Statistical Analysis Plan Version 2 I8B-MC-ITTC

A Study to Investigate Local Infusion Site Pain after Infusion of Excipients across Infusion Sites and Infusion Depths

NCT05067270

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STATISTICAL ANALYSIS PLAN

A Study to Investigate Local Infusion Site Pain after Infusion of Excipients across Infusion Sites and Infusion Depths

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1. TABLE OF CONTENTS

2. ABBREVIATIONS

Abbreviations pertain to the Statistical Analysis Plan (SAP) only (not the tables, figures and listings [TFLs]).

AE	Adverse event
CI	Confidence interval
CRU	Clinical Research Unit
CSII	Continuous subcutaneous insulin infusion
CSR	Clinical Study Report
CV	Coefficient of variation
ECG	Electrocardiogram
ICH	International Conference on Harmonisation
ISR	Infusion site reaction
LSMeans	Least-squares means
MedDRA	Medical Dictionary for Regulatory Activities
SAP	Statistical Analysis Plan
SD	Standard deviation
T1D	Type 1 diabetes mellitus
TFLs	Tables, Figures, and Listings
VAS	Visual analog scale
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 18 May 2021, protocol amendment (a) dated 08 September 2021, protocol amendment (b) dated 28 September 2021 and protocol amendment (c) dated 14 October 2021).

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

The intent of this document is to provide guidance for the statistical analyses of data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Eli Lilly and Company. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. For open-label studies, this SAP must be signed off prior to first participant visit for this study. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon with Eli Lilly and Company and identified in the CSR. Any minor deviations from the TFLs may not be documented in the CSR.

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

4. STUDY OBJECTIVES AND ENDPOINTS

4.1 Part A

4.1.1 Primary Objective and Endpoint

Primary Objective

To investigate local infusion site pain for infusions of sodium citrate and treprostinil in Humalog diluent with magnesium chloride (without insulin) in the abdominal, arm, thigh, and buttock areas in participants with type 1 diabetes mellitus (T1D) on continuous subcutaneous insulin infusion (CSII).

Primary Endpoint

VAS pain score.

4.1.2 Secondary Objective and Endpoint

Secondary Objective

To investigate local infusion site pain of 2 different cannula insertion depths (6 mm and 9 mm) in participants with T1D on CSII.

Secondary Endpoint

VAS pain score.

4.1.3 Exploratory Objective and Endpoint

Exploratory Objective

To assess local infusion site reactions (ISR) using the exploratory CCI Platform.

Exploratory Endpoint

Characterization and measurement of incidence and severity of local ISR data.

5. STUDY DESIGN

Study I8B-MC-ITTC is a 1-/2-center, participant-(Part A CCI) and investigator-CCI blind, 2-part randomized crossover study in adults (18 to 69 years of age, inclusive) with T1D on CSII. Approximately 46 participants will be randomly assigned to study intervention such that approximately 40 evaluable participants complete Part A CCI

Part A of this study will be a 1-/2-center, randomized, 1 day 5-period crossover based on the order of infusion sites and depths, blinded (between infusion depths), open-label single-treatment study conducted in adults with T1D.

CCI

For CCI Part A CCI , the participant will continue using his or her personal insulin pump system at the currently employed infusion site and will be responsible for performing the required actions to maintain its functionality. Participants will be instructed to avoid the use of the central abdominal area for their personal infusion sets during the CCI and prior to arrival at the clinical research unit (CRU).

5.1 PART A

1. Following an informed consent and a screening visit, participants will come to the CRU in the evening (after dinner) of Day -1 for Part A.
2. Prior to the insertion of the first infusion set, the thickness of the SC adipose tissue layer at the abdomen, arm, thigh, and buttock areas will be assessed by ultrasound and the measurement recorded in mm in the electronic case report form. The evaluated site should be identified with a unique identifier.
3. The infusion sites will be assessed, and an image of each local infusion site will be collected using the CCI Platform prior to insertion of the corresponding infusion set.
4. Each Medtronic™ MiniMed™ 770G pump reservoir will be filled by a qualified site staff member with 3 mL of study treatment (sodium citrate and treprostinil in Humalog diluent with magnesium chloride [without insulin]).
5. Five pumps will be used for each participant to assess infusions into the abdominal, arm, thigh, and buttocks areas. Participants will be randomly assigned to 1 of 5 infusion site sequences to indicate the order of the infusion sites being evaluated.
6. Six mm cannula will be inserted into each of the designated areas (abdomen [at least 5 cm away from the umbilicus in the left or right lower quadrants], posterior aspect of the upper arm, anterior or lateral thigh, and upper buttock), avoiding areas of lipohypertrophy or surgical scars. At the abdominal area only, a 9 mm cannula will also be inserted into the opposite side of the lower abdomen.

