

Statistical Analysis Plan I8B-MC-ITTA (1.0)

A 26-Week, Multicenter, Open-Label, Single-Arm, Phase 4 Study to Assess the Safety of Lyumjev in Adult Patients with Type 2 Diabetes Mellitus in India

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List of Abbreviations

Abbreviation	Definition
AE	adverse event
ANCOVA	analysis of covariance
BG	blood glucose
BMI	body mass index
CI	confidence interval
CRF	case report form
CSR	clinical study report
ECG	Electrocardiogram
eCRF	electronic case report form
ED	early discontinuation
EDC	electronic data capture
EMA	European medicines agency
FAS	Full Analysis Set
FDA	food and drug administration
HbA1c	hemoglobin A1c
HR	heart rate
IP	investigational product
ITSQ	Insulin Treatment Satisfaction Questionnaire

Abbreviation	Definition
IWRS	interactive web response system
LOCF	last-observation-carried-forward
MedDRA	medical dictionary for regulatory activities
MDI	multiple daily injection
MMRM	mixed model for repeated measurements
O	office visit
P	phone visit
PPG	postprandial glucose
SAE	serious adverse event
SAF	Safety Population
SAP	statistical analysis plan
SD	standard deviation
SMBG	self-monitored blood glucose
SOC	system organ class
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event
WHO-DD	world health organization drug dictionary
WOCBP	woman of childbearing potential

1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Eli Lilly and Company protocol number I8B-MC-ITTA (c) (A 26-Week, Multicenter, Open-Label, Single-Arm, Phase 4 Study to Assess the Safety of Lyumjev in Adult Patients with Type 2 Diabetes Mellitus in India), dated 03 January 2024, version 1.0. Reference materials for this statistical plan include the protocol and the accompanying sample data collection documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials (ICH, 1998). All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association (ASA, 2018) and the Royal Statistical Society (RSS, 2014), for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The statistical plan described hereafter is an *a priori* plan. It will be approved prior to first subject first visit.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective is to assess the risk of hypoglycemia in adult subjects with type 2 diabetes mellitus (T2DM) in India who will be administered Lyumjev.

2.1.2. Secondary Objectives

The secondary objectives are:

- To assess the adverse events and other safety parameters in adult subjects with T2DM in India
- To assess the efficacy of Lyumjev in adult subjects with T2DM in India

2.2. Study Endpoints

2.2.1. Safety Endpoints

2.2.1.1. Primary Safety Endpoint

The primary safety endpoint of this study is the incidence (percent of subjects with at least 1 event) and rate (events/subject/year) of all documented hypoglycemia (blood glucose [BG]<54 mg/dL) from baseline through Week 26.

2.2.1.2. Secondary Safety Endpoints

The secondary safety endpoints of this study include the following:

- Serious adverse event (SAEs) and treatment-emergent adverse event (TEAEs) from baseline through study follow-up
- Incidence and rate (events/subject/year) of severe hypoglycemic events from baseline through Week 26
- Incidence and rate (events/subject/year) of nocturnal hypoglycemia (BG <54 mg/dL) from baseline through Week 26
- Incidence and rate (events/subject/year) of nocturnal and all documented hypoglycemic events (BG<70 mg/dL) from baseline through Week 26
- Change in body weight from baseline to Week 26
- Change in Insulin Treatment Satisfaction Questionnaire (ITSQ) scores from baseline to Week 26

2.2.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study includes the following:

- Change in hemoglobin A1c [HbA1c] from baseline to Week 26
- Percentage of subjects achieving HbA1c <7% at Week 26
- Change in 1- and 2-hour postprandial glucose [PPG] (estimated from self-monitored blood glucose (SMBG)) values from baseline to Week 26
- Change in bolus insulin dose, basal insulin dose, and basal:bolus ratio from baseline to Week 26
- Change in 9-point SMBG values from baseline to Week 26

3. Overall Study Design and Plan

Study I8B-MC-ITTA (referred as Study ITTA henceforth) is a Phase 4, prospective, open-label, single-arm, outpatient, multicenter study to assess safety of Lyumjev in subjects with T2DM in India. The study includes a 1-week screening period, a 4-week lead-in period, followed by a 26-week treatment period, and a 2-week safety follow-up period.

