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Statistical Analysis Plan

OLP-1002 – A First-in-human, Double blind, Placebo controlled, Single and Multiple Subcutaneous Dose, Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Study in Healthy Male and Female Subjects

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LIST OF ABBREVIATIONS

Abbreviations pertain to the statistical analysis plan (SAP) only (not the tables, figures, and listings [TFLs]).

ADaM	analysis data model
AE	adverse event
AUC	area under the plasma concentration-time curve
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time 0 extrapolated to infinity
$AUC_{0-tlast}$	area under the plasma concentration-time curve from time 0 to the time of last quantifiable plasma concentration (t_{last})
$AUC_{0-\tau}$	area under the plasma concentration-time curve calculated over the dosing interval (τ)
BLQ	below the limit of quantification
CDISC	Clinical Data Interchange Standards Consortium
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
CRU	Clinical Research Unit
CSR	clinical study report
DN	dose normalized
ECG	electrocardiogram
E_{max}	maximum pain intensity
ICF	informed consent form
ICH	International Council for/Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NC	not calculated
NR	no result
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
R^2-adj	adjusted coefficient for determination of exponential fit
$RAAUC_{0-\tau}$	observed accumulation ratio based on $AUC_{0-\tau}$
RAC_{max}	observed accumulation ratio based on C_{max}
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation

$t_{1/2}$	apparent plasma terminal elimination half-life
TCP	temporal change parameter
TEAE	treatment-emergent adverse event
tE_{max}	time of maximum pain intensity
TFL	table, figure, and listing
t_{max}	time of maximum observed plasma concentration
WHODrug	World Health Organization Drug Dictionary
$\%AUC_{extrap}$	percentage of AUC that is due to extrapolation from the last measurable plasma concentration to infinity

1. INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Version 5 dated 27 September 2019) and electronic case report form.

This SAP describes the planned analysis of the pharmacokinetic (PK), pharmacodynamic (PD), and safety and tolerability data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shells document.

In general, the analyses are based on information from the protocol, unless they have been modified by agreement with OliPass Corporation. A limited amount of information about this study (eg, objectives, study design) is given to help the reader's interpretation. This SAP must be finalized prior to the lock of the clinical database for this study. When the SAP and TFL shells are approved, they will serve as the template for this study's CSR.

This SAP supersedes any statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified accordingly in the CSR. Any substantial deviations from this SAP will be agreed with OliPass Corporation and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 guideline *Statistical Principles for Clinical Trials* and ICH E3 guideline *Structure and Content of Clinical Study Reports*.[1,2]

The document history is presented in Appendix 1.

2. STUDY OBJECTIVES

The primary objective of the study is to assess the safety and tolerability of single and multiple subcutaneous (SC) doses of OLP-1002 in healthy subjects.

The exploratory objectives of the study are to evaluate the PD effect of OLP-1002 following single SC doses in healthy volunteers using a capsaicin pain model, and to monitor the effects of single SC doses of OLP-1002 on cardiac QT interval. Where possible, single and/or multiple subcutaneous dose PK of OLP-1002 in healthy subjects will be determined.

3. STUDY ENDPOINTS

3.1. Primary Endpoints

The primary safety endpoints for this study are as follows:

- incidence and severity of adverse events (AEs)
- vital signs measurements (blood pressure, pulse rate, respiratory rate)
- 12-lead electrocardiogram (ECG) parameters

- incidence of clinical laboratory abnormalities, based on clinical chemistry, hematology, and urinalysis test results
- physical examinations
- injection site assessment
- demonstrate that exposure to OLP-1002 does not exceed pre-defined exposure limits from non-clinical studies.

3.2. Exploratory Endpoints

The following exploratory objectives will be assessed:

- pain intensity and duration will be assessed by area under the curve (AUC), maximum pain intensity (E_{max}), and time of maximum pain intensity (tE_{max}), calculated using a capsaicin-evoked pain model. The exploratory endpoint of secondary hyperalgesia will be assessed by the area of secondary area of hyperalgesia (Part A only).
- continuous (24-hour) ECG monitoring will be recorded in this study and archived for potential future analysis of OLP-1002 effects on the QT interval (Part A only).
- heat pain threshold measurements and heat pain tolerance measurements.
- For Part A, the single ascending dose, PK outcome endpoints of OLP-1002 are as follows:

  Primary PK

  - area under the plasma concentration-time curve (AUC) from time 0 to infinity ($AUC_{0-\infty}$) (actual and dose normalized [DN])
  - AUC from time 0 to the time of the last quantifiable concentration ($AUC_{0-tlast}$) (actual and DN)
  - maximum observed plasma concentration (C_{max}) (actual and DN)

  Secondary PK

  - time of the maximum observed plasma concentration (t_{max})
  - apparent plasma terminal elimination half-life ($t_{1/2}$)

- For Part B, the multiple ascending dose PK outcome endpoints of OLP-1002 are as follows:

  Primary PK

  - AUC over a dosing interval ($AUC_{0-\tau}$) (actual and DN)
  - $AUC_{0-\infty}$ (actual and DN)

- C_{max} (actual and DN)

Secondary PK

- minimum observed plasma concentration (C_{min})
- t_{max}
- $t_{1/2}$
- observed accumulation ratio based on $AUC_{0-\tau}$ ($RAAUC_{0-\tau}$)
- observed accumulation ratio based on C_{max} (RAC_{max}).
- Temporal change parameter (TCP)

Other PK parameters may also be added if deemed necessary.

