Authentic partnerships in challenging drug development

25 August 2025

Protocol: **NKF-INS(A)-101**
NCT No.: **06492226**
Subject: **Cover Letter for Statistical Analysis Plan (SAP)**

SAP V1.0 21OCT2024 for NKF-INS(A)-101 is attached with NCT06492226.

Sincerely,

Chris Schroth
Clinical Project Manager | Xentria, Inc.

scigenix

STATISTICAL ANALYSIS PLAN

Protocol title: A single-center, single-dose, double-blind, randomized, three-period, three-treatment, six-sequence, crossover study to demonstrate pharmacokinetic and pharmacodynamic similarity between NKF-INS(A), US-NovoLog®, and EU-NovoRapid® using the euglycemic clamp technique in healthy male adult volunteers.	
Protocol number: NKF-INS(A)-101	**Applicable Protocol Version:** Version 2.0, 6-May-2024
Author: Anna Fastovsky, Biostatistician	**Internal reviewer(s):** Xan Swart, Biostatistician **Sponsor representative(s):** Tom Matthews, Vice President of Clinical Development
Revision history: Version 1.0	**Date:** 21-Oct-24

The layout of this document is based on the Guideline on the International Conference on Harmonization (ICH E9).

TABLE OF CONTENTS

Signature page

Authored by:

Anna Fastovsky
Biostatistician
Scigenix (Pty) Ltd

Signature and date

Internal reviewer(s):

Xan Swart
Biostatistician
Scigenix (Pty) Ltd

Signature and date

Sponsor representative(s):

Tom Matthews
Vice President of Clinical Development
Xentria, Inc.

Signature and date

Glossary of abbreviations

Abbreviation	Description
AE	Adverse event
ADL	Activities of daily living
ALT	Alanine aminotransferase
ANOVA	Analysis of Variance
Anti-HBc	Antibody to hepatitis B core antigen
AST	Aspartate aminotransferase
BLQ	Below the limit of quantification
BMI	Body mass index
CI	Confidence interval
CL/F	Clearance
COVID-19	Coronavirus disease 2019
CRU	Clinical research unit
CSP	Clinical study protocol
CSR	Clinical Study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DILI	Drug-Induced Liver Injury
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of study
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GIR	Glucose infusion rate
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgM	Immunoglobin M
INR	International normal ratio
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time
NCA	Noncompartmental analysis
NCI	National Cancer Institute

PASS	Power Analysis & Sample Size Software
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Pharmacokinetic parameters
QTcF	QT-interval corrected by Fredericia's formula
RBC	Red blood cell
SAE	Serious adverse events
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SC	Subcutaneous(ly)
SD	Standard deviation
SDTM	Study data tabulation model
SOC	System organ class
SOP	Standard Operating Procedure
$t^1/_2z$	Apparent terminal half life
TEAE	Treatment emergent adverse events
TGV	Target Glucose Values
TLF	Tables, listings and figures
US	United States
V/F	Volume of distribution
WBC	White blood cell
λz	Apparent terminal elimination rate constant

1. Overview

1.1 Introduction

This document describes the rules and conventions to be used in the presentation and analysis of Xentria, Inc. study titled “a single-center, single-dose, double-blind, randomized, three-period, three-treatment, six-sequence, crossover study to demonstrate pharmacokinetic and pharmacodynamic similarity between NKF-INS(A), US-NovoLog®, EU-NovoRapid® using the euglycemic clamp technique in healthy male adult volunteers”.

This statistical analysis plan (SAP) is based on Protocol NKF-INS(A)-101, Version 2.0, dated 06-May-24. This SAP describes all preplanned analyses as specified in the protocol, adding clarification and details where appropriate. If circumstances should arise during the study rendering the analysis inappropriate, or if in the meantime improved methods of analysis should come to light, different analyses may be made. Any deviations from the statistical methodology, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in the clinical study report (CSR).

This will be a double-blind, randomized, crossover study to demonstrate pharmacokinetic and pharmacodynamic similarity between NKF-INS(A), US-NovoLog®, EU-NovoRapid® using the euglycemic clamp technique in healthy male adult volunteers at a single study center.

2. Study objectives

The following objectives are those stated in the protocol.

2.1 Primary objectives

- To compare the PK of NKF-INS(A) to US-approved and EU-authorized insulin aspart to demonstrate PK similarity for insulin aspart.
- To compare the PD of NKF-INS(A) to US-approved and EU-authorized insulin aspart injection by examining GIR profiles after a single SC dose.

2.2 Secondary objectives

- To evaluate additional PK parameters of NKF-INS(A) compared to US-approved and EU-authorized insulin aspart.
- To evaluate additional PD parameters of NKF-INS(A) compared to US-approved and EU-authorized insulin aspart.
- To assess the safety of NKF-INS(A).

2.3 Exploratory objectives

- To assess endogenous insulin suppression via C-peptide measurements, which includes both corrected and uncorrected C-peptide concentrations.

3. End points

3.1 Primary endpoints

- Aspart concentration-time curve from 0 to 12 hours (AUC_{0-t}).
- Maximum observed insulin aspart concentration (C_{max}).

- Area under the GIR-time curve from 0 to 12 hours ($AUCGIR_{0-t}$).
- Maximum GIR (GIR_{max}) of glucose.

3.2 Secondary endpoints

- PK parameters for serum insulin aspart concentrations: AUC_{0-4h}, AUC_{0-6h}, AUC_{6-12h}, AUC_{0-12h}, T_{max}, $AUC_{0-\infty}$.
- Time to half-maximum before C_{max} (t50%-early).
- Time to half-maximum after C_{max} (t50%-late).
- The terminal elimination half-life ($t_{1/2}$).
- AUCGIR from 0 to 4 hours ($AUCGIR_{0-4h}$), from 0 to 6 hours ($AUCGIR_{0-6h}$), and from 6 hours until the end of clamp ($AUCGIR_{6-last}$).
- Time to maximum GIR (T_{max}.GIR).
- Time to half-maximum glucose infusion rate before GIR_{max} (tGIR, 50%-early).
- Time to half-maximum glucose infusion rate after GIR_{max} (tGIR, 50%-late, indicator of end of duration of action).
- Time from study drug administration until the blood glucose concentration has decreased by at least 5mg/dL from baseline (onset of action).
- The difference between tGIR, 50%-late and the onset of action (duration of action).
- AE assessments (including injection site reactions), clinical laboratory investigations (hematology, clinical chemistry, [including glucose], coagulation, and urinalysis), vital signs, physical examinations, 12-lead ECG, prior and concomitant medication assessments.