3.1. Overall Design

The study is designed to evaluate risk of hypoglycemia in adult subjects with T2DM during 26 weeks of Lyumjev treatment.

The purpose of the lead-in period will be to titrate basal insulin, obtain preliminary diagnostic laboratory tests, and determine baseline hypoglycemia rates.

Subjects treated with multiple daily injection (MDI) therapy will be eligible for inclusion in the trial. The subjects can be on

- a) basal insulin in combination with at least 1 prandial injection of bolus insulin OR
- b) premixed analog or human insulin regimens with any basal and bolus insulin combination injected at least twice daily, except for IDegAsp (insulin degludec + insulin aspart; Ryzodeg) injected once daily (Inclusion Criterion [4])

Subjects should use basal insulin glargine 100 U/mL (Basaglar) throughout the trial once daily. Subjects using other basal insulin regimens or premixed insulins will be transitioned at Visit 2 to an insulin glargine 100 U/mL. Subjects treated with 1 to 2 prandial injections a day, premixed insulin, or prandial insulin other than insulin lispro 3 times a day prior to study entry will be transitioned to 3 injections a day of insulin lispro (Humalog) at the beginning of the lead-in period. Basal insulin will be titrated during the 4-week lead-in period to allow the subject to reach the target fasting BG by the end of this period.

At Visit 3, subjects will stop taking Humalog and will transition to Lyumjev unit-for-unit. Subjects will start taking Lyumjev at each meal (breakfast, lunch, and dinner). Prandial insulin doses should be titrated as necessary to meet the target SMBG levels. It is expected that adjustments to prandial and basal insulin doses will continue throughout the 26-week treatment period to maintain glycemic control or for safety reasons such as hypoglycemia or unacceptable hyperglycemia.

The 26-week treatment period will be followed by a 2-week safety follow-up period.

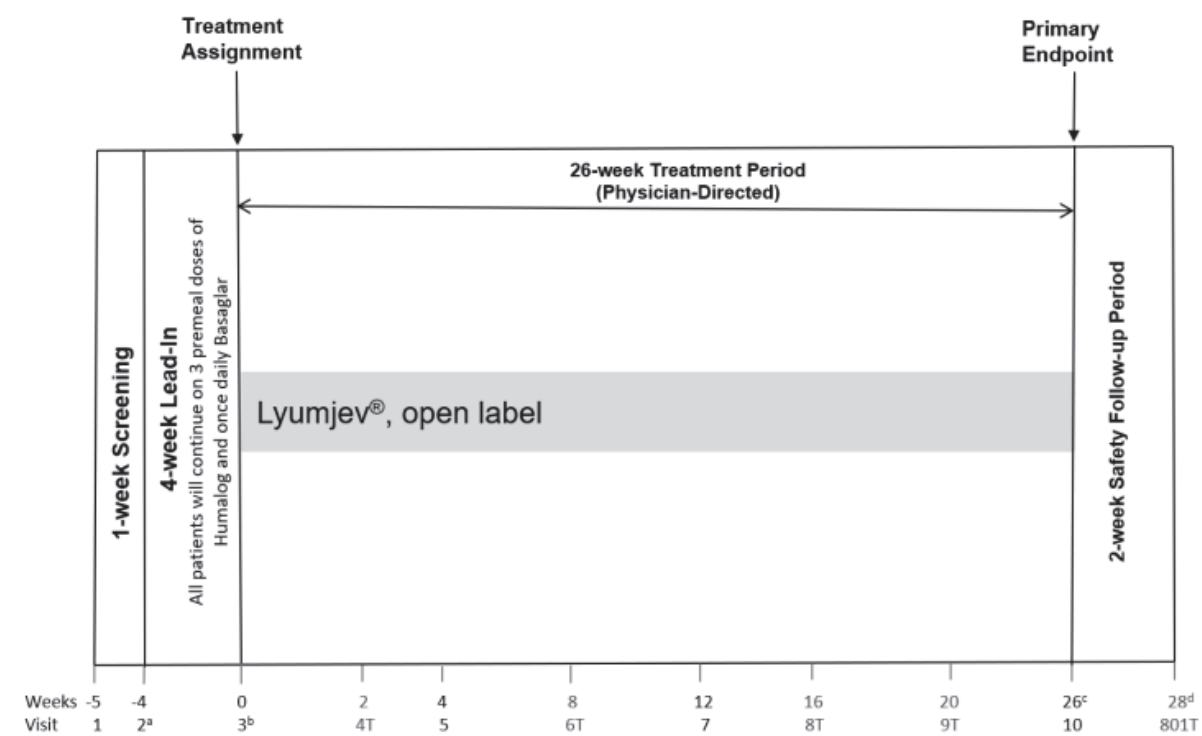
In conclusion, this single-arm study includes the following study periods: 1-week screening, 4-week lead-in, 26-week treatment, and 2-week safety follow-up. All subjects will use open-label Lyumjev and Basaglar® during the treatment period.