4. STUDY DESIGN

This will be a double-blind, randomized, placebo-controlled, single and multiple SC dose study conducted in 2 parts.

4.1. Part A

Part A will comprise a single-dose, sequential-group design. Overall, 68 healthy subjects will be studied in 11 groups.

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Potential subjects for Groups A2, A4, A6, A9, A10, and A11 will attend a pre-screening visit for an intradermal capsaicin test.

Each subject will participate in 1 treatment period only, and will reside at the Clinical Research Unit (CRU) from Day -2 (2 days before dosing) to Day 3. All subjects will return for non-residential visits on Days 4, 7 (±2 days), 10 (±2 days), and 14 (±2 days), and for a poststudy visit on Day 28 (±2 days).

Based on the ongoing review of the safety and tolerability, additional non-residential visits may be required. The number of additional visits per subject will not exceed 3 and will not extend beyond Day 28 (±2 days).

Doses will be administered in an escalating manner following satisfactory review of safety and tolerability data up to Day 10 (216 hours postdose) from the lower dose levels. For doses ≥12 µg, PK data will also be reviewed up to Day 7 prior to dose escalation.

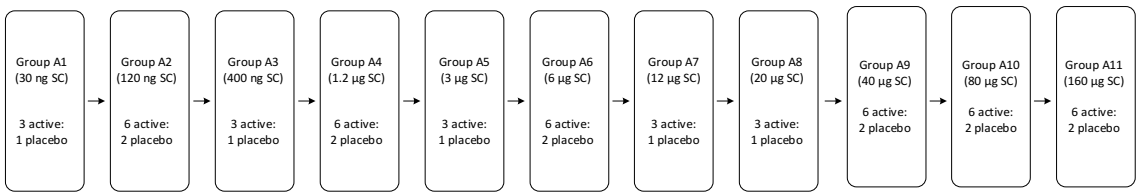
In Part A, Groups A1, A3, A5, A7, and A8 will consist of 4 subjects; 3 subjects will receive OLP-1002 and 1 subject will receive placebo. To assess PD parameters, Groups A2, A4, A6, A9, A10, and A11 will consist of 8 subjects; 6 subjects will receive OLP-1002 and 2 subjects will receive placebo.

Sentinel dosing will be employed for all groups in Part A. To maintain the blind in a 4-subject group, the first subject will be dosed 48 hours before the second subject, and the second subject will be dosed 48 hours prior to the third and fourth subjects. In PD assessment groups, 2 subjects (1 active: 1 placebo) will be dosed 48 hours before the remaining 6 subjects (5 active: 1 placebo).

The total duration of study participation for each subject (from Screening through Follow-up visit) is anticipated to be approximately 8 weeks.

A schematic of the study design is presented in Figure 1.

Figure 1: Study Design (Part A)



Active = OLP-1002; SC = subcutaneous
6 groups consist of 8 subjects (6 active: 2 placebo); all other groups will consist of 4 subjects (3 active: 1 placebo).

4.2. Part B

Part B will comprise a multiple-dose, sequential-group study. Overall, 32 subjects will be studied in 4 groups (Groups B1 to B4), with each group consisting of 8 subjects. Up to 2 additional groups (16 subjects in total) may be included for further assessment of safety and tolerability.

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Each subject will participate in 1 treatment period only and reside at the CRU from Day -1 until Day 15.

All subjects will return for non-residential visits on Days 18 (±2 days), 22 (±2 days), 25 (±2 days), and 29 (±2 days), and for a poststudy visit on Day 57 (±2 days).

In each of Groups B1 to B4, 6 subjects will receive OLP-1002 and 2 subjects will receive placebo. For all subjects, a single SC dose will be administered on Days 1, 4, 7, 10, and 13. Prior to each dosing occasion a physician will review the available safety and tolerability data from each subject to confirm it is acceptable to continue dosing. The dosing frequency in Part B may be changed following review of data from groups in Part A.

