12-lead ECG with leads placed on the patient's limbs and on the surface of the chest will be collected at Screening and on Days 1 and 56.

7.5 Stool Sample Collection/Fecal Calprotectin

Stool samples will be collected and split for enteric pathogens such as *Clostridium difficile* and for fecal calprotectin, a marker of UC treatment activity, within 2 weeks after Informed Consent and for fecal calprotectin at Day 28 and Day 56.

7.6 Clinical Laboratory Tests

Viral/bacterial infection (hepatitis B, hepatitis C, HIV, COVID-19, TB) tests will be performed at Screening.

The following clinical laboratory assessments will be performed at the Screening, Day 1, Day 14, Day 28 and Day 56 Visits (or Early Termination Visit), as well as the visits every 2 months during the active treatment extension.

Hematology: white blood cell counts with differential, hemoglobin, hematocrit, platelet count, ESR (screening) and red blood cell count.

Serum chemistry: albumin, total protein, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, total bilirubin, blood urea nitrogen, calcium, bicarbonate, chloride, creatinine, glucose, and sodium, potassium, T3, T4, TSH, cholesterol and triglycerides.

Urinalysis: Specific Gravity, pH, protein, glucose, ketone, bilirubin, urobilinogen, blood, nitrite, and leukocytes.

Venous blood samples will be collected and prepared using standard procedures and sent to a certified central laboratory for processing and reporting. Details for collection, handling, processing and shipping of specimens are described in a Study Laboratory Manual (provided separately).

7.7 Urine drug screen, alcohol breathalyzer

A standard urine drug panel screen and alcohol breathalyzer will be administered at Screening.

7.8 Urine pregnancy test/Contraception

Female patients who are pre-menopausal or who have not been surgically sterilized will take a urine pregnancy test at Screening and on Day 1. Female patients who have a negative pregnancy test at Screening and Day 1 and who agree to use adequate birth control methods throughout the entire study (and extension, if applicable) will be enrolled.

Highly effective methods of contraception (i.e., pregnancy rate of less than 1% per year) are: a stable regimen of combined estrogen and progesterone hormonal contraception with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone releasing system, bilateral tubal occlusion or have a vasectomized partner. Agreement to continuous abstinence is also acceptable.

Non-vasectomized male patients who are sexually active with female partners of childbearing potential must agree to the use condoms during every penile-vaginal intercourse and not donate semen during the trial or within 90 days after the last

investigational product administration. In addition, the female partner of childbearing potential must use a highly effective method of contraception (see above). Non-vasectomized male patients may also agree to continuous abstinence from heterosexual sexual contact.

7.9 Concomitant Medications

Concomitant medications (prescription medications, over-the-counter medications including multi-vitamins and herbal remedies) must be reviewed for all subjects during screening and at every study visit. Vaccines (i.e., influenza, COVID-19) will only be allowed in the active treatment extension period.

If use of a permitted concomitant medication occurs during the study, subjects will be instructed to report all such medications taken and to report any changes to existing medications while on study through the follow-up period; it is the responsibility of the Investigator to ensure that details regarding the medication(s) are recorded in full in the subject's medical records.

Prohibited concomitant medications in this study are listed in Section 8.5.

7.10 Adverse Events

Adverse events (AEs) will be recorded and monitored for all subjects who are enrolled in the study (sign an informed consent form and receive at least one dose of study drug).

7.11 Modified Mayo Clinical Score (MMCS)

The Mayo Score will be determined within 2 weeks after Screening and following the Day 56 sigmoidoscopy to evaluate the potential efficacy of SPH3127 as a treatment for mild-to-moderate UC. The MMCS will also be determined at the end of the active treatment extension (D336). Stool frequency and rectal bleeding scores will be taken at the D56 and D336 visits; the endoscopy score will be determined from the sigmoidoscopy performed within 2 days of these visits. The Modified Mayo Score in this study does not include the Physician's Global Assessment component. Directions will be provided to patients on ratings of Stool Frequency and Rectal Bleeding and will be recorded on an electronic patient diary or by patient recall (at Screening). Patients may be sedated for flexible sigmoidoscopy which will be recorded and scored by a blinded central reader.