The study design is shown in

Figure 1.



Figure 1: Summary of Study Design.



Abbreviation: T = telephone visit.

- ^a At Visit 2, subjects treated with insulin aspart, insulin glulisine, regular insulin, or premixed insulin will be transferred to insulin lispro 100 U/mL (Humalog) administered 0 to 2 minutes before meals 3 times a day. At Visit 2, subjects treated with a basal insulin regimen other than insulin glargine will be transferred to insulin glargine 100 U/mL once daily. Subjects will titrate basal insulin during the lead-in period.
- ^b At Visit 3, subjects will stop taking Humalog and will transition to Lyumjev unit-for-unit. Subjects will start treatment with Lyumjev administered 0 to 2 minutes before meals 3 times a day and continue once-daily Basaglar. Subjects will titrate Lyumjev during the 26-week treatment period.
- ^c Subjects will discontinue study insulins at Week 26 and be transferred to nonstudy insulin as determined by the principal investigator.
- ^d Subjects will return for a safety follow-up visit at Week 28.

3.2. Sample Size

CCI [REDACTED]
[REDACTED] the target is to have a minimum of 100 subjects completing the study.

3.3. Study Population

The study population consists of adults more than 18 years of age with T2DM and duration of type 2 diabetes more than or equal to 1 year; for women of child bearing potential a reliable method of contraception is to be used during the duration of the trial. More detailed in section 5 of the Protocol.

Full list of inclusion/exclusion criteria are described in the protocol section 5.1 and 5.2.

3.4. Treatments Administered

All subjects will be treated with Lyumjev injected immediately (0 to 2 minutes) prior to each meal in combination with insulin glargine 100 U/mL (Basaglar®) once daily as basal insulin.

3.5. Method of Assigning Subjects to Treatment Groups

This is a single-arm treatment study and there is no randomization involved.

3.6. Blinding and Unblinding

No study treatments will be blinded or masked.

3.7. Schedule of Events

Please see the protocol section 1.3 for a detailed schedule of events.

4. Statistical Analysis and Reporting

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will primarily use SAS (release 9.4 or higher). If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

Continuous (quantitative) variable summaries will include the number of subjects (n) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum for both the actual and the change from baseline measurements. Least-square means and standard errors derived from the analysis models will also be displayed for the actual and the change from baseline measurements.