3.3 Exploratory endpoints

- Corrected and uncorrected C-peptide concentrations.
- If possible, i.e., if the terminal phase of serum concentration-time profile has sufficient data points, apparent terminal elimination half-life ($t^1/_2z$), apparent terminal elimination rate constant (λz), mean residence time (MRT), clearance (CL/F), and volume of distribution (V/F) will be calculated.

4. Study design

4.1 Design overview

Study NKF-INS(A)-101 is a Phase 1, 12-hour euglycemic glucose clamp study conducted using a randomized, double-blind, three-period, three-treatment, six-sequence crossover design. The study will compare single doses of the proposed insulin biosimilar (NKF-INS(A)) with respective EU- and US- reference products in healthy male participants.

Written informed consent will be obtained from all participants, and the study will be conducted in accordance with the principles of Good Clinical Practice (GCP) as defined by the International Conference of Harmonization (ICH).

The study will comprise:

- A screening period of up to 4 weeks (Days -28 to -1) to obtain informed consent and assess eligibility for participation,

- Three treatment periods each consisting of 1-day dose administrations and euglycemic clamp periods (periods 1, 2, and 3) separated by a washout period of 3-14 calendar days between treatment periods 1 and 2, and a washout period of 5-21 calendar days between treatment periods 2 and 3, and
- A follow up period of 2-11 days after last dose.

The entire study duration will be a maximum of 11 weeks. Procedures listed for the post-study visit will be performed in the event of early withdrawal from the study.

Three insulin products (NKF-INS(A), EU-NovoRapid®, and US-NovoLog®) will be administered over three treatment periods. Upon admission to the clinical research unit (CRU) on Day -1, participants will be randomized to one of six treatment sequences in a 1:1:1:1:1:1 ratio, receiving a single subcutaneous (SC) dose of 0.3 U/kg administration of one of the three study drugs on each dosing day.

A 12-hour euglycemic glucose clamp will be conducted using a manual clamp technique, which will monitor the participant's blood glucose and administer glucose infusion rate (GIR) to maintain blood glucose close to the target blood glucose concentration. The clamp procedure will be initiated, maintained, and terminated, in accordance with the site standard operating procedures (SOPs). The participant's blood glucose will be maintained within a pre-defined target window per site SOP and clinical judgement for the participant by manually adjusting the GIR.

Blood samples will be collected at pre-specified intervals before and up to 12 hours after dosing for measurement of blood glucose, serum insulin, and C-peptide.

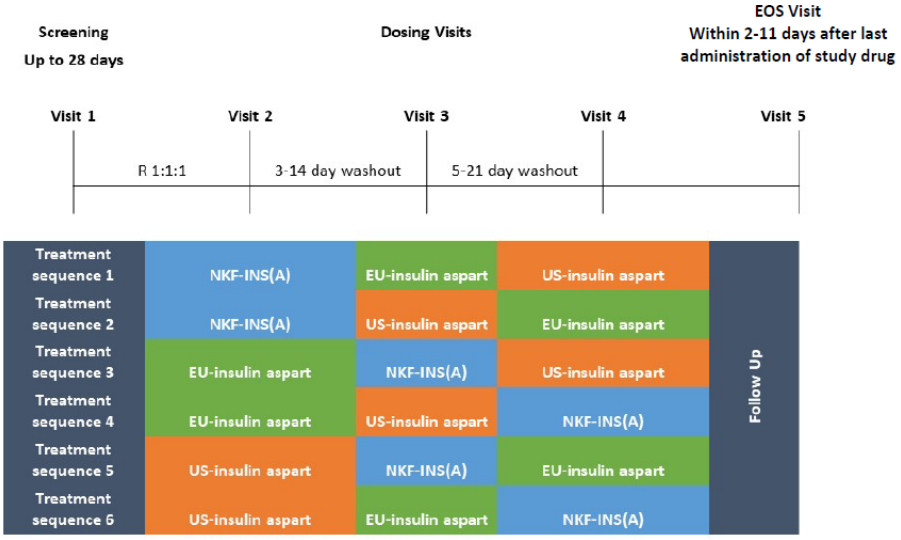
4.1.1 Sample Size Considerations

A literature review of similar studies was conducted in order to inform the assumptions for the sample size, for the primary endpoints of AUC0-∞ and Cmax (see Table 9 in the NKF-INS(A)-101 CSP; Version 2.0, 6-May-2024).

The CV value ranged from 23.8% to 30.8%, with a mean value of 25.4%. The CV of the Innovator study was 25.3%. Based on the above data, the CV value is selected as 26%.

The sample size was calculated using PASS software [2] with following parameters including 90% power, dropout rate 20%, α=0.05, 90% confidence interval (CI), assumed actual ratio 0.95 within 80-125%, N=40; taking account of 20% dropout, the sample size is determined as N=54 to have at least 36 evaluable participants.

Figure 4.1: Study Design Schematic (from Protocol v2.0, 06-May-2024)



Abbreviations: EU = European Union; US = United States

4.2 Schedule of events

Please refer to Table 3 in the CSP for NKF-INS(A)-101 v2.0 06-May-2024.

Table 4.2: Pharmacokinetic, pharmacodynamic, C-peptide and glucose sampling schedule (from Protocol v2.0, 06-May-2024).

	Pre-dose (minutes)			Post-dose (minutes)																		
Sample	60	30	0	5	10	20	30	40	50	60	75	90	105	120	135	150	180	210	240	300	600	720 (12 hours)
Insulin (serum)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-peptide (serum)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood glucose				Every 3 minutes →										Every 5 minutes →					Every 10 minutes →			

5. Analysis populations

Agreement and authorization of participants included/excluded from each analysis population will be reached prior to final database hard lock. The Sponsor will supply a list of all participants to be excluded from the relevant analysis populations, including the reason(s) for exclusion from the analysis populations.

All protocol deviations (major or minor) that occur during the study will be considered for their severity/impact in terms of adversely influencing the integrity or reliability of results and may be taken into consideration when participants are assigned to analysis populations. All analysis exclusions will be clearly documented with reasons for exclusion.

