PROTOCOL: SHP681-101

TITLE:	A Randomized, Double-blind, Placebo-controlled, Phase 1 Study to Assess the Safety, Tolerability, and Pharmacokinetics of Ascending, Subcutaneous, Single and Multiple Doses of SHP681 (GLP-2 analog-Fc fusion) in Healthy Adult Subjects
DRUG:	SHP681 (Glucagon-like peptide-2 (GLP-2) analog-Fc fusion protein)
IND:	139424
EUDRACT NO.:	Non-EUDRACT
SPONSOR:	Shire Human Genetic Therapies, Inc. (Shire) 300 Shire Way, Lexington, MA 02421 USA
PRINCIPAL/ COORDINATING INVESTIGATOR:	[redacted]
PROTOCOL HISTORY:	Original Protocol: 29 Oct 2018 Amendment 1: 11 Feb 2019 Amendment 2: 10 May 2019 Amendment 3: 08 Oct 2019 Amendment 4: 19 Nov 2019

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [redacted]	Date: [redacted]

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP681-101.

Title: A Randomized, Double-blind, Placebo-controlled, Phase 1 Study to Assess the Safety, Tolerability, and Pharmacokinetics of Ascending, Subcutaneous, Single and Multiple Doses of SHP681 (GLP-2 analog-Fc fusion) in Healthy Adult Subjects

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)	_____
	_____
	_____

Signature: _____ **Date:** _____

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **4**	**Amendment Date** **19 Nov 2019**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
Changed the Medical Monitor to [redacted]		Protocol Signature Page, Emergency Contact Information
Corrected oversights from previous amendment: • Corrected the total number of subjects to 102 and the number of MAD subjects to 72. • Added the interim analysis of first 3 SAD cohorts that was included the body of protocol.		Synopsis
Extended the planned study period.		Synopsis
An interim analysis was performed after the last subject from the 3rd MAD cohort completed the Day 39 visit, to determine the dose level of the 6th MAD cohort, and to assess safety and pharmacodynamics, [redacted]. The absorption of TAK-681 following SC dosing was slow, with absorption half-life ranging from 12.7 hours to 30.7 hours. The apparent clearance and volume of distribution were 0.105 L/hours and 14.3 L, respectively. The mean elimination half-life of TAK-681 ranged from 89.8 hours to 104 hours (ie, 3.7 days to 4.3 days) across dose levels. TAK-681 PK properties were observed to be linear and time-independent. Using a noncompartmental analysis, the area under the concentration-time curve from time zero to infinity of TAK-681 after multiple doses increased in a dose-proportional manner from 0.2 mg/kg to 1 mg/kg. Based on these results, a dose of 4 mg/kg SHP681 (or placebo) every 2 weeks over a 6-week period (3 doses) was nominated for the 6th MAD cohort.		Synopsis, Section 3.1.1, Section 6.2.2
One subject in the 2 mg/kg MAD cohort developed a progressive rise in aminotransferases, total and direct bilirubin, and alkaline phosphatase during the 5-week treatment period, consistent with an idiosyncratic mixed cholestatic and hepatocellular injury pattern. Ultrasound and magnetic resonance cholangiopancreatography showed stones and sludge within the gallbladder which were likely present at baseline. The relationship of these gallbladder findings and the liver injury is unclear. To minimize ambiguity in safety assessments in the final MAD cohort, the following exclusion criteria has been added: 20. Findings of subclinical hepatobiliary disease, such as gallstones, on abdominal ultrasound at screening as determined by the Investigator in consultation with the Medical Monitor.		Synopsis, Section 4.2

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **4**	**Amendment Date** **19 Nov 2019**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
Abnormal gallbladder wall thickness and gallbladder diameter which were noted in the subject above may be related to pharmacodynamic effects of SHP681. To characterize changes in the biliary tree caused by SHP681, abdominal ultrasound will be obtained during screening and at the end of treatment in the final MAD cohort.		Table 7, Table 10, Table 11, Section 3.1.2, Section 7.2.2.10, Section 9.9
Removed the analysis of crypt depth as this data was not collected.		Synopsis, Section 9.10
Clarified that PK samples drawn beyond Day 2 cannot deviate by more than ±10% of the specified time from the first dose.		Table 7, Table 9, Table 10, Section 7.1, Section 7.2.3
Deleted the Day 43 abbreviated physical exam to be consistent with MAD cohorts 1-5 and overall schedule of assessments for MAD cohort 6.		Table 7
The visit windows were updated to allow for subject flexibility.		Table 7, Table 9, Table 10
Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made.		Throughout the protocol

See Appendix 1 for protocol history, including all amendments.

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form within 24 hours to the Shire Global Drug Safety Department. Applicable fax numbers and e-mail address (drugsafety@shire.com) can be found on the form (sent under separate cover). A copy of this form must also be sent to the contract research organization (CRO)/Shire medical monitor by fax or e-mail using the details below.

For protocol- or safety-related issues, the investigator must contact the Shire medical monitor:

[redacted]

Telephone (24-hour coverage):

[redacted]

ADDITIONAL CONTACT INFORMATION

In case of any other issues, including non-safety-related issues or if the medical monitor is unable to be reached, the investigator must contact the Shire Study Lead:

[redacted]

Telephone:

[redacted] (business hours)

[redacted] (24-hour coverage)

If unavailable, please contact:

[redacted]

Telephone:

[redacted] (business hours)

[redacted] (24-hour coverage)

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 8.

Please use the information below as applicable to report the Product Quality Complaint:

Origin of Product Quality Complaint	E-mail Address
North and South America	[redacted]
European Union and Rest of World	[redacted]

Telephone numbers (provided for reference if needed):

Shire, Lexington, MA (USA)

[redacted]

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ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
β-hCG	beta-human chorionic gonadotropin
CRC	clinical research center
CRF	case report form
CRO	contract research organization
DMC	data monitoring committee
EC	ethics committee
ECG	electrocardiogram
EU	European Union
FDA	Food and Drug Administration
FIH	first in human
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IP	investigational product
IRB	Institutional Review Board
MAD	multiple ascending dose
nADA	neutralizing anti-drug antibody
PK	pharmacokinetic
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SBS	short bowel syndrome
US	United States

STUDY SYNOPSIS

Protocol number: SHP681-101	**Drug:** SHP681
Title of the study: A Randomized, Double-blind, Placebo-controlled, Phase 1 Study to Assess the Safety, Tolerability, and Pharmacokinetics of Ascending, Subcutaneous, Single and Multiple Doses of SHP681 (GLP-2 analog-Fc fusion) in Healthy Adult Subjects	
Number of subjects (total and for each treatment arm): A total of 102 subjects (30 for the single ascending dose [SAD] portion and 72 subjects for the multiple ascending dose [MAD] portion) are planned to be enrolled for this study.	
Investigator(s): [redacted]	
Site(s) and Region(s): [redacted]	
Study period (planned): Feb 2019-Jan 2020	**Clinical phase:** 1

Objectives:

Primary: To assess the safety and tolerability of single and multiple, ascending, subcutaneous (SC) doses of SHP681 in healthy adult subjects

Secondary: To characterize the pharmacokinetics (PK) of SHP681 following single and multiple, ascending SC doses in healthy adult subjects

Rationale:

SHP681 has been engineered with a significant half-life extension compared to teduglutide. This extended half-life is expected to allow once weekly injection with similar safety and efficacy as teduglutide.

The present study is a first in human study to assess the safety, tolerability, and pharmacokinetics of SHP681 when administered as single and multiple ascending SC doses.

Investigational product, dose, and mode of administration:

- Investigational product (IP): SHP681 refers to a glucagon-like peptide-2 (GLP-2) analog-Fc fusion protein, abbreviated as GLP-2 analog-Fc fusion. The IP will be referred to as SHP681 through this document
- SAD portion of the study- Dose escalation with single SC doses of SHP681: 0.2 mg/kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg, and 4 mg/kg vs. placebo.
- MAD portion of the study- Sequential dose escalation of SC doses of SHP681: 0.2 mg/kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg, and 4 mg/kg. Each of the first 5 MAD cohorts will receive SHP681 (or placebo) once weekly for 5 weeks. The 6th MAD cohort will receive 4 mg/kg SHP681 once every 2 weeks for 6 weeks (3 doses).
- All subjects (both SAD and MAD portions) will have the IP administered in the abdomen.

Methodology:

SAD- Part 1: The plan is to enroll 30 subjects in 5 cohorts. Each cohort will include 6 subjects. Subjects will be randomized within each cohort such that 5 subjects receive SHP681 and 1 subject receives placebo. Dose escalation will proceed sequentially to assess the following SC doses of SHP681: 0.2 mg/kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg, and 4 mg/kg. After a single administration of SHP681 or placebo in each cohort, if the dose is assessed as safe and tolerable during a dose escalation meeting, the next cohort will be administered a SC dose of SHP681 at the next higher dose level or placebo. During dose escalation, protocol defined dose levels may be reduced, repeated, discontinued, or an intermediate increase may be added depending on the outcome of the blinded safety data review between dose escalations. Upon completion of these 5-dose cohorts, additional doses may be studied based on emergent safety data.

The study duration of the SAD portion of the study will consist of a screening period of up to 28 days and

1 treatment period of 29 days. A total of 8 overnight stays are required for the SAD portion of the study. Blood samples for pharmacokinetic analysis of SHP681 will be collected through 672 hours post dose in each dosing period. The last study visit is scheduled at Day 29 and will include final safety assessments; there will be no further follow up.

MAD- Part 2: This portion of the study may initiate upon completion of a pharmacokinetic and safety data review of SAD Cohort 1, SAD Cohort 2, and partial data from SAD Cohort 3 (see Part 1). The plan is to enroll 72 subjects within 6 MAD cohorts. Each cohort will include 12 subjects. Subjects will be randomized within each cohort such that 10 subjects receive SHP681 and 2 subjects receive placebo.

Subjects in each of the first 5 cohorts will receive SHP681 (or placebo) once weekly for 5 weeks. After the first cohort has been administered 2 doses of SHP681 (or placebo) over 2 weeks and the dose is assessed as safe and tolerable during a dose escalation meeting, the next MAD cohort will commence. Dose escalation will proceed sequentially to include the following SC doses: 0.2 mg/kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg, and 4 mg/kg. During dose escalation, protocol defined dose levels may be reduced, repeated, discontinued, or an intermediate increase may be added depending on the outcome of the blinded safety data review between dose escalations.

An interim analysis was performed after the last subject from the 3rd MAD cohort completed the Day 39 visit, to determine the dose level of the 6th MAD cohort, and to assess safety and pharmacodynamics. [redacted]. The absorption of TAK-681 following SC dosing was slow, with absorption half-life ranging from 12.7 hours to 30.7 hours. The apparent clearance and volume of distribution were 0.105 L/hours and 14.3 L, respectively. The mean elimination half-life of TAK-681 ranged from 89.8 hours to 104 hours (ie, 3.7 days to 4.3 days) across dose levels. TAK-681 PK properties were observed to be linear and time-independent. Using a noncompartmental analysis, the area under the concentration-time curve from time zero to infinity of TAK-681 after multiple doses increased in a dose-proportional manner from 0.2 mg/kg to 1 mg/kg. Based on these results, a dose of 4 mg/kg SHP681 (or placebo) every 2 weeks over a 6-week period (3 doses) was nominated for the 6th MAD cohort.

The study duration of the MAD portion will comprise of a screening period up to 28 days and a treatment period of 57 days for each cohort. A total of 21 overnight stays are required for the first 5 cohorts and 16 overnight stays are required for the 6th cohort for this portion. The inhouse period may be revised due to operational issues pending approval by the PI and Sponsor.

For the first 5 cohorts, blood samples for pharmacokinetic analysis of SHP681 will be collected over 24 hours on Day 1 and at predose on Day 8, Day 15, Day 22, and Day 29 in each treatment period. On Day 29, blood samples for the pharmacokinetic analysis of SHP681 will be collected through 672 hours post-last dose in each dosing cohort. The last study visit is scheduled at Day 57 and will include final safety assessments; there will be no further follow up.

For the 6th cohort blood samples for pharmacokinetic analysis of SHP681 will be collected over 24 hours on Day 1 and at predose on Day 15 and Day 29. On Day 29, blood samples for the pharmacokinetic analysis of SHP681 will be collected through 672 hours post-last dose. The last study visit is scheduled at Day 57 and will include final safety assessments; there will be no further follow up.

Inclusion and exclusion criteria:

Inclusion Criteria:

1. Ability to voluntarily provide written, signed, and dated informed consent to participate in the study.
2. An understanding, ability, and willingness to fully comply with study procedures and restrictions.
3. Age 18-50 inclusive at the time of consent. The date of signature of the informed consent is defined as the beginning of the screening period. This inclusion criterion will only be assessed at the first screening visit.
4. Male, or non-pregnant, non-lactating female who agrees to comply with any applicable contraceptive requirements of the protocol or females of non-childbearing potential.
5. Considered "healthy" by the investigator. Healthy status is defined by absence of any active or chronic disease or condition based on a detailed medical and surgical history, a complete physical.
6. Body mass index between 18.0 and 30.0 kg/m^2 inclusive with a body weight 50-100 kg (110-220 lbs). This inclusion criterion will only be assessed at the first screening visit.

Exclusion Criteria:

1. History of any hematological, hepatic, respiratory, cardiovascular, renal, neurological or psychiatric disease, gallbladder removal, or current or recurrent disease that could affect the action, absorption, or disposition of the investigational product, or clinical or laboratory assessments.
2. Current or relevant medical history of physical or psychiatric illness, any medical disorder that may require treatment or render the subject unlikely to complete the study, or any condition that presents undue risk from the investigational product or procedures.
3. Known or suspected intolerance or hypersensitivity to the investigational product(s), closely-related compounds, or any of the stated ingredients.
4. Significant illness, as judged by the investigator, within 2 weeks of the first dose of investigational product.
5. Known history of alcohol or other substance abuse within the last year.
6. Donation of blood or blood products (eg, plasma or platelets) within 60 days prior to receiving the first dose of investigational product.
7. Within 30 days prior to the first dose of investigational product:
    a. Have used an investigational product (if elimination half-life is <6 days, otherwise 5 half-lives).
    b. Have been enrolled in a clinical study.
    c. Have had any substantial changes in eating habits, as assessed by the investigator.
8. Use of DPP-4 inhibitors within 30 days or 5 half-lives, whichever is greater, prior to administration of the investigational product.
9. Confirmed systolic blood pressure >139mmHg or <89mmHg, and diastolic blood pressure >89 mmHg or <49 mmHg.
10. Twelve-lead ECG demonstrating QTcF >450 msec at screening. If QTcF exceeds 450 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF values should be used to determine the subject's eligibility.
11. Positive screen for alcohol or illicit drugs at screening or Day -1.
12. Male subjects who consume more than 21 units of alcohol per week or 3 units per day. Female subjects who consume more than 14 units of alcohol per week or 2 units per day. (1 alcohol unit=1 beer or 1 wine (5 oz/150 mL) or 1 liquor (1.5 oz/40 mL) or 0.75 oz alcohol).
13. Positive HIV, HBsAg, or HCV antibody screen.
14. Use of tobacco in any form (eg, smoking or chewing) or other nicotine-containing products in any form (eg, gum, patch). Ex-users must report that they have stopped using tobacco for at least 30 days prior to receiving the first dose of investigational product.
15. Routine consumption of more than 2 units of caffeine per day or subjects who report developing headaches associated with caffeine withdrawal. (1 caffeine unit is contained in the following items: one 6 oz (180 mL) cup of coffee, two 12 oz (360 mL) cans of cola, one 12 oz cup of tea, three 1 oz (85 g) chocolate bars. Decaffeinated coffee, tea, or cola are not considered to contain caffeine).
16. Prior screen failure (unless Sponsor approval is given), randomization, participation, or enrollment in this study or prior exposure to any GLP-2 analogs.
17. Unresected GI polyp, known polyposis condition, or premalignant changes in the GI tract.
18. Any history of malignancy in the GI tract or treatment for any other malignancy in the previous 5 years.
19. Current use of any medication (including over-the-counter, herbal, or homeopathic preparations; with the exception of hormonal replacement therapy or hormonal contraceptives and occasional use of ibuprofen or acetaminophen and pre-approved medication for sedation or other medications required during or after the endoscopy). Current use is defined as use within 14 days of the first dose of investigational product.
20. Findings of subclinical hepatobiliary disease, such as gallstones, on abdominal ultrasound at screening as determined by the Investigator in consultation with the Medical Monitor.