Categorical (qualitative) variable summaries will include the frequency and percentage of subjects who are in the particular category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population for the analysis set of interest (e.g., the Full Analysis Set (FAS)), unless otherwise specified. Confidence intervals will be calculated at 95%, 2-sided.

The minimum and maximum will be reported with the same degree of precision (ie, the same number of decimal places) as the observed data. Measures of location (mean and median) will be

reported to 1 degree of precision more than the observed data and measures of spread (SD) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified.

Confidence intervals (CIs) will be presented to 1 decimal place. All *P* values will be displayed in four decimals and rounded using standard scientific notation (eg, 0.XXXX). If a *P* value less than 0.0001 occurs it will be shown in tables as < 0.0001.

Unless otherwise indicated, all statistical tests will be conducted at the 0.05 significance level using 2-tailed tests, and *P* values will be reported. Corresponding 2-sided 95% CIs will be presented for statistical tests.

Baseline is defined as the last nonmissing measurement at or before the treatment assignment (Visit 3) unless otherwise specified. An ANCOVA will be used to analyze continuous variables that are planned to be collected only for baseline and endpoint, and a restricted-maximum-likelihood-based, mixed model repeated measures (MMRM) analysis will be used to analyze continuous longitudinal variables collected at baseline and more than 1 scheduled postbaseline visits.

The ANCOVA model will include baseline as a covariate. Unless otherwise stated, missing endpoints will be imputed using the last-observation-carried-forward (LOCF) approach, using only postbaseline data.

For the MMRM analyses, all the longitudinal observations at each scheduled postbaseline visit will be included in the analysis. The model will include fixed class effect of visit and the covariate of baseline. An unstructured covariance structure will be used to model the within-subject errors. If this structure fails to converge, the following covariance structures will be used in order until one converges:

- Toeplitz with heterogeneity
- Autoregressive with heterogeneity
- Compound symmetry with heterogeneous variances
- Toeplitz without heterogeneity
- Autoregressive, and
- compound symmetry without heterogeneous variances.

Significance tests will be based on least-squares means and Type III tests. SAS® PROC MIXED will be used to perform the analysis. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

4.2. Interim Analysis and Data Monitoring

An interim analysis of baseline characteristics (focus on demographics, prior and concomitant medications, and disease characteristics) will be done when all patients have been administered

at least 1 dose of the investigational product. Limited information is available on baseline characteristics of patients in India with T2DM on basal bolus insulin therapy. This analysis will help understand this missing information.

There is no data monitoring committee for this study. There will be ongoing medical reviews on listings and AEs reported at monthly intervals during the duration of the study.

4.3. Trial Level Safety Review

A trial level safety review will be done twice. The first time will be done when all patients have been administered at least 1 dose of the investigational product. The second time will be done 2 weeks after last patient will have last visit.

5. Analysis Populations

The following analysis populations are planned for this study:

- **Full analysis set (FAS)/ Safety Population (SAF):** The FAS/Safety Population includes all subjects who are exposed to at least one dose of study intervention (Lyumjev).
- **Efficacy analysis set:** The Efficacy Analysis Set includes all subjects in the FAS/Safety Population who have baseline and at least one postbaseline value present for the efficacy endpoints.
- **Enrolled Population:** The Enrolled Population includes all subjects who are entering Visit 2 (lead-in).

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

The last non-missing measurement at or before the treatment assignment (Visit 3), unless otherwise specified, will be used as the baseline observation for all calculations of change from baseline.

The hypoglycemic events recorded during the lead-in period is going to be considered as baseline.

6.1.2. Adjustments for Covariates

The ANCOVA model will include baseline as a covariate.

The MMRM model will include fixed class effect of visit and the covariate of baseline

6.1.3. Multiple Comparisons

No adjustments will be made for multiple comparisons.