Sentinel dosing will only occur in Part B at dose levels where exposure to OLP-1002 at steady state is predicted to exceed exposures that have been shown to be safe and well

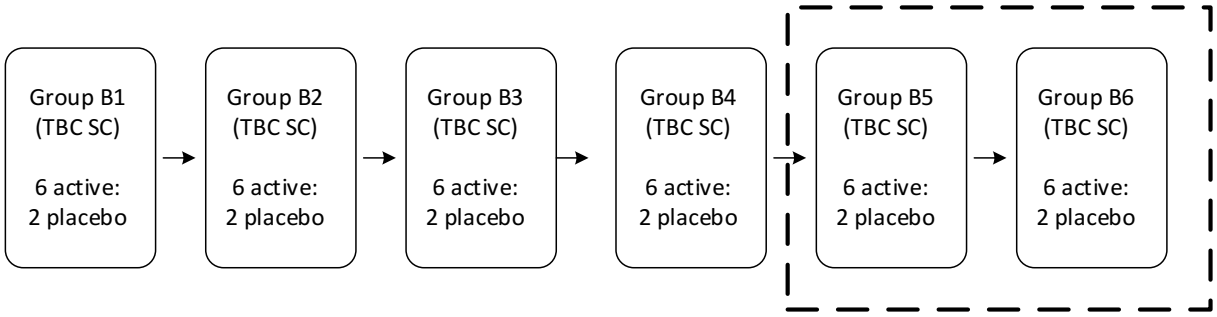
tolerated in earlier groups in Parts A or B. In the event of sentinel dosing, 2 subjects (1 active, 1 placebo) will be dosed at least 4 days prior to the remaining 6 subjects (5 active: 1 placebo). Safety data for the sentinel subjects from at least 2 additional doses will be reviewed prior to dosing the remaining subjects (i.e. sentinel subjects' safety data after doses 1 and 2 will be reviewed prior to the remaining subjects receiving dose 1). In addition, safety data from each subject will be reviewed by a physician prior to each dose to approve continued dosing.

Doses will be administered in an escalating manner following satisfactory review of safety, tolerability, and PK data up to Day 22 (216 hours post-final dose) from the lower dose levels. Part B may start after a review of the safety, tolerability, and available PK for Groups A1 to A6. The total daily dose administered will not exceed the highest single dose given in Part A.

The total duration of study participation for each subject (from Screening through Follow-up visit) is anticipated to be approximately 12 weeks.

A schematic of the study design is presented in Figure 2.

Figure 2: Study Design (Part B)



Active = OLP-1002; SC = subcutaneous; TBC = to be confirmed.
All doses will be confirmed based on results of Part A and previous groups in Part B
Groups B5 and B6 will be included if required.

5. SAMPLE SIZE JUSTIFICATION

No formal statistical assessment, in terms of sample size, has been conducted as this is the first time OLP-1002 is being administered to humans. However, the number of subjects in each part of the present study is common in early clinical pharmacology studies and is considered sufficient to achieve the objectives of the study. As part of Protocol Version 5, 3 additional groups will be included in Part A (Groups A9, A10, and A11) and 1 additional group will be included in Part B (Group B4). Up to 2 additional groups of 8 subjects may be added to Part B (6 active; 2 placebo).

6. STUDY TREATMENTS

6.1. Part A

The study treatment names and ordering to be used in the TFLs are presented in Table 1.

Table 1: Presentation of Study Treatments in TFLs (Part A)

Group	Study Treatment	Order in TFLs
A1 to A11	Placebo[a]	1
A1	30 ng OLP-1002	2
A2	120 ng OLP-1002	3
A3	400 ng OLP-1002	4
A4	1.2 µg OLP-1002	5
A5	3 µg OLP-1002	6
A6	6 µg OLP-1002	7
A7	12 µg OLP-1002	8
A8	20 µg OLP-1002	9
A9[b]	40 µg OLP-1002	10
A10[b]	80 µg OLP-1002	11
A11[b]	160 µg OLP-1002	12

[a] Placebo will be pooled across all groups
[b] Groups to be included if required

All treatments described above are the planned treatments. The TFLs will reflect the actual treatments received, and dose levels will be displayed in increasing order.

6.2. Part B

The study treatment names and ordering to be used in the TFLs are presented in Table 2.

Table 2: Presentation of Study Treatments in TFLs (Part B)

Group	Study Treatment	Order in TFLs
B1 to B6	Placebo[a]	1
B1	XX µg OLP-1002	2
B2	XX µg OLP-1002	3
B3	XX µg OLP-1002	4
B4[b]	XX µg OLP-1002	5
B5[b]	XX µg OLP-1002	6
B6[b]	XX µg OLP-1002	7

[a] Placebo will be pooled across all groups
[b] Groups to be included if required

The TFLs will reflect the actual treatments received, and dose levels will be displayed in increasing order. The following footnote will be applied in all applicable Part B TFLs: "Dosing regimen was a single subcutaneous dose administered on Days 1, 4, 7, 10 and 13."