Maximum duration of subject involvement in the study:

SAD-Part1

- *Planned duration of screening period: 28 days*
- *Planned duration of treatment period: 29 days*

  The maximum total duration of study participation for a subject is 57 days (approximately 2 months)

MAD-Part2

- *Planned duration of screening period: 28 days*
- *Planned duration of treatment period: 57 days*

  The maximum total duration of study participation for a subject is 85 days (approximately 3 months)

Endpoints and statistical analysis:

Endpoints and Statistical Analysis

Subject populations are separately defined to analyze the data in the SAD portion and the MAD portion:

SAD

- The SAD safety analysis data set includes subjects who have received at least 1 dose of SHP681or placebo in the SAD portion.
- The SAD PK analysis data set consists of subjects who have received at least 1 dose of SHP681 and have at least 1 evaluable post-dose PK concentration value in the SAD portion.

MAD

- The MAD safety analysis data set includes subjects who have received at least 1 dose of SHP681or placebo in the MAD portion.
- The MAD PK analysis data set consists of subjects who have received at least 1 dose of SHP681 and have at least 1 evaluable post-dose PK concentration value in the MAD portion.

Pharmacokinetic Endpoints:

- Pharmacokinetic parameters including exposure and property parameters will be calculated for individual subjects using plasma SHP681 concentration-time data and non-compartmental analysis for both SAD and MAD parts and all calculations will be based on actual sampling times. Effect of anti-drug antibody (ADA) and neutralizing anti-drug antibody (nADA) on PK will be evaluated.

The PK analysis will be based on the PK analysis set.

Pharmacokinetic parameters will be calculated from plasma SHP681 concentration-time data using non-compartmental methods and all calculations will be based on actual sampling times. Pharmacokinetic parameters will include, but not be limited to, the following:

SAD

- C_{max}: Maximum concentration occurring at t_{max}
- t_{last}: Time of the last measurable concentration
- t_{max}: Time of maximum observed concentration sampled during a dosing interval
- $AUC_{0\text{-}last}$: Area under the curve from the time of dosing to the last measurable concentration
- $AUC_{0\text{-}\infty}$: Area under the curve extrapolated to infinity
- $t_{1/2}$: Terminal half-life
- λ_z: First order rate constant associated with the terminal (log-linear) portion of the curve
- CL/F: Apparent total body clearance for extravascular administration divided by the fraction of dose absorbed calculated as dose divided by AUC0-$_\infty$.
- V_z/F: Apparent volume of distribution following extravascular administration divided by the fraction of dose absorbed calculated as CL/F divided by λ_z.

MAD

Post first dose

- AUC_{0-24}: Area under the curve from the time of dosing to the 24 hours post first dose
- $C_{max,24}$: Maximum concentration occurring during 24 hours after first dose
- $t_{max,24}$: Time of maximum observed concentration during 24 hours after first dose

Between the first dose and last dose

- C_{trough}: Observed concentration at the end of each dosing interval (immediately before next dose for the first 5 cohorts and immediately before 2nd and 3rd dose of the 6th MAD cohort)

Post last dose

- C_{max}: Maximum concentration during the dosing interval occurring at t_{max}
- T_{last}: Time of the last measurable concentration
- t_{max}: Time of maximum observed concentration during the dosing interval
- AUC_{tau}: Area under the curve for the defined interval between doses (only calculated if interpretable)
- AUC_{0-last}: Area under the curve from the time of dosing to the last measurable concentration post last dose
- $AUC_{0-\infty}$: Area under the curve (post last dose) extrapolated to infinity, calculated using the observed value of the last non-zero concentrations (only calculated if interpretable)
- $t_{1/2}$ Terminal half-life
- λ_z First order rate constant associated with the terminal (log-linear) portion of the curve
- CL/F Apparent total body clearance following extravascular administration divided by the fraction of dose absorbed calculated as dose divided by AUC_{tau}
- V_z/F Apparent volume of distribution following extravascular administration divided by the fraction of dose absorbed calculated as CL/F divided by λ_z

Safety Endpoints:

For both the SAD and MAD portions, the safety and tolerability of escalating SC doses of SHP681 will be evaluated by examining for each cohort: number, severity, seriousness and causality of all treatment-emergent adverse events (TEAEs), including injection site and hypersensitivity reactions, changes in vital signs, ECGs, abdominal ultrasounds, and clinical laboratory results (hematology, chemistry, and urinalysis) from baseline to post-baseline timepoints, incidence of anti-drug antibodies (ADA) to SHP681 and incidence of neutralizing anti-drug antibodies (nADA) to SHP681.

Sample Size Justification:

SAD

It is planned that dose escalation will proceed for up to 5 dose levels. Each cohort will include 5 subjects treated with SHP681 and 1 subject treated with placebo for a planned total of 30 subjects. However, if dose levels are repeated, modified, or not conducted or if additional dose levels are studied, the total number of subjects may change. The number of subjects is expected to provide reasonable information on initial testing of SHP681 for safety and PK while exposing as few subjects as possible to investigational drug materials. The number of subjects in this study is not based on statistical hypothesis testing and power considerations as this is the first in human study. The statistical analyses are primarily descriptive, and no hypothesis testing is specified for this portion.

MAD

It is planned that the MAD portion of the study will include 6 cohorts. Each cohort will include 10 subjects treated with SHP681 and 2 subjects treated with placebo for a planned total of 72 subjects. The number of subjects is expected to provide reasonable information on initial testing of SHP681 for safety and PK while exposing as few subjects as possible to investigational drug materials. The number of subjects in this study is not based on

statistical power considerations as this is the first time in human study. The statistical analyses are primarily descriptive, and no hypothesis testing is specified in the study.

Exploratory Endpoints:

[redacted]

Statistical Methodology for Safety Endpoints:

For both SAD and MAD, statistical analysis of safety data will be based on the safety analysis data set for the portion. Safety data will be listed by subject and summarized for each dose cohort of SHP681 and a pooled placebo group of all subjects who were administered placebo, using descriptive statistics.

Continuous variables will be summarized by sample size, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized by number of subjects and the percent of subjects in each category.

Treatment-emergent adverse events will be analyzed for each dose cohort, using the number and percentage of subjects reporting events, as well as the number of events, by system organ class and preferred term, severity, and causal relationship to the study treatment. Injection site reactions will be analyzed in an analogous fashion. Laboratory tests, vital signs, and ECG assessments and corresponding changes from baseline in each dose cohort will be summarized by study visit where baseline will be defined as the last non-missing assessment prior to the first dose. Immunogenicity in each dose cohort will be analyzed by number and percent of subjects testing positive for ADA or nADA predose and by post-dose study visit. The results of abdominal ultrasound tests will be listed.

Statistical Methodology for Pharmacokinetic Endpoints:

Pharmacokinetics of SHP681 following single dose will be characterized based on information collected during the **SAD portion** as follows:

- All individual concentration data (using nominal timepoints) and pharmacokinetic parameters following single dosing will be listed for each subject and dose cohort together with descriptive summary statistics such as geometric mean, median, arithmetic mean, standard, deviation, coefficient of variation, and geometric coefficient of variation, minimum and maximum grouped by dose cohort. The time until C_{max} is reached (ie, t_{max}) will be also listed for each subject and summarized by medians, minimum and maximum grouped by dose cohort. The number of timepoints of the terminal log-linear phase used to estimate the terminal rate constant and the residual area will be also provided for each subject and dose cohort.

Pharmacokinetics of SHP681 following multiple ascending doses will be based on information collected during the **MAD portion** as follows:

- All individual concentration data (using nominal timepoints) and pharmacokinetic parameters following dosing will be listed for each subject and dose cohort together with descriptive summary statistics such as geometric mean, median, arithmetic mean, standard, deviation, coefficient of variation, and geometric coefficient of variation, minimum and maximum grouped by dose cohort. The time until $C_{max,24}$ and C_{max} is reached (ie, $t_{max;24}$ and t_{max}) will be also listed for each subject and treatment and summarized by medians, minimum and maximum grouped by dose cohort. The number of timepoints of the terminal log-linear phase used to estimate the terminal rate constant following repeat dosing will be also provided for each subject and dose cohort.

Statistical Methodology for Exploratory Endpoints:

[redacted]

Interim Analysis

To support an initiation of the MAD phase and confirm the dosing interval, an interim data analysis will be required. Blinded plasma data obtained after dosing in Cohort 1, Cohort 2, and part of Cohort 3 in the SAD portion will be evaluated and justified for this purpose.

An interim analysis will be performed after the last patient from the 3rd MAD cohort has completed the Day 39 visit, to determine the dose level of the 6th MAD cohort, and to assess any safety, tolerability, or pharmacokinetic questions based on the safety review. The data for this analysis will be source data verified and cleaned according to the Interim Snapshot Plan. This analysis will unblind all completed SAD cohorts and the first 3 MAD cohorts for the Sponsor. MAD cohorts 4, 5 and 6 will not be unblinded to any parties due to this interim analysis.

STUDY SCHEDULE(S)

Table 1 Schedule of Assessments (SAD Portion)

Visit	Screening		Treatment Period (All Cohorts)										
Study Day	**–28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**11**	**15**	**22**	**29**
Informed consent	X												
Inclusion/exclusion criteria	X	X											
Demographics and medical/medication history	X												
Physical examination (Including Height and Weight)[a,b]	X	X							X				X
Vital signs (body temperature, blood pressure, pulse)[a,c]	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (12-lead)[a, d]	X	X	X	X	X				X				X
Biochemistry, hematology, and urinalysis[a, j, l]	X	X	X		X				X		X[m]		X
HIV, HBsAg, and HCV antibodies	X												
Pregnancy test (women only)[a, e]	X	X							X	X	X	X	X
Urine drug and alcohol screening[f]	X	X								X	X	X	X
Randomization			X[i]										
SHP681 or placebo administration			X										
Pharmacokinetic blood sampling[g]			X	X	X	X	X	X	X	X	X	X	X
ADA and nADA sampling			X										X
Admit to CRC		X											
Discharge from CRC[h]									X				
Outpatient visit										X[k]	X[k]	X[k]	X[k]
Adverse events/serious adverse events[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication[a]	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1 Schedule of Assessments (SAD Portion)

Visit	Screening		Treatment Period (All Cohorts)										
Study Day	–28 to -2	-1	1	2	3	4	5	6	8	11	15	22	29

β-hCG=beta human chorionic gonadotropin; CRC=clinical research center; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus
[a] In the event a subject prematurely withdraws or is discontinued from the study, every attempt should be made to complete these assessments.
[b] Height will be recorded at the screening visit only.
[c] Vital signs will be obtained while the subject is seated for 5 minutes on study days noted. Oral temperature should be taken by placing a digital thermometer under the tongue for at least 30 seconds and the temperature reported in degrees Celsius. Tympanic temperature may also be used. Whichever procedure is used should be the same procedure throughout the study.
[d] 12-lead electrocardiograms will be performed at each timepoint; these assessments should be performed within 15 minutes of the planned timepoint. The subject should not have exercised or consumed caffeine, alcohol, or nicotine within 30 minutes prior to collection. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG.
[e] Serum β-hCG test at screening is required for all women. Urine pregnancy test is required for all women at subsequent scheduled timepoints
[f] Drugs of abuse at screening and drugs of abuse and alcohol on Day -1, Day 11, Day 15, Day 22, and Day 29; a breathalyzer test for alcohol may be done if more convenient than a urine alcohol test.
[g] See Table 2 for detailed collection timepoints.
[h] Subject to be discharged following the completion of all assessments on Day 8.
[i] Randomization to SHP681 or placebo will occur on Day -1 or Day 1 only.
[j] Urine collections should be from the first void of the day while the subjects are confined to the unit; during outpatient visits, urine may be obtained at any time during the visit.
[k] A window of +/- 1 day is allowed for outpatient visits on Days 11, 15, 22, and 29 to allow for subject flexibility.
[l] Full thyroid panel (T3, T4, TSH, Free T3 and Thyroxine-binding globulin [TBG]) on Day 1 (Predose), Day 8 and Day 15.
[m] On Day 15, only a full thyroid panel (T3, T4, TSH, Free T3, and Thyroxine-binding globulin [TBG]) will be collected.

Table 2 Detailed Schedule of Assessments for SAD

Study Day	**Day 1**					**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 8**	**Day 11**	**Day 15**	**Day 22**	**Day 29**
Hour (relative to dosing time)	**Pre dose**	**0**	**3**	**6**	**12**	**24**	**48**	**72**	**96**	**120**	**168**	**240**	**336**	**504**	**672**
Physical examination (Including Height and Weight)[a, b]											X				X
Vital signs (body temperature , blood pressure, pulse)[a, c]	X[e]		X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (12-lead)[a,d]	X[e]		X	X	X	X	X				X				X
Biochemistry, hematology, and urinalysis[a, f, g]	X[e]						X				X		X[h]		X
SHP681 or placebo administration		X													
Pharmacokinetic blood sampling	X[e]		X	X	X	X	X	X	X	X	X	X	X	X	X
ADA and nADA blood sampling	X[e]														X
Adverse events/serious adverse events[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] In the event a subject is prematurely discontinued from the study or withdraws, every attempt should be made to complete these assessments.

[b] Height will be recorded at the screening visit only.

[c] Vital signs will be obtained while the subject is seated for 5 minutes on study days noted. Oral temperature should be taken by placing a digital thermometer under the tongue for at least 30 seconds and the temperature reported in degrees Celsius. Tympanic temperature may also be used. Whichever procedure is used should be the same procedure throughout the study.

[d] 12-lead electrocardiograms will be performed at each timepoint; the subject should not have exercised or consumed caffeine, alcohol, or nicotine within 30 minutes prior to collection. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG.

[e] These assessments should be performed within 30 minutes prior to dose administration.

[f] Urine collections should be from the first void of the day while the subjects are confined to the unit; during outpatient visits, urine may be obtained at any time during the visit.

[g] Full thyroid panel (T3, T4, TSH, Free T3 and Thyroxine-binding globulin [TBG]) on Day 1 (Predose), Day 8 and Day 15.

[h] On Day 15, only a full thyroid panel (T3, T4, TSH, Free T3, and Thyroxine-binding globulin [TBG]) will be collected.

Table 3 Schedule of Assessments (MAD Portion for Cohorts 1-5)-Part 1

Visit	Screening		Treatment Period (Cohorts 1-5)												
Study Day	**–28 to -2**	**-1**	**1**	**2**	**3**	**4**	**7**	**8**	**10**	**14**	**15**	**18**	**21**	**22**	**24**
Informed consent	X														
Inclusion/exclusion criteria	X	X													
Demographics and medical/medication history	X														
Physical examination (Including Height and Weight) [a,b]	X	X				X	X[k]			X[k]			X[k]		
Vital signs (body temperature, blood pressure, pulse)[a,c]	X	X	X	X	X	X	X	X		X	X		X	X	
Electrocardiogram (12-lead)[a,d]	X	X	X	X	X	X		X			X			X	
Biochemistry, hematology, and urinalysis[a,l]	X	X	X		X	X		X			X			X	
HIV, HBsAg, and HCV antibodies	X														
Pregnancy test (women only)[a, e]	X	X				X	X		X	X		X	X		X
Urine drug and alcohol screening[f]	X	X					X			X			X		
Randomization			X[j]												
SHP681 or placebo administration			X					X			X			X	
Pharmacokinetic blood sampling[g]			X	X				X			X			X	
ADA and nADA blood sampling			X					X			X			X	
[redacted]			X												
Admit to CRC		X					X			X			X		
Discharge from CRC[i]						X			X			X			X
Outpatient visit															
Upper GI endoscopy with biopsy	X														
Adverse events/serious adverse events[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

βhCG=beta human chorionic gonadotropin; CRC=clinical research center; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus

[a] In the event a subject prematurely withdraws or is discontinued from the study, every attempt should be made to complete these assessments.

[b] Height will be recorded at the screening visit only.

[c] Vital signs will be obtained while the subject is seated for 5 minutes on study days noted. Oral temperature should be taken by placing a digital thermometer under the tongue for at least 30 seconds and the temperature reported in degrees Celsius. Tympanic temperature may also be used. Whichever procedure is used should be the same procedure throughout the study.

[d] 12-lead electrocardiograms will be performed at each timepoint; these assessments should be performed within 15 minutes of the planned timepoint. The subject should not have exercised or consumed caffeine, alcohol, or nicotine within 30 minutes prior to collection. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG.

[e] Serum β-hCG test at screening is required for all women. Urine pregnancy test is required for all women at subsequent scheduled timepoints

[f] Drugs of abuse at screening and drugs of abuse and alcohol on Day -1, Day 7, Day 14, Day 21, Day 28; Day 39, Day 43, Day 50, Day 57 a breathalyzer test may be done if more convenient than a urine alcohol test.