Components of the Modified Mayo Clinical Score:

Stool Frequency
0 = Normal
1 = 1–2 stools/day more than normal
2 = 3–4 stools/day more than normal
3 = >4 stools/day more than normal
Rectal bleeding*
0 = None
1 = Visible blood with stool less than half the time
2 = Visible blood with stool half of the time or more
3 = Passing blood alone
Mucosal appearance at endoscopy
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)

*A score of 3 for bleeding requires patients to have at least 50% of bowel motions accompanied by visible blood and at least one bowel motion with blood alone.

7.12 UC-100 Score

The composite UC-100 score (i.e., 1 + 16 × Mayo Clinic stool frequency subscore [0 to 3] + 6 × Mayo Clinic endoscopic subscore [0 to 3] + 1 × Robarts Histopathology Index score [0 to 33]), which ranges from 1 (no disease activity) to 100 (severe disease activity) will be calculated based on the respective subscores collected within 2 weeks after Screening and following the Day 56 sigmoidoscopy (within 2 days of visit). The UC-100 Score will also be determined at the end of the active treatment extension (D336; within 2 days of visit).

7.13 Robarts Histopathology Index (RHI)

The Robarts Histopathology Index includes 4 grading domains: chronic inflammatory infiltrate, lamina propria neutrophils, neutrophils in the epithelium, and erosions or ulcerations. Lesion tissue samples will be graded according to this scale within 2 weeks after Screening and following the Day 56 sigmoidoscopy (within 2 days of visit). The

RHI will also be determined at the end of the active treatment extension (D336; within 2 days of visit).

Components of the Robarts Histopathology Index:

Chronic inflammatory infiltrate
0=No increase
1=Mild but unequivocal increase
2=Moderate increase
3=Marked increase
Lamina propria neutrophils
0=None
1=Mild but unequivocal increase
2=Moderate increase
3=Marked increase
Neutrophils in epithelium
0=None
1=<5% crypts involved
2=<50% crypts involved
3=>50% crypts involved
Erosion or ulceration
0=No erosion, ulceration or granulation tissue
1=Recovering epithelium+adjacent inflammation
1=Probable erosion—focally stripped
2=Unequivocal erosion
3=Ulcer or granulation tissue

7.14 Flexible Sigmoidoscopy

To prepare for flexible sigmoidoscopy, recommendations will be given to patients the day before the scheduled sigmoidoscopy at Screening (within 2 weeks of the Screening visit) and for the Day 56 site visit (within 2 days of visit). The same instructions will be

given to patients prior to the Day 336 site visit (within 2 days of visit), for those participating in the active treatment extension. The recommendations may include:

- Follow a special diet the day before the exam. Patients may be asked to not eat the day before the exam. Drinks may be limited to clear liquids — plain water, broth, carbonated beverages, and tea and coffee without milk or cream. Patients may be asked not to eat or drink anything after midnight the night before the exam.
- Take a laxative the night before the exam.
- Use an enema kit. Patients will need to use an over-the-counter enema kit, typically a few hours before the exam to empty their colon.

During the exam, patients may be sedated. The sigmoidoscopy will be recorded and scored by a blinded central reader. There is a high degree of correlation in assessments of UC activity made by rectosigmoidoscopy vs. colonoscopy (Colombel et al., 2016).

7.15 UC Histology Assessment

Samples of UC tissue will be taken at the time of flexible sigmoidoscopy. Tissue samples will be evaluated for histology (and graded using the MMCS and Robarts Histopathology Index) and tissue biomarker levels (e.g., angiotensin II, complement C3, cytokines IL-1β, IL-17A, TNF-α, IL-6, and IL-23).

7.16 Plasma Biomarkers

Blood samples (3 mL/time point) will be collected once at each time point (-10”, 1’, 2’, 4’, 8’) for plasma biomarker (e.g., cytokines IL-1β, IL-17A, TNF-α, IL-6, and IL-23) analysis into anticoagulant tubes containing EDTA-K_2 and centrifuged for 15 min. The pretreated plasma biomarker plasma samples will be frozen and sent for determination of biomarker levels. Sample collection will occur over 8 hours at the study site on Days 1, 28 and 56.