7. DEFINITIONS OF POPULATIONS

Any protocol deviations will be considered prior to database lock for their importance and taken into consideration when assigning subjects to populations.

7.1. All Subjects Population

The all subjects population will include all subjects who signed the informed consent form (ICF) and had any study assessment recorded in the database per the protocol.

7.2. Safety Population

The safety population will include all subjects who received a dose of study treatment (OLP-1002 or Placebo).

7.3. Pharmacokinetic Population

The PK population will include all subjects who received a dose of study treatment (OLP-1002), have at least 1 quantifiable PK concentration, and have had no AEs or protocol deviations considered to impact PK.

7.4. Pharmacodynamic Population

The PD population will include all subjects who received at least 1 dose of study treatment (OLP-1002 or Placebo) and have at least 1 postdose PD assessment.

8. STATISTICAL METHODOLOGY

8.1. General

Listings will be provided for all data captured in the database, with the exception of medical history. Listings will include all subjects assigned to the all subjects population and include data up to the point of study completion or discontinuation. Any subject who discontinued the study will be identified accordingly in the listings. Summaries will include the subjects assigned to the relevant population based on data type.

Data analysis will be performed using the SAS® statistical software package Version 9.4 (or higher if upversioned during the study).

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1 (or higher if upversioned during the study) and CDISC ADaM Implementation Guide Version 1.1 (or higher if upversioned during the study). Pinnacle 21 Community Validator Version 2.2.0 (or higher if upversioned during the study) will be utilized to ensure compliance with CDISC standards.

Where reference is made to ‘all calculations’, this includes, but is not limited to, summary statistics, baseline derivation, changes from baseline, and any parameter derivations.

8.1.1. Calculation of the Summary Statistics

For continuous data the following rules will be applied:

- Missing values will not be imputed, unless specifically stated otherwise.
- Unrounded data will be used in the calculation of summary statistics.

- If number of subjects with valid observations (n) <3, summary statistics will not be calculated, with the exception of n, minimum, and maximum.

- As Early Termination data is not associated with any scheduled timepoint, it will be excluded from all calculations of summary statistics.

For categorical data the following rules will be applied:

- If the categories of a parameter are ordered (eg, AE severity), all categories between the possible minimum and maximum categories will be included, even if n = 0 for a given category. If the categories are not ordered (eg, race), only those categories for which there is at least 1 subject represented will be included.

- Missing values will not be imputed, with the exception of AEs where the 'worst-case' approach will be taken (see Section 8.7.1), or unless specifically stated otherwise. A 'missing' category will be included for any parameter for which information is missing. This will ensure that the population size totals are consistent across different parameters.

8.1.2. Triplicate Readings

For vital signs data only, where triplicate readings are taken, the median of triplicate readings will replace the original readings in all calculations.

For electrocardiogram (ECG) data only, where triplicate readings are taken, the mean of triplicate readings will replace the original readings in all calculations.

In case of incomplete triplicate readings (eg, only 2 out of 3 readings were recorded), the mean and/or medians will be calculated based on the number of readings available.

8.1.3. Repeat and Unscheduled Readings

For vital signs and ECG data only, any predose value recorded in addition to the original value or a postdose value recorded within 15 minutes of the original value will be defined as a repeat value; any postdose value recorded more than 15 minutes after the original value will be defined as an unscheduled value. For all other data types (eg, laboratory parameters), any value recorded in addition to the original value will be defined as an unscheduled value.

The original value will be replaced by the last associated repeat value in all calculations, with the exception of the ECG outlier analysis (see Section 8.7.4).

As unscheduled values are not associated with any scheduled timepoint, they will be excluded from all calculations, with the exception of the baseline derivation (see Section 8.1.4) and ECG outlier analysis (see Section 10.7.4).

8.1.4. Definitions of Baseline and Change from Baseline

The baseline will be defined as the last value recorded prior to dosing (Part A) or the first dose (Part B). If the date/time of the value is incomplete or missing, it will be excluded from

the baseline calculation, unless the incomplete date/time indicates the value was recorded prior to dosing (Part A) or the first dose (Part B).

Individual changes from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The mean change from baseline will be defined as the mean of the individual changes from baseline for all subjects.

See Section 8.1.3 for more detail on handling repeat and unscheduled readings in the calculations. See Section 8.1.2 for more detail on handling of triplicate readings in the calculations.

8.2. Subject Disposition and Population Assignment

Subject disposition and population assignment will be listed.

A summary table by treatment will be provided, based on the all subjects population.

8.3. Screening Demographics

The screening demographics including age, sex, race, ethnicity, height, body weight, and body mass index will be listed.

A summary table by treatment will be provided, based on the safety population.

8.4. Prior and Concomitant Medication

Prior medication will be defined as medication that ends prior to dosing (Part A) or the first dose (Part B). Concomitant medication will be defined as medication that starts after dosing (Part A) or the first dose (Part B) or starts but does not end prior to dosing (Part A) or the first dose (Part B).