5.1 Screening Analysis Set

This analysis population will include all participants who provided written informed consent, and provided demographic and/or baseline screening assessments, regardless of the participant's randomization status. Screening failures will be included in this analysis population.

5.2 Enrolled Analysis Set/ Full Analysis Set (FAS)

This analysis population includes all individuals who signed the ICF.

5.3 Safety Analysis Set (SAF)

This analysis population will include all participants who received any amount of study treatment. Analyses based on the SAF population will reflect the actual IP administered to participants, regardless of the randomization list. This population will be used for the analysis of safety.

5.4 Pharmacokinetic Concentration Analysis Set (PKCS)

The PK Concentration population will include all participants in the SAF who received any amount of study treatment and have at least 1 post-baseline reportable PK result.

5.5 Pharmacokinetic Parameter Analysis Set (PKPS)

The PK Parameter Population will include all participants in the PKC who have at least 1 PK parameter derived.

5.6 Pharmacodynamic Parameter Analysis Set (PDS)

The PD Parameter Population will include all participants in the SAF who have at least 1 PD parameter derived.

6. General considerations

6.1 Visit and date conventions

Visit day will be calculated from the reference start date which will be used to present start/stop day of assessments and events. The *reference start date* is defined as the date of first IP administration. The following conventions will be used for visit references:

- $Visit\ day = date\ of\ event - reference\ start\ date + 1$
- $Visit\ week = \frac{visit\ day}{7},\ rounding\ up\ to\ next\ whole\ number$
- $Visit\ month = \frac{visit\ day}{30.44},\ rounding\ up\ to\ next\ whole\ number$

No visit windowing (i.e. remapping of visits based on visit windows) will be performed for this study. The assigned nominal visit will be used for by-visit summaries. In the situation where the assessment/event date is partial or missing, visit day/week/month, and any corresponding durations will appear missing in the data listings. Unscheduled measurements will not be included in by-visit summaries. In the case of a retest (same visit number assigned), the last available measurement for that visit will be presented for by-visit summaries. Data listings will include scheduled, unscheduled, retest and early discontinuation data. Study visit will be assigned as delineated in Table 6.1:

	Screen	Euglycemic Clamp Procedure Treatment Periods 1-3				Post-Study Visit
		Admission		Clamp Procedure	Post Clamp	
Visit Day	-28 to -1	Period 1	-1	1	2	16 - 52
		Period 2	5 - 16	6 - 17	7 - 18	
		Period 3	12 - 39	13 - 40	14 - 41	
Visit No.	1	Period 1	2	3	3	8
		Period 2	4	5	5	
		Period 3	6	7	7	

Washout periods vary between treatment periods: washout period of 3-14 calendar days between treatment period 1 and 2, and a washout period of 5-21 calendar days between treatment periods 2 and 3.

6.2 Baseline

Unless stated otherwise, baseline is defined as the last non-missing observation made prior to the first administration of IP.

6.3 Statistical tests

Bioequivalence is assumed if 90% (PK) / 95% (PD) of the test and reference ratio of the primary PK/PD parameters confidence intervals (CIs) fall within the limits of 80%-125%.

6.4 Common calculations

For quantitative measurements, change from baseline will be calculated as: (Test value at Visit Day X – Baseline value), where the baseline value is defined as the last non-missing observation taken prior to first exposure to IP.

6.5 Software

All analyses will be performed using R Version 4.4.1 or higher. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.r-project.org/ [2].

7. Statistical considerations

7.1 Missing data

Missing safety data will not be imputed for this study. All missing or incomplete safety and PK data, including dates and times, are treated as such.

8. Output presentations

Summary tables will be stratified by treatment sequence randomized to, unless otherwise specified.

The templates provided in the separate output templates document describe the format and content for presentation of tables, listings and figures (TLFs).

Categorical variables will be summarized and presented with the following nomenclature: n = frequency and % = percentage. Categories of NOT REPORTED, MISSING, and/or UNKNOWN may be excluded from summaries if null (0)

For continuous variables, data will be summarized with the number of participants (N), arithmetic mean, standard deviation (SD), minimum, median and maximum by treatment group.

All percentages (%) for a specific summary are calculated using the total number of participants included in the relevant analysis population as the denominator, unless otherwise specified. Tables will summarize relevant data from the eCRF.

Data listings will be based on all participants randomized to IP, unless otherwise specified.

9. Primary endpoint assessments

For PK and PD analysis, refer to sections 22 and 23, respectively. For safety and tolerability analysis, refer to sections 19, 20 and 21.

10. Secondary endpoint assessments

For PK and PD analysis, refer to sections 22 and 23, respectively. For safety and tolerability analysis, refer to sections 19, 20 and 21.

11. Exploratory endpoint assessments

For the exploratory endpoint assessments refer to section 24.

12. Participant disposition and withdrawal

12.1 Variables and derivations

End of study classifications are defined as follows:

12.1.1 Screening failure

Participants for whom informed consent was obtained and documented in writing (i.e. the participant signed an informed consent form), but who were not randomized to IP. Individuals who do not meet the criteria for participation in this study may be rescreened only once, at the discretion of the Investigator.

12.1.2 Completed treatment

A participant will have fulfilled the requirements for treatment completion if/when the participant has completed all three treatment periods.

12.1.3 Early withdrawal

Participants may withdraw from the study at any time with or without reason. The Investigator also has the right to discontinue or terminate participants from the study in the event of concomitant disease, AEs, or any reason that would benefit the participant. If a participant withdraws from the study for any reason, the study site must immediately notify the clinical monitor. The date and reason for study discontinuation must be recorded in the electronic case report form (eCRF). Participants who discontinue early, irrespective of the reason for discontinuation from the study, will be asked to complete the EOS assessments at the time of the participant's withdrawal, as outlined in the schedule of assessments (*Table 3 in the CSP for NKF-INS(A)-101*).

12.1.4 Completed study

A participant will have fulfilled the requirements for study completion if/when the participant has completed all three treatment periods, and the end of study (EOS) visit within 2-11 days after last administration of the IP. The participant will be considered as having "completed study" in the event of the EOS visit occurs outside the scheduled 2-11 days after the last IP administration window.