7.17 SPH3127 Pharmacokinetics

Blood samples (3 mL/time point) will be collected once at each time point (-10” pre-dose, 15”, 30”, 1’, 2’, 4’, 8’) for PK analysis into anticoagulant tubes containing EDTA-K_2 and centrifuged for 15 min. The pretreated PK plasma samples will be frozen and sent for determination of SPH3127 levels. Sample collection will occur over 8 hours at the study site on Days 1, 28 and 56.

8 STUDY DRUG MANAGEMENT

8.1 Description

8.1.1 Formulation

SPH3127 50 mg tablets or matching placebo tablets will be packed in blister cards (PVC with foil back) containing a 2-week supply (one tablet per day) plus 2 extra tablets to account for Visit scheduling (i.e., 2 x 8 configuration). Each blister card is packed individually in a foil pouch. Subjects will receive 2 blister cards (in foil pouches) for each 2-week period and will take one tablet orally from each blister card daily.

The study drug products (SPH3127 and placebo tablets) will be packaged with the following labeling information:

- serial number (for blinding and randomization)
- protocol number
- Sponsor's identification
- investigational new drug statement
- drug product name and potency
- drug product manufacturer
- route of administration
- instructions for use and storage
- precautionary statements

8.1.2 Storage

The supplied drug product should be stored at room temperature (15°C to 25°C).

8.2 Packaging and Shipment

The blister cards in foil pouches will be provided in cardboard packaging.

Access to study drug will be limited to designated study personnel.

Neither the Investigator nor any designees may provide study drug to any subjects who are not participating in this study.

8.3 Dose and Administration

A total of 30 eligible patients will be randomly assigned to one of three treatment arms (10 subjects per treatment group):

- Treatment A: 50 mg SPH3127 (given as one 50 mg tablet in the morning and one placebo tablet in the evening) PO daily for 8 weeks;
- Treatment B: 100 mg SPH3127 (given as one 50 mg tablet in the morning and one 50 mg tablet in the evening) PO daily for 8 weeks;
- Treatment C: Matching placebo tablets PO daily (one tablet in the morning and one tablet in the evening) for 8 weeks.

All randomized subjects will have the opportunity to enter an active treatment extension after the last main study visit (Day 56). Medication will be dispensed at 8-week intervals in the same 2-week blister packs as the main study for an additional 10 months in the active treatment extension. Those subjects receiving Treatment A (50 mg SPH3127 total daily dose) and who choose to enter the extension will continue on Treatment A in a blinded manner (will not know SPH3127 dose). Those subjects receiving Treatment B (100 mg SPH3127 total daily dose) and who choose to enter the extension will continue on Treatment B in a blinded manner (will not know SPH3127 dose). Those subjects receiving Treatment C (placebo) and who choose to enter the extension will be

randomized to receive Treatment A or Treatment B in a blinded manner (will not know SPH3127 dose).

8.4 Accountability

The study pharmacist or coordinator and clinical Investigator will maintain accurate records of receipt of all study drug, including dates of receipt. Study personnel will maintain accurate records regarding when and how much study drug is dispensed to and used by each subject in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At completion of the study, to satisfy regulatory requirements regarding study drug accountability, all study drug will be reconciled and retained or destroyed according to applicable state and federal regulations and International Conference on Harmonisation (ICH) guidelines.

8.5 Prohibited Concomitant Therapy

Patients treated with oral mesalamine >2.5 g/d, systemic steroids or rectal steroids within 4 weeks prior to randomization, rectal mesalamine (within 2 weeks), immunomodulators or immunosuppressant drugs, including, but not limited to, IL-6 inhibitors, TNF inhibitors, anti-IL-1 agents and JAK inhibitors within 5 half-lives prior to randomization, antibiotics, anti-diarrheals (within 2 weeks), drugs blocking the renin-angiotensin system (e.g., direct renin inhibitors, angiotensin converting enzyme (ACE) inhibitors, or angiotensin II receptor blockers (ARBs)) (within 4 weeks) or administration of any investigational drug (within 4 weeks) will be excluded from the study. Because SPH3127 is a direct renin inhibitor with the potential to reduce blood pressure, other classes of antihypertensives (e.g., calcium channel blockers, beta blockers, diuretics, direct vasodilators, alpha blockers, central α2 antagonists) (within 4 weeks) will also be excluded from the study. These medications will also be prohibited during the study unless required to treat medical conditions and approved by the Medical Monitor.