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) Global, Format B3, Version March 2018 (or later if upversioned during the study). Prior and concomitant medications will be listed.

8.5. Pharmacokinetic Assessments

8.5.1. Pharmacokinetic Analysis

The following PK parameters will be determined where possible from the plasma concentrations of OLP-1002 using non-compartmental methods performed using Phoenix WinNonlin (Version 8.1 or higher):

Part A

Parameter	Definition
$AUC_{0\text{-}tlast}$	area under the plasma concentration-time curve from time 0 to the time of last quantifiable plasma concentration (t_{last}), calculated using the linear trapezoidal rule for increasing plasma concentrations and the logarithmic rule for decreasing plasma concentrations

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time 0 extrapolated to infinity
$\%AUC_{extrap}$	percentage of AUC that is due to extrapolation from the last measurable plasma concentration to infinity
C_{max}	maximum observed plasma concentration
t_{max}	time of maximum observed plasma concentration
$t_{1/2}$	apparent plasma terminal elimination half-life

Part B

Parameter	Definition
$AUC_{0-\tau}$	area under the plasma concentration-time curve calculated over the dosing interval (τ)
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time 0 extrapolated to infinity
$\%AUC_{extrap}$	percentage of AUC that is due to extrapolation from the last measurable plasma concentration to infinity
C_{max}	maximum observed plasma concentration
C_{trough}	concentration observed at the end of the dosing interval
t_{max}	time of maximum observed plasma concentration
$t_{1/2}$	apparent plasma terminal elimination half-life
$RAAUC_{0-\tau}$	observed accumulation ratio based on $AUC_{0-\tau}$, calculated as $AUC_{0-\tau}$ on profile day 15 / $AUC_{0-\tau}$ on profile day 1
RAC_{max}	observed accumulation ratio based on C_{max}, calculated as C_{max} on profile day 15 / C_{max} on profile day 1
TCP	temporal change parameter, calculated as $AUC_{0-\tau}$ on profile day 15 / $AUC_{0-\infty}$ on profile day 1

The DN $AUC_{0-\infty}$, DN $AUC_{0-tlast}$ and DN C_{max} will be calculated by dividing the original PK parameter by dose.

Additional PK parameters may be determined where appropriate.

The PK analysis will, where possible, be carried out using actual postdose times recorded in the raw data. If actual times are missing, nominal times may be used.

Concentrations are used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory.

C_{max} and t_{max} will be obtained directly from the plasma concentration-time profiles.

For multiple peaks, the highest postdose concentration will be reported as C_{max}. In the case that multiple peaks are of equal magnitude, the earliest t_{max} will be reported.

8.5.1.1. Criteria for handling concentrations below the limit of quantification in Pharmacokinetic analysis

- Concentration values that are below the level of quantification (BLQ) will be set to 0, with defined exceptions as follows;

- Any embedded BLQ value (between 2 quantifiable concentrations) and BLQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis.

- If there are late positive concentration values following 2 BLQ concentration values in the apparent terminal phase, these values will be evaluated. If these values are considered to be anomalous, they will be set to missing.

- If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.

- If a predose concentration is missing in Part A or on Day 1 of Part B, these values may be set to 0 with sponsor approval.

8.5.1.2. Criteria for the Calculation of an Apparent Terminal Elimination Half-Life

8.5.1.2.1. Number of Data Points

- At least 3 data points will be included in the regression analysis and preferably should not include C_{max}.

8.5.1.2.2. Goodness of Fit

- When assessing terminal elimination phases, the adjusted coefficient for determination of exponential fit (R^2-adj) will be used as a measure of the goodness of fit of the data points to the determined line.

- Regression based parameters ($AUC_{0-\infty}$, $t_{1/2}$) will only be calculated if the R^2-adj ≥ 0.7.

8.5.1.2.3. Period of Estimation

- Time period used for the estimation of $t_{1/2}$, where possible, will be over at least 2 half-lives. The regression listing will include the time period over which the $t_{1/2}$ was derived as a ratio of the determined $t_{1/2}$ for each subject.

- Where an elimination half-life is estimated over a time period <2 half-lives, it will be flagged in the data listings at the discretion of the pharmacokineticist, and the robustness of the value should be discussed in the CSR.

8.5.1.3. Calculation of AUC

- The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least 1 of these concentrations following C_{max}.

- For any partial AUC determination (i.e. AUC over a dosing interval), nominal time will generally be used for the end of the interval. Actual times for partial AUC intervals may be used at the discretion of the Pharmacokineticist.

