Statistical Analysis Plan B5K-MC-IBHD (V2)

Safety and Efficacy of Human Regular U-500 Insulin Administered by Continuous Subcutaneous Insulin Infusion versus Multiple Daily Injections in Subjects with Type 2 Diabetes Mellitus: A Randomized, Open-Label, Parallel Clinical Trial

NCT02561078

Approval Date: 31-May-2017

1. Statistical Analysis Plan B5K-MC-IBHD: Safety and Efficacy of Human Regular U-500 Insulin Administered by Continuous Subcutaneous Insulin Infusion versus Multiple Daily Injections in Subjects with Type 2 Diabetes Mellitus: A Randomized, Open-Label, Parallel Clinical Trial

(VIVID: Evaluating U-500R Infusion versus Injection in Type 2 Diabetes Mellitus)

Humulin R U-500 (LY041001)

This is a Phase 3b, randomized, open-label, parallel study comparing human regular insulin U-500 delivered by continuous subcutaneous insulin infusion (OmniPod® Insulin Management System for use with regular human insulin U-500) to delivery by multiple daily injections in high-dose insulin-requiring patients with type 2 diabetes mellitus who have inadequate glycemic control on existing high dose insulins (with or without other insulins/antihyperglycemic agents).

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Protocol B5K-MC-IBHD
Phase 3b

Statistical Analysis Plan Version 1 approved: 17 September 2015
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly on date provided below.

Approval Date: 31-May-2017 GMT

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3. Revision History

This is the second version of the Statistical Analysis Plan (SAP) for Study B5K-MC-IBHD (IBHD). This version is based on protocol amendment B5K-MC-IBHD(a) approved on 07 December 2016. The first version of the SAP for Study IBHD was approved on 17 September 2015 based on original protocol B5K-MC-IBHD.

Some changes in the SAP were made on request from the US Food and Drug Administration (FDA).

The overall changes and rationale for the changes made to this SAP are as follows:

- Elaborated on the safety and efficacy analyses and handling of missing data in "Statistical and Analytical Plans" (Sections 5.2, 5.9, 5.10). The SAP now provides for multiple analysis methods of the primary and key secondary objectives to account for missing data. Based on US FDA request, the Intent-to-Treat (ITT) estimand that accounts for all observed data, including those for subjects who have stopped study drug but continued in the study, will be used for the primary analysis of the All Randomized Set (ARS) and will be analyzed using copy reference multiple imputation analyses with analysis of covariance (ANCOVA). For publications and regulatory purposes in other regions, the efficacy estimand that includes only data observed while subjects were receiving study drug (excludes data after subjects discontinued study drug but remained in study) will be used for the primary analysis using mixed model repeated measures (MMRM). Two sets of similar analysis approaches (MMRM and multiple imputation based ANCOVA) as those for the primary objective will be used for key secondary endpoints.
- The Disposition section (Section 5.4) was edited to remove non-essential summary analyses.
- Edited "Concomitant Therapy" (Section 5.6) to remove analyses typically not included in parallel studies.
- Non-essential listings were removed from the SAP.
- The analyses for the different groups (Group A and Group A+B) were clarified. Analyses for primary and key secondary objectives will be done for Group A and Group A+B. Analyses not for primary and key secondary objectives (including exploratory objectives and safety evaluations not used to assess secondary objectives) will be done for Group A+B only. Subgroup analyses will be done for the primary objective and for Group A only.
- Edited "Hypoglycemic Analyses" (Section 5.13.2.1) to exclude analyses based on the alternative definition of hypoglycemia with blood glucose <50 mg/dL. The 24-hour analysis by 2-hour interval of the 1-year rates of documented symptomatic and severe hypoglycemia was added.
- In Section 5.8 (Protocol Deviations), the table for the important protocol deviations was updated.

- A new section for the study unblinding plan was added (Section 6).

4. Study Objectives

4.1. Primary Objective

The primary objective is to demonstrate the change in hemoglobin A1c (HbA1c) of Humulin® R U-500 (U-500R) administered by continuous subcutaneous insulin infusion (CSII) is noninferior to U-500R administered by multiple daily injection (MDI) therapy from baseline to the 26-week in high-dose insulin-requiring patients with type 2 diabetes mellitus (T2DM) who have inadequate glycemic control on high-dose non U-500R (>200 and ≤600 units per day) insulins (CSII or MDI) and/or high-dose U-500R insulin (MDI) without use of glucagon-like peptide-1 (GLP-1) receptor agonists or sodium-glucose cotransporter 2 (SGLT2) inhibitors and with or without other insulins/antihyperglycemic agents (AHAs). This population is referred to as Group A.