Vaccinations are prohibited within 4 weeks of randomization and throughout the study (main and active treatment extension phases). Influenza and COVID-19 vaccinations are permitted during the active treatment extension phase of the study.

Although SPH3127 is mainly metabolized by CYP3A4, the impact of CYP3A4 inhibitors or inducers on SPH3127 PK has not been characterized in humans. Consequently, drugs, herbal medicines and substances that inhibit or induce CYP3A4 will be prohibited during the study. Examples of strong and moderate inhibitors and inducers of CYP3A4 include, but are not limited to:

- Strong inhibitors - boceprevir, cobicistat, danoprevir, ritonavir, elvitegravir, grapefruit juice, itraconazole, ketoconazole, lopinavir, paritaprevir and (ombitasvir and/or dasabuvir), posaconazole, saquinavir, tipranavir, telithromycin, troleandomycin, voriconazole;
- Moderate inhibitors - aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil;
- Strong inducers - apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John’s wort; and,

- Moderate inducers - bosentan, efavirenz, etravirine, phenobarbital, primidone.

8.6 Compliance

Patients will be asked to return their blister card(s) at each post-randomization study visit (except Day 1).

9 ADVERSE EVENTS

An adverse event can be any unfavorable or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) drug, whether or not it is related to the medicinal (investigational) drug.

9.1 Documenting Adverse Events

The recording of AEs (regardless of their relationship to study drug) will begin with the Screening Visit until the Final Visit (Day 56) or Early Termination Visit. If the Investigator is made aware of an AE up to 7 days after the last dose of study drug the AE will be followed to resolution. For those patients who enter the optional active treatment extension, Investigator(s) will query patients for AEs when they visit the site to pick up their medication every 8 weeks. Investigator(s) will monitor each patient closely for AEs. At each visit, the Investigator will document all observed or volunteered AEs.

The Investigator(s) should always attempt to group signs and symptoms into a single term that constitutes a single unifying diagnosis. Adverse Events will be classified using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) classification system. AEs reported from the first dose of IP until 7 days after the last dose of IP will be considered as treatment-emergent AEs (TEAEs) and will be summarized descriptively. The Investigator's opinion of the association of each AE to study drug, the duration (date of onset / date of resolution), frequency, intensity, countermeasures (treatment), and the outcome of each AE will be documented. Each adverse event must be recorded separately. Multiple occurrences of a single PT in a patient will only be counted once at the maximum severity/grade. All AEs will be summarized by relatedness to IP. Any AEs leading to death or discontinuation of IP will also be summarized.

Any medical condition or laboratory abnormality that is present at subject screening and prior to the first dose of study drug should be considered as baseline, recorded in medical history, and should not be reported as an AE. However, if the medical condition worsens at any time during the study after the first dose of study drug it should be recorded as an adverse event.

9.2 Assessment of Intensity and Causality

The event's **relationship to the study drug or treatment procedure** should be indicated according to the following definitions:

Definite	The adverse event *is clearly related* to the treatment or procedure.
Possible	The adverse event *may be related* to the treatment or procedure.
Unlikely	The adverse event *is doubtfully related* to the treatment or procedure.
Not Related	The adverse event *is clearly not related* to the treatment or procedure.

The **frequency** of the event should be indicated according to the following definitions:

Single episode	This is the first and only experience/episode of the event in the trial.
Recurrent	The event has occurred before in the trial.
Continuous	The event is continuing.

The **intensity** grade of the event should be indicated according to the following definitions:

Mild	The event is easily tolerated by the subject and does not affect the patient's usual daily activities.
Moderate	The event causes the subject sufficient discomfort and interferes with the patient's usual daily activities.
Severe	The event is incapacitating and causes considerable interference with the subject's usual daily activities.