7. The first infusion site will be initiated, and a basal infusion rate of 1 U/h will be started. The same procedure will occur at the subsequent infusion sites according to the randomly assigned sequence with an approximately 30-minute interval between initiation of the previous infusion site. In case of immediate infusion set intolerance, a new infusion set can be inserted within the first 10 minutes of initiation of the infusion site.
8. Approximately 3 hours after the start of the basal infusion at 1 U/hr, a bolus dose of 15 U will be delivered at quick bolus speed (15 U/min) to each infusion site according to the treatment sequence with an approximately 30-minute interval between infusion sites.
9. A second bolus of 15 U given at quick speed (15 U/min) will be delivered approximately 6 hours after the start of the basal infusion to each infusion site according to the treatment sequence with an approximately 30-minute interval between infusion sites.
10. A third bolus dose of 15 U given at quick speed (15 U/min) will be delivered approximately 9 hours after the start of the basal infusion to each infusion site according to the treatment sequence with an approximately 30-minute interval between infusion sites.
11. Participants will rate the pain at each infusion site after each bolus dose at the following approximate time points: 5 minutes before the administration of a bolus dose and 1 and 15 minutes after the start of each bolus dose.
12. Study infusion sets with cannula and pumps will be removed.
13. Infusion sites will be evaluated for acute local ISRs and an image of each local infusion site will be collected using the CCI Platform.
14. Following the final evaluation, the participants will have the option to spend the night or be discharged from the CRU.

6. INFUSION SITE LOCATIONS/TREATMENTS

The following is a list of the study infusion site locations/treatment abbreviations that will be used in the TFLs.

6.1 Part A

Infusion site location	Infusion site location order in TFL
Arm	1
Thigh	2
Abdomen 6 mm	3
Abdomen 9 mm	4
Buttock	5

CCI

7. SAMPLE SIZE JUSTIFICATION

Approximately 46 participants with T1D will be enrolled in Study I8B-MC-ITTC so that approximately 40 participants complete CCI Part A CCI of the study. CCI Forty completing participants will provide approximately 80% power to demonstrate approximately a 55% increase in the VAS pain score between the infusion site locations in Part A CCI . Testing will be done at alpha-level of 0.05 with a 2-sided confidence interval (CI). The variability was estimated by analyzing a Lilly internal study that showed a log-scale standard deviation of within- participant difference in VAS pain scores of 0.95.

Participants who discontinue the study before completing the assessments may be replaced at the discretion of the sponsor and investigator to ensure that approximately 40 participants complete the study. The replacement participant will be assigned to the same treatment sequence as the discontinued participant

8. DEFINITION OF ANALYSIS SETS

The "Full" analysis set will consist of all randomized participants. Participants will be included in the analyses according to the randomly assigned sequences.

The "Safety" analysis set will consist of all randomized participants who receive at least 1 infusion. Participants will be analyzed according to the infusions they actually received.

Data related to a site where an infusion set cannula is accidentally pulled out of an infusion site or data following a pump occlusion alarm during a bolus infusion will not be used in the analysis for that particular site only/part of the study.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when participants are assigned to analysis populations before database lock.

9. STATISTICAL METHODOLOGY

9.1 General

Data listings will be provided for all data that is databased. Summary statistics and statistical analysis will only be presented for data where detailed in this SAP. For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation (SD), median, min, max and n; for log-normal data, the geometric mean and geometric coefficient of variation (CV%) will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all participants up to the point of withdrawal, with any participants excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for participants included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Mean change from baseline is the mean of all individual participants' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual participant's baseline value from the value at the timepoint. The individual participant's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

Data analysis will be performed using SAS® Version 9.4 or greater.

9.2 Demographics and Participant Disposition

Participant disposition will be summarized and listed. The demographic variables age, sex, race, site ID, body weight, height, and body mass index will be summarized by part and listed. All other demographic variables will be listed only.

9.3 Safety and Tolerability Assessments

9.3.1 Primary Endpoint

Descriptive statistics

Infusion site pain assessed using the VAS pain score will be listed and summarized using standard descriptive statistics including the geometric mean and CV% by bolus time (3, 6, and 9 hours after initiation of basal infusion) and VAS assessment time point (5 minutes prior to bolus and 1 and 15 minutes after bolus). For Part A, the summary will also be by infusion site location. The 5 infusion site locations include the assessment of 2 cannula depths at the

abdominal site. CCI [redacted] The relevant timepoint windows will also be displayed in the labelling of the timepoints in the output.

It is possible that VAS scores will be 0; if so, all scores will be analyzed as log (VAS+1) to allow for the inclusion of the 0 values in the geometric descriptive statistics. This transformation will be applied for the calculation of the geometric statistics only and will not be applied to the arithmetic statistics. This transformation (VAS+1) will also be applied to all data prior to the calculation of the ratio of the post-bolus time points to the pre-bolus time point if there are occurrence of 0.

Frequencies and percentages of VAS pain scores in each of the categories of 0, 1 to 10, 11 to 20, 21 to 45, and 46 to 100 mm will be summarized by bolus time, infusion site location/study treatment, and time point.

Geometric mean profile plots will be presented by bolus time, infusion site location/study treatment, and time point.