6.1.4. Handling of Dropouts or Missing Data

Any subject with missing ITSQ analyzed with ANCOVA will be imputed using the LOCF approach, using only postbaseline data. If any baseline value is missing or only available value is baseline (no records and no other previous or unscheduled measurement before week 26 and post-baseline), that subject will be excluded for the analysis. If any post-baseline value is missing, the Unscheduled visit or other previous visit as LOCF value will be used, if present.

The ITSQ is a validated instrument containing 22 items that assess treatment satisfaction for subjects taking insulin. If an item score is missing for a subject within the domain (or overall), the mean of the items in the domain (or overall) will be imputed for the missing item score(s).

6.1.5. Analysis Visit Windows

Analyses of all variables for this study, unscheduled and/or repeated measurements will only be included if a scheduled measurement is not available, early discontinuation, and the unscheduled/repeated measurement falls within the analysis visit windows as described in Table 2. Otherwise, visits will be analyzed as scheduled, and unscheduled/repeated measurements falling outside of the visit windows will be excluded from analysis and only listed. In case two unscheduled visits fall in the same time window, the visit the closest to the target day will be considered (taking the first unscheduled in case of equal difference with the target day).

Table 2: Analysis Visit Windows

Analysis Day*	Analysis Visit	Week	Study Day	Lower Limit (Study Day)	Upper Limit (Study Day)
Screening	Visit 1	Weeks -5	-35	-77 (within 42 days from Visit 2)	-22
Lead-in	Visit 2	Weeks -4	-28	-35	-21
Baseline/Day 1	Visit 3	Week 0	1	1	1
Day 15	Visit 4	Week 2	15	8	22
Day 29	Visit 5	Week 4	29	15	43
Day 57	Visit 6	Week 8	57	43	71

Day 85	Visit 7	Week 12	85	71	99
Day 113	Visit 8	Week 16	113	99	127
Day 141	Visit 9	Week 20	141	127	155
Day 183	Visit 10	Week 26	183	169	197
Day 197/ Safety follow-up	Visit 801	Week 28	197	183	211

*Analysis day is calculated from Baseline being the last non-missing measurement at or before the treatment assignment (Visit 3).

6.1.6. Pooling of Sites

There will be no pooling of sites.

6.1.7. Derived Variables

- Aggregate Hypoglycemia rate= summed hypoglycemia episodes divided by the cumulative days on treatment from all patients, multiplied by 365. Compliance rate= $[(\text{Total} - \text{Non-compliances}) / (\text{Total})] \times 100\%$. Non-compliance is defined as missing at least one insulin dose. Subjects who miss the insulin dose or will not attend the scheduled visits are non-compliant.
- Hypoglycemia event rate (events/subject/year)= summed hypoglycemia episodes divided by the cumulative days on treatment for each patient, multiplied by 365.
- Hypoglycemia incidence= proportion will be calculated through number of patients with at least 1 documented hypoglycemic event divided by the total number of patients.

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- Change from baseline = value at current time point – value at baseline.
- 9-point SMBG for each patient by visit and timepoint= for each patient, visit and timepoint average SMBG episodes from cumulative non-missing data days(days 1,2 and 3). The timepoints will be pre-morning meal, 1-hour post breakfast, 2 hours post breakfast, pre-midday meal, 1-hour post lunch, 2-hour post lunch, pre-dinner meal, 1-hour post dinner and 2-hour post dinner.
- 4-point SMBG for each patient by visit and timepoint= for each patient, visit and timepoint average SMBG episodes from cumulative non-missing data days(days 1,2 and 3). The timepoints will be pre-morning meal, pre-midday meal, pre-dinner meal, and post dinner.
- Average bolus insulin dose for each patient by visit = for each patient and visit summed

number of daily units (day 1, 2 and 3) of bolus insulin dose divided by the cumulative non-missing data days.

- Average basal insulin dose for each patient by visit = for each patient and visit summed number of daily units (day 1, 2 and 3) of basal insulin dose divided by the cumulative non-missing data days.
- Basal:bolus ratio for each patient and visit = average of basal insulin dose divided by average of bolus insulin dose.
- Treatment-emergent adverse events (TEAE) = any adverse event newly reported after the first dose of IP used or reported to worsen in severity from baseline to 26-week of treatment period.

