STATISTICAL ANALYSIS PLAN

Study: DV0012

Product: Zilucoplan

AN OPEN-LABEL, SINGLE CENTER, RANDOMIZED, 2-WAY CROSSOVER, SINGLE-DOSE, BIOEQUIVALENCE STUDY OF ZILUCOPLAN INJECTED SUBCUTANEOUSLY EITHER BY A PREFILLED SYRINGE OR AN AUTO-INJECTOR IN HEALTHY ADULT PARTICIPANTS

SHORT TITLE:

An open-label, single center, randomized, 2-way crossover, single dose, bioequivalence study of zilucoplan injected subcutaneously in healthy adult participants

Sponsor Name:
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Confidentiality Statement

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VERSION HISTORY

This Statistical Analysis Plan (SAP) is based on Protocol Amendment 1 dated 19 March 2024.

SAP Version	Date	Change	Rationale
1	11 Nov 2024	Not Applicable	Original version

1 INTRODUCTION

The purpose of this SAP is to provide all the information that is necessary to perform the required statistical analysis of DV0012. The SAP is based on the protocol and details what will be provided in the tables, figures, and listings (TFLs) in the final clinical study report (CSR). The TFL specifications are contained in a separate document and are based on the UCB Standard TFL Shells.

Unless specified in the sections below, the study will be analyzed as described in the most recent version of the protocol. If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this SAP will be amended accordingly. In addition, if the methodology for the analysis of key endpoints must be modified or updated prior to database lock, a SAP amendment will be required. If, after database lock, additional analysis is required to supplement the planned analysis described in this SAP, the changes will be described in the CSR together with the associated rationale. Other minor changes to non-key analysis will also be documented in the CSR.

The content of this SAP is compatible with the International Council for Harmonisation (ICH) E9 Guidance documents (Phillips and Haudiquet, 2003).

Changes to protocol-planned analyses are described in Section 4.8.

1.1 Objectives and endpoints

The objectives of the study and associated endpoints are presented in Table 1–1.

Table 1–1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To establish the bioequivalence of ZLP pharmacokinetics (PK) after a single sc injection with ZLP safety syringe (ZLP- PFS) and ZLP-AI	• Area under the plasma concentration-time curve from time 0 to infinity (AUC) • Area under the plasma concentration-time curve from time 0 to time t (AUC_{0-t}) • Maximum observed plasma concentration (C_{max})
Secondary	
• To evaluate the safety and tolerability of ZLP after a single sc injection with ZLP-PFS and ZLP-AI	• Occurrence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse device effects (ADEs, serious and nonserious) from Day 1 up to the End of Study (EOS) or Early Termination (ET) Visit

Table 1–1: Objectives and Endpoints

Exploratory	
• To further evaluate the safety and tolerability of ZLP after a single sc injection with ZLP-PFS and ZLP-AI • To further evaluate the PK of ZLP after a single sc injection with ZLP-PFS and ZLP-AI • To evaluate device deficiencies	• Change from Baseline in clinical laboratory tests (hematology, clinical chemistry, and urinalysis) • Terminal half-life ($t_{½}$) • Apparent plasma clearance (CL/F) • Time to maximum observed concentration (t_{max}) • Apparent volume of distribution (V_z/F) • Device deficiencies as reported via the electronic case report form (eCRF)

sc=subcutaneous; ZLP=zilucoplan; ZLP-AI=zilucoplan-autoinjector; ZLP-PFS=zilucoplan-prefilled syringe

1.2 Study design

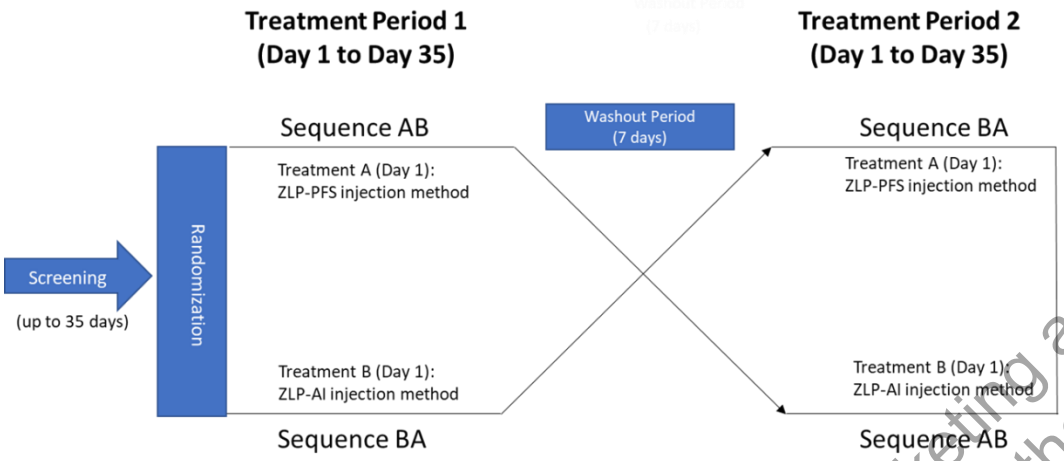
DV0012 is a Phase 1, open-label, single-center, randomized, 2-way crossover study in 14 healthy study participants designed to establish bioequivalence in zilucoplan (ZLP) pharmacokinetics (PK) between a single sc injection of ZLP from a safety syringe (ZLP-PFS; reference product) and an auto-injector (ZLP-AI; test product), and to investigate the PK, safety, and tolerability in healthy study participants who receive a single sc injection of ZLP.

Fourteen healthy study participants from a single cohort will be randomized 1:1 to treatment sequence AB or BA, where treatment A is ZLP-PFS and treatment B is ZLP-AI. Following completion of the first Treatment Period and a 7-day Washout Period, study participants will then complete the second Treatment Period with the same dose level as in Treatment Period 1 but using the alternate device.

- Sequence AB: 7 study participants to receive ZLP-PFS followed by ZLP-AI
- Sequence BA: 7 study participants to receive ZLP-AI followed by ZLP-PFS

Study participants who withdraw or are withdrawn from the study after dosing will not be replaced. However, if the number of dropouts exceeds initial expectations (see Section 5), study participants who withdraw or are withdrawn might be replaced at the discretion of the Sponsor.

Figure 1–1: Study schematic



The total maximum study duration per study participant will be up to 15 weeks, as follows:

- Screening Period: Up to 35 days (Days -35 to -2).
- In-Clinic Period: 1 day (Day -1) in each Treatment Period.
- Treatment Period 1 and Treatment Period 2: 5 weeks each (Days 1-35; approximately 5 times the half-life of ZLP). Each Treatment Period includes:
  - a 2-day In-Clinic Period (Days 1 and 2).
  - a 33-day Observation Period.
- Washout Period between Treatment Period 1 and Treatment Period 2: 1 week (7 days).
- The End of Study (EOS) Visit procedures will be performed on Day 35 of Treatment Period 2 (ie, on Study Day 78).