Statistical Analysis

A mixed effects model will be used to analyze the log transformed VAS pain score for each bolus time and VAS time point. The statistical model for Part A will include terms for infusion site location, period (order of infusions), bolus time, VAS time point, the 2- and 3-way interactions between infusion site location, bolus time, and VAS time point as fixed effects and participant as a random effect. Comparisons will be made between infusion site locations for the abdominal infusion site for each bolus time and VAS time point.

CCI [redacted]

Least-squares means (LSMeans), infusion site location/treatment differences in LSMeans, and the corresponding 95% confidence intervals (CIs) for the infusion site location/treatment differences will be estimated and back-transformed from the log scale to provide estimates of the ratio of geometric LSMeans and 95% CI for the ratio of these means. It is possible that VAS scores will be 0; if so, all scores will be analyzed as log (VAS+1) to allow for the inclusion of the 0 values in the analysis.

The same model will also be used to analyze the change from the pre-bolus time point (5 minutes prior to the bolus) to the post-bolus time points of (1 and 15 minutes after bolus).

Example SAS code for Part A is shown below, CCI

```
proc mixed data=xxx;
class location period bolus_time vas_time subjid;
model logVAS = period location|bolus_time|vas_time /residual ddfm=kr2;
random intercept / subject=subjid;
lsmeans location*bolus_time*VAS_time / cl pdiff alpha=0.05;
ods output lsmeans=lsm;
ods output diffs=estims;
run;
```

9.3.2 Secondary Endpoint

For Part A, the comparison of cannula depths at the abdominal infusion site location will be analyzed as part of the same mixed effects model used for the primary endpoint.

9.3.3 Exploratory Endpoint

Local ISR data (erythema, induration, categorical pain, pruritus, and edema) will be listed and summarized by infusion site location (Part A) CCI in frequency tables. Data from the exploratory CCI Platform will not be included in the CSR but may be presented in a separate report.

9.3.4 Adverse Events

Where changes in severity are recorded in the Case Report Form, each separate severity of the adverse event (AE) will be reported in the listings, only the most severe will be used in the summary tables. A pre-existing condition is defined as an AE that starts before the participant has provided written informed consent and is ongoing at consent. A non-treatment emergent AE is defined as an AE which starts after informed consent but prior to dosing. A treatment-emergent AE is defined as an AE which occurs postdose or which is present prior to dosing and becomes more severe postdose.

All AEs will be listed. Treatment-emergent AEs will be summarized by study part and by infusion site location/study treatment, severity, and relationship to the study drug/protocol procedure. The frequency (the number of AEs, the number of participants experiencing an AE and the percentage of participants experiencing an AE) of treatment-emergent AEs will be summarized by infusion site location/study treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 system organ class, and preferred term. The summary and frequency AE tables will be presented for all causalities and those considered related to the study drug by the investigator and repeated for those considered related to the protocol procedure. Any serious AEs will be listed. Summaries by infusion site location/study treatment will only be possible where a particular AE is able to be attributed to a particular infusion site location, AE data will also be summarized by study part.

Discontinuations due to AEs will be listed.

9.3.5 Concomitant Medication

Concomitant medication will be coded using the WHO drug dictionary (Version March 2021). Concomitant medication will be listed.

9.3.6 Clinical Laboratory Parameters

Samples for clinical laboratory data will be performed for inclusion/exclusion criteria purposes only and will not be presented.

9.3.7 Vital Signs

Vital signs data including subcutaneous layer thickness data will be listed.

9.3.8 Electrocardiogram (ECG)

ECGs will be performed for inclusion/exclusion criteria purposes only and will not be presented.

9.3.9 Hepatic Monitoring

Not applicable.

9.3.10 Immunogenicity Assessments

Immunogenicity assessments are not evaluated in this study.

9.3.11 Hypersensitivity Reactions

For all hypersensitivity reactions that occur, additional follow-up data will be collected to assess the patient's medical history, alternative causes, and symptoms.

These data will be listed.

9.3.12 Other Assessments

All other safety assessments not detailed in this section will be listed but not summarized or statistically analyzed. If there is an impact on the study due to COVID-19, additional data presentations/considerations may be required. This will be assessed prior to the database lock.

10. INTERIM ANALYSES

No interim statistical analyses are planned.

11. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

12. REFERENCES

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

13. DATA PRESENTATION

13.1 Decimal Places

N and percentage values should be reported as whole numbers. The geometric mean, arithmetic mean, median and SD will be presented to 1 decimal place more than the original data..

13.2 Missing Data

Missing data will not be displayed in listings.

13.3 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of participants or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No serious adverse events occurred for this study.”

14. APPENDICES

Appendix 1: Document History

Status and Version	Date of Change	Summary/Reason for Changes
Final Version 1.0	NA	NA; the first version.
Final Version 2.0	01 February 2022	Added reference to and updates from protocol amendment (c) Added clarification for the VAS data handling Other minor clarifications

NA = not applicable

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