- $AUC_{0-\infty}$ values where the percentage extrapolation <20% will be reported. $AUC_{0-\infty}$ values where the percentage extrapolation is between 20 to 30% will be flagged and included in the summary statistics, whilst $AUC_{0-\infty}$ values where the percentage extrapolation is >30% will be reported and flagged but excluded from summary statistics.

- If $AUC_{0-\infty}$ cannot be determined for all subjects or all dose levels, an alternative AUC measure, such as AUC to a fixed time point, may be used in the assessment of dose proportionality.

8.5.1.4. Anomalous Values

- If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude this point from the PK analysis. However, the exclusion of data must have strong justification and will be documented in the raw data and CSR.

- Embedded BLQ values may be considered anomalous depending on the route of administration and the characteristics of the drug.

- Positive predose value(s) >5% of C_{max} may be excluded from the summary statistics of PK tables and statistical analysis at the discretion of the pharmacokineticist.

8.5.2. Presentation Pharmacokinetic Plasma Concentration Data

- The following rules will be applied if there are values that are BLQ or if there are missing values in a plasma concentration data series to be summarized.

  - For the calculation of summary statistics, BLQ values will be set to 0.

  - If an embedded BLQ value is considered anomalous within the concentration-time profile, this value will be excluded from the summary statistics.

  - If the value of the arithmetic mean or median is BLQ, these values will be presented as 0 and the geometric mean and geometric coefficient of variation will not be calculated.

  - Concentrations collected with a time deviation from nominal time >10% will be reported and flagged but excluded from summary statistics.

8.5.3. Pharmacokinetic Statistical Methodology

All PK concentrations and parameters will be listed.

Summary tables, mean (+ standard deviation [SD]) figures, overlaying individual figures, and individual figures by treatment and time postdose will be provided for plasma PK concentrations. All figures will be produced on both linear and semi-logarithmic scales, with the exception of figures across all days (for Part B only), which will be produced on the linear scale only. The +SD bars will be only displayed on the linear scale.

Summary tables by treatment will be provided for all PK parameters, with the exception of regression-related PK parameters.

No inferential statistical analyses are planned.

8.6. Pharmacodynamic Assessments (Part A Only)

Capsaicin intradermal test will be performed for subjects in Groups A2, A4, A6, A9, A10 and A11. Each subject will be tested at a pre-screening visit before being tested twice during the study (1 predose and 1 postdose).

8.6.1. Capsaicin-evoked Pain Model

The capsaicin model will be conducted by intradermal injection of capsaicin (100 µg in 100 µL of sterile saline containing 8% [w/w] Tween 80) into the skin of the anterior aspect of the forearm, midway between the elbow and the wrist. The bleb area (wheal) will be a sign of local plasma extravasation. An assessment of the pain intensity related to capsaicin injection will be estimated by repeated use of a VAS from injection to 5 minutes post-injection or until the pain intensity returned to 0. The AUC, E_{max}, and tE_{max} will be calculated and reported using dedicated software.

8.6.2. Secondary Hyperalgesia

The area of secondary hyperalgesia will be quantified with a 60-g weighted von Frey hair, by stimulating along 8 linear paths (4 vectors crossing at the location of the injection site) arranged vertically and horizontally around the stimulation site in 5-mm steps (starting approximately 6 cm away from the injection site). The area of secondary hyperalgesia will be evaluated at 5 and 30 minutes post-capsaicin injection.

8.6.3. Pharmacodynamic Statistical Methodology

All PD data and parameters will be listed.

Summary tables and mean figures by treatment and timepoint will be provided for all PD parameters.

Values recorded as $<x$, $\leq x$, $>x$, or $\geq x$ will be displayed in the listings as recorded. For the derivation of listing flags, calculation of summary statistics, and presentation in the figures, $<x$ and $\leq x$ values will be set to half of x, whereas $>x$ and $\geq x$ values will be set to x.

No inferential statistical analyses are planned.

8.7. Safety and Tolerability Assessments

8.7.1. Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0 (or higher if upversioned during the study).

A treatment-emergent adverse event (TEAE) will be defined as an AE that starts during or after dosing (Part A) or the first dose (Part B), or starts prior to dosing (Part A) or the first dose (Part B) and increases in severity after dosing (Part A) or the first dose (Part B).

A treatment-related TEAE will be defined as a TEAE with a relationship of possibly related or related to the study treatment, as determined by the investigator.

All AEs will be listed. In addition to the data recorded in the database, the listings will include derived onset time and duration. Onset time will be calculated from the time of dosing TEAEs only.