2 STATISTICAL HYPOTHESES

Hypotheses to be tested for each primary endpoint (AUC, AUC_{0-t}, and C_{max}) to establish bioequivalence are:

H0: T/R < 0.80 vs H1: T/R ≥ 0.80

and

H0: T/R > 1.25 vs H1: T/R ≤ 1.25

where T/R is the ratio of the geometric means of ZLP-AI (test [T]) versus ZLP-PFS (reference [R]).

A confidence interval (CI) approach to assess the hypotheses will be used. For each primary endpoint, 90% CIs will be used to summarize the two one-sided tests at the 5% significance level on the log-transformed (base e) endpoints for the differences in means for each treatment, producing the geometric mean ratios when back-transformed to the original scale.

Rejection of the null hypothesis in both cases can be undertaken if the 90% CI of the geometric mean ratio is contained in the interval (0.8000, 1.2500). If the 90% CI for each of the 3 primary endpoints is contained within the interval, then bioequivalence will be concluded.

2.1 Multiplicity adjustment

There will be no accounting for multiplicity in this study because all 3 primary endpoints (AUC, AUC_{0-t}, and C_{max}) must satisfy the bioequivalence requirements, i.e. bioequivalence will not be established for the individual endpoints separately. The ICH E9 guideline states that if the purpose of the trial is to demonstrate effects on all of the designated primary variables, there is no need for adjustment of the type I error.

3 POPULATIONS FOR ANALYSIS

The All Study Participants Set (ASPS) will consist of all study participants who signed the informed consent. This set includes screening failures and will be used for disposition and demographics of study participants. The ASPS will also be used for the listing of all adverse events (AEs).

The Randomized Set (RS) will consist of all study participants who are randomized. The RS will be used for disposition and demographics of study participants. Note: This set will only be produced if it differs from the Safety Set.

The Safety Set (SS) will consist of all study participants who are randomized and receive at least 1 dose of ZLP. In this context, 'dose of ZLP' includes the use of the device with the administration of the drug (either partial or full dose received). Study participants will be classified according to the treatment sequence in which they actually received the treatments. The SS will be used for all safety analyses.

The Pharmacokinetic Set (PKS) will consist of all study participants who are randomized, receive at least 1 dose of ZLP (defined as per SS above), and have at least 1 observable PK concentration measurement. The PKS will be used for analyses of PK endpoints. If a study participant in the PKS is missing concentrations at individual time points or these are otherwise unobservable, the study participant will be included in the PKS but those values will be omitted from the summaries of PK concentrations, as appropriate. Note that some study participants in the PKS may not have a complete set of PK parameters as some parameters may not be able to be calculated based on the PK concentrations collected.

4 STATISTICAL ANALYSES

4.1 General considerations

Statistical analysis and generation of tables, figures, and study participant data listings will be performed using SAS® (SAS Institute, Cary, NC, US) Version 9.4 or higher using validated program code according to relevant SOP.

Analysis data will adhere to Clinical Data Interchange Standards Consortium (CDISC) guidance documents for Analysis Data Model (ADaM) and follow the UCB interpretation. The PK noncompartmental analysis (NCA) will be performed by a designated Clinical Research Organization (CRO) using Phoenix WinNonlin® v8.3.4 or higher (Certara L.P., Princeton, NJ, US) for PK parameters estimation.

Tables and figures will be presented by treatment (or treatment sequence for demographics and disposition), visit, and timepoint (as applicable) and, unless otherwise stated, listings will be presented by treatment sequence, study participant, visit, and timepoint (as applicable).

Summary statistics will be presented for continuous endpoints including number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Geometric mean, geometric coefficient of variation (CV), and 95% CI for the geometric mean will also be presented in the summaries of PK concentration data and PK parameters. In addition, geometric SD will be presented for PK concentration summaries. Further details on standard reporting procedures for PK data can be found in Section 6.10.

Categorical endpoints will be summarized using frequency counts and percentages. Unless otherwise stated, the denominator for the percentage calculations will be based on the number of study participants in the respective analysis set, treatment group, visit, and timepoint (as applicable) with non-missing data. If there are any study participants with missing values for a categorical endpoint, an additional row displaying the number of study participants with missing data will be added.

When reporting descriptive statistics, the following rules will apply in general:

- Mean (arithmetic and geometric), SD (arithmetic and geometric), standard error (SE), CI, and median will use 1 decimal place more, or 1 significant figure more – depending on the reporting format of the original data – than the original data
- Coefficient of variation (CV) will be reported as a percentage to 1 decimal place
- Minimum and maximum will be reported using the same number of decimal places or significant figures as the original value
- If no participants have data at a given timepoint, then only n=0 will be presented. If n<3, then only the n, minimum, and maximum will be presented. If n=3, then only n, minimum, median, and maximum will be presented. The other descriptive statistics will be left blank
- Unless otherwise noted, all percentages will be displayed to 1 decimal place. No percentages will be displayed for zero counts and no decimal will be presented when the percentage is 100%

Time windows for PK sampling and maximum deviations from scheduled sampling times considered irrelevant for PK are documented in the protocol (Protocol Section 8.1). Time deviations considered relevant for PK will be reviewed by the PK Scientist. Any important deviations will be flagged in the PK listings and the plasma concentrations will be excluded from the summary statistics.

Statistical model output will be placed in the ‘Documentation of Statistical Methods’ appendix of the CSR.

4.1.1 Analysis time points

4.1.1.1 Study Day and Period Day for listings

There is no Study or Period Day 0. For the purpose of the study participant data listings, Study Day and Period Day will not be calculated if the event/measurement date is partial. Instead, Study Day and Period Day will be presented as ‘--‘ in the relevant study participant data listing.

Study Day for an event or measurement occurring before the date of the first dose will be calculated as follows:

Study Day = (Event/Measurement Date−Date of First Dose)

Study Day for an event or measurement occurring on the date of the first dose is 1. Study Day for an event or measurement occurring on or after the date of the first dose to the date of the last dose will be calculated as follows:

Study Day = (Event/Measurement Date−Date of First Dose) + 1

For events or measurements occurring after the date of the last dose, Study Day will be prefixed with '+' in the data listings and will be calculated as follows:

Study Day = + (Event/Measurement Date−Date of Last Dose)

In addition, a variable for Period Day will be defined for each Period based on the date of the single dose in each Treatment Period. Period Day will range from Day -1 to Day 41.

For the purpose of calculating the relative Day within each Period, the day before dosing in Treatment Period 1, and the washout period between the first and last dose are calculated relative to the first dose. Similarly, the day before dosing in Treatment Period 2, and the days between this dose and the EOS visit, are calculated relative to the last dose. If a study participant withdraws from the study early, the days between the last dose received and the Early Termination Visit (ETV) are calculated from the last dose they received and will be in either Treatment Period 1 or Treatment Period 2.

4.1.1.2 Analysis periods

The analysis periods consist of:

- Screening Period (Study Day -35 to -2).
- Treatment Period 1 consists of 36 days (Period Day -1 to 35).
- Washout Period consists of 7 days and occurs between the end of Treatment Period 1 and the start of the In-Clinic Period in Treatment Period 2 (i.e. between Treatment Period 1 Day 35 and Treatment Period 2 Day -1).
- Treatment Period 2 consists of 36 days (Period Day -1 to 35).

A study participant is defined as having started a Treatment Period if they receive a sc injection containing a single dose of ZLP in that period.