[g] See Table 4 and Table 5 for detailed collection timepoints.

[h] Subjects must fast for at least 8 hours prior to collection

[i] Subject to be discharged following the last assessment on study days noted. The inhouse period may be revised due to operational issues pending approval by the PI and Sponsor.

Table 3 Schedule of Assessments (MAD Portion for Cohorts 1-5)-Part 1

Visit	Screening		Treatment Period (Cohorts 1-5)												
Study Day	–28 to -2	-1	1	2	3	4	7	8	10	14	15	18	21	22	24

[j] Randomization to SHP681 or placebo will occur on Day -1 or Day 1 only.
[k] Abbreviated physical exam will be performed (includes minimally general appearance; head, eyes, ears, nose, and throat; cardiovascular; respiratory; neurological; abdomen; and skin) on study days noted.
[l] Urine collections should be from the first void of the day while the subjects are confined to the unit; during outpatient visits, urine may be obtained at any time during the visit.

Table 3 Schedule of Assessments (MAD Portion for Cohorts 1-5)-Part 2

Visit	Treatment Period (Cohorts 1-5)											
Study Day	28	29	30	31	32	33	34	36	39	43	50	57
Informed consent												
Inclusion/exclusion criteria	X											
Demographics and medical/medication history												
Physical examination (Including Height and Weight) [a,b]	X[j]				X			X[j]				X
Vital signs (body temperature, blood pressure, pulse)[a,c]	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (12-lead)[a, d]	X	X	X	X				X				X
Biochemistry, hematology, and urinalysis[a, l]	X	X		X				X				X
HIV, HBsAg, and HCV antibodies												
Pregnancy test (women only)[a, e]	X							X	X	X	X	X
Urine drug and alcohol screening[f]	X								X	X	X	X
Randomization												
SHP681 or placebo administration		X										
Pharmacokinetic blood sampling[g]		X	X	X	X	X	X	X	X	X	X	X
ADA and nADA blood sampling		X						X				X
[redacted]								X				X
Admit to CRC	X											
Discharge from CRC[l]								X				
Outpatient visit									X[m]	X[m]	X[m]	X[m]
Upper GI endoscopy with biopsy								X[k]				
Adverse events/serious adverse events[a]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication[a]	X	X	X	X	X	X	X	X	X	X	X	X

Table 3 Schedule of Assessments (MAD Portion for Cohorts 1-5)-Part 2

Visit	Treatment Period (Cohorts 1-5)											
Study Day	28	29	30	31	32	33	34	36	39	43	50	57

βhCG=beta human chorionic gonadotropin; CRC=clinical research center; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus
[a] In the event a subject prematurely withdraws or is discontinued from the study, every attempt should be made to complete these assessments.
[b] Height will be recorded at the screening visit only.
[c] Vital signs will be obtained while the subject is seated for 5 minutes on study days noted. Oral temperature should be taken by placing a digital thermometer under the tongue for at least 30 seconds and the temperature reported in degrees Celsius. Tympanic temperature may also be used. Whichever procedure is used should be the same procedure throughout the study.
[d] 12-lead electrocardiograms will be performed at each timepoint; these assessments should be performed within 15 minutes of the planned timepoint. The subject should not have exercised or consumed caffeine, alcohol, or nicotine within 30 minutes prior to collection. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG.
[e] Serum β-hCG test at screening is required for all women. Urine pregnancy test is required for all women at subsequent scheduled timepoints.
[f] Drugs of abuse at screening and drugs of abuse and alcohol on Day -1, Day 7, Day 14, Day 21, Day 28, Day 39, Day 43, Day 50, Day 57 a breathalyzer test may be done if more convenient than a urine alcohol test.
[g] See Table 6 for detailed collection timepoints. PK timepoints post day 33 can have a -/+ one day window.
[h] Subjects must fast for at least 8 hours prior to collection
[i] Subject to be discharged following the last assessment on study days noted. The inhouse period may be revised due to operational issues pending approval by the PI and Sponsor.
[j] Abbreviated physical exam will be performed (includes minimally general appearance; head, eyes, ears, nose, and throat; cardiovascular; respiratory; neurological; abdomen; and skin) on study days noted
[k] This procedure will be performed on Day 36 (ie, window of +/-3 days).
[l] Urine collections should be from the first void of the day while the subjects are confined to the unit; during outpatient visits, urine may be obtained at any time during the visit.
[m] A window of +/- 1 day is allowed for outpatient visits on Days 39, 43, 50, and 57 to allow for subject flexibility.

Table 4 Detailed Schedule of Assessments for MAD Cohorts 1-5 (Day 1 to Day 4)

Study Day	**Day 1**					**Day 2**	**Day 3**	**Day 4**
Hour (relative to dosing time)	**Pre dose**	**0**	**3**	**6**	**12**	**24**	**48**	**72**
Physical examination (Including Height and Weight)[a, b]								X[g]
Vital signs (body temperature , blood pressure, pulse)[a, c]	X[f]		X	X	X	X	X	X
Electrocardiogram(12-lead)[a,d]	X[f]		X	X	X	X	X	X
Biochemistry, hematology, and urinalysis[a, h]	X[f]						X	X
SHP681 or placebo administration		X						
Pharmacokinetic blood sampling	X[f]		X	X	X	X		
ADA and nADA blood sampling	X[f]							
[redacted]	X[f]							
Upper GI endoscopy with biopsy								
Adverse events/serious adverse events[a]	X	X	X	X	X	X	X	X
Concomitant medication[a]	X	X	X	X	X	X	X	X

[a] In the event a subject is prematurely discontinued from the study or withdraws, every attempt should be made to complete these assessments.
[b] Height will be recorded at the screening visit only.
[c] Vital signs will be obtained while the subject is seated for 5 minutes on study days noted. Oral temperature should be taken by placing a digital thermometer under the tongue for at least 30 seconds and the temperature reported in degrees Celsius. Tympanic temperature may also be used. Whichever procedure is used should be the same procedure throughout the study.
[d] 12-lead electrocardiograms will be performed at each timepoint; the subject should not have exercised or consumed caffeine, alcohol, or nicotine within 30 minutes prior to collection. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG.
[e] Subjects must fast for at least 8 hours prior to collection.
[f] These assessments should be performed within 30 minutes prior to dose administration.
[g] Abbreviated physical exam will be performed (includes minimally general appearance; head, eyes, ears, nose, and throat; cardiovascular; respiratory; neurological; abdomen; and skin) on study days noted.
[h] Urine collections should be from the first void of the day while the subjects are confined to the unit; during outpatient visits, urine may be obtained at any time during the visit.

Table 5 Detailed Schedule of Assessments for MAD Cohorts 1-5 (Day 7 to Day 22)

Study Day	**Day 7**	**Day 8**		**Day 14**	**Day 15**		**Day 21**	**Day 22**	
Hour (relative to dosing time)	**0**	**Predose**	**0**	**0**	**Predose**	**0**	**0**	**Predose**	**0**
Physical examination (Including Height and Weight)[a, b]	X[g]			X[g]			X[g]		
Vital signs (body temperature , blood pressure, pulse)[a, c]	X	X[f]		X	X[g]		X	X[g]	
Electrocardiogram (12-lead)[a,d]		X[f]			X[g]			X[g]	
Biochemistry, hematology, and urinalysis[a, h]		X[f]			X			X	
SHP681 or placebo administration			X			X			X
Pharmacokinetic blood sampling		X[f]			X[g]			X[g]	
ADA and nADA blood sampling		X[f]			X[g]			X[g]	
[redacted]									
Upper GI endoscopy with biopsy									
Adverse events/serious adverse events[a]	X	X	X	X	X	X	X	X	X
Concomitant medication[a]	X	X	X	X	X	X	X	X	X

[a] In the event a subject is prematurely discontinued from the study or withdraws, every attempt should be made to complete these assessments.
[b] Height will be recorded at the screening visit only.
[c] Vital signs will be obtained while the subject is seated for 5 minutes on study days noted. Oral temperature should be taken by placing a digital thermometer under the tongue for at least 30 seconds and the temperature reported in degrees Celsius. Tympanic temperature may also be used. Whichever procedure is used should be the same procedure throughout the study.
[d] 12-lead electrocardiograms will be performed at each timepoint; the subject should not have exercised or consumed caffeine, alcohol, or nicotine within 30 minutes prior to collection. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG.
[e] Subjects must fast for at least 8 hours prior to collection.
[f] These assessments should be performed within 30 minutes prior to dose administration.
[g] Abbreviated physical exam will be performed (includes minimally general appearance; head, eyes, ears, nose, and throat; cardiovascular; respiratory; neurological; abdomen; and skin) on study days noted.
[h] Urine collections should be from the first void of the day while the subjects are confined to the unit; during outpatient visits, urine may be obtained at any time during the visit.

Table 6 Detailed Schedule of Assessments for MAD Cohorts 1-5 (Day 28 to Day 57)

Study Day	**Day 28**	**Day 29**					**Day 30**	**Day 31**	**Day 32**	**Day 33**	**Day 34**	**Day 36**	**Day 39**	**Day 43**	**Day 50**	**Day 57**
Hour (relative to dosing time)	**0**	**Predose**	**0**	**3**	**6**	**12**	**24**	**48**	**72**	**96**	**120**	**168**	**240**	**336**	**504**	**672**
Physical examination (Including Height and Weight)[a, b]	X[g]								X[g]			X[g]				X
Vital signs (body temperature , blood pressure, pulse)[a, c]	X	X[f]		X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (12-lead)[a,d]	X	X[f]		X	X	X	X	X				X				X
Biochemistry, hematology, and urinalysis[a, i]	X	X[f]						X				X				X
SHP681 or placebo administration			X													
Pharmacokinetic blood sampling		X[f]		X	X	X	X	X	X	X	X	X	X	X	X	X
ADA and nADA blood sampling		X[f]										X				X
[redacted]												X				X
Upper GI endoscopy with biopsy												X[h]				
Adverse events/serious adverse events[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] In the event a subject is prematurely discontinued from the study or withdraws, every attempt should be made to complete these assessments.
[b] Height will be recorded at the screening visit only.
[c] Vital signs will be obtained while the subject is seated for 5 minutes on study days noted. Oral temperature should be taken by placing a digital thermometer under the tongue for at least 30 seconds and the temperature reported in degrees Celsius. Tympanic temperature may also be used. Whichever procedure is used should be the same procedure throughout the study.
[d] 12-lead electrocardiograms will be performed at each timepoint; the subject should not have exercised or consumed caffeine, alcohol, or nicotine within 30 minutes prior to collection. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG.
[e] Subjects must fast for at least 8 hours prior to collection.
[f] These assessments should be performed within 30 minutes prior to dose administration.
[g] Abbreviated physical exam will be performed (includes minimally general appearance; head, eyes, ears, nose, and throat; cardiovascular; respiratory; neurological; abdomen; and skin) on study days noted.
[h] This procedure will be performed on Day 36 (ie, window of +/- 3 days).
[i] Urine collections should be from the first void of the day while the subjects are confined to the unit; during outpatient visits, urine may be obtained at any time during the visit.

Table 7 Schedule of Assessments for 6th MAD Cohort (Day 1 to Day 57)

Visit	Screening		Treatment Period (Cohort 6)																				
Study Day	-28	-1	1	2	3	4	8	14	15	18	22[n]	28	29	30	31	32	33	34	36	39	43	50[o]	57[p]
Informed consent	X																						
Inclusion/exclusion criteria	X	X										X											
Demographics and medical/medication history	X																						
Physical examination (Including Height and Weight)[a, b]	X	X				X	X[k]	X			X[k]	X[k]				X			X[k]				X
Vital signs (body temperature, blood pressure, pulse)[a, c]	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (12-lead)[a, d]	X	X	X	X	X	X	X		X		X	X	X	X	X				X				X
Biochemistry, hematology, and urinalysis[a, m]	X	X	X		X	X	X		X		X	X	X		X				X				X
HIV, HBsAg, and HCV antibodies	X																						
Pregnancy test (women only)[a, e]	X	X				X	X	X		X	X	X							X	X	X	X	X
Urine drug and alcohol screening[f]	X	X					X	X			X	X								X	X	X	X
Randomization			X[j]																				
SHP681 or placebo administration			X						X				X										
Pharmacokinetic blood sampling[g]			X	X					X				X	X	X	X	X	X	X	X	X	X	X
ADA and nADA blood sampling			X				X		X		X		X						X				X
[redacted]			X																X				X
Admit to CRC		X						X				X											

Table 7 Schedule of Assessments for 6th MAD Cohort (Day 1 to Day 57)

Visit	Screening		Treatment Period (Cohort 6)																				
Study Day	**-28**	**-1**	**1**	**2**	**3**	**4**	**8**	**14**	**15**	**18**	**22 [n]**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**36**	**39**	**43**	**50 [o]**	**57 [p]**
Discharge from CRC[i]						X				X									X				
Outpatient visit							X				X									X	X	X	X
Upper GI endoscopy with biopsy	X																		X[l]				
Abdominal ultrasound[a]		X																	X[l]				
Adverse events/serious adverse events[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

βhCG=beta human chorionic gonadotropin; CRC=clinical research center; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus

[a] In the event a subject prematurely withdraws or is discontinued from the study, every attempt should be made to complete these assessments.

[b] Height will be recorded at the screening visit only.

[c] Vital signs will be obtained while the subject is seated for 5 minutes on study days noted. Oral temperature should be taken by placing a digital thermometer under the tongue for at least 30 seconds and the temperature reported in degrees Celsius. Tympanic temperature may also be used. Whichever procedure is used should be the same procedure throughout the study.

[d] 12-lead electrocardiograms will be performed at each timepoint; these assessments should be performed within 15 minutes of the planned timepoint. The subject should not have exercised or consumed caffeine, alcohol, or nicotine within 30 minutes prior to collection. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG.

[e] Serum β-hCG test at screening is required for all women. Urine pregnancy test is required for all women at subsequent scheduled timepoints

[f] Drugs of abuse at screening and drugs of abuse and alcohol on the remainder of study days as indicated. A breathalyzer test may be done if more convenient than a urine alcohol test.

[g] See Table 8, Table 9, and Table 10 for detailed collection timepoints. PK samples drawn beyond Day 2 cannot deviate by more than ±10% of the specified time from the first dose.

[h] Subjects must fast for at least 8 hours prior to collection

[i] Subject to be discharged following the last assessment on study days noted. The inhouse period may be revised due to operational issues pending approval by the PI and Sponsor.

[j] Randomization to SHP681 or placebo will occur on Day -1 or Day 1 only.

[k] Abbreviated physical exam will be performed (includes minimally general appearance; head, eyes, ears, nose, and throat; cardiovascular; respiratory; neurological; abdomen; and skin) on study days noted.

[l] This procedure will be performed on Day 36 (window of +/-3 days).

[m] Urine collections should be from the first void of the day while the subjects are confined to the unit; during outpatient visits, urine may be obtained at any time during the visit.

[n] A window of + / - 2 days is allowed for Day 22 visit to allow for subject flexibility.

[o] A window of +/- 3 days is allowed for Day 50 visit to allow for subject flexibility.

[p] A window of +/- 4 days is allowed for Day 57 visit to allow for subject flexibility.

Table 8 Detailed Schedule of Assessments for MAD Cohort 6 (Day 1 to Day 4)

Study Day	**Day 1**					**Day 2**	**Day 3**	**Day 4**
Hour (relative to dosing time)	**Pre dose**	**0**	**3**	**6**	**12**	**24**	**48**	**72**
Physical examination (Including Height and Weight)[a, b]								X[g]
Vital signs (body temperature , blood pressure, pulse)[a, c]	X[f]		X	X	X	X	X	X
Electrocardiogram(12-lead)[a,d]	X[f]		X	X	X	X	X	X
Biochemistry, hematology, and urinalysis[a, h]	X[f]						X	X
SHP681 or placebo administration		X						
Pharmacokinetic blood sampling	X[f]		X	X	X	X		
ADA and nADA blood sampling	X[f]							
[redacted]	X[f]							
Upper GI endoscopy with biopsy								
Adverse events/serious adverse events[a]	X	X	X	X	X	X	X	X
Concomitant medication[a]	X	X	X	X	X	X	X	X

[a] In the event a subject is prematurely discontinued from the study or withdraws, every attempt should be made to complete these assessments.
[b] Height will be recorded at the screening visit only.
[c] Vital signs will be obtained while the subject is seated for 5 minutes on study days noted. Oral temperature should be taken by placing a digital thermometer under the tongue for at least 30 seconds and the temperature reported in degrees Celsius. Tympanic temperature may also be used. Whichever procedure is used should be the same procedure throughout the study.
[d] 12-lead electrocardiograms will be performed at each timepoint; the subject should not have exercised or consumed caffeine, alcohol, or nicotine within 30 minutes prior to collection. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG.
[e] Subjects must fast for at least 8 hours prior to collection.
[f] These assessments should be performed within 30 minutes prior to dose administration.
[g] Abbreviated physical exam will be performed (includes minimally general appearance; head, eyes, ears, nose, and throat; cardiovascular; respiratory; neurological; abdomen; and skin) on study days noted.
[h] Urine collections should be from the first void of the day while the subjects are confined to the unit; during outpatient visits, urine may be obtained at any time during the visit.