The frequency of subjects with TEAEs and the number of TEAEs will be summarized for the following categories:

- TEAEs (overall, serious, leading to discontinuation, and leading to death) by treatment
- TEAEs by severity and treatment
- Treatment-related TEAEs (overall, serious, leading to discontinuation, and leading to death) by treatment
- Treatment-related TEAEs by severity and treatment

The frequency of subjects will be summarized separately for TEAEs and treatment-related TEAEs by the following:

- System organ class, preferred term, and treatment
- Preferred term and treatment
- System organ class, preferred term, day of onset, and treatment (Part B only)

For the AE data the following rules will apply:

- For the derivation of TEAE status: If the start date/time of an AE is incomplete or missing, an AE will be assumed to be a TEAE, unless the incomplete start date/time or the end date/time indicates an AE started prior to dosing (Part A) or the first dose (Part B).
- For the derivation of treatment-related TEAE status: If the study treatment relationship for a TEAE is missing, a TEAE will be assumed to be a treatment-related TEAE.
- For the derivation of onset time: If the start date/time of an AE is missing, onset time will not be calculated. If the start date/time of an AE is incomplete, where possible, the minimum possible onset time will be calculated and presented in '≥DD:HH:MM' format (eg, if the date/time of dosing is 01MAY2019/08:00 and recorded start date/time of an AE is 03MAY2019, then the minimum possible onset time will be calculated by assuming the an AE started at the first hour and minute of 03MAY2019 [03MAY2019/00:00], thus will be presented as onset time ≥01:16:00 in the listing).

- For the derivation of duration: If the end date/time of an AE is missing, duration will not be calculated. If the start or end date/time of an AE is incomplete, where possible, the maximum possible duration will be calculated and presented in '≤DD:HH:MM' format (eg, if the start of an AE date/time is 01MAY2019/08:00 and its recorded end date/time is 03MAY2019, then the maximum possible duration will be calculated by assuming the AE ended at the last hour and minute of 03MAY2019 [03MAY2019/23:59], thus will be presented as duration ≤02:15:59 in the listing).

- For the calculation of summary statistics: If the severity of a TEAE is missing, a TEAE will be counted under the maximum severity possible.

- For the calculation of summary statistics: If a subject experienced multiple TEAEs with the same preferred term for the same treatment, this will be counted as 1 TEAE for that treatment under the maximum severity recorded.

8.7.2. Clinical Laboratory Parameters

All clinical laboratory parameters will be listed; any value outside the clinical reference range will be flagged. Separate listings will be provided for any parameter for which there is any individual subject value outside the respective clinical reference range.

Summary tables and boxplots by treatment and timepoint will be provided for clinical chemistry and hematology parameters.

Values recorded as <x, ≤x, >x, or ≥x will be displayed in the listings as recorded. For the derivation of listing flags, calculation of summary statistics, and presentation in the figures, <x and ≤x values will be set to half of x, whereas >x and ≥x values will be set to x.

8.7.3. Vital Signs Parameters

All vital signs parameters, with changes from baseline will be listed; any value outside the clinical reference range will be flagged.

Summary tables and boxplots by treatment and timepoint will be provided for all vital signs parameters with changes from baseline.

8.7.4. 12-lead Electrocardiogram Parameters

All 12-lead ECG parameters, with changes from baseline will be listed; any value outside the clinical reference range will be flagged.

Summary tables and boxplots by treatment and timepoint will be provided for all 12-lead ECG parameters, with changes from baseline.

An outlier analysis will be performed for QT interval corrected for heart rate using Bazett's formula (QTcB) and QT interval corrected for heart rate using Fridericia's formula (QTcF). The analysis will include all individual original, repeat, and unscheduled postdose values.

The maximum postdose values will be summarized by treatment according to the following categories:

- ≤450 ms
- >450 and ≤480 ms (all instances flagged in the listing)
- >480 and ≤500 ms (all instances flagged in the listing)
- >500 ms (all instances flagged in the listing)

The maximum increases from baseline will be summarized by treatment according to the following categories:

- ≤30 ms
- >30 and ≤60 ms (all instances flagged in the listing)
- >60 ms (all instances flagged in the listing)

8.7.5. Heat Pain Threshold and Tolerance Tests

Heat pain threshold and tolerance level tests will be conducted using a computer-controlled thermal sensory analyzer device on the subject's thigh.

For the heat pain threshold and heat pain tolerance tests, each test will be performed 3 times at each scheduled timepoint and the computer will record the mean time recording from the 3 experiments for that timepoint.

All heat pain threshold and tolerance tests data, with changes from baseline will be listed.

Summary tables by treatment and timepoint will be provided for heat pain threshold and tolerance tests data, with changes from baseline.

8.7.6. Injection Site Assessments

Injection site assessments will involve evaluation of the dosing site for the following criteria:

- Pain will be evaluated according to the following scale:

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
None	Does not interfere with activity	Interferes with activity or repeated use of non-narcotic pain reliever	Prevents daily activity or repeated use of narcotic pain reliever	Requires medical intervention greater than analgesia

- Redness will be assessed by estimating the size of the red patch at the injection site across its widest point, and will be evaluated according to the following scale:

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
0-24 mm	25-50 mm	51-100 mm	More than 100 mm	Requires medical intervention greater than analgesia

- Swelling will be assessed by estimating the size of the raised area around the injection site across its widest point, and will be evaluated according to the following scale:

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
0-24 mm	25-50 mm and does not interfere with activity	51-100 mm or interferes with activity	More than 100 mm and prevents daily activity	Requires medical intervention greater than analgesia

  In addition, how the swelling affects the subject in their daily routing activities will be considered.