A study participant is considered to have completed Treatment Period 1 if they are not withdrawn from the study between Treatment Period 1 Day 1 and Treatment Period 2 Day -1, which includes the Washout Period. A study participant is considered to have completed Treatment Period 2 if they are not withdrawn from the study between Treatment Period 2 Day 1 and Treatment Period 2 Day 35.

End of study (EOS) procedures will be performed on the last sampling day (Day 35) of Treatment Period 2, in addition to the Day 35 procedures. Study participants who prematurely withdraw from the study will return to the study center for the Early Termination (ET) Visit as soon as possible after the time of withdrawal and will have all Day 35 (ie, Day 35 of the Treatment Period in which they withdrew from the study) and EOS procedures performed.

A study participant is considered to have completed the study if they have completed all periods of the study, including Treatment Period 1 and Treatment Period 2, and the EOS Visit assessments. Study participants have both Day 35 and EOS procedures performed on the last sampling day (Treatment Period 2 Day 35). Since Day 35 is part of Treatment Period 2, those who have completed the study have also completed all the required treatments and procedures.

The end of the study is defined as the date of the last EOS Visit for the last participant in the study.

4.1.2 Definition of Baseline values

In the protocol, the Baseline visit is defined as the first day of the first In-Clinic Period (Day -1). Baseline for the study is defined as the last non-missing measurement collected at the first day of the first In-Clinic Period (Day -1) for both Treatment Periods.

Endpoint-specific Baseline definitions are presented in Table 4–1. Scheduled or unscheduled measurements may be used as the Baseline value.

Table 4–1: Definition of Baseline

Endpoint	Definition of Baseline
Hematology, clinical chemistry, urinalysis	Baseline for each treatment period is defined as the value on Day -1 of the respective treatment period. If these values are missing or multiple assessments occur, the last measure prior to dosing on Day 1 in each treatment period will be used as Baseline for that treatment period. Baseline for the EOS/ET visit assessment is defined as the Screening assessment. Note: No assessments for these endpoints are scheduled on Day 1 prior to dosing in both treatment periods. If an unscheduled sample is taken on Day 1 prior to dosing in either treatment period, this will be considered as the Baseline value for that treatment period.
Vital signs	Baseline is defined as the value (or mean value if measurement is taken in triplicate) on Treatment Period 1 Day -1. If this value is missing or multiple assessments occur, the last measure prior to dosing in Treatment Period 1 will be used as Baseline.

4.1.3 Mapping of assessments performed at Early Termination Visit

Unscheduled measurements performed for the ET Visit will be assigned to the EOS Visit and analyzed accordingly as an EOS Visit.

4.1.4 Treatment assignment

Treatment assignment for the SS and PKS will be according to the actual treatment received.

4.1.5 Multicenter studies

This is a single center trial.

4.1.6 Handling repeated and unscheduled measurements

Repeated and unscheduled measurements will be presented in the data listings. Repeated measurements are defined as more than 1 measurement at the same visit. The following general rules will apply to all repeated and unscheduled measurements:

- For repeated measurements obtained prior to the single dose of study treatment within each treatment period, the latest value (which may be scheduled or unscheduled) will be used in the calculation of the descriptive statistics.
- For repeated measurements obtained at the time of the designated Baseline measurement (see Table 4–1) the latest value (which may be scheduled or unscheduled) will be defined as the Baseline provided that this occurred prior to the single dose of study treatment within each Treatment Period.
- Unscheduled and repeated measurements will not be used in the descriptive statistics at timepoints after the single dose of study treatment in each Treatment Period.
- Unscheduled measurements performed for the ET Visit will be assigned to the EOS Visit and analyzed accordingly as an EOS Visit.

4.2 Primary endpoints analysis

This section includes both primary and sensitivity analyses of the primary endpoints.

4.2.1 Definition of endpoints

The primary endpoints are:

- Area under the plasma concentration-time curve from time 0 to infinity (AUC)
- Area under the plasma concentration-time curve from time 0 to time t (AUC_{0-t})
- Maximum (or peak) observed plasma concentration (C_{max})

Pharmacokinetic parameters will be determined by non-compartmental analysis in Phoenix WinNonlin using the PKS. Details of the PK parameter calculations are described in Section 6.9.

The PK parameters of ZLP will be computed using the actual blood sampling timepoints.

4.2.2 Main analytical approach

The primary analysis to establish bioequivalence and sensitivity analyses are described in Section 4.2.2.1 and Section 4.2.2.2, respectively. Details of the standard reporting procedures of plasma concentrations and PK parameters are described in Section 6.10. Study specific instructions for producing tables, figures, and listings for plasma concentrations and PK parameters are provided below.

All PK statistical analysis, summaries, and listings will be performed using the PKS.

For plasma concentrations:

- In the event that a study participant does not receive a full dose of ZLP in either one or both treatment periods, they will be excluded from the statistical summaries for the relevant periods.

For PK parameters:

- In the event that a study participant does not receive a full dose of ZLP in either one or both treatment periods, the study participant will be excluded from the primary analysis to establish bioequivalence, but will be included in a sensitivity analysis and statistical summaries for the Treatment Period in which they received a full dose.
- If a study participant withdraws early from either Treatment Period (before Day 3 for C_{max} or before Day 35 for AUC and AUC_{0-t}) the study participant's PK parameters for that Treatment Period will be excluded from the primary analysis to establish bioequivalence, the planned sensitivity analyses, and statistical summaries. Parameters associated with the primary endpoints will also be excluded from statistical summaries for that study participant.

4.2.2.1 Primary analysis to establish bioequivalence

The analysis of the primary endpoints will be used to establish the bioequivalence of ZLP PK after a single sc injection with ZLP-PFS and ZLP-AI.

The primary analysis to determine if bioequivalence is established will use data from study participants who have evaluable primary PK endpoints for both treatments. Each primary PK endpoint will be analyzed separately. An analysis flag will be created to indicate whether the PK endpoint was included in the primary statistical analysis. Any values excluded will be flagged in the listings of the primary PK endpoints. Other analysis flags may be created for the sensitivity analyses.

Log-transformed PK parameters of AUC, AUC_{0-t}, and C_{max} will be analyzed using a mixed-effects model with period, treatment and sequence as fixed effects and study participant as a random effect. The ZLP-PFS device will be considered the reference treatment for the comparisons.

The least squares (LS) means and their associated 95% CIs for each treatment, and the difference in LS means and its 90% CI between the 2 treatments (ZLP-AI versus ZLP-PFS) will be estimated. All estimates will be back-transformed to provide geometric means and 95% CI for each treatment, and the ratio of geometric means (ZLP-AI/ZLP-PFS) and its 90% CI will also be provided. The point estimates and CIs for the ratios will be presented to 4 decimal places. Inter- and intra-participant variability of PK parameters will be derived from the results of this analysis. The intra-participant variability will be reported as CV.