Table 9 Detailed Schedule of Assessments for MAD Cohort 6 (Day 8 to Day 22)

Study Day	Day 8	Day 14	Day 15		Day 22[i]
Hour (relative to dosing time)	**0**	**0**	**Predose**	**0**	**0**
Physical examination (Including Height and Weight)[a, b]	X[g]	X[g]			X[g]
Vital signs (body temperature , blood pressure, pulse)[a, c]	X	X	X[f]		X
Electrocardiogram (12-lead)[a,d]	X		X[f]		X
Biochemistry, hematology, and urinalysis[a, h]	X		X[f]		X
SHP681 or placebo administration				X	
Pharmacokinetic blood sampling[j]			X[f]		
ADA and nADA blood sampling	X		X[f]		X
[redacted]					
Upper GI endoscopy with biopsy					
Adverse events/serious adverse events[a]	X	X	X	X	X
Concomitant medication[a]	X	X	X	X	X

[a] In the event a subject is prematurely discontinued from the study or withdraws, every attempt should be made to complete these assessments.
[b] Height will be recorded at the screening visit only.
[c] Vital signs will be obtained while the subject is seated for 5 minutes on study days noted. Oral temperature should be taken by placing a digital thermometer under the tongue for at least 30 seconds and the temperature reported in degrees Celsius. Tympanic temperature may also be used. Whichever procedure is used should be the same procedure throughout the study.
[d] 12-lead electrocardiograms will be performed at each timepoint; the subject should not have exercised or consumed caffeine, alcohol, or nicotine within 30 minutes prior to collection. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG.
[e] Subjects must fast for at least 8 hours prior to collection.
[f] These assessments should be performed within 30 minutes prior to dose administration.
[g] Abbreviated physical exam will be performed (includes minimally general appearance; head, eyes, ears, nose, and throat; cardiovascular; respiratory; neurological; abdomen; and skin) on study days noted.
[h] Urine collections should be from the first void of the day while the subjects are confined to the unit; during outpatient visits, urine may be obtained at any time during the visit.
[i] A window of + / - 2 days is allowed for Day 22 visit to allow for subject flexibility.
[j] PK samples drawn beyond Day 2 cannot deviate by more than ±10% of the specified time from the first dose.

Table 10 Detailed Schedule of Assessments for MAD Cohort 6 (Day 28 to Day 57)

Study Day	**Day 28**	**Day 29**					**Day 30**	**Day 31**	**Day 32**	**Day 33**	**Day 34**	**Day 36**	**Day 39**	**Day 43**	**Day 50[j]**	**Day 57[k]**
Hour (relative to dosing time)	**0**	**Predose**	**0**	**3**	**6**	**12**	**24**	**48**	**72**	**96**	**120**	**168**	**240**	**336**	**504**	**672**
Physical examination (Including Height and Weight)[a, b]	X[g]								X[g]			X[g]				X
Vital signs (body temperature, blood pressure, pulse)[a, c]	X	X[f]		X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (12-lead)[a,d]	X	X[f]		X	X	X	X	X				X				X
Biochemistry, hematology, and urinalysis[a, i]	X	X[f]						X				X				X
SHP681 or placebo administration			X													
Pharmacokinetic blood sampling[l]		X[f]		X	X	X	X	X	X	X	X	X	X	X	X	X
ADA and nADA blood sampling		X[f]										X				X
[redacted]												X				X
Upper GI endoscopy with biopsy												X[h]				
Abdominal ultrasound[a]												X[h]				
Adverse events/serious adverse events[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] In the event a subject is prematurely discontinued from the study or withdraws, every attempt should be made to complete these assessments.
[b] Height will be recorded at the screening visit only.
[c] Vital signs will be obtained while the subject is seated for 5 minutes on study days noted. Oral temperature should be taken by placing a digital thermometer under the tongue for at least 30 seconds and the temperature reported in degrees Celsius. Tympanic temperature may also be used. Whichever procedure is used should be the same procedure throughout the study.
[d] 12-lead electrocardiograms will be performed at each timepoint; the subject should not have exercised or consumed caffeine, alcohol, or nicotine within 30 minutes prior to collection. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG.
[e] Subjects must fast for at least 8 hours prior to collection.
[f] These assessments should be performed within 30 minutes prior to dose administration.
[g] Abbreviated physical exam will be performed (includes minimally general appearance; head, eyes, ears, nose, and throat; cardiovascular; respiratory; neurological; abdomen; and skin) on study days noted.
[h] This procedure will be performed on Day 36 (window of +/-3 days).
[i] Urine collections should be from the first void of the day while the subjects are confined to the unit; during outpatient visits, urine may be obtained at any time during the visit.
[j] A window of +/- 3 days is allowed for Day 50 visit to allow for subject flexibility.
[k] A window of +/- 4 days is allowed for Day 57 visit to allow for subject flexibility.
[l] PK samples drawn beyond Day 2 cannot deviate by more than ±10% of the specified time from the first dose.

Table 11 Early Discontinuation Assessments

Study Procedure	Early Discontinuation Visit[a,b]
Concomitant medications	X
Physical examination (including weight)[c]	X
Vital signs (blood pressure, pulse)[d]	X
Biochemistry, hematology, and urinalysis	X
Pregnancy testing[e]	X
Abdominal ultrasound	X
ADA and nADA blood sampling	X
Adverse events/serious adverse events[f]	X

[a] Rules for data collection when subjects are discontinued from the study are provided in Section 4.5 of the protocol.
[b] The early discontinuation visit will be conducted at 28 (±7) days after the last dose of investigational product
[c] Abbreviated physical exam on all subjects (includes minimally general appearance; head, eyes, ears, nose, and throat; cardiovascular; respiratory; neurological; abdomen; and skin).
[d] Vital signs will be measured with the subject in a seated position using standard methods/equipment at the CPU. Subjects should be in a seated position for at least 5 minutes prior to the procedure. Vital signs should be measured before the collection of blood (eg, safety labs).
[e] A urine pregnancy test will be performed for all female subjects.
[f] All AEs are collected from the time the informed consent is signed through 7 days after the last dose of investigational product. Investigators will report all SAEs that occur ≤30 days after the last dose of investigational product and related SAEs that occur >30 days after the last dose of investigational product to Shire Global Safety Department.

1. BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

SHP681 is the Glucagon-like peptide-2 (GLP-2) analog-Fc fusion protein, abbreviated as GLP-2 analog-Fc fusion. The IP will be called SHP681 through this document.

SHP681, a long acting glucagon like peptide-2 (GLP-2) analog, is being developed for treating patients with short bowel syndrome (SBS).

Short bowel syndrome is a rare, serious, disabling, socially incapacitating, and potentially life-threatening condition (Nightingale and Woodward, 2006) resulting from surgical resection or congenital loss of most of the absorptive surface area of the small intestine (O' Keefe et al., 2006). Short bowel syndrome is characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balances when on a conventionally accepted, normal diet (O' Keefe et al., 2006). Causes of SBS in adults include Crohn's disease, mesenteric ischemia, volvulus, trauma, surgical complications, and cancer.

The prevalence of adults with intestinal failure due to SBS is estimated at 2-4 million, (Bakker et al., 1999; Kelly et al., 2014; Mughal and Irving, 1986) while the incidence of neonatal SBS is estimated at 24.5 per 100,000 live births (Wales et al., 2004). It is estimated that 83% of pediatric cases of SBS begin during infancy (Guarino and De Marco, 2003).

Patients with SBS are highly prone to malnutrition, diarrhea, dehydration, electrolyte disturbances, malabsorption of nutrients, gastric hypersecretion, metabolic acidosis, cholelithiasis, nephrolithiasis, steatorrhea, small bowel bacterial overgrowth and an inability to maintain weight due to the reduced intestinal capacity to absorb macronutrients, water, and electrolytes (Dudrick et al., 1991; Nightingale, 1999; Rombeau and Rolandelli, 1987; Shanbhogue and Molenaar, 1994; Vanderhoof and Langnas, 1997; Wilmore et al., 1997; Nightingale and Woodward, 2006; O' Keefe et al., 2006). Complications common to SBS include d-lactic acidosis, hyperoxaluria, intestinal failure associated liver disease, and anastomotic ulcers.

Short bowel syndrome is the leading cause of intestinal failure, defined as the requirement for parenteral support (intravenous nutrition and/or fluids) to maintain health and/or growth (Pironi et al., 2016). Although parenteral support (PS) is considered life-saving, it is also well associated with serious complications such as catheter-associated bloodstream infections, catheter breakage, central venous thrombosis, metabolic bone disease, and liver disease. The risks of these complications increase commensurately with the duration of intestinal failure, and as a result, patients with intestinal failure have higher mortality rates than those with intestinal insufficiency (Amiot et al., 2013; Goulet et al., 2005).

Some patients with SBS are able to adapt metabolically and compensate for their malabsorption of fluids, electrolytes, trace elements, vitamins, or nutrients by increasing oral/enteral intake (Messing et al., 1999; Jeppesen and Mortensen, 2000) such that they can attain enteral autonomy (independence from parenteral support) even though they continue to have symptoms of malabsorption (intestinal insufficiency).

However, there are limits to the adaptive capacity of the small intestine, especially in cases where the distal ileum and colon have been removed. Such patients often have a compromised adaptive response due in part to deficiency in glucagon-like peptide 2 (GLP-2), a hormone produced by L-type enteroendocrine cells that reside in these segments of bowel.

In response to the presence of unabsorbed nutrients in the distal ileum and colon, L-type enteroendocrine cells release GLP-2, which acts on receptors in sub-epithelial myofibrobasts and enteric neurons. This triggers the release of growth factors that stimulate intestinal epithelial stem cell proliferation and inhibit epithelial apoptosis, resulting in increases in villus height and crypt depth, thereby increasing the absorptive surface area of the remaining gut. Other downstream effects include increases in splanchnic blood flow, inhibition of gastric acid production, and slowing of gastric emptying.

1.2 Product Background

Teduglutide is a recombinant human GLP-2 analog with an Ala2Gly substitution, which increases the half-life from 7 minutes to approximately 2 hours in healthy subjects and 1.3 hours in adult SBS subjects.

SHP681 is a fusion protein containing 2 moieties of teduglutide, a polypeptide linker, and human IgG1Fc. Based on animal models, the predicted half-life in humans for SHP681 is approximately 4 days, which may allow once weekly dosing.

1.2.1 Preclinical Information

SHP681 demonstrated in animal models a longer half-life than teduglutide. The present study is a first in human (FIH) study to assess the safety, tolerability, and pharmacokinetics of SHP681 when administered as single and multiple, ascending subcutaneous (SC) doses.

Refer to the Investigator's Brochure provided under separate cover for more information.

1.2.2 Clinical Information

Teduglutide has been shown in clinical trials to reduce parenteral support requirements in patients with SBS. It is approved in the US (as Gattex®) for the treatment of adults with SBS who are dependent on parenteral support, and in Europe (as Revestive®) for treatment of patients aged 1 year and above with SBS who are stable following a period of intestinal adaptation after surgery. Teduglutide is administered at 0.05 mg/kg subcutaneous once daily.

Always refer to the latest version of the SHP681 investigator's brochure for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics, efficacy, and safety of SHP681.

1.3 Risk/Benefit and Ethical Assessment

There is no anticipated benefit from taking part in this study.

Risks for subject exposure to SHP681 are listed in the current investigator brochure.

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

SHP681 is a long acting glucagon like peptide-2 (GLP-2) analog intended for treating patients with short bowel syndrome (SBS). The current marketed GLP-2 analog product in the US (Gattex®) and the EU (Revestive®) has a half-life of approximately 2 hours in healthy subjects and 1.3 hours in adult SBS subjects and the dose regimen for the indication is SC 0.05 mg/kg daily. SHP681 has been engineered with a significant half-life extension. Based on animal models, the predicted half-life in humans for SHP681 is approximately 4 days, which may allow once weekly dosing. The non-clinical development program of SHP681, which included preclinical pharmacology studies and 1-month GLP toxicity investigation studies, support the first in human testing. The present study is a FIH study to assess the safety, tolerability, and pharmacokinetics of SHP681 when administered as single and multiple ascending SC doses.

2.2 Study Objectives

2.2.1 Primary Objectives

The primary objective for this study is to assess the safety and tolerability of single and multiple, ascending, SC doses of SHP681 in healthy adult subjects.

2.2.2 Secondary Objectives

The secondary objective of this study is to characterize the pharmacokinetics (PK) of SHP681 following single and multiple, ascending SC doses in healthy adult subjects.

2.2.3 Exploratory Objectives

[redacted]

3. STUDY DESIGN

3.1 Study Design and Flow Chart

This study is a randomized, double-blind, placebo-controlled, Phase 1 study to assess the safety and tolerability, and pharmacokinetics of SHP681 following single and multiple, ascending, SC doses in healthy adult subjects. This study will be conducted at a single center and 5 dose levels are planned for both the single-ascending dose (SAD) and multiple-ascending dose (MAD) parts of this study. A total of 102 subjects (30 for the SAD portion and 72 subjects for the MAD portion) are planned to be enrolled for this study.

The plan is to enroll in the SAD portion of the study 30 subjects in 5 cohorts. Each cohort will include 6 subjects. Subjects will be randomized within each cohort such that 5 subjects receive SHP681 and 1 subject receives placebo.

The MAD portion of this study may initiate upon completion of a pharmacokinetic and safety data review of SAD Cohort 1, SAD Cohort 2, and partial data from SAD Cohort 3 (see Part 1). The plan is to enroll 72 subjects within 6 MAD cohorts. Each cohort will include 12 subjects. Subjects will be randomized within each cohort such that 10 subjects receive SHP681 and 2 subjects receive placebo.

The study design is shown in the study schema in Figure 1 and Figure 2.