6.1.8. Data Adjustments/Handling/Conventions

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included only in the data listings.

Adverse events will be coded using the MedDRA version 26.1. Medications will be coded using World Health Organization Drug Dictionary (WHO-DD) Drug-Global B3 format Sept,1 2023.

If partial dates occur, the convention for replacing missing dates for the purpose of statistical analysis is as follows: if just day is missing then the day assigned is the first day of the month or the date of first dose (if in the same month), whichever is later; if just month is missing then the month assigned is the month of the first dose, unless that results in a date before the first dose in which case the month after the first dose is used; and if both month and day are missing then the month assigned is the month of the first dose and the day assigned is either the first day of the month or the first dose date, whichever is later.

7. Study Patients/Subjects and Demographics

These analyses will be conducted for the Enrolled population and FAS/Safety population.

7.1. Disposition of Patients/Subjects and Withdrawals

Number of subjects screened, enrolled, failed screening and the reasons for screen failure, treated, completed, continued without study treatment (Lyumjev), continued without Basaglar, and discontinued will be summarized. In addition, patient disposition, including reasons for study discontinuation will be summarised descriptively.

All disposition information will be listed.

7.2. Protocol Violations and Deviations

Protocol deviations classified by major/minor will be summarized and listed.

7.3. Demographics and Other Baseline Characteristics

Summary statistics for age, sex, race, childbearing potential, menopausal status, height, weight, and body mass index (BMI) will be presented.

The number and percent of subjects reporting various medical histories, grouped by MedDRA system organ class and preferred term (coded using MedDRA v.26.1), will be tabulated.

These analyses will be conducted for the Enrolled population and FAS/Safety population.

7.4. Exposure and Compliance

Total Humalog Kwik Pens dispensed, total Humalog Kwik Pens taken, number of Humalog Kwik Pens returned, total Lyumjev Kwik Pens dispensed, total Lyumjev Kwik Pens taken, number of Lyumjev Kwik Pens returned, total Basaglar Kwik Pens dispensed, total Basaglar Kwik Pens taken, number of Basaglar Kwik Pens returned, number of doses administered, number of dose interruptions, dose level administered, and compliance rate by insulin type will be presented in tabular form.

These analyses will be conducted for the Enrolled population and FAS/Safety population.

8. Safety and Tolerability Analysis

The analysis of safety assessments in this study belongs to primary and secondary endpoints and will include summaries of the following categories of safety and tolerability data collected for each patient:

- Incidence and rate of hypoglycemic with BG < 54 mg/dL
- Incidence and rate of hypoglycemia with BG < 70 mg/dL
- Incidence and rate of nocturnal hypoglycemic
- Incidence and rate of severe hypoglycemic
- Adverse Events
- Change in ITSQ
- Physical examination
- Electrocardiogram (ECG results)
- Change in vital sign
- Change clinical laboratory values

The safety analysis will be based on the FAS/Safety Population.

8.1. Primary Safety Analysis

The primary safety endpoint is to estimate the incidence and rate of all documented hypoglycemia with BG < 54 mg/dL. There will be no statistical hypothesis tested.

Hypoglycemic events will be summarized by visits. The hypoglycemic events recorded during

the lead-in period is going to be considered as baseline. The proportion of patients with at least 1 documented hypoglycemic event with BG<54 mg/dL (incidence) will be summarized by visit and overall period. The 1-year rate of documented hypoglycemia will be summarized. The aggregate rate will be calculated using the total number of hypoglycemia episodes divided by the cumulative days on treatment from all patients, multiplied by 365.

These analyses will be conducted for the FAS/Safety Population.

8.2. Secondary Safety Analysis

These analyses will be conducted for the FAS/Safety Population.