4.2.2.2 Sensitivity analyses

The following sensitivity analyses will be carried out if required:

- If one or more study participants do not have evaluable primary PK endpoints for both Treatment Periods, an analysis using the same model as the primary analysis with the inclusion of Satterthwaite's correction for degrees of freedom will be carried out using data from study participants with evaluable PK endpoints in one or both Treatment Periods. (Sensitivity Analysis 1)
- If one or more study participants do not have evaluable primary PK endpoints for both Treatment Periods, an analysis using the same model as in the primary analysis will be carried out but will only include the study participants who have all three evaluable

primary PK endpoints (AUC, AUC_{0-t}, and C_{max}) in both Treatment Periods. (Sensitivity Analysis 2)

Other sensitivity analyses may be performed if necessary, and will be dependent on the PK data.

4.3 Secondary endpoints analysis

The analysis of the secondary endpoints will be used to evaluate the safety and tolerability of ZLP after a single sc injection with ZLP-PFS and ZLP-AI.

4.3.1 Definition of endpoints

The secondary endpoints are the occurrence of treatment-emergent serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), and adverse device effects (ADEs, serious and nonserious) from Study Day 1 (post dose) up to the EOS or ET Visit.

4.3.2 Main analytical approach

All safety analyses will be performed using the SS. The secondary endpoints will be analyzed as detailed in Section 4.5.2.

4.4 Exploratory endpoints analysis

4.4.1 Safety and tolerability endpoints analysis

The objective of the exploratory endpoint is to further evaluate the safety and tolerability of ZLP after a single sc injection with ZLP-PFS and ZLP-AI.

4.4.1.1 Definition of endpoints

The exploratory endpoints are:

- Change from Baseline in clinical laboratory tests (hematology, clinical chemistry, and urinalysis)

4.4.1.2 Main analytical approach

All safety analyses will be performed using the SS. The safety endpoints above will be analyzed as detailed in Section 4.5.3.1.

4.4.2 Pharmacokinetic endpoints analysis

The objective of the exploratory endpoint is to further evaluate the PK of ZLP after a single sc injection with ZLP-PFS and ZLP-AI.

4.4.2.1 Definition of endpoints

The exploratory endpoints are:

- Terminal half-life ($t_{½}$)
- Apparent plasma clearance (CL/F)
- Time to maximum observed concentration (t_{max})
- Apparent volume of distribution (V_z/F)

4.4.2.2 Main analytical approach

Pharmacokinetic analyses will be performed using the PKS.

The PK parameters $t_{½}$, CL/F, and V_z/F will be summarized by treatment using descriptive statistics as for the PK parameters described in Section 4.2.2. For the PK parameter t_{max}, only median, minimum, and maximum will be reported. Other PK parameters or diagnostics that support the derivation of the primary or exploratory PK endpoints, as defined in Table 1–1, will also be listed and summarized (e.g. AUC_{extr}, λ_z, t_{last}, and MRT [mean residence time]).

4.4.3 Device deficiency analysis

4.4.3.1 Definition of endpoints

The exploratory endpoints are:

- Device deficiencies as reported via the electronic case report form (eCRF)

4.4.3.2 Main analytical approach

The device deficiency analysis will be performed using the SS.

Device deficiencies will be listed by treatment sequence and their occurrence and incidence will be summarized by treatment if there are sufficient data.

4.5 Other safety analysis

The safety analyses will be performed using the SS.

Other safety data, for example previous medical procedures and pregnancy, may be reviewed as part of safety reviews (Excel or Spotfire), but data will only be formally listed in TFLs/CSR if these events contribute to a decision-making process or outcomes of study participants.

4.5.1 Extent of exposure

Administration of treatments will be listed for all study participants in the SS by treatment sequence. The listing will include study participant ID, visit, treatment, and the date and time of administration of the dose.

4.5.2 Adverse events

All AEs (including effects associated with the use of the device that fulfil the definition of an AE, ie, ADEs) will be coded using the most recent MedDRA and characterized as pretreatment (prior to the first dose) and treatment-emergent according to the administration of ZLP.

A TEAE is defined as any AE with a start date/time on or after the first injection in Treatment Period 1 or any unresolved event already present before administration of treatment that worsens in intensity following exposure to the treatment. TEAEs will be attributed to the most recent treatment received. TEAEs that occur in the week between the 2 Treatment Periods (ie, Washout Period), and up to Treatment Period 2 Day 1 predose, will be assigned as treatment-emergent with regards to the treatment received in Treatment Period 1.

The occurrence and incidence of TEAEs will be summarized by MedDRA system organ class (SOC), preferred term (PT), and by treatment.

The occurrence and incidence of TEAEs will also be summarized by intensity, and TEAEs by relationship to ZLP.

Summaries of TEAEs will include the following:

- Incidence of TEAEs - overview (including number and percentage of study participants with any TEAEs, serious TEAEs, discontinuations due to TEAEs, drug-related TEAEs, device-related TEAEs (ADEs), severe TEAEs and TEAEs leading to death, AEs of Special Monitoring [*Neisseria meningitidis* infection], and AEs of Special Interest [Hy's Law]; event counts will also be included).
- Incidence of TEAEs
- Incidence of serious TEAEs
- Incidence of TEAEs by maximum intensity
- Incidence of TEAEs by maximum relationship to study drug
- Incidence of non-serious TEAEs above reporting threshold of 5% of study participants
- Incidence of TEAEs by preferred term

The AEs of special interest and special monitoring are detailed in Section 6.11.

Summary tables will contain counts of study participants, percentages of study participants in parentheses, and the number of events where applicable. A participant who has multiple events in the same SOC and PT during a given treatment will be counted only once in the participant counts for that treatment, but all events will be included.

Adverse device effects (serious and nonserious) will be coded using the MedDRA and grouped into the SOC Product Issues. They will be listed by treatment sequence and their occurrence and incidence summarized by MedDRA SOC, PT, and treatment if there are sufficient data.

In summaries including relationship to study drug, the following relationships will be summarized: 'Not related', 'Related'. If participants experience the same event multiple times and at least one of the occurrences of the event is considered to be related to study drug, then all occurrences of the event will be considered to be related to study drug. Events with missing relationship will be considered as 'Related' for summary purposes but recorded as missing in the listings.

In summaries including intensity, the following intensity categories will be summarized: 'Mild', 'Moderate', 'Severe'. Participants who experience the same event multiple times will be included in the most severe category for tabulations by maximum intensity. Events with missing intensity will be considered as 'Severe' events for summary purposes but recorded as missing in the listings.

Adverse event summaries will be ordered alphabetically by SOC and decreasing frequency of PT within SOC in the ZLP-AI treatment column for tables including event counts (except for summaries by maximum intensity and maximum relationship). For tables including only the number and percentage of study participants, summaries will be ordered alphabetically by SOC and decreasing incidence of PT within SOC in the ZLP-AI treatment column.

All listings (except the listing of study participant numbers by TEAE, see below) will be presented for the ASPS by treatment sequence and study participant number, and will include the onset date/time and outcome date/time of the event, the most recent treatment received, the treatment period and period day at onset, the event duration (derived), time to onset (derived), pattern of event, intensity, relationship to study drug and/or device, seriousness, action taken

with study drug and/or device, and outcome. AEs that led to discontinuation, AEs of special monitoring, AEs of special interest, and SAEs will be flagged. The SAEs and reasons considered serious will also be listed separately.