The following alternative hypothesis will be tested for the primary objective:

H1: CSII is noninferior to MDI in change in HbA1c using a noninferiority margin (NIM) of 0.4%.

The family-wise type I error rate for the primary objective and the following key secondary objectives will be controlled at a 2-sided 5% level by the graphical approach (see Section 5.3 for details).

4.2. Secondary Objectives

4.2.1. Key Secondary Objectives

The following 4 key (alternative hypotheses [H#]) secondary objectives at Week 26 are to demonstrate for the main study population (Group A [without use of GLP-1 receptor agonists or SGLT2 inhibitors, Section 4.4]) that:

H2: CSII is superior to MDI in change in fasting plasma glucose (FPG).

H3: CSII is superior to MDI in proportions of subjects achieving HbA1c targets/values <7.0%.

H4: CSII is superior to MDI in change in HbA1c.

H5: CSII is superior to MDI in proportions of subjects achieving HbA1c targets/values <7.5%.

The following 5 key (alternative hypotheses [H#]) secondary objectives are to demonstrate the objectives at Week 26 for the total study population (Group A [without use of GLP-1 receptor agonists or SGLT2 inhibitors] and Group B [those who use GLP-1 receptor agonists or SGLT2 inhibitors use, Section 4.4]) that:

H6: CSII is noninferior to MDI in change in HbA1c using NIM of 0.4%.

H7: CSII is superior to MDI in change in FPG.

H8: CSII is superior to MDI in proportions of subjects achieving HbA1c targets/values <7.0%.

H9: CSII is superior to MDI in change in HbA1c.

H10: CSII is superior to MDI in proportions of subjects achieving HbA1c targets/values <7.5%.

4.2.2. Other Secondary Objectives

Additional secondary objectives of the study are to compare the efficacy and safety of U-500R given by CSII versus MDI at Week 26 for the main study population Group A and Group A+B (the total study population) respectively (separately), with respect to the following:

- Proportions of subjects achieving HbA1c targets/values (≤6.5% and <8.0%).
- Mean change in 7-point self-monitored blood glucose (SMBG) including mean SMBG for each time point measurement.
- Change in total daily insulin dose (TDD) (unit and unit/kg).
- Proportions of subjects achieving HbA1c targets/values (≤6.5%, <7.0%, <7.5%, and <8.0%) without documented symptomatic hypoglycemia (SMBG <50 mg/dL).
- Rate and incidence of hypoglycemia (documented [documented symptomatic, asymptomatic, and unspecified], severe, and nocturnal).
- Change in body weight between treatment groups and as a function of change in HbA1c.

4.3. Exploratory Objectives

Exploratory objectives of the study are the following and will be assessed for the total study population (Group A+B):

- The change in patient reported outcomes including Treatment-Related Impact Measure for Diabetes (TRIM-D) and TRIM-D for Diabetes Device (TRIM-DD) surveys from baseline to 26-week value.
- Assess subject-reported OmniPod pump experience via OmniPod U-500 System Exit Questionnaire.
- Assess proportion of subjects with an HbA1c ≥9% and <9% at the 26-week value.
- Postprandial contributions to total glycemic burden at baseline to 26-week values using area under the curve (AUC) analysis of 7-point SMBG profiles.
- Glycemic variability using 7-point SMBG profiles (including within day and day-to-day standard deviation [SD], coefficient of variation, average daily risk range, and mean of daily differences).
- Examine the relationship between gene variants including, but not limited to, insulin receptor, insulin like growth factor-1, melatonin receptor 1B1, adiponectin, transcription factor 7-like 2, phosphoinositide-3-kinase, regulatory subunit 1 and B-cell CLL/lymphoma 11A on clinical outcomes.

- Evaluate subgroups of baseline TDD >2 and ≤2 units/kg, TDD >200 units at baseline that fall below TDD 200 units during the study, baseline TDD >400 and ≤400 units, users of GLP-1 receptor agonists or SGLT2 inhibitors, and geriatric subjects (age ≥65 years and ≥75 years) on each of the primary and secondary objectives.
- Functionality and safe use of the OmniPod U-500 system.