Figure 1 Study Design Flow Chart for the SAD portion

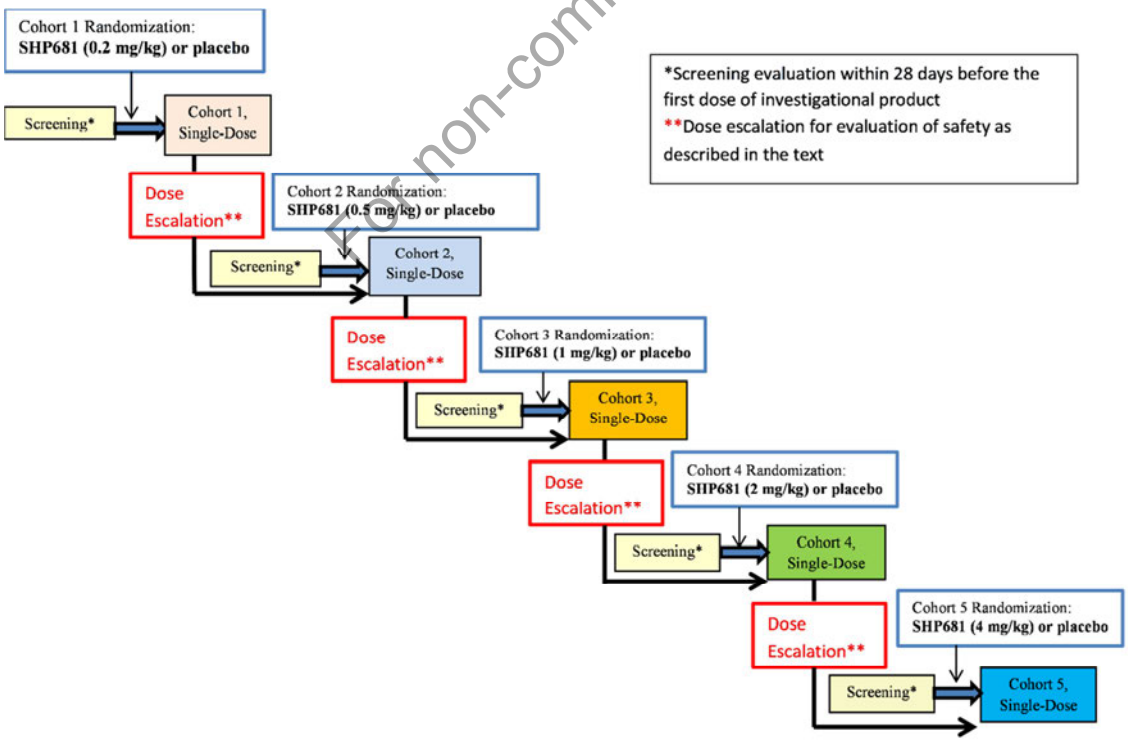
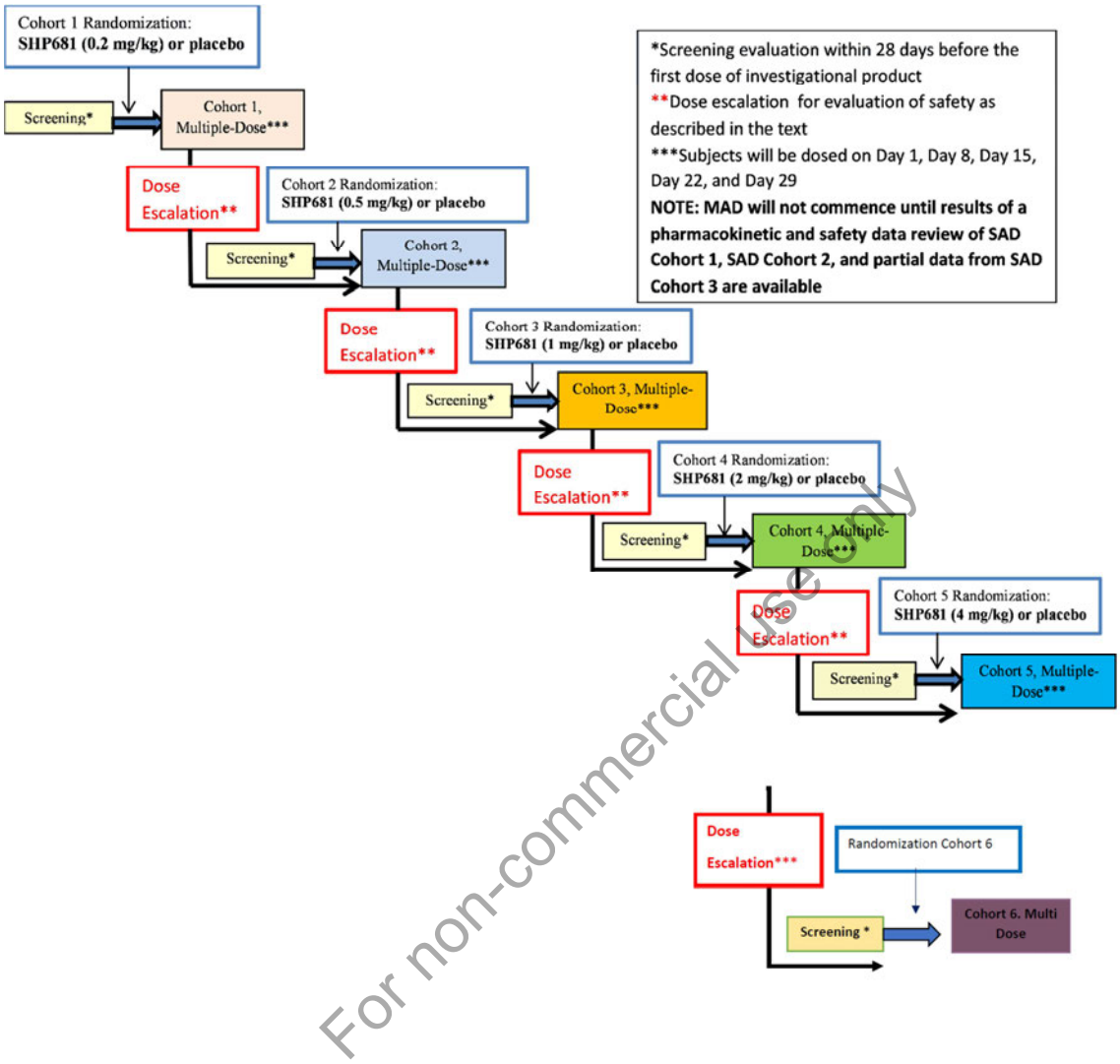


Figure 2 Study Design Flow Chart for the MAD portion



3.1.1 Dose selection, rationale and administration

SAD(Part1)

Dose escalation will proceed sequentially to assess the following SC doses of SHP681: 0.2 mg/kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg, and 4 mg/kg. After a single administration of SHP681 or placebo in each cohort, if the dose is assessed as safe and tolerable during a dose escalation meeting, the next cohort will be administered a SC dose of SHP681 at the next higher dose level or placebo. All subjects will have the IP administered in the abdomen. During dose escalation, protocol defined dose levels may be reduced, repeated, discontinued, or an intermediate increase may be added depending on the outcome of the blinded safety data review between dose escalations. Upon completion of these 5-dose cohorts, additional doses may be studied based on emergent safety data.

MAD (Part 2)

The MAD part will not commence until results of a pharmacokinetic and safety data review of SAD Cohort 1, SAD Cohort 2, and partial data from SAD Cohort 3 are available. Each cohort will receive SHP681 (or placebo) once weekly for 5 weeks. After the first cohort has been administered 2 doses of SHP681 (or placebo) over 2 weeks and the dose is assessed as safe and tolerable during a dose escalation meeting, the next MAD cohort will commence. All subjects will have the IP administered in the abdomen. Dose escalation will proceed sequentially to include the following SC doses: 0.2 mg/kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg, and 4 mg/kg weekly.

An interim analysis was performed after the last subject from the 3rd MAD cohort completed the Day 39 visit, to determine the dose level of the 6th MAD cohort, and to assess safety and pharmacodynamics. As of the interim analysis, TAK-681 was well-tolerated and dose-dependent [redacted]. The absorption of TAK-681 following SC dosing was slow, with absorption half-life ranging from 12.7 hours to 30.7 hours. The apparent clearance and volume of distribution were 0.105 L/hours and 14.3 L, respectively. The mean elimination half-life of TAK-681 ranged from 89.8 hours to 104 hours (ie, 3.7 days to 4.3 days) across dose levels. TAK-681 PK properties were observed to be linear and time-independent. Using a noncompartmental analysis, the area under the concentration-time curve from time zero to infinity of TAK-681 after multiple doses increased in a dose-proportional manner from 0.2 mg/kg to 1 mg/kg. Based on these results, a dose of 4 mg/kg SHP681 (or placebo) every 2 weeks over a 6-week period (3 doses) was nominated for the 6th MAD cohort.

During dose escalation, protocol defined dose levels may be reduced, repeated, discontinued, or an intermediate increase may be added depending on the outcome of the blinded safety data review between dose escalations.

3.1.2 Screening and Treatment Period

SAD (Part 1)

The SAD portion of the study will consist of a screening period of up to 28 days and one treatment period of 29 days. A total of 8 overnight stays are required for the SAD portion of the study.

The first dose will occur within 28 days of screening. Subjects will be admitted to the clinical research center (CRC) on Day -1 and randomized to SHP681 or placebo on Day -1 or the morning of Day 1 as indicated in Figure 1. Subjects will not participate in more than 1 treatment cohort.

Safety and tolerability will be assessed by treatment-emergent AEs (TEAEs), vital signs, electrocardiogram (ECG) findings, and clinical laboratory evaluations.

Blood samples for pharmacokinetic analysis of SHP681 will be collected through 672 hours post dose in each dosing period. The last study visit is scheduled at Day 29 and will include final safety assessments; there will be no further follow up. Additionally, blood draws for determination of anti-drug antibodies (ADAs) and neutralizing antidrug antibody (nADA) will be

collected prior to dose on Day 1 and at 672 hours post dose. Subjects with detectable ADAs in their plasma might require additional visits and blood collection for follow-up assessments of antibody titers up to a year post-dose.

MAD (Part 2)

The study duration of the MAD portion will comprise of a screening period up to 28 days and a treatment period of 57 days. A total of 21 overnight stays are required for the first 5 cohorts and 16 overnight stays are required for the 6th cohort for this portion. The inhouse period may be revised due to operational issues pending approval by the PI and Sponsor.

First dose will occur within 28 days of screening. Subjects will be admitted to the CRC on Day -1 and randomized to SHP681 or placebo on Day -1 or the morning of Day 1 as indicated in Figure 2. Subjects will not participate in more than 1 treatment cohort.

Safety and tolerability will be assessed by treatment-emergent AEs (TEAEs), vital signs, ECG findings, abdominal ultrasounds, and clinical laboratory evaluations.

For the first 5 MAD cohorts, blood sample for pharmacokinetic analysis of SHP681 will be collected over 24 hours on Day 1 and at predose on Day 8, Day 15, Day 22, and Day 29 in each dosing period. On Day 29, blood samples for the pharmacokinetic analysis of SHP681 will be collected through 672 hours post-dose in each dosing period. The last study visit is scheduled at Day 57 and will include final safety assessments; there will be no further follow up.

For the 6th MAD cohort, blood samples for pharmacokinetic analysis of SHP681 will be collected over 24 hours on Day 1 and at predose on Day 15 and Day 29. On Day 29, blood samples for the pharmacokinetic analysis of SHP681 will be collected through 672 hours post-dose in each dosing period. The last study visit is scheduled at Day 57 and will include final safety assessments; there will be no further follow up.

Additionally, blood draws for determination of ADAs and nADAs will be collected prior to each dose, 7 days after the last dose (Day 36), and 28 days after the last (Day 57) dose in each cohort.

Subjects with detectable ADAs in their plasma on Day 57 might require additional visits and blood collection for follow-up assessments of antibody titers up to a year post-dose.

[redacted]

3.2 Duration and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 2 months in the SAD and approximately 3 months in the MAD portion, if the maximum screening and treatment durations are used. The study will be completed in approximately 6 months.

The Study Completion Date is defined as the date the LAST subject, completes their final protocol-defined assessments.

Please note that this includes the last visit or contact, whichever is later. The Study Completion Date is used to ascertain timing for study results posting and reporting.

3.3 Sites and Regions

This study will be conducted at 1 CRC in the United States.

4. STUDY POPULATION

Each subject must participate in the informed consent process and provide written informed consent before any procedures specified in the protocol are performed.

4.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below. Subjects cannot be randomized before all inclusion criteria (including test results) are confirmed.

1. Ability to voluntarily provide written, signed, and dated informed consent to participate in the study.
2. An understanding, ability, and willingness to fully comply with study procedures and restrictions.
3. Age 18-50 inclusive at the time of consent. The date of signature of the informed consent is defined as the beginning of the screening period. This inclusion criterion will only be assessed at the first screening visit.
4. Male, or non-pregnant, non-lactating female who agrees to comply with any applicable contraceptive requirements of the protocol or females of non-childbearing potential.
5. Considered "healthy" by the investigator. Healthy status is defined by absence of evidence of any active or chronic disease or condition based on a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, and urinalysis.
6. Body mass index between 18.0 kg/m² and 30.0 kg/m² inclusive with a body weight 50-100 kg (110-220 lbs). This inclusion criterion will only be assessed at the first screening visit.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. History of any hematological, hepatic, respiratory, cardiovascular, renal, neurological or psychiatric disease, gall bladder removal, or current or recurrent disease that could affect the action, absorption, or disposition of the investigational product, or clinical or laboratory assessments.
2. Current or relevant history of physical or psychiatric illness, any medical disorder that may require treatment or render the subject unlikely to fully complete the study, or any condition that presents undue risk from the investigational product or procedures.
3. Known or suspected intolerance or hypersensitivity to the investigational product(s), closely- related compounds, or any of the stated ingredients.
4. Significant illness, as judged by the investigator, within 2 weeks of the first dose of investigational product.
5. Known history of alcohol or other substance abuse within the last year.

6. Donation of blood or blood products (eg, plasma or platelets) within 60 days prior to receiving the first dose of investigational product.
7. Within 30 days prior to the first dose of investigational product:
   a. Have used an investigational product (if elimination half-life is <6 days, otherwise 5 half-lives).
   b. Have been enrolled in a clinical study.
   c. Have had any substantial changes in eating habits, as assessed by the investigator.
8. Use of DPP-4 inhibitors within 30 days or 5 half-lives, whichever is greater, prior to administration of the investigational product.
9. Confirmed systolic blood pressure >139mmHg or <89mmHg, and diastolic blood pressure >89 mmHg or <49 mmHg.
10. Twelve-lead ECG demonstrating QTcF >450 msec at screening. If QTcF exceeds 450 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF values should be used to determine the subject's eligibility.
11. Positive screen for alcohol or illicit drugs at screening or Day -1.
12. Male subjects who consume more than 21 units of alcohol per week or 3 units per day. Female subjects who consume more than 14 units of alcohol per week or 2 units per day. (1 alcohol unit=1 beer or 1 wine (5 oz/150 mL) or 1 liquor (1.5 oz/40 mL) or 0.75 oz alcohol).
13. Positive HIV, HBsAg, or HCV antibody screen.
14. Use of tobacco in any form (eg, smoking or chewing) or other nicotine-containing products in any form (eg, gum, patch). Ex-users must report that they have stopped using tobacco for at least 30 days prior to receiving the first dose of investigational product.
15. Routine consumption of more than 2 units of caffeine per day or subjects who experience headaches associated with caffeine withdrawal. (1 caffeine unit is contained in the following items: one 6 oz (180 mL) cup of coffee, two 12 oz (360 mL) cans of cola, one 12 oz cup of tea, three 1 oz (85 g) chocolate bars. Decaffeinated coffee, tea, or cola are not considered to contain caffeine).
16. Prior screen failure (unless Sponsor approval is given), randomization, participation, or enrollment in this study or prior exposure to any GLP-2 analogs
17. Unresected GI polyp, known polyposis condition, or premalignant changes in the GI tract.
18. Any history of malignancy in the GI tract or treatment for any other malignancy in the previous 5 years.
19. Current use of any medication (including over-the-counter, herbal, or homeopathic preparations; with the exception of hormonal replacement therapy or hormonal contraceptives and occasional use of ibuprofen or acetaminophen and pre-approved medication for sedation or other medications required during or after the endoscopy). Current use is defined as use within 14 days of the first dose of investigational product.
20. Findings of subclinical hepatobiliary disease, such as gallstones, on abdominal ultrasound at screening as determined by the Investigator in consultation with the Medical Monitor.

4.3 Restrictions

1. Subjects should refrain from taking DPP4 inhibitors through the course of the study.
2. Subjects should refrain from strenuous physical exercise 48 hours prior to admission to the CRC and during the in-house stays at the CRC.
3. Subjects should refrain from alcohol 48 hours prior to admission to the CRC and during the in-house stay at the CRC.
4. Subjects should refrain from use of tobacco or any products containing nicotine within 30 days of Day 1 of the first treatment period through the completion of the last treatment period.
5. Subjects should refrain from taking or regularly using any medication (including over-the counter multivitamin, herbal, or homeopathic preparations) with the exception of those listed in Section 5.2 from 14 days prior to receiving the first dose of the investigational product through the completion of the discharge assessments and procedures.
6. Subjects should refrain from foods or beverages containing caffeine/xanthine 48 hours prior to admission to the CRC and during the in-house stay at the CRC.
7. Subjects will be required to follow standardized meal schedules and eat the meals provided by the site while housed in the CRC. No outside food or beverages (including gum, mints, etc.) will be permitted. Menus will be identical for all subjects at the CRC. Subjects are not required to complete the entire meal but must meet their individual nutritional requirements to maintain stable weight. Copies of the menus will be provided to the sponsor for approval prior to the start of the study.

4.4 Reproductive Potential

4.4.1 Female Contraception

Sexually active females of childbearing potential should be using an acceptable form of contraception. Females of childbearing potential must be advised to use acceptable contraceptives throughout the study period and for 30 days following the last dose of investigational product. If hormonal contraceptives are used, they should be administered according to the package insert. Females of childbearing potential who are not currently sexually active must agree to use acceptable contraception, as defined below, if they become sexually active during the period of the study and 30 days following the last dose of investigational product.