12.1.5 Lost to follow-up

The participant stopped coming for visits and study personnel were unable to contact the participant. In cases in which the participant is deemed lost to follow up, prior to this designation, the Investigator (or designee) must make every effort to contact the participant (e.g., telephone calls, certified letter to the participant's last known mailing address, or local equivalent methods, and efforts to reach the participant's emergency contact). The site will make 3 attempts to regain contact with the participant. These contact attempts must be documented in the participant's medical records.

12.2 Analysis

Participant disposition and withdrawals will be summarized and presented in data listings for the screening population set.

The number of participants included in the relevant analysis populations, as well as the number of participants excluded with reasons for exclusion from the relevant analysis populations (Section 5) and protocol violations/deviations will be summarized for the SAF population and listed in data listings for the FAS population.

13. Participant demographics and other baseline characteristics

13.1 Variables and derivations

The following demographic and other baseline characteristics will be summarized by treatment sequence:

- Age (Years) (Calculated relative to date of informed consent, as provided by the participant and recorded in the eCRF)
- Sex
- Race
- Ethnicity
- Height (cm) at Screening
- Weight (kg) at Screening
- BMI (as collected in the eCRF)

The following demographic and baseline characteristics will be listed:

- The date of written informed consent
- Year of birth

13.2 Analysis

Demographic data and other baseline characteristics will be summarized by treatment sequence randomized to for the SAF population and presented in data listings for the screening analysis population.

14. Exposure to IP

14.1 Variables and derivations

The date of first IP administration will be derived as the first date of dosing from the IP administration eCRF page. As this is a single dose study, the date of the first IP administration will also be the last date of the particular IP's administration.

14.2 Analysis

Exposure to IP will be presented in data listings for the SAF populations.

15. IP compliance

15.1 Variables and derivations

Administration of the study treatment will be supervised by unblinded study site personnel to ensure compliance. An unblinded monitor will periodically review the study records to ensure compliance. Discontinuation for compliance is at the Investigator's discretion and is to be noted in the eCRF.

15.2 Analysis

Overall treatment compliance to IP will be summarized for each treatment group for the SAF population and presented in data listings. Dosing administration errors will be listed for the same population, citing the treatment sequence, and treatment concerning the dose error and participant number.

16. Medical and treatment history

16.1 Variables and derivations

Medical history will be coded using MedDRA. See the relevant Data Management Plan for details.

Medical history will be recorded at screening. The recorded medical history will be updated, if necessary, at admission to treatment period 1. Investigators should document the occurrence, signs, and symptoms of the participant's preexisting conditions, including all prior significant illnesses. Medical history will include alcohol consumption and smoking history, if applicable.

Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs in the eCRF in accordance with Section 12.6 in the CSP of NKF-INS(A)-101 v2.0 06-May-2024. All changes that are not present at baseline or described in the medical history and identified as clinically noteworthy must be recorded as AEs.

16.2 Analysis

Medical history will be listed for each participant, by system organ class (SOC) and preferred term, for the FAS population.

17. Prior, concomitant and other medications

17.1 Variables and derivations

Prior, concomitant and other medications will be coded using WHODrug Global. See relevant Data Management Plan for details.

Medications taken by or administered to the participant for the period before screening will be recorded in the eCRF as prior medications. Restricted therapies include over-the-counter medication within 7 days or prescription medication within 14 days prior to dosing (apart from vitamin/mineral supplements, occasional paracetamol, thyroid placement, or birth control methods).

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) other than NKF-INS(A), US-NovoLog® and EU-NovoRapid® that the participant is receiving at the time of enrolment, or receives during the study, must be recorded in the eCRF as concomitant medications along with:

- Reasons for use.
- Dates of administration including start and end dates
- Dosage information including dose, regimen, route and frequency

Relevant prior concomitant medication given within 3 weeks before screening and all medication given from screening until the EOS visit (within 2-11 days after last administration of the study drug) must be recorded.

The participant must be told to notify the investigational site about any new medications taken after administration of the study treatment. All previous and on study Coronavirus disease 2019 (COVID-19) vaccinations should be recorded in the eCRF.

Other than those medications explicitly prohibited (*please refer to Section 8.6.1 in the CSP of NKF-INS(A)-101, v2.0 06-May-2024*), concomitant medication decisions will be left to the discretion of the Investigator.

17.2 Analysis

Prior- and concomitant medications will be presented in data listings for each participant, only for the FAS population. All medications captured on the concomitant medications panel of the eCRF will be categorised (prior/concomitant) and listed. Prohibited medications will be identified with an asterisk (*) in the relevant data listings.

18. Adverse events

18.1 Variables and derivations

Adverse Events (AEs) will be coded using MedDRA. See the relevant Data Management Plan for details.

Treatment-emergent adverse events (TEAEs) are defined as AEs that started at the time of, or after the first IP administration as well as those events that started prior to the first study drug administration, but which worsened after the first study drug administration.

Imputations will only be performed where at least the year is provided. The imputations derived for partial dates will be as follows:

- Missing days will default to the first of the month for start dates and the last day of the month for stop dates.
- Missing months will default to the first month (January) for start dates and to the last month (December) for stop dates.
- There will be no default for a missing year field.

In the case where it is impossible to define an AE as treatment-emergent or not, the AE will be classified by the worst case assigned, i.e. a TEAE.

18.2 Analysis

An overall summary will be presented as the number of participants within each of the event type categories described in the sub-sections below, including the incidence of TEAEs by SOC and preferred term, unless otherwise specified. Both number of participants, number of mentions (i.e., events) and percentage will be provided.

All TEAEs will be summarized by treatment sequence and period of event as follows:

- All AEs,
- Grade ≥ 3 AEs
- AEs related to study treatment, including related Grade ≥ 3 AEs,
- All adverse drug reactions, and
- SAEs

All AEs will be listed by participant, along with information regarding onset, duration, relationship, and severity to study treatment, action taken with study treatment, treatment of event, and outcome as captured in the EDC.

18.2.1 Incidence of TEAEs

The incidence of all TEAEs by SOC and preferred term and severity will be presented by treatment of event.