Action Taken should be indicated according to the following definitions:

None	No treatment was required and no changes were made to study drug administration and dose.
Treatment	Subject received treatment, e.g., medications or procedures as a result of the AE.
Discontinued from Study	Subject was discontinued from study.
Discontinued study drug	Study drug was discontinued and not restarted.
Study drug interrupted	Dosing was stopped or delayed due to the AE.
Other	Specify

The **outcome** should be indicated according to the following definitions:

Recovered without sequelae	Patient recovered completely from the AE.
Recovered with sequelae	Patient has recovered from the AE but displays other symptoms.
Ongoing	Patient continues to exhibit symptoms of the AE. The patient will be followed until the AE is resolved.
Death	Patient died. (The date of death should be entered as the SAE resolution date)
Unknown	Outcome is unknown due to loss to follow-up.

9.3 Clinical Laboratory Changes

Clinically significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an adverse event. Examples of these include abnormal laboratory results that are associated with symptoms or require treatment. Whenever possible, the underlying diagnosis should be listed in lieu of abnormal laboratory values. Laboratory abnormalities deemed not clinically significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

All clinically significant abnormal laboratory test results will be repeated until they return to within normal limits or are at levels that are regarded as clinically non-significant by the Investigator.

9.4 Pregnancy

Pregnancy is neither an AE nor an SAE. However, all pregnancies occurring in subjects or their partner will be followed to assess for pregnancy-associated AEs or SAEs such as congenital anomaly. If, at any time between the first study drug dispensing and 7 days after the last dose of study drug, a pregnancy is suspected, the patient/partner will be instructed/requested to return to the study center within 48 hours and undergo a serum

pregnancy test, as confirmation of pregnancy. All confirmed pregnancies must be immediately reported using the appropriate form.

Upon confirmation of a subject pregnancy, no further investigational treatment will be administered. All pregnancies with study drug exposure will be followed until resolution (i.e., termination [voluntary or spontaneous] or birth).

9.5 Adverse Event Follow-up

For this study, the Investigator will follow AEs until the last day of study participation or up to 7 days thereafter, until the adverse event is resolved or the Investigator determines that the subject is stable, whichever is earlier. Appropriate action may be taken if judged clinically necessary. All AEs identified on the last scheduled contact must be recorded on the AE Case Report Form (CRF) and/or electronic record and the current status (ongoing or resolved) will be noted. In addition, SAEs will be reported to the Sponsor according to the reporting outlines identified in Section 9.8.

9.6 Serious Adverse Event

9.7 Definition of Serious Adverse Event

A SAE is any event that meets any of the following criteria:

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received SPH3127
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:
  - Intensive treatment in an emergency room or at home for allergic bronchospasm
  - Blood dyscrasias or convulsions that do not result in inpatient hospitalization
  - Development of drug dependency or drug abuse.

Definition of Terms

Life threatening: An AE is life threatening if the subject was at immediate risk of death from the event as it occurred; i.e., it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug-induced hepatitis can be fatal.

Hospitalization: AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'non-serious' according to the usual criteria.

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

Disability/incapacitating: An AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.

9.8 Reporting Serious Adverse Events

The recording of SAEs (regardless of their relationship to study drug) will begin with the Screening visit until the Final Visit (Day 56 or 336 (if entering the extension) or Early Termination Visit. Any SAE, including death due to any cause, which occurs during the conduct of this study, regardless of relationship to study drug, must be reported within 24 hours of the Investigator’s (or designee’s) first awareness of the event.

An initial Serious Adverse Event Form (SAE form) should be completed and submitted through the CRF (or paper form as a backup) per the SAE form instructions.

The Investigators should attempt to group signs and symptoms into a single term that constitutes a single unifying diagnosis and indicated the serious criteria that are applicable to the SAE (the list of serious criteria is also provided in the above section. The Investigator’s opinion of the relationship of the SAE to study drug, the duration, intensity, frequency, actions taken with study drug, and the outcome of the SAE will be documented using the definitions/criteria in Section 9.2.

All serious adverse events are to be reported to the Institutional Review Board (IRB) by the Investigator.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

Unexpected adverse reactions are adverse reactions, the nature, severity, consequences, or frequency of which are not consistent with the anticipated risks described in current relevant information (e.g., investigator's brochure) for the investigational product. The investigator's brochure serves as a primary document to provide safety reference information to determine whether an adverse reaction is expected or unexpected. Prior to submitting the appropriate IND safety report, the Sponsor will ensure that the event meets all three of the definitions for “suspected adverse reaction”, “serious”, and “unexpected”.