Female subjects should be either:

- Medically confirmed postmenopausal surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 6 weeks post-sterilization, or
- Females of childbearing potential with a negative serum beta-human chorionic gonadotropin (β-hCG) pregnancy test at screening and negative urine pregnancy test on Day -1. Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Acceptable methods of contraception are:

- Intrauterine devices plus condoms
- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam)
- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the first dose of investigational product, plus condoms. Note: If subject becomes sexually active during the study, they should use one of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

4.4.2 Male Contraception

Male subjects must be advised to use acceptable contraceptives throughout the study period and for 3 months following the last dose of investigational product. Male subjects must be advised not to donate sperm during the course of the study and within 3 months of the last dose of investigational product. The acceptable method of contraception for male subjects is a double-barrier method (eg, condom with spermicidal gel or foam).

4.5 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject from investigational product with the medical monitor when possible.

If investigational product is discontinued, regardless of the reason, the early withdrawal evaluations listed in are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified follow-up. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for termination and date of stopping investigational product must be recorded in the case report form (CRF) and source documents.

Randomized subjects who discontinue from the study may be replaced at the sponsor's discretion.

4.5.1 Reasons for Discontinuation

The reason for withdrawal must be determined by the investigator and recorded in the subject's medical record and on the case report form (CRF). If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the CRF.

Reasons for discontinuation include but are not limited to:

- Adverse event
- Protocol deviation/violations

- Withdrawal by subject
- Lost to follow-up
- Other (Note: If "Other" is selected, then the specific reason will need to be recorded in the CRF)

4.5.2 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any timepoint prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and return any unused investigational product.

4.5.3 Stopping Criteria for Dose Escalation

Dose escalation will not continue to the next planned dose/cohort if any of the following criteria are met:

- A serious adverse event (SAE) related to active drug (according to Investigator assessment) occurs in 1 or more subjects receiving active drug. No further subjects will be enrolled or dosed until further evaluation of the available data is made by the medical monitor and investigator to determine whether to stop or proceed with the study. Following a safety review of the event, study enrollment or dosing of currently enrolled subjects may be restarted if the medical monitor and the investigator determine that it is safe to proceed with the study.
- Two or more subjects experience a treatment emergent adverse event (TEAE) of National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v5.0) Grade 3 or higher in the same system organ class (SOC).
- If 2 or more subjects experience a treatment emergent adverse event (TEAE) of at least moderate severity (such as National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE v5.0] Grade 3 or higher) in the same system organ class (SOC).

Individual Stopping Criteria

Individual subjects should be discontinued if any of the following laboratory findings are observed:

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 8 × upper limit of normal (ULN)
- AST or ALT > 5 × ULN for 2 weeks;
- AST or ALT > 3 × ULN and either total bilirubin > 2 × ULN or international normalized ratio (INR) > 1.5;

- AST or ALT > 3 × ULN with symptoms consistent with hepatic disease or injury (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia >5%)
- Any other drug related event occurs in subjects receiving active drug and is deemed to pose an unacceptable risk to subjects by the investigator or medical monitor after further evaluation.
- Dosing will be discontinued in an individual subject if that subject has a laboratory abnormality or TEAE of CTCAE v5.0 Grade 3 or higher that is considered possibly related to study drug by the investigator.

Should any of the apparent stopping criteria be met, the data under examination will be unblinded to ensure the criteria have been met with respect to those subjects receiving active drug. The Shire Medical Monitor and/or principal investigator can request unblinding of the data at any time in order to further evaluate a possible safety concern for an individual subject or entire cohort.

In case one of these dose-limiting events occurs, it will be assumed that the minimum intolerable single dose or multiple doses has been reached. Further once-weekly dosing will be at a dose, determined by the Shire Medical Monitor and the principal investigator, below the minimum intolerable once-weekly dose and when needed in consultation with the Shire Safety Officer.

5. PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Treatment

Prior treatment includes all treatment (including but not limited to herbal treatments, vitamins, non-pharmacological treatment such as psychotherapy as appropriate) received within 30 days (or pharmacokinetic equivalent of 5 half-lives, whichever is longer) of the date of first dose of investigational product. Prior treatment information must be recorded on the appropriate source documentation.

5.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product and the last study visit (or last contact with the subject, whichever comes first), inclusive. Concomitant treatment information must be recorded on the appropriate source documentation.

5.2.1 Permitted Treatment

Subjects should refrain from taking any medications (excluding those medications listed below) during the course of the study. Any medication which is considered necessary for the subject's safety and well-being may be given at the discretion of the investigator. The administration of all medications (including investigational products) must be listed on the appropriate source documentation.

Medications permitted during the study are listed below:

- Hormonal contraceptives for females of childbearing potential administered according to the package insert (see Section 4.4.1)
- Hormone replacement therapy
- Occasional use of ibuprofen or acetaminophen

5.2.2 Prohibited Treatment

Refer to Section 4.3 on restrictions for prohibited treatment.

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The test product is SHP681 which will be provided in vials.

The reference/comparator product is a placebo which will be provided in vials. Additional information related to SHP681, including preparation and administration, is provided in the current SHP681 investigator brochure, and in an investigational product preparation and administration manual that will be provided.

6.1.1 Blinding the Treatment Assignment

This is a randomized, double-blind, placebo-controlled study. The actual treatment given to individual subjects is determined by a randomization schedule. The associated treatment assignments giving details of individual subject treatment are in the form of vendor randomization schedule held at the investigational site which will be provided by the biostatistics vendor.

The randomization code will be sent to the unblinded dispenser at the site in a password protected file. This code will be opened by the unblinded dispenser and will be kept in a sealed envelope under locked conditions.

The investigator should assign the responsibility of unblinded dispenser to a person who will not participate in the evaluation of any study subject. This permits all other participants to remain blinded. A member of the staff of the CRU or clinical pharmacy should fulfill this role and should be fully trained in the relevant aspects of the study. His/her role should be documented on the site's delegation of authority log. The unblinded dispenser may not administer the investigational product to study subjects. The unblinded dispenser must give the investigational product to the investigator or designee for administration. The unblinded dispenser will draw up the dose into a syringe and apply a colored wrap to the dosing syringe(s) to ensure blinding, as the active investigational product has a yellow-brown tinge compared to the placebo. The unblinded dispenser may not administer the investigational product to study subjects. Contact between the unblinded dispenser and study subjects should be kept to a minimum. The investigator, study coordinator, and any study participants other than the unblinded dispenser must not be allowed to know the investigational product assigned to any study subject and must not be allowed to see the randomization doe, investigational product containers, or treatment records. For emergency circumstances, please see Section 6.2.3.

Aside from unblinding for the interim analysis, the treatment assignment must not be broken during the study except in emergency situations where the identification of the investigational product is required for further treatment of the subject(s) or to assess any safety, tolerability, or pharmacokinetic questions based on the safety review.

Treatment assignments in the SAD cohorts and the first 3 MAD cohorts will be unblinded for an interim analysis after the last subject in the 3rd MAD cohort completes the Day 39 assessments.

Each vial of SHP681 and placebo will be assigned a unique packaging identification number. When a vial of SHP681 or placebo is assigned to a subject, the packaging identification number will be recorded in the drug accountability records. Each subject will be assigned a specific vial or multiple vials of investigational product.

6.2 Administration of Investigational Product(s)

6.2.1 Allocation of Subjects to Treatment

This is a randomized, double-blind, placebo-controlled study.

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation. This will be a 4-digit number starting at 0001.

The actual treatment given to individual subjects is determined by a randomization schedule. The randomization number represents a unique number representing study portion (SAD/MAD) as well as cohort and corresponds to investigational product allocated to the subject. This randomization number will be assigned prior to dosing after eligibility has been determined.

For the SAD portion Cohort 1, this unique 4-digit randomization number will be assigned as follows:

Cohort	Patient/Order of Randomization	Randomization #
Cohort 1	First Patient Randomized in the First SAD Cohort	1101
Cohort 1	Second Patient Randomized in the First SAD Cohort	1102
Cohort 1	Third Patient Randomized in the First SAD Cohort	1103
Cohort 1	X Patient randomized in the First SAD Cohort	110X

For the MAD portion Cohort 1, this unique 4-digit randomization number will be assigned as follows:

Cohort	Patient/Order of Randomization	Randomization #
Cohort 1	First Patient Randomized in the First MAD Cohort	2101
Cohort 1	Second Patient Randomized in the First MAD Cohort	2102
Cohort 1	Third Patient Randomized in the First MAD Cohort	2103
Cohort 1	X Patient randomized in the First MAD Cohort	210X

If a randomization number is allocated incorrectly the study monitor must be notified as soon as the error is discovered. Once a randomization number has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study.

Investigational product packaging identification numbers, separate from randomization numbers/unique identifiers, may also be assigned to subjects for specific treatment assignment as dictated by the study. In these cases, the same investigational product packing identification number may not be assigned to more than 1 subject.

6.2.2 Dosing

After satisfying all screening and entry criteria, SHP681or placebo will be administered in the abdomen to all subjects according to the following schedule:

SAD portion of the study

The plan is to enroll 30 subjects in 5 cohorts. Each cohort will include 6 subjects. Subjects will be randomized within each cohort such that 5 subjects receive SHP681 and 1 subject receives placebo. After a single administration on Day 1 of each treatment period of SHP681 or placebo in each cohort, if the dose is assessed as safe and tolerable during a dose escalation meeting, the next cohort will be administered a SC dose of SHP681 at the next higher dose level or placebo.

Dose escalation will proceed sequentially to assess the following SC doses of SHP681: 0.2 mg/kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg, and 4 mg/kg. During dose escalation, protocol defined dose levels may be reduced, repeated, discontinued, or an intermediate increase may be added depending on the outcome of the blinded safety data review between dose escalations.

MAD portion of the study

The plan is to enroll 72 subjects within 6 MAD cohorts. Each cohort will include 12 subjects. Subjects will be randomized within each cohort such that 10 subjects receive SHP681 and 2 subjects receive placebo. Subjects in the first 5 MAD cohorts will receive SHP681 (or placebo) once weekly for 5 weeks, on Day 1, 8, 15, 22 and 29. After the first cohort has been administered 2 doses of SHP681 (or placebo) over 2 weeks and the dose is assessed as safe and tolerable during a dose escalation meeting, the next MAD cohort will commence. Dose escalation will proceed sequentially to include the following SC doses: 0.2 mg/kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg, and 4 mg/kg. Subjects in the 6th MAD cohorts will receive 4 mg/kg SHP681 (or placebo) once every 2 weeks, on Day 1, 15, and 29.

During dose escalation, protocol defined dose levels may be reduced, repeated, discontinued, or an intermediate increase may be added depending on the outcome of the blinded safety data review between dose escalations.

6.2.3 Unblinding the Treatment Assignment

Treatment assignments in the SAD cohorts and the first 3 MAD cohorts will be unblinded for an interim analysis after the last subject in the 3rd MAD cohort completes the Day 39 assessments.

Aside from unblinding for the interim analysis, the treatment assignment must not be broken during the study except in emergency situations where the identification of the investigational product is required for further treatment of the subject. The investigator should contact the medical monitor as soon as possible after the blind has been broken.

In the event that the treatment assignment is broken, the date, the signature of the person who broke the code and the reason for breaking the code are recorded on the source documents. Upon breaking the blind, the subject is withdrawn from the study, but should be followed up for safety purposes. Any code-breaks that occur must be reported to the sponsor and contract research organization (CRO). Code-break information is held by the unblinded dispenser at the site.

6.2.4 Labeling

Labels containing study information and pack identification are applied to the investigational product(s) container.

All investigational product is labeled with a minimum of the protocol number, medication identification number, dosage form (including product name and quantity in pack), directions for use, storage conditions, batch number, and/or packaging reference, the statements "For clinical trial use only," and/or "CAUTION: New Drug - Limited by Federal (or US) Law to Investigational Use," and "Keep out of reach of children," and the sponsor's name and address.

Space is allocated on the label so that the site representative can record a unique subject identifier and date of dispensation.

Additional labels (eg, those used when dispensing marketed product) may, on a case-by-case basis, be applied to the investigational product in order to satisfy local or institutional requirements, but must not:

- Contradict the clinical study label
- Obscure the clinical study label
- Identify the study subject by name

Additional labels may not be added without the sponsor’s prior full agreement.

6.2.5 Packaging

One vial of investigational product is packaged in one labeled carton.

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.

6.2.6 Storage

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

Investigational products are distributed by the unblinded dispenser or nominated member of the study team.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), eg, fumigation of a storage room.

6.3 Drug Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed-upon number of subjects.

The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for administering investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will administer the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All administered medications will be documented on the CRFs and/or other investigational product record.
No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

With the written agreement of the sponsor, at the end of the study all unused stock, and empty/used investigational product packaging may be destroyed at the site or a local facility. In this case, destruction records identifying what was destroyed, when and how, must be obtained with copies provided to the sponsor. Destruction of investigational products must be in accordance with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

6.4 Subject Compliance

Compliance must be assessed by observation of dosing by the investigator or designee. The investigator/nominated person will record details on the drug accountability log(s) and/or source documents. In addition, details of the dosing time (time and date) will be captured in the appropriate CRF.

6.5 Retention of Bioavailability and Bioequivalence Testing Samples

Not applicable.

7. STUDY PROCEDURES

7.1 Study Schedule

See the Study Schedules for study procedures to be followed in the study.

The following "priority order" will be in effect when more than 1 procedure or assessment is required at a particular timepoint.

- Spontaneous or solicited adverse event (AE) reporting
- Vital signs
- Electrocardiogram (ECG)
- Physical examination
- [redacted]
- Blood sampling for ADA and nADA
- Pharmacokinetic blood sampling
- Clinical laboratory tests
- Pregnancy testing

NOTE: Blood sampling for PK evaluation must be performed at the precise protocol-scheduled time. Actual sampling time(s) must be accurately recorded in the source document and appropriate CRF. Pharmacokinetic blood collection must not deviate from the nominal collection time set forth in the protocol by more than ±5 minutes from samples drawn within 4 hours after the first dose or by more than ±15 minutes for samples drawn between 4 hours and 24 hours after the first dose. Samples drawn beyond study day 2 cannot deviate by more than 10% of the specified time from the first dose.

7.1.1 Screening Period

For both SAD and MAD part of the study, screening procedures must be completed within 28 days prior to receiving the first dose of investigational product. All screening assessments and procedures are to be performed by the principal investigator or a qualified designee. See the Study Schedules for a complete list of screening procedures to be performed.

Written, signed, and dated informed consent from each subject prior to the performance of any study-related procedures must be obtained by the principal investigator or a designee. A copy of the signed informed consent must be given to the subject and/or subject's parent/LAR for their records.

7.1.1.1 Screening Failure

A screen failure is a subject who has given informed consent and failed to meet the inclusion and/or met at least 1 of the exclusion criteria and has not been randomized and/or enrolled or administered investigational product(s).

Subjects who fail to meet all inclusion/exclusion criteria will not be permitted to be rescreened for the study at any point.

Eligible subjects who meet all inclusion/exclusion criteria but are unable to participate in the study due to scheduling conflicts/timing may be rescreened based on investigator discretion and sponsor approval should their availability to participate fall outside the screening window. In these cases, a new subject number must be assigned for each subject who is rescreened and a new informed consent form must be signed.

7.1.2 Treatment Period

SAD (Part 1)

7.1.2.1 Admission to the CRC (Day -1)

Following the screening visit, eligible subjects will return to the CRC on Day -1 of the study. See the Study Schedules for a list of procedures and assessments to be completed upon admission to the CRC. Subjects who successfully complete the pre-admission procedures and assessments will be admitted to the CRC on Day -1 and randomized and assigned a randomization number on Day -1 or Day 1 as described in Section 6.2.1.

7.1.2.2 Treatment Period (Day 1 through Day 29)

Subjects will be admitted to the CRC after eligibility is confirmed on Day -1. Subjects will be confined at the CRC from Day -1 until after completion of the assessments on Day 8 as indicated in the Study Schedules. SHP681 or placebo will be administered on Day 1 of the treatment period for each cohort. On Day 8 subjects will be discharged from the CRC. From Day 11 to Day 29 the subjects will be back at the CRC for outpatient visits to complete the study procedures, safety and pharmacokinetic assessments as indicated in the Study Schedules.

MAD (Part 2)

7.1.2.3 Admission to the CRC (Day -1)

Following the screening visit, eligible subjects will return to the CRC on Day -1 of the study. See the Study Schedules for a list of procedures and assessments to be completed upon admission to the CRC. Subjects who successfully complete the pre-admission procedures and assessments will be admitted to the CRC on Day -1 and randomized and assigned a randomization number on Day -1 or Day 1 as described in Section 6.2.1.