18.2.2 TEAEs by severity

The Investigator will use the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 to describe the severity of AEs. AEs not listed in the CTCAE will be graded as follows:

- **Grade 1**: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2:** Moderate; minimal, local, or non-invasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL). ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Self-care ADL refers to bathing, dressing & undressing, feeding self, using the toilet, taking medications, and not bedridden.
- **Grade 4:** Life-threatening consequences; urgent intervention indicated.
- **Grade 5:** Death related to the AE.

The incidence of all TEAEs will be presented by SOC, preferred term and severity for each treatment of event.

18.2.3 Drug-related TEAEs

Classification of Adverse Events by relationship to study treatment:

- **NOT RELATED:** There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.
- **RELATED:** The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.

The incidence of all drug-related TEAEs will be presented by SOC and preferred term for each treatment of event. *"Treatment of event"* will be derived as the last treatment exposed to prior to the onset of the AE.

18.2.4 Serious TEAEs

Any untoward medical occurrence, in the view of the Investigator or Sponsor, that:

- Results in death
- Is life-threatening: An AE is life threatening if the participant was at immediate risk of death from the event as it occurred (i.e., it does not include a reaction that might have caused death if it had occurred in a more serious form).
- Requires or prolongs inpatient hospitalization: A hospitalization is defined as ≥ 24 hours in hospital or overnight stay. Complications occurring during hospitalization are AEs and SAEs if they cause prolongation of the current hospitalization. Hospitalization for elective treatment of preexisting, non-worsening conditions is not, however, considered an AE. The details of such hospitalizations must be recorded in the medical history/procedures or physical examination page of the eCRF.
- Results in persistent or significant disability/incapacity: An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the participant's ability to carry out normal life functions.
- Results in a congenital anomaly/birth defect.
- Is another medically important event

Other important medical events that may not be immediately life threatening or result in death or hospitalization, based upon appropriate medical judgement, are considered SAEs if they are thought to jeopardize the participant and/or require medical or surgical intervention to prevent one of the outcomes defining an SAE. SAEs are critically important for the identification of significant safety problems; therefore, it is important to consider both the Investigator's and Sponsor's assessment.

The incidence of all serious TEAEs will be presented by SOC and preferred term for each treatment of event. A data listing of serious adverse events (SAEs) will also be presented.

18.2.5 TEAEs leading to early withdrawal from study

TEAEs leading to early withdrawal from study are defined as, in the Investigator's judgement, continued participation would pose unacceptable risk to the participant or to the integrity of the study data.

The incidence of all serious TEAEs leading to early withdrawal will be presented by SOC and preferred term for each treatment of event. A data listing of AEs leading to early withdrawal from study will be presented.

18.2.6 TEAEs leading to death

Treatment-emergent adverse events (TEAEs) leading to death are defined as TEAEs where there is a reasonable possibility of death occurring due to the IP.

The incidence of all TEAEs leading to death will be presented by SOC and preferred term for each treatment of event. A data listing of all AEs for deceased participants will be presented.

19. Safety laboratory tests

All summaries for Safety laboratory tests will be based on the SAF population, unless otherwise specified. Data listings will be based on the SAF population.

19.1 Variables and derivations

For safety laboratory data, baseline will be defined as the last observation made prior to the first administration of IP.

The following laboratory tests (haematology, clinical chemistry and urinalysis) to be included in the analysis:

19.1.1 Hematology

Ethylenediaminetetraacetic acid (EDTA) tubes:

- Full and differential blood count,
- White blood cell (WBC) count,
- Red blood cell (RBC) count,
- Hemoglobin (Hb),
- Hematocrit (HCT),
- Mean corpuscular volume (MCV),
- Mean corpuscular hemoglobin (MCH),
- Mean corpuscular hemoglobin concentration (MCHC),
- Absolute differential count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) and
- Platelets

19.1.2 Clinical Chemistry

Serum separator tubes (SST):

- Potassium,
- Sodium,
- Urea,
- Chloride,
- Phosphorus,
- Creatinine,
- Calcium,
- Albumin,
- Total and direct bilirubin,
- Creatine kinase,
- Alkaline phosphates (ALP),
- Gamma glutamyl transferase (GGT),
- Aspartate aminotransferase (AST),
- Alanine aminotransferase (ALT),
- Lactate dehydrogenase,
- Total cholesterol,
- Triglycerides,
- Glucose

19.1.3 Blood coagulation tests

Citrated tubes:

- Prothrombin time (PT),
- Activated partial thromboplastin time (aPTT)
- International normalized ratio (INR)

19.1.4 Urinalysis

- Appearance,
- Glucose,

- bilirubin,
- ketone,
- specific gravity,
- Blood,
- pH,
- protein,
- urobilinogen,
- nitrite
- leucocytes.

Abnormal urinalysis results may be repeated at the discretion of the investigator.

Quantitative laboratory measurements reported as "< X.XX", i.e. below limit of quantitation, or "> X.XX", i.e. above the upper limit of quantification, will be converted to X.XX for quantitative summaries, but will be presented as recorded, i.e. as "< X.XX" or "> X.XX" in the data listings.

19.2 Analysis

The SAF population alone will be used to analyse safety laboratory data.

Summaries of haematology, clinical chemistry, blood coagulation and urinalysis laboratory tests for each treatment sequence, by visit and by time point, will include descriptive statistics of the following:

- Actual and change from baseline (for quantitative measurements)
- Frequencies and percentages (n and %) (for qualitative measurements)

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges and categorised as:

- Low: Below the lower limit of the laboratory reference range
- Normal: Within the laboratory reference range (upper and lower limit included)
- High: Above the upper limit of the laboratory reference range

These categorizations will only be presented in data listings. Other laboratory results (apart from haematology, clinical chemistry and urinalysis laboratory tests), e.g. urine microscopy, will be listed. A separate listing containing clinically significant laboratory results will be presented.

20. Vital signs

All summaries, and data listings, for vital signs will be based on the SAF population, unless otherwise specified.

Vital signs will be measured after the participant has been resting quietly in a seated position for at least 5 minutes. Vital sign measurements will be repeated if clinically significant abnormal or machine/equipment errors occur. Out-of-range blood pressure, respiratory rate, or heart rate measurements may be repeated at the Investigator's discretion. Any confirmed, clinically significant abnormal vital sign measurements must be recorded as AEs.

20.1 Variables and derivations

For vital signs, baseline is defined as the last observation made prior to the first administration of IP.