9.9 Discontinuation of Treatment/Study Termination Criteria

If a participant in the trial meets criteria for discontinuation and the Investigator is unable to determine whether the adverse event is related to study treatment, the participant should discontinue treatment and be taken off the treatment phase of the study after discussion with the Medical Monitor. The adverse event should be assessed consistent with the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Unblinding for individual patients may be warranted after consultation with the Medical Monitor for adverse events of CTCAE grade ≥ 3.

Study treatment should be permanently discontinued for the following:

- The investigator believes that for safety reasons or tolerability reasons (e.g., AE), it is in the best interest of the participant to discontinue study treatment.
- Any Grade 3 non-skin, drug-related AE lasting > 7 days, or recurs with the following exceptions for hypotension (without associated AEs (e.g., dizziness)), diarrhea, or colitis-related symptoms.

The study must be terminated if any of the following criteria are met:

- Two or more study drug-related ≥ Grade 4 AEs or SAEs (unblinding required) of a similar nature that occur in participants that have received SPH3127 and the study team believe that participants would incur undue risk by continuing the study.
- Death (CTCAE grade 5) of any participant in which the cause of death is assessed to be related to study treatment and the participant was found to have received SPH3127.

Study termination requires that no additional participants will be administered study treatment. Participants who have already received study treatment will continue to be followed for safety through the remainder of the planned follow-up period.

9.10 Overdose

Any instance of overdose (suspected or confirmed and irrespective of whether or not it involved SPH3127) must be communicated to Shanghai Pharma Biotherapeutics USA Inc. or a specified designee. Details of any signs or symptoms and their management should be recorded including details of any antidote(s) administered.

10 STATISTICS

10.1 General Procedures

Descriptive statistical methods will be used to summarize the data from this exploratory study, with the term descriptive statistics referring to the number of subjects (n), mean, median, standard deviation (SD), minimum, and maximum for continuous data and frequencies and percentages for categorical data. Analyses will be performed at both the end of the main 8-week study and the active treatment extension. All statistical testing will be 2-sided and performed using a significance (α) level of 0.05. Statistical comparisons to placebo will be to the individual and pooled doses of SPH3127. The

statistical analyses will be conducted with the SAS software package version 9.1.3 or higher (SAS Institute, Inc, Cary, North Carolina).

10.2 Sample Size

No formal sample size and power calculations were made for this exploratory study.

10.3 Safety Analyses

The safety and tolerability of SPH3127 will be monitored by physical examinations, ECGs, clinical laboratory tests, vital signs, concomitant medications and AEs. Safety will be monitored through Day 63 (Main Study) or through the active treatment extension period, if applicable.

All treatment-emergent AEs will be summarized by treatment group and Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms for each group of participants.

10.3.1 Adverse Events

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the MedDRA. Treatment-emergent adverse events are AEs with onset during the treatment phase or that are a consequence of a preexisting condition that has worsened since baseline. All reported AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by treatment group. Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, or who experience a severe AE or a SAE.

10.3.2 Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point. Changes from baseline results will be presented in pre- versus post-treatment cross-tabulations (with classes for below, within, and above normal ranges). A listing of participants with Grade 2 or higher abnormal laboratory results based on FDA Guidance (FDA 2007) will be provided.

10.3.3 Electrocardiogram (ECG)

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and corrected QT (QTc) interval using some or all of the following correction methods: QT corrected according to Bazett's formula (QTcB), QT corrected according to Fridericia's formula (QTcF).

Descriptive statistics of QTc intervals and changes from baseline will be summarized. The percentage of participants with QTc interval >450 milliseconds, >480 milliseconds, or >500 milliseconds will be summarized, as will the percentage of participants with QTc interval increases from baseline >30 milliseconds or >60 milliseconds.

10.3.4 Vital Signs

Descriptive statistics of temperature, pulse/heart rate, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time

point. The percentage of participants with values beyond clinically important limits will be reported.

10.3.5 Physical Examination

Participants with abnormal post-dose physical examination results will be listed by treatment group and by scheduled time points.

10.4 Other Analyses

10.4.1 Pharmacokinetic Analyses

Data will be listed for all patients with available plasma concentrations in the SPH3127 group. Patients will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (e.g., missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation).