4.4. Summary of Study Design

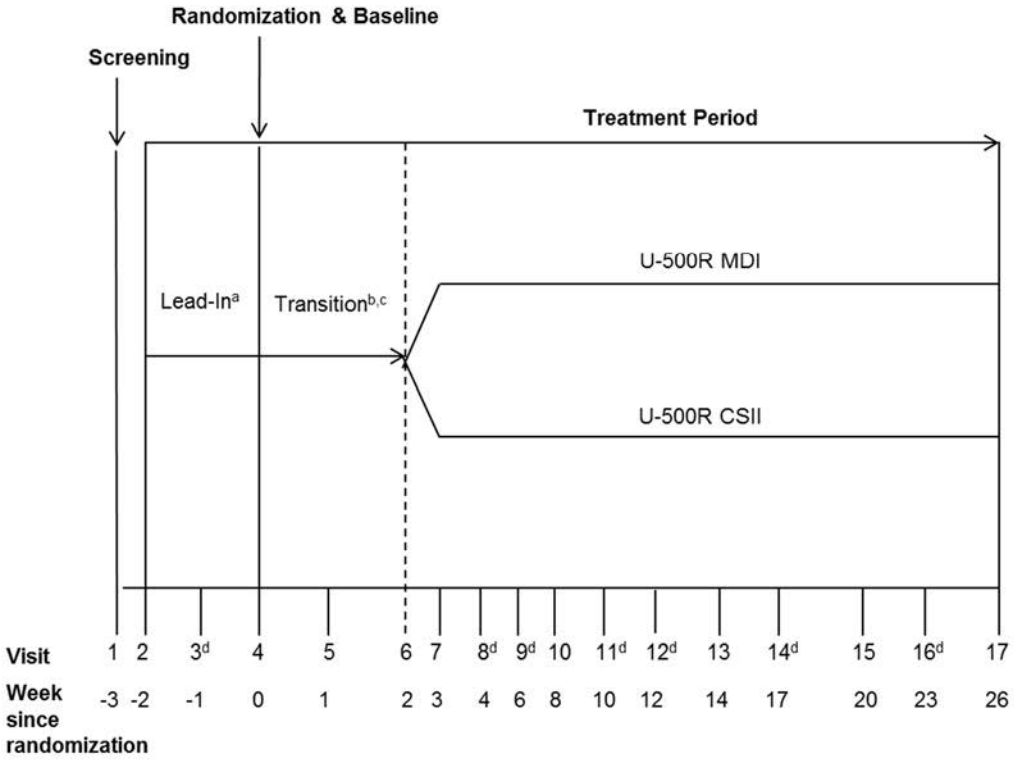
Study IBHD is a Phase 3b, multicenter, randomized, open-label, parallel clinical trial comparing U-500R administered by CSII (OmniPod U-500 system) to U-500R administered MDI in high-dose insulin-requiring subjects with T2DM who have inadequate glycemic control on high-dose non U-500R (>200 and ≤600 units per day) insulins (CSII or MDI) and/or U-500R insulin (MDI) with or without other insulins/AHAs. The trial design includes: 1-week screening period, 2-week lead-in period, and a 26-week treatment period (2 week transition to U-500R MDI administered TID, 12 weeks titration and 12 weeks maintenance U-500R CSII or MDI). As shown in the following recruitment plan (Table IBHD.4.1), approximately 320 subjects requiring high-dose insulin without use of GLP-1 receptor agonists or SGLT2 inhibitors (Group A) and approximately 64 to 96 additional subjects who are using GLP-1 receptor agonists or SGLT2 inhibitors (Group B) with or without other AHAs will be randomized based on a 1:1 ratio to 2 treatment arms. After Group A has been fully enrolled, Lilly may stop enrollment for Group B, even if the minimum recruitment goal for Group B has not been met. Approximately 240 (Group A) and 48 to 72 (Group B) subjects are expected to complete the 26-week treatment period (assuming a 25% dropout rate).

Table IBHD.4.1. Planned Subject Recruitment

	Group A	Group B GLP-1 or SGLT2 users (Target range)
Entered	450	90 to 136
Enrolled/Randomized	320	64 to 96
Completed	240	48 to 72

Abbreviations: GLP-1 = glucagon-like peptide-1; SGLT2 = sodium-glucose cotransporter 2.

The end of the study for each subject is Visit 17 or the early termination (ET) visit for subjects who discontinue early. Figure IBHD.4.1 illustrates the study design.



Abbreviations: CSII = continuous subcutaneous insulin infusion; GLP-1 = glucagon-like peptide-1; HbA1c = hemoglobin A1c; MDI = multiple daily injections; SGLT2 = sodium-glucose cotransporter 2.

a Subjects will continue their pre-study insulin regimens.

b Subjects will be stratified and randomly assigned equally between treatment arms by nonusers (Group A) versus users (Group B) of GLP-1 receptor agonists or SGLT2 inhibitors, entry HbA1c ≥8.5% or <8.5%, and U-500R at entry versus other insulins.

c MDI or CSII and will be transitioned to U-500R by MDI.

d Telephone visits.