7.1.2.4 MAD Cohorts 1-5 Treatment Period (Day 1 through Day 57)

Eligible subjects will be confined to the CRC from the morning of Day -1 until completion of all procedures and assessments on Day 4. SHP681 or placebo will be administered on Day 1 of the treatment period for each cohort. On Day 4 subjects will be discharged from the CRC. They will then be readmitted in the CRC on Day 7, Day 14, Day 21 and Day 28 and discharged from the CRC respectively on Day 10, Day 18, Day 24 and Day 36 after completion of the assessments as indicated in the Study Schedules. From Day 39 to Day 57 the subjects will

return to the CRC for outpatient visits to complete the study procedures, safety and pharmacokinetic assessments as indicated in the Study Schedules.

7.1.2.5 MAD Cohort 6 Treatment Period (Day 1 through Day 57)

Eligible subjects will be confined to the CRC from the morning of Day -1 until completion of all procedures and assessments on Day 4. SHP681 or placebo will be administered on Day 1 of the treatment period for each cohort. On Day 4 subjects will be discharged from the CRC. They will then be readmitted in the CRC on Day 14 and Day 28 and discharged from the CRC, respectively, on Day 18 and Day 36 after completion of the assessments as indicated in the Study Schedules. From Day 39 to Day 57 the subjects will return to the CRC for outpatient visits to complete the study procedures, safety and pharmacokinetic assessments as indicated in the Study Schedules.

7.1.3 Follow-up Period

There will be no further follow up.

7.1.4 Additional Care of Subjects after the Study

No aftercare is planned for this study.

7.2 Study Evaluations and Procedures

7.2.1 Demographic and Other Baseline Characteristics

Demographic characteristics such as date of birth, sex, weight, height and body mass index will be collected according to the Study Schedules.

7.2.2 Safety

The name and address of each third-party vendor (eg, clinical laboratory) used in this study will be maintained in the investigator's and sponsor's files.

Actual safety assessment times will be monitored and recorded. The sponsor's expectation is that the investigator will ensure that every effort is made to perform all assessments at the precise protocol-scheduled time. Any safety assessment that deviates from the scheduled assessment time set forth in the protocol by more than ±15 minutes will be considered a protocol deviation.

An AE is any unfavorable and unintended sign, ie, any clinically significant worsening from baseline of an abnormal laboratory finding, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995). Treatment emergent AEs (TEAEs) are adverse events that occur after initiation of either the investigational product or placebo (see Section 8 for more information).

7.2.2.1 Medical and Medication History

A complete medical and medication history, as well as demographic information, will be performed at the screening visit/timepoints described in the Study Schedules by a qualified licensed physician, physician's assistant, nurse practitioner, or a delegated study coordinator/assistant. The medical history will be reviewed and recorded, including:

- Date of birth
- Sex
- Race and ethnicity
- Recent ingestion of medication (30 days prior to entering the screening period)
- History of respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, psychiatric, and other diseases
- Smoking habits

7.2.2.2 Physical Examination (Including Height and Weight)

Complete or abbreviated physical examinations will be performed as specified at the time points described in the Study Schedules by a qualified licensed physician, physician's assistant, or nurse practitioner.

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

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

Abnormalities identified at the screening visit will be documented in the subject's source documents and on the medical history CRF. Changes after the screening visit that are considered clinically significant by the investigator will be captured as AEs on the AE CRF page.

7.2.2.3 Adverse Event Collection

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?").

Adverse events are collected from the time informed consent is signed. (Please refer to Section 8, Adverse and Serious Adverse Events Assessment.)

7.2.2.4 Vital Signs

Blood Pressure and Pulse Rate

Blood pressure and pulse rate will be measured at times specified in the Study Schedules of this protocol. Additional blood pressure and pulse rate measurements may be performed, as determined by the investigator, in order to ensure appropriate monitoring of subject safety and accurate recording of vital sign measurements. Any changes from baseline which are deemed clinically significant by the investigator are to be recorded as an AE.

The same method for obtaining blood pressure measurement (auscultatory or oscillometric) should be used throughout the study for all subjects (and documented). In addition, the conditions of vital sign measurements should be controlled and as consistent as possible during the study, in order to minimize external variability of the readings. It is advised that measurements be collected at a comfortable room temperature with little to no background noise, using the same (appropriately sized) cuff placed at the same location of the same arm during the study.

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

The cuff should have a bladder length that is 80% and a width that is at least 40% of arm circumference (a length-to-width ratio of 2:1).

The subject should be asked to remove all clothing that covers the location of cuff placement. The subject should not have exercised or consumed caffeine, alcohol, or nicotine within 30 minutes of collection. The subject should be instructed to relax as much as possible for at least 5 minutes prior to collection. The subject should remain quiet during this time and through the measurement.

The subject should be sitting comfortably, with the legs uncrossed. The arm should be supported with a pillow, such that the middle of the cuff on the upper arm is at the level of the right atrium (approximately halfway between the bed and the level of the sternum).

At the screening visit, blood pressure should be compared between both arms. If, after a single measurement is taken, there is a difference between arms in either systolic or diastolic blood pressure of >10 mmHg, the site will perform triplicate BP measurements in each arm to determine the arm with the higher BP. The arm with the higher BP (based on the average of the 3 BP measurements for each arm) should be used for inclusion at screening, and the last of the 3 measurements recorded in the eCRF as the screening BP. The same (right or left) arm with the higher blood pressure will be used throughout the study.

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

Body Temperature

Oral temperature should be taken by placing a digital thermometer under the tongue for at least 30 seconds and the temperature reported in degrees Celsius. Tympanic temperature may also be used.

7.2.2.5 Clinical Laboratory Evaluations

All clinical laboratory assays will be performed according to the laboratory's normal procedures. Reference ranges are to be supplied by the laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

The following clinical laboratory assessments will be performed:

Biochemistry

Blood samples (8.5 mL) for serum biochemistry will be collected into a gel separator tube at the timepoints described in the Study Schedules. The following parameters will be assessed:

Sodium	Phosphorus	β-hCG[a]
Potassium	Total protein	
Glucose	Total CO_2 (Bicarbonate)	
Blood urea nitrogen	Albumin	
Creatinine	Aspartate transaminase	
Amylase	Lipase	
Calcium	Alanine transaminase	
Chloride	Gamma glutamyl transferase	
Thyroid stimulating hormone (TSH)	Free T3[b]	
T3[b]	Thyroxine-binding Globulin[b]	
T4[b]	Alkaline phosphatase	
Uric acid	Total bilirubin	

β-hCG = beta-human chorionic gonadotropin

[a] Females only

[b] These parameters will only be calculated on Day 1, Day 8, and Day 15 for the SAD portion of the study. An additional 3.5 mL of blood will be collected from each subject on Days 1 and 8 for the assessment of TBG. T3, T4, and Free T3 will be assessed from the 8.5 mL collected for the biochemistry. On Day 15, an additional 7 mL of blood will be collected from each subject for the assessment of T3, T4, Free T3, and TBG

Hematology

Blood samples (4 mL) for hematology will be collected into an EDTA (ethylenediaminetetraacetic acid) tube at the timepoints described in the Study Schedules. The following parameters will be assessed:

Hemoglobin	Total neutrophils (absolute)
Hematocrit	Eosinophils (absolute)
Red blood cells	Monocytes (absolute)
Platelet count	Basophils (absolute)
White blood cell count; total and differential	Lymphocytes (absolute)

Urinalysis

A urine sample for urinalysis will be collected at the timepoints described in the Study Schedules. The following parameters will be assessed:

pH	Blood	Nitrites
Glucose	Ketones	Leukocyte esterase
Protein	Bilirubin	Specific gravity

Microscopic examination will be conducted if protein and/or blood is/are detected during urinalysis. At a minimum the microscopic examination will consist of red blood cells, white blood cells, casts, and bacteria.

7.2.2.6 Pregnancy Test

For all female subjects (regardless of reproductive potential status), a serum pregnancy test is performed at the screening visit, while urine pregnancy test will be performed at subsequent scheduled timepoints as indicated in the Study Schedules if pregnancy is suspected; or on withdrawal of the subject from the study.

7.2.2.7 Drug and Alcohol Screen

A urine screen for drugs of abuse and alcohol breath test will be performed at the timepoints described in the Study Schedules. Additional drug and alcohol screens may be performed at the investigator's discretion.

Urine samples are to be tested for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, opiate metabolite, and phencyclidine.

Results of urine drug and alcohol screens will be reviewed and verified by the study monitor but will not be collected in the CRF database.

Any positive result for drugs of abuse or alcohol at screening or on Day -1 will exclude the subject from further participation in the study. If during the study, the subject becomes positive for drugs of abuse (except ethanol <0.08 mg/dl or cannabinoids), the subject will be withdrawn from the study.

7.2.2.8 Serology Screen

At the screening visit, a blood sample of approximately 8.5 mL will be drawn into a serum separator tube to test for the presence of HIV, HBsAg, and HCV antibody.

The test results must be confirmed negative prior to enrollment in the study. If a test result is positive, the subject will be excluded from entering the study. Results of the virology screen will be reviewed and verified by the study monitor but will not be collected in the CRF database.

7.2.2.9 Electrocardiogram

Twelve-lead ECGs will be performed at the times specified in the Study Schedules. All ECGs will be performed using the equipment supplied by the CRC.

The following parameters will be recorded on the appropriate CRF page: heart rate, PR, RR, QRS, and QT intervals. The QTcB and QTcF will be derived from the data in the database. The investigator's assessment of the ECG tracing as normal or abnormal must be documented, and if abnormal, his/her determination of whether the abnormality is clinically significant or not will be documented on the tracing and recorded in the source documentation.

The subject should be asked to remove all clothing that covers the location of lead placement. The subject should not have exercised or consumed caffeine, alcohol, or nicotine within 30 minutes prior to collection. The subject must be resting in the supine position for at least 5 minutes prior to collecting the ECG.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings.

Triplicate recording, including a 10-second rhythm strip, will be obtained approximately 2-4 minutes apart for all assessments excluding the screening visit (wherein a single ECG assessment is required). Each ECG parameter obtained with the 3 assessments will be recorded in the CRF. The average of the triplicate ECG measurements collected at each nominal timepoint will be used for analysis. The 3 recordings should be immediately assessed as valid recordings and if not valid, they should be repeated in order to obtain a total of 3 valid recordings. Invalid recordings will not be entered in the CRF.

When triplicate ECGs are obtained: The average of the triplicate ECG measurements collected predose on Day 1 will serve as the subject's baseline ECG.

To ensure safety of the subjects, a qualified individual at the investigational site will make comparisons to baseline measurements.

If the QTcF interval (calculated online on site) is increased by >45 msec from the baseline, or an absolute QTcF value is >500 msec for any scheduled ECG, then 2 additional ECGs will be collected, approximately 2-4 minutes apart, to confirm the original measurement.
If either of the QTcF values from these repeated ECGs remains above the threshold value (>45 msec increase from the baseline; or >500 msec), then a single ECG must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement. When triplicate ECGs are collected, the mean of the triplicate measurements should be used to trigger the decision to collect follow-up ECGs.

If QTcF values remain above 500 msec (or >45 msec from the baseline) for >4 hours (or sooner at the discretion of the investigator) or QTcF intervals get progressively longer, the subject should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF intervals do not return to <500 msec (or to <45 msec above the baseline) after 8 hours of monitoring (or sooner at the discretion of the investigator). If a machine-read QTcF/QTcB value is prolonged, as defined above, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTcF/QTcB values are in the acceptable range.

7.2.2.10 Abdominal Ultrasound

An abdominal ultrasound will be performed at the times specified in the Study Schedules.

7.2.3 Pharmacokinetic Procedures

The name and address of the bioanalytical laboratory(ies) for this study will be maintained in the investigator's files at the/each site and in the Trial Master File at the sponsor. A laboratory manual fully describing the schedule and method of sample handling will be provided to the site. Actual pharmacokinetic blood sample collection times versus time of dosing will be monitored. The sponsor's expectation is that the investigator will ensure that every effort is made to collect all pharmacokinetic blood samples at the precise protocol scheduled time but must record the actual clock time (AM/PM or 24-hr) of the sample collection. Pharmacokinetic blood collection must not deviate from the nominal collection time set forth in the protocol by more than ±5 minutes for samples drawn within 4 hours after the first dose or by more than ±15 minutes for samples drawn between 4 hours to 24 hours after the first dose. Samples drawn beyond study day 2 cannot deviate by more than ±10% of the specified time from the first dose. Samples drawn outside these parameters will be considered a protocol deviation.

7.2.3.1 Blood Sample Collection and Handling Procedures

Blood samples will be collected at the time specified in the Study Schedules to measure plasma concentrations of SHP681.

A full description of the PK blood collection, handling, storage, and shipping can be found in the laboratory manual.

Plasma sample tubes for bioanalysis must be freezer-safe and identified with freezer-safe labels provided by the CRC. The labels will contain the following information:

- Study number (SHP681-101)
- Subject identifier
- Treatment Dose and portion of the study (SAD or MAD)
- Period
- Nominal day (Day 1, Day 2, etc.)
- Nominal time
- Matrix identifier (plasma for PK)
- Split (primary or backup or aliquot 1 or aliquot 2)

7.2.3.2 Shipment of Plasma Pharmacokinetic Samples

All pharmacokinetic samples should be placed in a cryo-box, double-bagged to contain leaks and packed with a sufficient quantity of dry ice to ensure that they remain frozen for at least 72 hours to allow for delays in shipment. All applicable shipping regulations must be followed. Shipments should be scheduled so that no samples arrive on the weekend and should be shipped Monday-Wednesday only. Samples should be transported to ensure that they arrive at the bioanalytical laboratory between the hours of 9:00 AM and 4:00 PM. The recipient and primary Shire contact must be notified by telephone or e-mail when the samples are shipped, and they must be provided with the shipment tracking number.

Full directions for shipment of all PK samples, (along with the corresponding documentation) can be found in the laboratory manual provided under separate cover.

Pharmacokinetic samples will be stored nominally at -70° C prior to and after analysis at the laboratory performing the assay until sample disposal is authorized by Shire.

7.2.3.3 Plasma Drug Assay Methodology

Plasma sample analysis will be performed according to the relevant Standard Operating Procedures at the contract bioanalytical lab.

Plasma concentrations will be measured using the most current validated bioanalytical method. In addition, selected plasma samples may be used to investigate incurred sample reproducibility (full details will be described in the bioanalytical study plan). The presence of other metabolites or artifacts may be monitored or quantified as appropriate. Raw data will be stored in the archive of the designated bioanalytical contract laboratory.

7.2.4 Pharmacodynamic Assessments

Not applicable.

7.2.5 Pharmacogenomic Assessments

Not applicable.

7.2.5.1 Immunogenicity Assessments

SAD (Part 1)

Additionally, blood draws (6 mL in K2EDTA tubes for each applicable time-point) for determination of anti-drug antibodies (ADAs) and neutralizing antidrug antibody (nADA) will be collected prior to dose on Day 1 and at 672 hours post dose. Subjects with detectable ADAs in their plasma might require additional visits and blood collection for follow-up assessments of antibody titers up to a year post-dose.

Full directions for shipment of samples can be found in the laboratory manual under separate cover.

MAD (Part 2)

Additionally, blood draws for determination of ADAs and nADAs will be collected (6 mL in K2EDTA tubes for each applicable time-point) prior to each dose, 7 days after the last dose (Day 36), and 28 days after the last (Day 57) dose in each cohort. Subjects with detectable ADAs in their plasma on Day 57 might require additional visits and blood collection for follow-up assessments of antibody titers up to a year post-dose.

Full directions for shipment of samples can be found in the laboratory manual under separate cover.

7.2.6 Exploratory Assessments

[redacted]

7.2.7 Volume of Blood to be Drawn from Each Subject

Table 12 Volume of Blood to be Drawn from Each Subject

Assessment		Sample Volume (mL)	Number of Samples	Total Volume (mL)
SAD (Part 1 of the study)				
Pharmacokinetic samples[a]		7	14	98
ADA and nADA samples		6	2	12
HBsAg, HIV, HCV		8.5	1	8.5
Safety	Biochemistry and β-hCG[b]	8.5	6	51
	Hematology	4	6	24
	Thyroid Panel[c]	3.5	4	14
Total mL				207.5
MAD Cohorts 1-5 (Part 2 of the study)				
Pharmacokinetic samples[a]		7	22	154
ADA and nADA samples		6	7	42
HBsAg, HIV, HCV		8.5	1	8.5
Safety	Biochemistry and β-hCG[b]	8.5	13	110.5
	Hematology	4	13	52
[redacted]		6	3	18
Total mL				385
MAD Cohort 6 (Part 2 of the study)				
Pharmacokinetic samples[a]		7	20	140
ADA and nADA samples		6	7	42
HBsAg, HIV, HCV		8.5	1	8.5
Safety	Biochemistry and β-hCG[b]	8.5	13	110.5
	Hematology	4	13	52
[redacted]		6	3	18
Total mL				371

β-hCG=beta-human chorionic gonadotropin; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus

[a] If a catheter is used, the first mL is to be discarded; then take 6 mL into appropriate tube for pharmacokinetic sample. A total of 7 mL of blood drawn has been used in determination of sample volume.