All plasma concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentations. Concentrations below the lower quantifiable concentration will be treated as zero in the summary statistics. All patients and samples excluded from the analysis will be clearly documented in the Clinical Study Report.

For each dose, descriptive statistics (including means, median, SDs and coefficient of variation [CVs]) will be calculated for the plasma concentrations at each sampling time and for PK parameters of SPH3127 (e.g., C_{max}, T_{max}, AUC_{last}, AUC_{inf}, $t_{1/2}$, CL/F, and Vz/F. Additional PK parameters may be determined, as appropriate.

10.4.2 Biomarker Analyses

UC tissue and plasma cytokine assays will be performed using standardized multiplex assays for each collection timepoint from all subjects. Fecal calprotectin will be determined in a standardized chemiluminescence assay. Descriptive statistical methods will be used to summarize the data from these exploratory measures.

10.4.3 Modified Mayo Clinical Score, UC-100, Robarts Histopathology Index

Descriptive statistical methods will be used to analyze the data from Modified Mayo Clinical Score and Mayo subscales, UC-100, and Robarts Histopathology Index.

10.4.4 Clinical remission/response, Endoscopic remission/response

Descriptive statistical methods will be used to analyze the data from definitions of clinical remission and response, and endoscopic remission and response.

Clinical remission:

Defined as a MMCS of 0 – 2, including the following three components:

1. Stool frequency subscore = 0 or 1;
2. Rectal bleeding subscore = 0; and,
3. Endoscopy subscore = 0 or 1.

Clinical response:

Defined as a decrease from baseline in MMCS of ≥ 2 points AND a 30% reduction from baseline PLUS a decrease from baseline in rectal bleeding subscore of ≥ 1 or an absolute rectal bleeding subscore of ≤ 1.

Endoscopic remission:

Defined as an endoscopic subscore = 0.

Endoscopic response:

Defined as a > 1-point reduction in endoscopic subscore.

11 ETHICS AND RESPONSIBILITIES

11.1 Good Clinical Practice

The Investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

11.2 Institutional Review Board (IRB)

Before the start of the study, the Investigator (or Sponsor where required) will provide the IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments.
- Sponsor-approved ICF (and any other written materials to be provided to the participants).
- Investigator's Brochure (or equivalent information) and amendments/addenda.
- Sponsor-approved participant recruiting materials.
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable.
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IRB).
- Information regarding funding, name of the Sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants.

- Any other documents that the IRB requests to fulfill its obligation.

This study will be undertaken only after the IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for patients, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and patient compensation programs, and the Sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IRB and the documents being approved.

During the study the Investigator (or Sponsor where required) will send the following documents and updates to the IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for patients, data or study conduct).
- Revision(s) to ICF and any other written materials to be provided to patients.
- If applicable, new or revised participant recruiting materials approved by the Sponsor.
- Revisions to compensation for study-related injuries or payment to patients for participation in the study, if applicable.
- New edition(s) of the IB and amendments/addenda.
- Summaries of the status of the study at intervals stipulated in guidelines of the IRB (at least annually).
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study treatment.
- New information that may adversely affect the safety of the patients or the conduct of the study.
- Deviations from or changes to the protocol to eliminate immediate hazards to the patients.
- Report of deaths of participants under the Investigator's care.
- Notification if a new Investigator is responsible for the study at the site.
- Development Safety Update Report and Line Listings, where applicable.
- Any other requirements of the IRB.

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for patients, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IRB for review and approval before implementation of the change(s).

At least once a year, the IRB will be asked to review and reapprove this study, where required.

At the end of the study, the Investigator (or Sponsor where required) will notify the IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

11.3 Informed Consent

Each patient must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the Sponsor and by the reviewing IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy.

Before enrollment in the study, the Investigator or an authorized member of the study-site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. Finally, they will be told that the Investigator will maintain a participant identification register and that their records may be accessed by health authorities and authorized Sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the patient is authorizing such access. It also denotes that the patient agrees to allow his or her study physician to recontact the patient for the purpose of obtaining consent for additional safety evaluations, if needed.

The patient will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the patient's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the patient.

Patients who are rescreened are required to sign a new ICF.