The listing of study participant numbers by TEAE will be presented for the SS by most recent treatment received, and will include intensity, relationship to study drug, relationship to study device, seriousness, number of individual occurrences of TEAE, and study participant number.

For results disclosure on public registries (eg, ClinicalTrials.gov), TEAEs and treatment-emergent SAEs will be published.

4.5.3 Additional safety assessments

4.5.3.1 Clinical laboratory evaluations

All laboratory results (clinical chemistry, hematology, and urinalysis) outside the normal ranges will be listed by treatment sequence, study participant number, visit, most recent treatment received, and parameter, including changes from Baseline (Day -1 of each Treatment Period) for numeric endpoints, the reference ranges, and a flag to indicate whether values are below the lower limit of the reference range or above the upper limit of the reference range. The listings will include any laboratory value out of normal range at the visit it occurred only.

Separate listings of clinical chemistry and hematology laboratory results for study participants who have a value outside the normal ranges will be provided. These listings will include all data for a parameter for which a study participant has at least one abnormal value during the study.

A separate listing for study participants with elevated liver function results will be provided. The listing will present the study participants who meet one or more of the following criteria at any timepoint:

- Alanine aminotransferase (ALT) > 3 (x upper limit of normal (ULN)
- Aspartate aminotransferase (AST) > 3 x ULN
- Alkaline phosphatase (ALP) > 1.5 x ULN
- Total bilirubin (TBL) > 1.5 x ULN

Potential Hy's Law cases will be identified using the following definition:

- Either AST or ALT > 3 x ULN with concurrent ALP < 2 x ULN and concurrent total bilirubin > 2 x ULN.

In order to meet the above criteria, a study participant must experience the elevation in bilirubin and ALT and AST (and the absence of the ALP elevation) on the same date.

Urinalysis results will be listed by treatment sequence, study participant number, visit, and most recent treatment received including changes from Baseline for numerical endpoints, the reference ranges and flags for values outside the normal ranges.

For tables and listings, laboratory endpoints will be grouped according to the laboratory function panel (e.g. lipids, endocrine) and categorized as normal, high or low, if applicable, based on the reference range supplied by the analytical laboratory.

Clinical chemistry and hematology parameters will be summarized by treatment and visit for both absolute values and changes from Baseline.

Measurements that are below the limit of quantification (BLQ) or above the limit of quantification (ALQ) will be presented as BLQ or ALQ in the listings. For the purpose of calculating change from Baseline or for descriptive statistics, BLQ values will be imputed with half of the lower limit of quantification (LLoQ) and ALQ values will be imputed to the upper quantification limit.

Any additional laboratory endpoints which were not collected for screening eligibility that are not included in the outputs described previously will be listed separately. These will include the following:

- Serology (if taken post screening)
- Alcohol breath test (if taken post screening)
- Serum pregnancy test (for women of childbearing potential, if taken post screening)
- Urine toxicology screen (if taken post screening)

4.5.3.2 Vital signs

Vital signs (DBP, SBP, pulse rate, oral temperature) and changes from Baseline will be listed by treatment sequence, study participant number, and visit. The listing will also include details of abnormal values. Vital signs and changes from Baseline will be summarized by treatment and visit. The mean of the triplicate values for the systolic and diastolic blood pressures will be used in the summary tables, in the calculation of the changes from Baseline, and in the assessment of abnormality.

Abnormality criteria to be applied in the assessment of vital signs are shown in Table 4–2.

Table 4–2: Abnormality criteria for vital signs

Endpoint	Unit	Low	High
Systolic blood pressure	mmHg	Value ≤90 and a decrease from Baseline ≥20	Value ≥160 and an increase from Baseline ≥20
Diastolic blood pressure	mmHg	Value ≤50 and a decrease from Baseline ≥15	Value ≥105 and an increase from Baseline ≥15
Pulse rate	bpm	Value ≤50 and a decrease from Baseline ≥15	Value ≥120 and an increase from Baseline ≥15
Oral temperature	ºC	n/a	Value >38.3 (101ºF)

bpm=beats per minute

4.5.3.3 Electrocardiograms

All standard 12-lead electrocardiogram (ECG) recordings will be taken in triplicate at the Screening Visit. Repeat or unscheduled measurements may be taken for safety reasons.

The following ECG parameters will be reported:

- Heart rate
- PR interval
- QT interval

- QRS interval
- QTc interval (QT corrected for heart rate using Fridericia's formula [QTcF] and Bazett's formula [QTcB])

The individual measurements will be reported in the listings, and will be presented by treatment sequence, study participant number, and visit. The listing will also include details of abnormal values. Abnormality criteria to be applied in the assessment of ECG values are shown in Table 4–3.

Abnormal findings for the ECG will also be listed.

Table 4–3: Abnormality criteria for ECG

Endpoint	Unit	Low	High
QT interval	ms	n/a	Value ≥500
QTcF	ms	n/a	Value ≥500
PR interval	ms	n/a	Value >200
QRS interval	ms	n/a	Value >100
Heart rate	bpm	Value <50	Value >120

bpm=beats per minute; ms=milliseconds; QTcF=QT interval corrected for heart rate using Fridericia's formula=$QT/RR^{1/3}$

4.5.3.4 Physical examinations

Physical examination findings will be listed by treatment sequence, study participant number, and visit, including clinical significance. Clinically significant physical examination abnormalities will be reported as AEs.

4.6 Other analyses

Not applicable.

4.7 Interim analyses

Not applicable.

4.8 Changes to protocol-planned analyses

Not applicable.

4.9 Data Monitoring Committee (DMC) or other review board

Not applicable.

5 SAMPLE SIZE DETERMINATION

The minimum required sample size for PK bioequivalence studies as recommended by the Food and Drug Administration (FDA; Statistical Approaches to Establishing Bioequivalence, 2022) is 12 study participants.

This study is designed to establish the bioequivalence of ZLP-PFS (reference) and ZLP-AI (test). Bioequivalence is established if the 90% CI for the geometric mean ratio is contained entirely

within the acceptance range of 0.8000 to 1.2500 for all 3 PK parameters (AUC, AUC_{0-t}, and C_{max}).

The sample size estimation is based on the intra-participant variability observed in UP0115. This was a recent study in healthy study participants which included the ZLP-PFS device to estimate the relative bioavailability when the ZLP-PFS device was used at different injection sites (1 group compared the abdomen and thigh, and a second group compared the abdomen and upper arm). Since each participant in UP0115 only had 1 injection in the abdomen, the intra-participant coefficient of variation (CV%) was estimated by pooling across injection sites. The highest intra-participant CV% reported for AUC_{0-t} or C_{max} was 7.74% and this was used in the sample size calculation.

Assuming a geometric mean ratio between 0.90 and 1.11, and intra-participant CV% of 7.74%, 12 study participants (6 study participants per treatment sequence) are required to have evaluable primary PK endpoints (AUC, AUC_{0-t}, and C_{max}) from the 2 Treatment Periods to have at least 95% power to establish bioequivalence.

Therefore, 12 study participants would fulfill FDA requirements and give more than adequate power to establish bioequivalence.