[b] β-hCG testing for females only.

[c] Thyroid Panels consist of T3, T4, Free T3, TSH, and Thyroxine-binding globulin (TBG); on Day 1 and Day 8, one 3.5 mL tube will be collected. On Day 15, two 3.5 mL tubes will be collected.

During this study, it is expected that approximately 207.5 mL of blood in the SAD portion of the study, and approximately 385 mL of blood in the MAD part will be drawn from the subjects, regardless of sex.

Note: The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment; however, the total volume drawn over the course of the study should be approximately 207.5 mL and 385 mL for the SAD subjects and MAD subjects, respectively. When more than 1 blood assessment is to be done at the timepoint/period, if they require the same type of tube, the assessments may be combined.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An **AE** is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 7.1.3. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the CRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE CRF.

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

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate CRF).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the CRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved With Sequelae
- Recovering/Resolving
- Unknown

8.1.4 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory, vital sign, or ECG assessment can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory, vital sign, or ECG values which were not present at the pretreatment value observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory, vital sign, or ECG parameter is clinically significant and therefore represents an AE.

8.1.5 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until last visit (or last contact with the subject) stated in Section 7.1.3.

Any report of pregnancy for any female study participant must be reported within 24 hours to the Shire Global Safety Department using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO/Shire medical monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 1 year post partum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β-hCG test or ultrasound result will determine the pregnancy onset date.

8.1.6 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- **Overdose** – Intentional or unintentional intake of a dose of investigational product higher than the protocol-prescribed dose
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of the unassigned treatment is/are always reportable as a medication error.

The administration and/or use of an expired investigational product should be considered as a reportable medication error. Violation of storage or refrigeration requirements for the investigational product is considered a reportable medication error and as such must be reported to the sponsor.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is the Investigator's Brochure which the sponsor has provided under separate cover to all investigators. However, this is the first clinical experience with SHP681 in humans. While major AEs are not anticipated, the investigator should proceed with caution. Equipment, supplies, and properly skilled medical personnel should be immediately available for emergency use in the event of an unexpected reaction. Subjects must be carefully selected and monitored closely.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Safety Department and the CRO/Shire medical monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.6) unless they result in an SAE.

The investigator must complete, sign, and date the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested) and fax or e-mail the form to the Shire Global Pharmacovigilance and Risk Management Department.

A copy of the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form (and any applicable follow-up reports) must also be sent to the CRO/Shire medical monitor using the details specified in the emergency contact information section of the protocol.

8.2.3 Serious Adverse Event Definition

A serious adverse event (SAE) is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.

  Note: Hospitalizations that are the result of elective or previously scheduled surgery for pre-existing conditions and have not worsened after initiation of treatment should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: 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 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.3 and must be reported to the Shire Global Pharmacovigilance and Risk Management Department and the CRO/Shire medical monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Global Pharmacovigilance and Risk Management Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

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

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject's death (ie, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product action of withdrawn should not be selected solely as a result of the subject's death.

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

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

In addition the sponsor is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP681 program.

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

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the CRF. A study monitor will visit each site in accordance with the monitoring plan and review the CRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is randomized, it is expected that site personnel will complete the CRF entry within a reasonable window of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the CRO data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Data Handling Considerations

Data that may potentially unblind the treatment assignment (ie, investigational product blood concentrations, antibodies to SHP681, [redacted], treatment allocation, and investigational product preparation/accountability data, will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, prior to unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

9.4 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent.

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the PK and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

Descriptive analysis will be performed to evaluate PK endpoints and safety endpoints. All analyses/summaries will be based on observed data, with missing data handling rules specified in Section 9.8.1 or the SAP.

Continuous endpoints will be summarized with the number of subjects (n), mean, standard deviation (SD), median, minimum and maximum value. As appropriate, raw (actual) values, changes from baseline, and percent changes from baseline will be summarized at each scheduled timepoint. Baseline is defined as the last non-missing value observed prior to dosing with SHP681 or placebo. Additional summary statistics will be provided for PK endpoints and are indicated in Section 9.8.1.

Categorical endpoints will be summarized, displaying counts and percentages. Summaries will include, where applicable: number and percentage of subjects with an outcome measure and shift tables (categorical change from baseline). Summaries will be presented by dose cohort and for the placebo group, and, if appropriate, by scheduled timepoint.

All data, including derived data, will be presented in subject data listings.

To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized prior to database lock.

The pharmacokinetic analysis will be conducted using Phoenix WinNonlin version 6.2 or higher (Pharsight Corporation, Mountain View, California, USA). The statistical analyses will be performed using SAS® (SAS Institute, Cary, NC 27513).

9.5 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

To support an initiation of the MAD phase and confirm the dosing interval, an interim data analysis will be required. Blinded plasma data obtained after dosing in Cohort 1, Cohort 2, and part of Cohort 3 in the SAD portion will be evaluated and justified for this purpose.

An interim analysis will be performed after the last patient from the 3rd MAD cohort has completed the Day 39 visit, to determine the dose level of the 6th MAD cohort, and to assess any safety, tolerability, or pharmacokinetic questions based on the safety review. The data for this analysis will be source data verified and cleaned according to the Interim Snapshot Plan. This analysis will unblind all completed SAD cohorts and the first 3 MAD cohorts for the Sponsor and external statistical groups. MAD cohorts 4, 5 and 6 will not be unblinded to any parties due to this interim analysis.

No adaptive design or data monitoring committee (DMC) is planned.

9.6 Sample Size Calculation and Power Considerations

SAD (Part 1)

It is planned that dose escalation will proceed for up to 5 dose levels. Each cohort will include 5 subjects treated with SHP681 and 1 subject treated with placebo for a planned total of 30 subjects. However, if dose levels are repeated, modified, or not conducted or if additional dose levels are studied, the total number of subjects may change. The number of subjects is expected to provide reasonable information on initial testing of SHP681 for safety and PK while exposing as few subjects as possible to investigational drug materials. The number of subjects in this study is not based on statistical hypothesis testing and power considerations as this is the first in human study. The statistical analyses are primarily descriptive, and no hypothesis testing is specified for this portion.

MAD (Part 2)

It is planned that the MAD portion of the study will include 6 cohorts. Each cohort will include 10 subjects treated with SHP681 and 2 subjects treated with placebo for a planned total of 72 subjects. The number of subjects is expected to provide reasonable information on initial testing of SHP681 for safety and PK while exposing as few subjects as possible to investigational drug materials. The number of subjects in this study is not based on statistical power considerations as this is the first time in human study. The statistical analyses are primarily descriptive, and no hypothesis testing is specified in the study.

9.7 Study Population

Subject populations are separately defined to analyze the data in the SAD portion and the MAD portion of the study:

SAD

- The safety analysis set includes subjects who have received at least 1 dose of SHP681 or placebo in the SAD portion.
- The PK analysis set consists of subjects who have received at least 1 dose of SHP681 and have at least 1 evaluable post-dose PK concentration value in the SAD portion.

MAD

- The safety analysis set includes subjects who have received at least 1 dose of SHP681or placebo in the MAD portion.

The PK analysis set consists of subjects who have received at least 1 dose of SHP681 and have at least 1 evaluable post-dose PK concentration value in the MAD portion.

9.8 Pharmacokinetic Analyses

9.8.1 Pharmacokinetic Analysis

The PK analysis will be based on the PK analysis set.

Pharmacokinetic parameters will be calculated from plasma SHP681 concentration-time data using non-compartmental methods and all calculations will be based on actual sampling times. Pharmacokinetic parameters will include, but not be limited to, the following:

SAD

- C_{max} Maximum concentration occurring at t_{max}
- t_{last} Time of the last measurable concentration
- t_{max} Time of maximum observed concentration sampled during a dosing interval
- $AUC_{0\text{-}last}$ Area under the curve from the time of dosing to the last measurable concentration
- $AUC_{0\text{-}\infty}$ Area under the curve extrapolated to infinity
- $t_{1/2}$ Terminal half-life
- λ_z First order rate constant associated with the terminal (log-linear) portion of the curve
- CL/F Apparent total body clearance for extravascular administration divided by the fraction of dose absorbed calculated as dose divided by AUC0-$_\infty$.
- V_z/F Apparent volume of distribution following extravascular administration divided by the fraction of dose absorbed calculated as CL/F divided by λ_z.

MAD

Post first dose

- $AUC_{0\text{-}24}$ Area under the curve from the time of dosing to the 24 hours post first dose
- $C_{max,24}$ Maximum concentration occurring during 24 hours after first dose
- $t_{max,24}$ Time of maximum observed concentration during 24 hours after first dose

Between the first dose and last dose

- C_{trough} Observed concentration at the end of each dosing interval (immediately before next dose for the first 5 cohorts and immediately before 2nd and 3rd dose of the 6th MAD cohort)

Post last dose

- C_{max} Maximum concentration during the dosing interval occurring at t_{max}

- T_{last} Time of the last measurable concentration
- t_{max} Time of maximum observed concentration during the dosing interval
- AUC_{tau} Area under the curve for the defined interval between doses (only calculated if interpretable)
- $AUC_{0\text{-}last}$ Area under the curve from the time of dosing to the last measurable concentration post last dose
- $AUC_{0\text{-}\infty}$ Area under the curve (post last dose) extrapolated to infinity, calculated using the observed value of the last non-zero concentrations (only calculated if interpretable)
- $t_{1/2}$ Terminal half-life
- λ_z First order rate constant associated with the terminal (log-linear) portion of the curve
- CL/F Apparent total body clearance following extravascular administration divided by the fraction of dose absorbed calculated as dose divided by AUC_{tau}
- V_z/F Apparent volume of distribution following extravascular administration divided by the fraction of dose absorbed calculated as CL/F divided by λ_z

9.8.1.1 Statistical Analysis of Pharmacokinetic Parameters

The pharmacokinetic analysis will be conducted by the pharmacokinetics CRO.

The applicable analysis conventions will be detailed in the statistical analysis plan, including the minimum number of quantifiable postdose concentrations to be used to derive AUC, handling rules of concentration values below the assay quantitation limit (BLQ), handling of potential anomalous predose concentration values, etc. Subjects randomized to SHP681 but excluded from the PK analysis set will be listed by subject and reason(s) leading to exclusion.

SAD

The PK analysis will be based on the PK analysis set for the SAD portion.

Individual subject's raw concentrations of SHP681and actual sampling time will be listed by nominal sampling timepoint. Individual subject's PK parameters will be listed by dose cohort, along with the number of timepoints of the terminal log-linear phase used to estimate the terminal rate constant and percentage of extrapolated AUC.

Raw concentrations for each nominal sampling timepoint and PK parameters except t_{max} and t_{last} will be summarized by dose cohort with descriptive statistics such as number of subjects, geometric mean, median, arithmetic mean, standard, deviation, coefficient of variation, and geometric coefficient of variation, minimum and maximum. The other parameters, t_{max} and t_{last}, will be summarized by median, minimum and maximum grouped by dose cohort.

Individual subject's concentration-time curves will be presented in linear/linear and log/linear scale using lattice plots, with one panel for each subject grouped by dose cohort. Figures showing the mean (with ±SD as error bar) as well as the median (with 25th to 75th quantiles as error bar) concentration time profiles will be presented in linear/linear and log/linear scale using lattice plots, with one panel for each dose cohort. Mean and median concentration time profiles for all dose cohorts will be also visualized in one plot.

MAD

The PK analysis will be based on the PK analysis set for the MAD portion.

Individual raw concentration data and actual sampling time will be listed by nominal sampling timepoint. Individual subject's PK parameters derived post the first dose and repeat doses (ie, after the last dose) will be listed by dose cohort, along with the number of timepoints of the terminal log-linear phase used to estimate the terminal rate constant and percentage of extrapolated AUC if applicable.

Raw concentrations for each nominal sampling timepoint and PK parameters post the first dose and repeat doses, except $t_{max,24}$, t_{max} and t_{last}, will be summarized by dose cohort with descriptive statistics such as number of subjects, geometric mean, median, arithmetic mean, standard, deviation, coefficient of variation, and geometric coefficient of variation, minimum and maximum where $t_{max,24}$, t_{max} and t_{last} will be summarized by median, minimum and maximum grouped by dose cohort.

Individual subject's concentration-time profile up to 24 hours after the first dose will be visualized with correspondingly superimposed concentration-time profile up to 24 hours following the 5th dose in linear/linear and log/linear scale using lattice plots, with one panel for each subject grouped by dose cohort.

Individual concentration-time curves following after the last dose will be presented in linear/linear and log/linear scale using lattice plots, with one panel for each subject grouped by dose cohort. Mean (with ±SD as error bar) as well as the median (with 25th to 75th quantiles as error bar) concentration time profiles will be presented in linear/linear and log/linear scale using lattice plots, with one panel for each dose cohort. Mean and median concentration time profiles for all dose cohorts will be superimposed in one plot.

9.9 Safety Analyses

For each portion, statistical analysis of safety data will be based on the safety analysis data set for the portion. Descriptive analysis, as described in Section 9.4 will be performed to evaluate all safety endpoints.

Safety data will be listed by subject and summarized for each dose cohort of SHP681 and a pooled placebo group of all subjects who were administered placebo, using descriptive statistics. Continuous variables will be summarized by sample size, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized by number of subjects and the percent of subjects in each category.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. Only treatment-emergent adverse events (TEAEs) will be analyzed. The number of events, incidence, and percentage of TEAEs will be calculated overall, by system organ class, preferred term, by dose cohort and with the placebo group.

Treatment−emergent adverse events will be further summarized by seriousness, severity and relationship to investigational product. Injection site reactions will be analyzed in an analogous fashion.

All AEs (TEAEs and non-TEAEs) will be provided in the AE subject listing. Serious adverse events (SAEs) and AEs leading to withdrawal will be listed as well.

Clinical laboratory tests, vital signs, and ECG assessments and corresponding changes from baseline in each dose cohort or placebo group will be summarized, as appropriate, by study visit. Safety data, including derived data, will be presented in subject data listings. Potentially clinically important findings will also be summarized or listed in subject data listing.

Immunogenicity in each dose cohort will be analyzed by number and percent of subjects testing positive for ADA or nADA predose and by post-dose study visit.

The results of abdominal ultrasound tests for MAD Cohort 6 will be listed.

Treatment-emergent adverse events will be further summarized by severity and relationship to investigational product. Adverse events related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.

9.10 Exploratory Analysis

[redacted]

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, and local ethical and legal requirements.

The name and address of each third-party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and CRFs in accordance with current GCP and the respective local and inter/national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.3 Indemnity/Liability and Insurance

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied to the investigator as necessary.

10.1.4 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance.

10.1.5 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub-investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator, in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or, for multicenter studies, the coordinating principal investigator, according to national provisions, and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

Case report forms are supplied by the sponsor and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto CRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Case report forms must be completed by the investigator or designee as stated in the site delegation log.

All data will have separate source documentation; no data will be recorded directly onto the CRF.

All data sent to the sponsor must be endorsed by the investigator.

The CRA/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, original clinical laboratory reports, and histology and pathology reports. All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The CRA/study monitor (and auditors, IRB/EC, or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays, etc.).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent from all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

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

10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

The applicant for an EC opinion can be the sponsor or investigator for sites within the EU; for multicenter studies, the applicant can be the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the clinical trial agreement. Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the sponsor has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; for sites within the EU, this can be done by the sponsor or investigator, or, for multicenter studies, it can be done by the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with HIPAA of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the sponsor.

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

After subjects have consented to take part in the study, the sponsor and/or its representatives' reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market SHP681; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (eg, to confirm that laboratory results have been assigned to the correct subject).

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

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (eg, Good Publication Practices 2) when forming a publication steering committee. The purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish, and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single-site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.

11. REFERENCES

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12. APPENDICES

Appendix 1 Protocol History

Document	Date	Global/Country/Site Specific
Original Protocol	29 Oct 2018	Global
Amendment 1	11 Feb 2019	Global
Amendment 2	10 May 2019	Global
Amendment 3	08 Oct 2019	Global
Amendment 4	19 Nov 2019	Global