12 RECORDS MANAGEMENT

12.1 Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: patient identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; treatment receipt/dispensing/return records; study treatment administration information; and date of study completion and reason for early discontinuation of study treatment or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (e.g., electronic source documents) as

well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the Sponsor. If eSource is utilized, references made to the CRF in the protocol include the eSource system, but information collected through eSource may not be limited to that found in the CRF.

12.2 Study Files and Record Retention

In compliance with the ICH/GCP guidelines, the Investigator/Institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The Investigator/Institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 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 until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the Investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation relating to this study, the Investigator/Institution must permit access to such reports.

13 AUDITING AND MONITORING

Representatives of the Sponsor or CRO clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Patient privacy must, however, be respected. The Investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the Sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The Investigator should immediately notify the Sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

The CRO will use a combination of monitoring techniques: remote and on-site monitoring to monitor this study.

The CRO will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will review the data entered into the eSource/eCRF system.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The Sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the Investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

14 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Shanghai Pharma Biotherapeutics USA Inc. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB and the Investigator must await approval before implementing the changes. Shanghai Pharma Biotherapeutics USA Inc. will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB, the Investigator, and/or Shanghai Pharma Biotherapeutics USA Inc., the amendment to the protocol substantially changes the study design and/or increases the potential risk to the subject and/or has an impact on the subject's involvement as a study participant, the currently approved written informed consent form will require similar modification. In such cases, informed consent will be renewed for subjects enrolled in the study before continued participation.

15 STUDY REPORT AND PUBLICATIONS

Shanghai Pharma Biotherapeutics USA Inc. is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

The publication policy of Shanghai Pharma Biotherapeutics USA Inc. is discussed in the Investigator's Clinical Research Agreement.

16 STUDY DISCONTINUATION

Both Shanghai Pharma Biotherapeutics USA Inc. and the Principal Investigator reserve the right to terminate the study at the Investigator's site at any time. Should this be necessary, Shanghai Pharma Biotherapeutics USA Inc. or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the Principal Investigator will inform the IRB of the same. In terminating the study, Shanghai Pharma Biotherapeutics USA Inc. and the Principal Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

17 CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from Shanghai Pharma Biotherapeutics USA Inc. However, authorized regulatory officials, IRB personnel, Shanghai Pharma Biotherapeutics USA Inc. and its authorized representatives are allowed full access to the records.

Identification of subjects and CRFs shall be by initials, date of birth, screening and treatment numbers only. If required, the subject's full name may be made known to an authorized regulatory agency or other authorized official.

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19 APPENDICES

19.1 APPENDIX I – Names of Study Personnel

Sponsor:	Shanghai Pharma Biotherapeutics USA Inc. 3545 John Hopkins Ct., Ste 160 San Diego, CA 92121 Phone: +1 858-775-5354
Medical Monitor:	Gabriela Radulescu, MD Alimentiv Inc. 100 Dundas Street, Suite 200 London ON N6A 5B6 Canada +1 226-270-7868
Clinical Research Organizations:	Alimentiv Inc. 100 Dundas Street, Suite 200 London ON N6A 5B6 Canada +1 226-270-7868
Central Laboratory:	Cerba Research 5 Delaware Dr Ste 2 New Hyde Park, NY, 11042-1100 +1 516-719-1052

19.2 APPENDIX II – Declaration of Helsinki

https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles

for

Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly

Helsinki, Finland, June 1964

and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)

55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)

59th WMA General Assembly, Seoul, Republic of Korea, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

PREAMBLE

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

GENERAL PRINCIPLES

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable

international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

RISKS, BURDENS AND BENEFITS

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

VULNERABLE GROUPS AND INDIVIDUALS

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

SCIENTIFIC REQUIREMENTS AND RESEARCH PROTOCOLS

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

RESEARCH ETHICS COMMITTEES

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers

must submit a final report to the committee containing a summary of the study's findings and conclusions.

PRIVACY AND CONFIDENTIALITY

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

INFORMED CONSENT

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

USE OF PLACEBO

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

POST-TRIAL PROVISIONS

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

RESEARCH REGISTRATION AND PUBLICATION AND DISSEMINATION OF RESULTS

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

UNPROVEN INTERVENTIONS IN CLINICAL PRACTICE

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.