The following vital signs will be reported for this study:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Heart rate (bpm)
- Body temperature (°C) (temporal or ear temperature measurements).
- Respiratory rate (breaths/min)

20.2 Analysis

The following summaries will be provided for vital signs data for each treatment sequence, by visit:

- Actual and change from baseline by visit
- Descriptive statistics (n, arithmetic mean, SD, minimum, median, maximum) for absolute values.

Abnormal quantitative vital signs will be identified in accordance with the following predefined abnormal criteria:

- Systolic blood pressure: 90 to 140 mmHg
- Diastolic blood pressure: 50 to 90 mmHg
- Heart rate: 40 to 100 bpm
- Body temperature: 35.5 to 37.5 °C

21. Other assessments

The following assessments will only be presented in data listings for the SAF population:

21.1 Physical examination data

A complete physical examination will be performed at screening (Visit 1). Physical examinations will be performed by a physician.

A full physical examination will include the following: evaluation for jaundice, pallor (anemia), cyanosis, clubbing, edema, and lymphadenopathy; skin evaluation: fundoscopy; ear, nose, and throat; cardiovascular assessment; respiratory assessment; abdominal examination; musculoskeletal assessment; neurological assessment. Other evaluations may be performed as deemed necessary by the Investigator.

Clinically significant findings must be recorded as AEs.

Physical examination data will be presented classified as normal or abnormal.

21.2 Electrocardiograms

A 12-lead, resting ECG will be obtained at the timepoints indicated in the schedule of assessments (Section 4.2; Protocol NKF-INS(A)-101, Version 2.0, dated 06-May-24). ECG should always be performed after the participant has been resting in a supine position for at least 5 minutes.

The frequency of abnormalities (e.g., heart rate, PR interval, QRS complex, and QTcF [Fridericia's corrected QT]) will be summarized by treatment group and scheduled visits using counts and percentages.

An assessment of normal, abnormal clinically significant, or abnormal not clinically significant will be recorded; if the ECG is considered abnormal, the abnormality will be documented in the eCRF. ECGs may be repeated if clinically significant abnormalities are observed, or artifacts are present. Any confirmed, clinically significant abnormal ECG findings must be recorded as AEs.

Participant ECG status (normal, abnormal clinically significant, or abnormal not clinically significant) may be summarized for each scheduled ECG and shifts from screening may be tabulated. Raw data and derivations will also be presented as a listing for the SAF population. Data will be analysed as outlined in ICH E14.

Abnormal ECG values will be identified in accordance with the following predefined normal criteria:

- PR Interval: 120 to 220 (msec)
- QRS Duration: < 120 (msec)
- Heart rate: 50 to 100 (bpm)
- QTc Interval: 350 to 450 (msec)
- For the QT, QTcF parameters, the following categorisations will be done:
  - x <= 450 ms (considered as normal range)
  - 450 < x <= 480 ms
  - 480 < x <= 500 ms
  - x > 500 ms

  and for change from baseline:
  - x <= 30 ms (considered as normal range)
  - 30 < x <= 60 ms
  - x > 60 ms
- For the PR parameter, the following categorisations will be done:
  - x < 120 ms
  - 120 <= x <= 220 ms (considered as normal range)
  - x > 220 ms
- For heart rate, the following categorisations will be done:
  - x < 50 bpm
  - 50 <= x <= 100 bpm (considered as normal range)
  - x > 100 bmp

21.3 Injection site assessment

The injection site and surrounding area will be assessed by the investigator at 1 min and 15 min post-dose on Day 1 and at the EOS visit. Reactions to the study drug injection will be documented using a numerical scoring system. The injection site assessment will be summarised (frequency and percentage) by type of assessment and timepoint for the SAF population. The injection site assessment will be listed for the SAF population.

22. Pharmacokinetic Analysis

The primary PK objective of this trial is to compare the PK of NKF-INS(A) to US-approved (US-NovoLog®) and EU-authorized (EU-NovoRapid®) insulin to demonstrate PK similarity for insulin aspart. The secondary PK objective is to evaluate additional PK parameters NKF-INS(A) compared to US-approved and EU-authorized insulin aspart. Details on the endpoints are provided in Section 3.

PK concentrations and parameter data will be listed and summarized descriptively (N, arithmetic and geometric mean, SD, CV%, median, minimum and maximum) and graphically by treatment.

Biosimilarity between the test product and the US-approved and EU-authorized insulin aspart will be considered separately, i.e., test product vs US-approved product and test product vs EU-authorized product. Biosimilarity of the test and reference products will be assessed on the basis of 90% CIs for estimates of the geometric mean ratios between the primary PK parameters of the test and reference products in relation to the conventional bioequivalence range of 80% to 125%.

Due to different regulatory requirements in terms of preferred statistical methods used in bioequivalence assessment, the test and respective reference insulin products will be analysed using two statistical models. Briefly, the Test-EU Reference comparison will be analysed using a model that only includes fixed effects and the Test – US-reference comparison will be analysed using a mixed effects model that includes both fixed and random effects.

22.1 Pharmacokinetic Concentrations

All PK blood sampling times, including time deviations, will be listed for all participants in the SAF population (to ensure data for participants excluded from the PK population are listed).

For geometric statistics, imputed BLQ values of zero will be omitted. In addition, the percentage and number of participants, with plasma concentrations below the BLQ will be presented at each timepoint. Natural log transformations will be used throughout the analysis, where applicable. CV% will be calculated as follows:

Arithmetic CV%$= \left(\frac{arithmetic\ standard\ deviation}{arithmetic\ mean}\right) * 100$

Geometric CV% $= (\sqrt{\exp(variance) - 1}) * 100$

All PK concentration data will be listed for all participants in the SAF population (to ensure data for participants excluded from the PK population are listed).

22.2 Pharmacokinetic Parameters

The PK parameters will be derived for NKF-INS(A), US-NovoLog®, and EU-NovoRapid® from serum concentrations by a validated PK analysis using linear up/ linear down non-compartmental analysis (NCA) (where data allow). A description of the PK parameters is provided in Table 22.2:

Table 22.2: PK Parameters and their descriptions.