8.2.1. Hypoglycemia with BG<70 mg/dL

The secondary endpoint of the incidence and rate of all documented hypoglycemia with BG<70 mg/dL will be summarized as described for the primary endpoint.

8.2.2. Nocturnal Hypoglycemia

The secondary endpoint of the incidence and rate of nocturnal hypoglycemia (BG<70 mg/dL) will be summarized as described for the primary endpoint.

The secondary endpoint of the incidence and rate of nocturnal hypoglycemia (BG< 54 mg/dL) will be summarized as described for the primary endpoint.

Nocturnal hypoglycemia is considered any hypoglycemic event (documented hypoglycemia or probable symptomatic hypoglycemia, including severe hypoglycemia) that occurs between bedtime and waking (11:59 PM to 5:59 AM).

8.2.3. Severe Hypoglycemia

The secondary endpoint of the incidence and rate of all documented severe hypoglycemia will be summarized as described for the primary endpoint.

Severe hypoglycemia is considered any hypoglycemic event where the patient requires assistance for recovery with or without hospitalization and is reported as a serious adverse event.

8.2.4. Adverse Events

All AEs, TEAEs, and SAEs will be coded using the MedDRA v.26.1.

The number and percent of subjects reporting TEAE, the number and percent of subjects reporting SAEs and the number and percent of subjects reporting AEs as the reason for discontinuation from the IP or study will be grouped by MedDRA system organ class and preferred term (coded using MedDRA v.26.1) sorted by decreasing frequency. TEAEs will also be summarized by preferred term sorted by decreasing frequency within the system organ class for all TEAEs, and by maximum severity. In the case of multiple occurrences of the same TEAE within the same subject, each

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subject will only be counted once for each preferred term. For events that are gender specific (as defined by Medical Dictionary for Regulatory Activities), the denominator and computation of the percentage will include only patients from the given gender.

In the summaries showing severity the event with the maximum severity (mild, severe) will be reported. If a particular event at baseline and post baseline is missing the severity will be imputed. Imputed analysis severity will only be used for derivation of TEAE. Summary tables and listings will use the collected (i.e., missing) severity.

- 1) If a particular event is missing the severity at baseline, then will be assumed for analysis severity "Mild". Events with missing severity at baseline will always be flagged as TEAE if severity worsened after the date of first dose.
- 2) If a particular event is missing the severity at post-baseline, then the strongest possible severity will be assumed for analysis (severity = severe).

In the AE data listings, all AEs will be displayed, including AEs during the lead-in period (4-week before first dose of the IP treatment period) and the safety follow-up period (2-week after 26-week treatment period). AEs that are not treatment-emergent will be flagged.

8.2.4.1. Adverse Events Leading to Discontinuation

A summary of frequencies and percentages of TEAEs leading to discontinuation of study drug will be grouped by SOC, and preferred term sorted by decreasing frequency. No inferential statistical tests will be performed.

A data listing of AEs leading to discontinuation of study drug will also be provided, displaying details of the event(s) captured on the CRF.

8.2.4.2. Deaths and Serious Adverse Events

Any deaths that occur during the study will be listed.

Serious adverse events will be listed and also tabulated by system organ class and preferred term and presented by treatment.

8.2.5. Insulin Treatment Satisfaction Questionnaire (ITSQ)

The ITSQ will evaluate treatment satisfaction of subjects taking insulin, contains 22 items measured on 7-point scale (lower scores reflect better outcomes) and constitute the 5 domains of satisfaction are categorized as

- Inconvenience of Regimen (5 items)
- Lifestyle Flexibility (3 items)
- Glycemic Control (3 items)
- Hypoglycemic Control (5 items), and
- Insulin Delivery Device (6 items).

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Descriptive summaries of ITSQ values will be calculated for items by visit and will be analyzed using the ANCOVA model including baseline as a covariate. Change from baseline in ITSQ overall score will be summarized by visit.