It is not planned to replace study participants who withdraw from the study; rather the number to be randomized has been increased to 14, if a dropout rate of 10% is assumed. If more than 1 study participant withdraws from each treatment sequence, then study participants who withdraw may be replaced at the Sponsor's discretion, and if replaced, the new study participant will be allocated to the same treatment sequence as the withdrawn study participant. The new study participant would be expected to complete both Treatment Periods.

6 APPENDIX: SUPPORTING DOCUMENTATION

6.1 Appendix 1: List of Abbreviations

List of Abbreviations

ADaM	Analysis Data Model
AE	Adverse Event
ALQ	Above the limit of quantification
ALT	Alanine aminotransferase
ANOVA	Analysis of Variance
ASPS	All Study Participants Set
AST	Aspartate aminotransferase
BLQ	Below the limit of quantification
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CRO	Clinical Research Organization

List of Abbreviations

CSR	Clinical Study Report
CV	Coefficient of variation
DBP	Diastolic blood pressure
DEM	Data Evaluation Meeting
ECG	Electrocardiogram
ETV	Early Termination Visit
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	US Food and Drug Administration
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational medicinal product
IND	Investigational New Drug
IPD	Important protocol deviations
LLoQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
NCA	Noncompartmental analysis
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic Set
PT	Preferred term
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SoC	Standard of care
SOC	System organ class
SS	Safety Set
TEAE	Treatment-Emergent Adverse Event
TFL	Tables, figures, and listings
ULN	Upper limit of normal
WHO-DD	World Health Organization Drug Dictionary
ZLP	Zilucoplan
ZLP-AI	Zilucoplan-autoinjector

List of Abbreviations

ZLP-PFS	Zilucoplan-prefilled syringe

6.2 Appendix 2: Coding dictionaries

Adverse events, ADEs, and medical history will be coded using MedDRA Version 27.0. Medications will be coded according to the World Health Organization Drug Dictionary (WHO-DD) Version MAR/2024. Medical procedures will not be coded.

6.3 Appendix 3: Participant disposition

Study participant disposition will be listed by treatment sequence for the ASPS and will include the following information: study participant status (screen failure, study completed or discontinued, treatment period completed or discontinued), date of informed consent, date of randomization, date of first and second dose of treatment, date of study termination (if applicable), and primary reason for study termination (if applicable). The listing will also include the date of final contact for the study participant and the previous study participant number, if a study participant was re-screened.

Study participant disposition will be summarized by treatment sequence and overall for the ASPS including the number of screen failures, reasons for screen failure, the number of participants randomized who did not receive any study treatment (if any), the number of participants who started the study, the number of study participants who completed the study, the number of participants who discontinued and reasons for discontinuation of study. The percentages for discontinuation will be calculated based on the number of participants in the SS.

The number and percentage of study participants included in each of the analysis sets will be summarized by treatment sequence.

6.4 Appendix 4: Baseline characteristics and demographics

A listing of demographics by study participant number and treatment sequence will be presented for the ASPS. This will include the year of birth, age (in years), gender, race, ethnicity, height (cm), weight (kg), and body mass index (BMI, in kg/m2 to 1 decimal place).

All demographic characteristics (except for year of birth) will be summarized for the ASPS by treatment sequence and overall (including study participants not randomized to a treatment sequence). The summary of age will include descriptive statistics and categorical summaries, the latter based on requirements for European Union Drug Regulating Authorities Clinical Trials (EudraCT) reporting.

6.5 Appendix 5: Protocol deviations

Important protocol deviations (IPDs) are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data for key safety and/or PK outcomes for an individual study participant or that may significantly affect a study participant's rights, safety, or well-being.

The criteria for identifying such protocol deviations will be defined within the IPD specifications document.

IPDs will be categorized as follows:

- Inclusion/exclusion criteria deviations
- Incorrect treatment or dose administered
- Procedural non-compliance
- Prohibited concomitant medication use
- Treatment non-compliance
- Withdrawal criteria deviation

All protocol deviations will be reviewed as part of the ongoing data cleaning and data evaluation process. All protocol deviations will be discussed at data cleaning meetings for identification of individual IPDs and will be classified by the deviation types in the IPD document. The IPDs identified at the data cleaning meetings will be listed and summarized by treatment for the SS and will include the deviation type and description.

At least one Data Evaluation Meeting (DEM) will be performed prior to the final database lock but after all data have been verified/coded/entered into the database, to decide whether any study participant or data need to be excluded from the analyses.

Participants may be excluded from the SS if they do not pass the inclusion/exclusion criteria. However, should a participant be mistakenly dosed, then their safety data would need to be reported. If the deviation is deemed to have the potential to bias the analyses for the duration of the study, then the whole participant may be removed in a sensitivity analysis on the key endpoints. The removal of the participant and the rationale will be clearly documented within the relevant TFLs.

6.6 Appendix 6: Medical history

Medical history and ongoing medical conditions will be listed and summarized by MedDRA SOC and PT for the SS by treatment sequence and overall. The reported term will be included in the listing. The summary will include the number and percentage of study participants and will be sorted alphabetically by SOC and, within each SOC, by descending incidence of PT, based on the 'All Study Participants' column.

6.7 Appendix 7: Prior / concomitant / follow-up medications

Prior medication definition:

Prior medications include any medications that started prior to the first date of dosing. This includes medications that started prior to the dosing and continued after.

Concomitant medication definition:

Concomitant medications include any medications that have been taken at least once from the time of first treatment administration in Treatment Period 1 to the end of the study. Any medications with missing dates and/or times will be handled as described in Section 6.8 to classify them as prior or concomitant.

Prior medications and concomitant medications will be listed for the SS by treatment sequence and study participant number and will include WHO-DD Anatomical Main Group [Level 1 term text], Pharmacological Subgroup [Level 3 term text], preferred name, and reported term. For

concomitant medications, the most recent treatment(s) received will also be included in the listing.

Prior medications will be summarized by treatment sequence, and concomitant medications will be summarized by treatment for the SS, and will include WHO-DD Anatomical Main Group [Level 1 term text], Pharmacological Subgroup [Level 3 term text], and preferred name.

Prior medication summaries will be sorted alphabetically by Level 1 term, alphabetical Level 3 term within Level 1 and decreasing frequency of preferred name in the 'All Study Participants' column.

Concomitant medication summaries will be sorted alphabetically by Level 1 term, alphabetical Level 3 term within Level 1 and decreasing frequency of preferred name in the ZLP-AI treatment column.

A separate listing for vaccinations will be provided for the SS.

6.8 Appendix 8: Data derivation rules

6.8.1 Handling of missing dates and times

Partial dates may be imputed for the following reasons:

- Classification of AEs as treatment-emergent
- Classification of medications as prior or concomitant

Imputed dates will not be shown in the listings; all dates will be displayed as reported in the database.