PK Parameter	Description
AUC_{0-4h}	concentration-time curve from 0 to 4 hours
AUC_{0-6h}	concentration-time curve from 0 to 6 hours
AUC_{6-12h}	concentration-time curve from 6 to 12 hours
AUC_{0-12h}	concentration-time curve from 0 to 12 hours/end of clamp
AUC_{0-t}	concentration-time curve from 0 hour to the last quantifiable concentration time
$AUC_{0-\infty}$	concentration-time curve from 0 hour to infinity
T_{max}	time to maximum serum concentration
C_{max}	maximum observed insulin aspart concentration
t50%-early	time to half-maximum before C_{max}
t50%-late	time to half-maximum after C_{max}
$t_{1/2}$	terminal elimination half-life

PK parameters will be estimated using non-compartmental analysis. Estimates of PK parameters will be listed and summarized (N, arithmetic and geometric mean, SD, CV%, median, minimum, and maximum) by treatment, descriptively and graphically.

Reliability of parameter estimates:

- The percentage of the extrapolated AUC (area under the curve) should not exceed 20% of AUC for an individual profile. For profiles where the percentage of extrapolated AUC is greater than 20%, the observations should be flagged in the SDTM PP dataset as unreliable, if applicable. Such observations should be listed, where possible, but not used in the preparation of summary statistics or any other statistical procedures.
- For terminal half-life, the following conditions should be met:
- It should be determined over a time interval equal to at least 1.5 times the terminal half-life.
- It should be estimated from at least 3 data points (primarily monotonically decreasing in magnitude), of which C_{last} (last observed quantifiable concentration) should be included, but not the datapoint at T_{max}.
- The adjusted coefficient of determination (adj-R^2) for the regression/fit should be at least 0.85.

If any one of the conditions are not met, an observation should be flagged as unreliable and listed, where possible, but not used in the preparation of summary statistics or any other statistical procedures. The observation should not be used in the NCA, unless specified otherwise.

22.3 Bioequivalence assessment (EU)

As specified in the *Guideline on the investigation of bioequivalence* [3] the test product will be compared to the reference product by means of

statistical analysis with respect to the primary PK parameters using an analysis of variance (ANOVA) with sequence, subject (sequence), treatment and period as fixed effects after logarithmic transformation of the relative PK parameter. Point estimates and 90% confidence intervals (CIs) for the "test/reference" geometric mean ratios of these parameters will be provided.

Bioequivalence will be established on the basis of the 90% CIs for estimates of the geometric ratios between the primary PK parameters of the test and EU-approved reference products are contained within the acceptance range of 80.00% to 125.00%. The primary PK parameters that will be used for the bioequivalence assessment are C_{max} and AUC_{0-t}. This method is equivalent to two one-sided tests with the null hypothesis of bioinequivalence at the 5% significance level.

22.4 Bioequivalence assessment (US)

As specified by *Guidance for industry: Statistical Approaches to Establishing Bioequivalence* [4] the test product will be compared to the reference product by means of statistical analysis with respect to the primary PK parameters using a linear mixed effects model following logarithmic transformation of the data. PK parameters will be estimated using treatment, period and sequence as fixed effects and participants as random effects. A difference in test and reference means and accompanying 90% CI will be back transformed from the log scale to provide estimates of the test/reference ratio of geometric means. Inter- and intra-subject variability will be estimated from the linear mixed effects model.

Point estimates and 90% CIs for the "test/reference" geometric mean ratios of these parameters will be provided. The primary PK parameters that will be used for the bioequivalence assessment are C_{max} and AUC_{0-t}. All other PK-related assessments of equivalence will be considered secondary.

Any missing samples or non-reportable concentration values will be disregarded in the PK analysis.

If terminal phase of serum concentration-time profile has sufficient data points, apparent terminal elimination half-life ($t^1/_2z$), apparent terminal elimination rate constant (λz), mean residence time (MRT), clearance (CL/F), and volume of distribution (V/F) will be calculated.

23. Pharmacodynamics Analysis

The primary PD objective is to compare the PD of NKF-INS(A) to US-approved (US-NovoLog®) and EU-authorized (EU-NovoRapid®) insulin aspart injection by examining GIR profiles after a single SC dose. The secondary PD objective is to evaluate the additional parameters NKF-INS(A) compared to US-approved and EU-authorized insulin aspart. Details on the endpoints are provided in Section 3.

PD GIR and parameter data will be listed and summarized descriptively (N, arithmetic and geometric mean, SD, CV%, median, minimum and maximum) by treatment and graphically.

As for PK similarity, biosimilarity between the test product and the US-approved and EU-authorized insulin aspart will be considered separately, i.e., test product vs US-approved product and test product vs EU-authorized product.

Due to different regulatory requirements in terms of preferred statistical methods used in bioequivalence assessment, the test and respective reference insulin products will be analysed using two statistical models. Briefly, the Test-EU Reference comparison will be analysed using a model that only includes fixed effects and the Test – US-reference comparison will be analysed using a mixed effects model that includes both fixed and random effects.

All PD analyses will be based on the PD parameter population.

23.1 Pharmacodynamic Glucose Infusion Rates

Blood samples for glucose and GIR values will be collected following exposure to NKF-INS(A), US-NovoLog®, and EU-NovoRapid® at the time points indicated in the sample schedule (refer to Table 4; Protocol NKF-INS(A)-101, Version 2.0, dated 06-May-24). The actual date and time of each blood sample and GIR changes will be recorded. Actual time will be used for the derivation of PD parameters.

23.2 Pharmacodynamic parameters

The PD similarity will be assessed using the parameters provided in Table 23.2 and by assessing:

- Time from study drug administration until the blood glucose concentration has decreased by at least 5mg/dL from baseline (onset of action).
- The difference between tGIR, 50%-late and the onset of action (duration of action).
- Total amount of glucose infused during clamp procedure (Gtot).

Table 23.2: PD Parameters and their descriptions.