Change from baseline in ITSQ transformed domain score and transformed overall score will be calculated and summarized descriptively and will be analyzed using ANCOVA model will include baseline as a covariate.

8.2.6. Physical Examination

The number and percentage of patients with normal and abnormal findings in the complete physical examination will be displayed.

8.2.7. Vital Signs

Descriptive summaries of actual values and changes from baseline will be calculated for systolic blood pressure, diastolic blood pressure, pulse rate, weight, and body temperature by visit.

Change in body weight from baseline will be summarized descriptively and will be analyzed using the MMRM model including fixed class effect of visit and the covariate of baseline.

8.2.8. Electrocardiograms

ECG results will be summarized descriptively including PR interval, QRS interval, QT interval, QTcB interval (QT interval with Bazette correction applied), heart rate (HR) and overall assessment.

8.2.9. Clinical Laboratory Evaluations

Laboratory test results at baseline and serum lipid profile at Week 26 will be summarized descriptively.

Change from baseline in laboratory parameters will be summarized descriptively.

8.2.10. Concomitant Medication

Prior and concomitant medications will be summarized descriptively using counts and percentages.

Prior medications will be presented separately from concomitant medications. Medications that started before first dose of Lyumjev will be considered prior medications whether or not they were stopped before first dose of Lyumjev. Any medications continuing or starting after first dose of Lyumjev will be considered to be concomitant. If a medication starts before first dose of Lyumjev and continues after first dose of Lyumjev it will be considered both prior and concomitant.

- Medications will be coded using WHO-DD Drug-Global B3 format Sept, 1 2023.

9. Efficacy Analysis

Efficacy analysis belongs to secondary endpoints.

9.1. Secondary Efficacy Analysis

These analyses will be performed on the Efficacy analysis set and FAS/Safety population.

9.1.1. HbA1c

The secondary endpoint of the percentage of subjects achieving HbA1c <7% will be summarized by visit.

Change in HbA1c from baseline will be summarized by visit. Change in HbA1c from baseline will be analyzed using the MMRM model including fixed class effect of visit and the covariate of baseline.

9.1.2. 9-point SMBG

The secondary endpoint of the SMBG will be summarized by visit, by day (1,2,3), including average by visit and by timepoint. Change in SMBG values from baseline will be summarized by visit and by timepoint.

Change in 1-hour and 2-hours postprandial glucose values from baseline will be analyzed using

the MMRM model including fixed class effect of visit and timepoint, and the covariate of baseline.

9.1.3. Insulin dose

The secondary endpoint of the average of units of insulin dose (bolus and basal) will be summarized by visit. Basal:bolus ratio will be summarized by visit. Average of units of insulin dose and basal:bolus ratio will be analyzed using the MMRM model including fixed class effect of visit, and the covariate of baseline.

Change in average of units of insulin dose (bolus and basal) from baseline will be summarized by visit, and will be analyzed using the MMRM model including fixed class effect of visit, and the covariate of baseline.

Change in Basal:bolus ratio from baseline will be summarized by visit and will be analyzed using the MMRM model including fixed class effect of visit, and the covariate of baseline.

Bolus insulin dose will be Lyumjev dose and basal insulin dose will be Basaglar dose.

9.1.4. Pharmacokinetic Analysis

No pharmacokinetic analysis is planned for this study.

10. References

- ASA. (2018) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April 2018. <http://www.amstat.org/about/ethicalguidelines.cfm>
- ICH (1998). ICH Harmonised Tripartite Guideline. Statistical Principles for Clinical Trials E9; 1998. https://database.ich.org/sites/default/files/E9_Guideline.pdf
- RSS. (2014) The Royal Statistical Society: Code of Conduct, 2014. <https://rss.org.uk/about/policy-and-guidelines/code-of-conduct/>.

11. Tables, Listings, and Figures

The TLF shells will be presented in a separate document.

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