The following rules will be applied for partial start dates:

- If only the month and year are specified and the month and year of the first dose of study treatment is not the same as the month and year of the start date then use the 1st of the month, or the date of screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use the 1st of the month). If time is missing this will be imputed as 00:00h

- If only the month and year are specified and the month and year of the first dose of study treatment is the same as the month and year of the start date, then the date of the first dose of study treatment will be used. If this results in an imputed start date that is after the specified end date, then use the 1st of the month, or the date of screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use the 1st of the month). If the imputed date is the date of dosing then time will be imputed as the start time of the dosing (i.e., event will be regarded as treatment emergent)

- If only the year is specified, and the year of the first dose of study treatment is not the same as the year of the start date then January 01 will be used. If time is missing this will be imputed as 00:00h

- If only the year is specified, and the year of the first dose of study treatment is the same as the year of the start date, then the date of the first dose of study treatment will be used. If this results in an imputed start date that is after the specified end date, then January 01, or the date of screening if this is later will be used (if the latter imputation results in an end date that is earlier

than the start date, then January 01 will be used). If the imputed date is the date of first dose of study treatment then time will be imputed as the start time of the study treatment intake (i.e., event will be regarded as treatment emergent).

In the event of ambiguity or incomplete data which makes it impossible to determine whether a medication/AE was concomitant/treatment-emergent or not, the medications/AEs will be considered as concomitant/treatment-emergent with respect to the first administration of study treatment.

The following rules will be applied to partial stop dates:

- If only the month and year are specified, then use the last day of the month
- If only the year is specified, then use December 31 of the known year
- If the stop date is completely unknown, do not impute the stop date

Missing or partially missing dates and/or times will be imputed as described in Table 6–1 for the calculation of duration of each event. Event duration is computed in and reported in day and time format: xx d hh:mm.

Table 6–1: Calculation rules for duration of events

Data availability	Onset date/time	Outcome date/time	Calculation rules
Complete data	D1/T1	D2/T2	Duration = [(D2 – D1)*24 + (T2 – T1)]/24 d
End time missing	D1/T1	D2/--	End time is substituted by time 23:59h (=23.98 in decimal format) Duration = <[(D2 – D1)*24 + (23.98 – T1)]/24 d
Start time missing	D1/--	D2/T2	Onset time is substituted by time 00:00h Duration = <[(D2 – D1)*24 + T2]/24 d
Start and end time missing	D1/--	D2/--	Duration = <D2 – D1 + 1
Start day and time missing	--/--	D2/T2	Duration = [(D2 – D0)*24 + (T2 – T0)]/24 d For a participant in the SS, D0 and T0 are the date and time of first administration of study intervention and for screen failures, D0 is the date of the screening visit and T0 = 00:00h
End day and time missing	D1/T1	--/--	If the stop date is missing, duration will not be calculated.
Start and end date missing	--/--	--/--	If the stop date is missing, duration will not be calculated.

6.9 Appendix 9: PK Parameter Calculations

Pharmacokinetic parameters will be calculated by non-compartmental analysis methods from the concentration-time data following these guidelines:

• Dosing times and actual PK sampling times will be recorded in hours and minutes. The relative actual time after dosing will be calculated from these using hours and minutes. The relative sampling time postdose in hours (decimals) will be recorded to at least 3 significant figures.

• Relative actual time after dosing will be used in the calculation of all derived pharmacokinetic parameters.

• There will be no imputation of missing data.

• If the predose concentration is ≤ 5 percent of the C_{max} value in that study participant, the study participant's data without any adjustments can be included in all pharmacokinetic measurements and calculations. It is recommended that if the predose value is > 5 percent of C_{max}, the study participant's data should be listed and flagged, but the study participant should be excluded from the bioequivalence evaluations (FDA, Guidance for Industry, 2022).

All pharmacokinetic parameters will be estimated according to the guidelines presented in Table 6–2.

Table 6–2: Pharmacokinetic Parameters and Estimation

Parameter	Guideline for Derivation
C_{max} and t_{max}	Obtained directly from the observed concentration-time data
AUC_{0-t}	The AUC from zero time (pre-dose) to the time of last quantifiable concentration (AUC_{0-t}) will be calculated using the linear up/log down trapezoidal rule. The AUC_{0-t} is the sum of areas up to the time of the last quantifiable sample: $AUC_{0-t} = \int_0^t C(t)dt$
AUC	The area from zero time extrapolated to infinite time will be calculated as follows: $AUC = AUC_{0-t} + \frac{C_t}{\lambda_z}$ where C_t is the last observed quantifiable concentration.
AUC_{extr}	The percentage of AUC obtained by extrapolation will be calculated as follows: $AUC_{extr} = \frac{AUC - AUC(0-t)}{AUC} \times 100$ Unless otherwise determined by PK Scientist's best knowledge and judgment, if the AUC_{extr} is greater than 20% the value, all dependent parameters (i.e. AUC, V_z/F, MRT, and CL/F) will be flagged in listings but will be included in summary tables and statistical analysis of PK parameters. The reason for flagging will be footnoted in parameter listings and summary tables.
AUMC	Area Under the first Moment Curve from 0 to infinity $AUMC = AUMC(0-t) + \frac{C_t * t}{\lambda_z} + \frac{C_t}{\lambda_z^2}$ where C_t is the last observed quantifiable concentration and t is the time of the last quantifiable sample
t_{last}	The time of the last quantifiable concentration

Table 6–2: Pharmacokinetic Parameters and Estimation

Parameter	Guideline for Derivation
λ_z and $t_{½}$	The apparent terminal phase rate-constant (λ_z) will be estimated by linear regression of concentration versus time data presented on a log-linear scale. Best fit option should be used in Phoenix WinNonlin but must be checked manually. Only those data points that are judged to describe the terminal log-linear decline will be used in the regression. A minimum number of three data points in the terminal phase will be used in calculating λ_z with the line of regression starting at any post-C_{max} data point (C_{max} should not be part of the regression slope). Unless otherwise determined by PK Scientist's best knowledge and judgment, if the adjusted correlation coefficient (R^2 adjusted) is <0.8, λ_z and all the λ_z dependent parameters (i.e. $t_{½}$, AUC, CL/F, MRT, and V_z/F) will be flagged but will be included in summary tables and statistical analysis of PK parameters. The reason for flagging will be footnoted in parameter listings and summary tables. Unless otherwise determined by PK Scientist's best knowledge and judgment, the interval used to determine λ_z should be equal to or greater than 2-fold the estimated $t_{½}$. If the interval is less than 2-fold then $t_{½}$ and λ_z, together with all the derived parameters (i.e. AUC, CL/F, MRT, V_z/F), will be flagged in listings but will be included in summary tables and statistical analysis of the PK parameters. The reason for flagging will be footnoted in parameter listings and/or summary tables. The $t_{½}$ will be calculated as follows: $t_{½} = \frac{Ln2}{\lambda_z} \approx \frac{0.693}{\lambda_z}$
CL/F	Apparent clearance of parent drug will be calculated from: $CL/F = \frac{Dose}{AUC}$
MRT	Mean Residence Time will be calculated from: $MRT = \frac{AUMC}{AUC}$
V_z/F	Apparent volume of distribution $V_z/F = \frac{CL/F}{\lambda z}$

6.10 Appendix 10: Standard Reporting Procedures

Standard reporting procedures for PK concentrations and PK parameters are described in Section 6.10.1 and Section 6.10.2, respectively. Instructions for producing tables, figures, and listings for plasma concentrations and PK parameters are described below.