PD Parameter	Description
$AUCGIR_{0\text{-}12h}$	Area under the GIR-time curve from 0 to 12 hours
GIR_{max}	The maximum GIR of glucose
$AUCGIR_{0\text{-}4h}$	Area under the GIR-time curve from 0 to 4 hours
$AUCGIR_{0\text{-}6h}$	Area under the GIR-time curve from 0 to 6 hours
$AUCGIR_{6\text{-}last}$	Area under the GIR-time curve from 6 hours until the end of clamp
$AUCGIR_{0\text{-}t}$	Area under the GIR-time curve from 0 hours to the last quantifiable concentration time
$AUCGIR_{0\text{-}\infty}$	Area under the GIR-time curve from 0 hours to the last quantifiable concentration time with extrapolation to infinity
$AUCGIR_{0\text{-}end}$ of clamp	Area under the GIR-time curve from 0 hours to end of clamp
T_{max}.GIR	Time to maximum GIR
tGIR,50%-early	Time to half-maximum GIR before GIR_{max}
tGIR,50%-late	Time to half-maximum GIRe after GIR_{max} (indicator of end of duration of action)

Estimates of PD parameters will be listed and summarized (N, arithmetic and geometric mean, SD, CV%, median, minimum and maximum) by treatment, descriptively and graphically.

Endogenous insulin suppression via C-peptide measurements will also be explored. These values include corrected and uncorrected C-peptide concentrations. C-peptide corrected estimates of exogenous insulin will be calculated using Owen's method [5].

23.3 Bioequivalence assessment (EU)

As specified in the *Guideline on the investigation of bioequivalence* [3] the test product will be compared to the reference product by means of statistical analysis with respect to the primary PD parameters using an ANOVA with sequence, subject (sequence), treatment and period as fixed effects after logarithmic transformation of the relative PD parameter. Point estimates and 95% confidence intervals (CIs) for the "test/reference" geometric mean ratios of these parameters will be provided.

Biosimilarity will be established on the basis of the 95% CIs for estimates of the geometric ratios between the primary PD parameters of the test and EU-approved reference products are contained within the acceptance range of 80% to 125%. The primary PD parameters that will be used for the bioequivalence assessment are GIR_{max} and $AUCGIR_{0\text{-}t}$.

23.4 Bioequivalence assessment (US)

As specified by *Guidance for industry: Statistical Approaches to Establishing Bioequivalence* [4] biosimilarity of the test and US-reference products will be assessed on the basis of 90% CIs for estimates of the geometric mean ratios between the primary PD parameters of the test and reference products in relation to the conventional bioequivalence range of 80% to 125%.

The test product will be compared to the reference product by means of statistical analysis with respect to the primary PD parameters using a linear mixed effects model after logarithmic transformation of the data. PD parameters will be estimated using treatment, period and sequence as fixed effects and participants as random effects. A difference in test and reference means and accompanying 90% CIs will be back transformed from the log scale to provide estimates of the test/reference ratios of geometric means. Inter- and intra-subject variability will be estimated from the linear mixed effects model.

Point estimates and 90% and CIs for the "test/reference" geometric mean ratios of these parameters will be provided. The primary PD parameters that will be used for the bioequivalence assessment are GIR_{max} and $AUCGIR_{0\text{-}t}$.

All other PD-related assessments of equivalence will be considered secondary.

24. Euglycemic Clamp Procedure and Performance

NKF-INS(A), US-NovoLog®, and EU-NovoRapid® will be administered using a euglycemic glucose clamp at targeted blood glucose concentrations. The euglycemic glucose clamp will be conducted using a manual clamp technique,

which will continuously monitor the participant's blood glucose and administer GIR to maintain blood glucose close to the target blood glucose concentration. The clamp procedure will be initiated, maintained, and terminated, in accordance with the site SOPs. The participant's blood glucose will be maintained within a predefined target window per site SOP and clinical judgement for the participant by manually adjusting the GIR.

The Target Glucose Value (TGV) for each participant is derived as follows (as described in the FARMOVS Standard Operating Procedure *Glucose Clamp Methodology CL14-v06 29-Jul-2024)*:

The TGV is derived as the mean baseline glucose value (mg/dL) subtracted by 5 mg/dL. The mean baseline glucose value will be derived as the mean (rounded to the whole number) of the glucose values obtained at the -60, -30 and 0 time points.

The upper limit of the TGV is the mean baseline glucose value, and the lower limit value is the derived TGV subtracted by 5. As far as possible, the post dose glucose values of participants should be maintained within the upper and lower limit values by adjusting the GIR accordingly.

Blood samples will be collected at pre-specified intervals before and up to 12 hours after dosing for measurement of blood glucose, serum insulin, and C-peptide as shown in the schedule of assessments.

High glucose clamp quality is important to precisely and reproducibly describe the time-action profiles of blood glucose (BG) lowering agents. To achieve high quality, that is, a GIR reflecting the correct PD effect, BG must be kept at the TGV as closely as possible.

Calculations of the mean values, root mean square deviation and CV of the BG concentrations will be used to provide an estimate of the performance of the clamp study. The mean ± SD difference between the clamp device and the target level reflects the "control deviation" and will be displayed in a figure. In this trial, the blood glucose CV% will be considered as a guide of good clamp technique. A blood glucose CV% below 10% has been suggested as the cut-off of sufficient clamp technique, i.e., CV % > 10% is considered poor clamp technique.

25. References

1. PASS 2024 Power Analysis and Sample Size Software (2024). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.
2. Team, R., RStudio: Integrated Development Environment for R. 2023: Boston, MA.
3. Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **20 January 2010)
4. Guidance for Industry on Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs--General Considerations FDA-2014-D-0204
5. Plum-Mörschel L, Singh G, Murugesan SNM, Marwah A, Panda J, Loganathan S, et al. Pharmacokinetic and pharmacodynamic equivalence of Biocon's biosimilar insulin-R with the US-licensed Humulin R formulation in healthy subjects: results from the RHINE-1 (Recombinant Human Insulin Equivalence-1) study. Diabetes Obes Metab. 2022;24:713-721.

6. Benesch C, Heise T, Klein O, Heinemann L, Arnolds S. How to assess the quality of glucose clamps? Evaluation of clamps performed with ClampArt, a novel automated clamp device. *J Diab Sci Technol*. 2015; **9**(4): 792-800.

26. Revision history

Version	Date	Change
Draft 01	05-Sep-2024	Initial draft
Draft 02	25-Sep-2024	Minor edits throughout SAP and clarifications where needed.
Draft 03	09-Oct-2024	Minor edits, clarifications and references were added where appropriate.
Draft 04	18-Oct-2024	PK and PD bioequivalence assessment models specified separately as regulatory requirements differ between EMA and FDA requirements in terms of models used. (fixed effects only for EMA and mixed effects for FDA)
Version 01	21-Oct-2024	Initial Version