- Tenderness will be evaluated using the following scale:

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
None	Mild pain to touch	Moderate Pain to touch	Severe pain to touch	Requires medical intervention greater than analgesia

- Bruising and ulceration will be evaluated as being present or absent

Local tolerability ratings of ≥Grade 3 and the presence of ulceration will be recorded as an AE.

All injection site assessment data will be listed.

Summary tables by treatment and timepoint will be provided for injection site assessment data.

8.7.7. Other Assessments

All other safety and tolerability assessments not detailed in the above sections will be listed only.

Medical history will not be listed.

8.7.8. Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

9. INTERIM ANALYSES

In Part A, doses will be administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, and tolerability data up to Day 10 (216 hours postdose) from groups that received lower doses of OLP-1002. For escalation to doses ≥12 µg, PK data up to Day 7 (144 hours postdose) will also be reviewed. All available safety, tolerability, and PK data from previous groups will be reviewed prior to dose escalation.

In Part B, doses will be administered in an escalating manner following satisfactory review of safety, tolerability, and PK data up to Day 22 (216 hours post-final dose) from groups that received lower doses of OLP-1002. Doses may be reduced and may be lower than the starting dose. Available safety, tolerability, and PK data from all previous groups will be reviewed prior to dose escalation.

Dose escalation in Part A will only occur if data from a minimum of 4 subjects (Groups A1, A3, A5, A7, and A8) or 6 subjects (Groups A2, A4, A6, A9, A10, and A11) have been reviewed from the previous lower dose group, such that data from a minimum of 3 or 4 subjects, respectively, who have received OLP-1002 will be used to make the dose-escalation decision. Dose escalation in Part B will only occur if data from a minimum of 6 subjects have been reviewed from the previous lower dose group, such that data from a minimum of 4 subjects who have received OLP-1002 will be used to make the dose-escalation decision.

The justification for this is as follows:

- The study drug is of a known pharmacological class for which the on-target effects in humans are well characterized. Based upon nonclinical data, no clinically important off-target effects are expected within the proposed dose range.

- A minimum of 3 subjects receiving the active drug is considered sufficient to characterize the safety profile for OLP-1002.

Between each dose escalation, the Investigator will review all available blinded data to ensure it is safe to proceed with the planned dose escalation. An interim safety report, summarizing results from all available safety assessments, will be sent to the Sponsor and a dose-escalation meeting will occur prior to the start of each successive group. Any clinically significant results will be discussed with the Sponsor before dose escalation continues. Interim PD data may also be reviewed on an ongoing basis. In the event of a disagreement between Sponsor and Investigator on the dose-escalation decision, the decision of the Investigator will be upheld.

10. SIGNIFICANT CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSES

There were no significant changes from the protocol-specified analyses.

11. REFERENCES

1. ICH. ICH Harmonised Tripartite Guideline: Statistical principles for clinical trials (E9). 5 February 1998.

2. ICH. ICH Harmonised Tripartite Guideline: Structure and content of clinical study reports (E3). 30 November 1995.

12. APPENDICES

Appendix 1: Document History

Version, Status	Date of Change	Summary/Reason for Change
Version 1, Final	NA	NA; the first version.

NA = not applicable

Statistical Analysis Plan Approval Form

Sponsor Name:	OliPass Corporation
Sponsor Protocol ID:	OLP-1002-001
Covance Study ID:	8379789
SAP Text Filename:	OLP-1002-001_SAP_Final V1.docx
TFL Shells Filename:	OLP-1002-001_TFL_Shells_Final V1.docx
Version:	Final V1
Date:	07 October 2019

Covance Approval(s):

[redacted] 11 Oct 2019
Date

[redacted]
Printed Name/Title - Statistician, Qualifications

[redacted] 11 OCT 2019
Signature Date

[redacted]
Printed Name/Title

Sponsor Approval(s):

By signing below when the statistical analysis plan (SAP) is considered final, the signatories agree to the analyses to be performed for this study; and to the format of the associated tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the TFLs based on this document can proceed. Any modifications to the SAP and TFLs made after signing may result in a work-scope change.

[redacted] Oct 11, 2019
Signature Date

[redacted]
Printed Name/Title

[redacted] Oct 11, 2019
Signature Date

[redacted]
Printed Name/Title

Please scan/email completed form(s) to the Lead Statistician listed below:

Printed Name/Title:	[redacted]
Email:	