Plasma concentrations of ZLP will be listed by treatment sequence and study participant. The listing will include treatment sequence, most recent treatment received, visit, actual blood sampling time, scheduled sampling time, and deviation from scheduled sampling time.

The plasma concentration-time profiles and PK parameters of ZLP will be listed by treatment and study participant and will be summarized by treatment using descriptive statistics.

Individual plasma ZLP concentration-time profiles will be displayed graphically by treatment on a linear-linear scale and semi-logarithmic scale. Spaghetti plots will be displayed by treatment with all study participants overlaid on the same plot on a linear-linear scale and semi-logarithmic scale. Geometric mean plasma concentration-time curves including their 95% CIs will be displayed by treatment.

Ping-pong plots for the individual primary PK endpoints will be displayed.

6.10.1 PK concentrations

When reporting individual data in listings the following rules will apply:

- Concentrations below the limit of quantification should be reported as BLQ (below the limit of quantification).
- Concentrations should be listed to the same number of significant figures supplied by the bioanalytical laboratory.

When reporting individual data in figures the following rules will apply:

- BLQ values prior to C_{max} should be set to 0 for purposes of plotting the figure (to capture lag-time).
- Actual sampling times should be used. Dosing times and PK sampling times will be recorded in hours and minutes.
- All times calculated relative to dosing time should be reported in hours to 3 significant figures, e.g. sampling at 2 minutes should be reported as 0.0333h (i.e. minutes/60 and 3 significant figures).

When summarizing the data in tables the following rules will apply:

- To calculate descriptive statistics, BLQ values should be set to half the LLoQ value and missing values should be excluded.
- When the total number of BLQ and missing values exceeds one third of the total then only minimum and maximum should be reported for this timepoint. Other descriptive statistics should be reported as missing. The minimum should be reported as “BLQ”.
- When the mean value includes one or more replaced BLQ values then a footnote should be included to say “contains one or more BLQ value replaced by half the LLoQ value”
- A minimum of 3 values are required to calculate summary statistics. If only 2 values are available then these should be presented as the minimum and maximum with other descriptive statistics reported as missing.
- If no participants have data, only n=0 will be presented. The other descriptive statistics will be left blank.
- Descriptive statistics will be reported to the same level of precision as the individual data for the minimum and maximum, and to 1 additional decimal place or 1 additional significant figure– depending on the reporting format of the original data with a maximum of 3 significant figures - for the mean (arithmetic and geometric), SD (arithmetic and geometric), CI, and median. Geometric CV will be reported as a percentage to 1 decimal place.

- Descriptive statistics of plasma concentrations will be calculated if at most 1/3rd of the individual data points are missing or are not quantifiable (<LLoQ) at the given time-point. Values that are BLQ will be replaced by the numerical value of the LLoQ/2 in this instance. However, if n<3, then only n, minimum and maximum will be presented, and the median will also be presented if n=3. The other descriptive statistics will be left blank.

- The geometric CV will be calculated using the following formula where SD is the standard deviation from the log-transformed data: Geometric CV (%) = sqrt[(exp (SD^2) – 1)] x 100

- The 95% CI for the geometric mean in the descriptive statistics should be calculated as: Exp[mean(log(endpoint)±$t_{0.975,df}$*sd(log(endpoint))/sqrt(n))]

When summarizing the data in figures the following rules will apply:

- The data plotted in the figure should match the data presented in the summary table, with the exception of missing values prior to C_{max} which should be set to 0 in the figure (to capture lag-time).

- For the individual figures, any plasma concentrations that are BLQ will be regarded as missing, except for predose BLQ measurements for all treatment periods, which will be imputed with zero for linear scale plots.

- Geometric mean should be plotted (as opposed to arithmetic mean) due to the log-normal distribution of concentrations. Variability should be plotted as 95% CI of the geometric mean.

- Nominal sampling times should be used.

- Both linear and semi-logarithmic scales should normally be presented

6.10.2 PK parameters

When reporting individual data in listings the following rules will apply:

- Individual PK parameters should be reported to 3 significant figures.

- If a parameter cannot be calculated, it should be reported as NE (not estimable i.e. if input data is missing which prevents calculation) or NC (not calculable i.e. if the data were available but the calculation was considered unreliable).

When summarizing the data in tables the following rules will apply:

- Generally descriptive statistics should be calculated on individual PK parameters that have 9 decimal places (exceptions include t_{max} i.e. discontinuous variables).

- For most PK parameters (i.e. for continuous variables) the following descriptive statistics should be calculated: mean, SD, geometric mean, 95% CI of the geometric mean, geometric CV, minimum, median and maximum. For t_{max} and t_{last} (i.e. for discontinuous variables) only median, minimum, and maximum should be reported.

- Descriptive statistics should be reported to 4 significant figures for the mean, SD, geometric mean, CI, and median and to 3 significant figures for the minimum and maximum. Geometric CV will be reported as a percentage to 1 decimal place.

- If at least two thirds of the study participants have a PK parameter reported then descriptive statistics will be calculated, otherwise only minimum and maximum will be reported for this PK parameter and all other descriptive statistics will be reported as NE (i.e. not estimable).

- A minimum of 3 values are required to calculate summary statistics. If only 2 values are available then these should be presented as the minimum and maximum with other descriptive statistics reported as missing.
- The geometric CV will be calculated using the following formula where SD is the standard deviation from the log-transformed data: Geometric CV (%) = sqrt[(exp (SD^2) – 1)] x 100
- The 95% CI for the geometric mean in the descriptive statistics should be calculated as: Exp[mean(log(endpoint)±$t_{0.975,df}$*sd(log(endpoint))/sqrt(n))]
- The CI for the geometric mean should be left blank if the geometric CV is 0.

6.11 Appendix 11: AEs of Special Interest and Special Monitoring

Adverse events of special interest relates to Hy's Law and any potential Hy's Law cases will be recorded on the eCRF.

Adverse events of special monitoring relates to *Neisseria meningitidis* infection and cases will be identified through the higher level term (HLT) = "Neisseria infections".

The AEs of special interest and special monitoring will be reported as per Section 4.5.2.

6.12 Appendix 12: Potentially Clinically Significant Criteria for safety endpoints

Refer to previous safety sections.

6.13 Appendix 13: Compliance

As dosing is performed in-house by the investigator or member of staff, no specific assessment or compliance is warranted. Any dosing deviation will be addressed in the DEM and described in the CSR.

7 REFERENCES

Food and Drug Administration. Guidance for Industry. Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs – General Considerations. US Dept of Health and Human Services, Center for Drug Evaluation and Research, Office of Clinical Pharmacology, 2022.

Guideline on performing NCA analysis, Global Exploratory Development (GED), 2017.

International Conference on Harmonisation: Statistical Principles for Clinical Trials (ICH E9)

ISO 14155:2011 Clinical Investigations of medical devices for human subjects – Good Clinical Practice.

Phillips A, Haudiquet V. ICH E9 guideline 'Statistical principles for clinical trials': a case study. Stat Med. 2003;22(1):1-11; discussion 13-7.

Posner K, Brent D, Lucas C, et al. Columbia-suicide severity rating scale (C-SSRS). Columbia University Medical Center, 2008.

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