Figure IBHD.4.1. Illustration of study design for clinical protocol B5K-MC-IBHD.

5. A Priori Statistical Methods

5.1. Sample Size Determination

Approximately 320 subjects requiring high-dose insulin without use of GLP-1 receptor agonists or SGLT2 inhibitors (Group A) and approximately 64 to 96 additional subjects with use of GLP-1 receptor agonists or SGLT2 inhibitors (Group B) will be randomized based on a 1:1 ratio to 2 treatment arms. Approximately 240 (Group A) and 48 to 72 (Group B) subjects are expected to complete the 26-week treatment period (assuming a 25% dropout rate).

The sample size was calculated based on the first primary objective for subjects without use of GLP-1 receptor agonists or SGLT2 inhibitors (Group A). The 240 completers will provide 80% statistical power to demonstrate the noninferiority (NIM is 0.4%; SD = 1.1%) of U-500R insulin CSII versus U-500R MDI in change in HbA1c at 26 weeks at 2-sided alpha = 0.05.

5.2. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (Lilly) or its designee.

As specified in Section 4.4, based on the use of GLP-1 receptor agonists or SGLT2 inhibitors, there are 2 patient populations in this study: Group A and Group B. Unless otherwise specified, all listings will be done for Group A and B combined (Group A+B), with group name included in the report. In general, analyses will be performed as follows:

- Summary analyses for primary and key secondary objectives will be done for Group A and for Group A+B.
- Analyses not for primary and key secondary objectives (including exploratory objectives and safety evaluations not used to assess secondary objectives) will be done for Group A+B only.
- Additional analyses of safety evaluations not used to assess secondary objectives may be performed for Group A if the graphical approach to test the primary and secondary efficacy objectives rejects only null hypotheses for Group A (Section 5.3).
- Analyses for Group B only may also be conducted if deemed appropriate and necessary (for example, for any safety concerns or signals).

The analysis population will also be specified for other analyses in the relevant sections such as subject characteristics, disposition, concomitant therapy, etc.

Also, the following 5 patient populations are defined for the analyses in this study:

All Randomized Set (ARS) Population: All entered subjects who were randomized at Visit 4 (Week 0) into this study.

Full Analysis Set (FAS) Population: All randomized subjects who received at least 1 dose of U-500R after randomization.

Completer Set (CS) Population: All FAS subjects who completed study treatment at the primary time point (Week 26).

Per-Protocol (PP) Population: All FAS subjects who completed the 26-week visit without important protocol deviations that will impact the primary outcome as defined in Section 5.8, and have both baseline and endpoint HbA1c measurements.

Continuous Glucose Monitoring (CGM) Population: A subset of the ARS population who also participate the CGM addendum.

Unless otherwise specified, both safety and efficacy analyses will be conducted on the ARS, including those who discontinued study treatment or were rescued. Sensitivity analyses may be done for the FAS, CS, and PP. The CGM population will be used for CGM analysis.

Separate efficacy analyses for primary and key secondary objectives will be conducted by either including or excluding post study treatment discontinuation data based on different purposes (see Section 5.9 and Section 5.10). In general, missing data will not be imputed, unless otherwise specified, for example, where the Last-Observation-Carried-Forward (LOCF) method or the copy reference multiple imputation method (per FDA's request) is mentioned.

Outcomes (laboratory, vital signs, weight, patient reported outcome questionnaires) measured within 5 days of last treatment dose will be considered on treatment and included in the analysis during the treatment period.

For data collected as a running record with an exact date stamp such as adverse events (AEs), SMBG, and hypoglycemia event where the dates of the measures were not tied with the date of an office visit, post-baseline data recorded at or prior to the last study drug dose date will be considered as data on treatment and included in the analysis during the treatment period.

Baseline will be the last value obtained at or prior to the randomization, unless otherwise stated.

For continuous measurements, summary statistics will include sample size, mean, median, SD, minimum, and maximum. Summary statistics for continuous measures will be provided for baseline, the actual measurements at each visit, and the change from baseline measurements to each visit. For all continuous variables, both the actual value and change from baseline (if available) will be analyzed.

An MMRM model will be used for continuous outcomes with repeated post-baseline measurements to compare treatment arms, unless otherwise noted. An ANCOVA or analysis of variance (ANOVA) model may also be used for continuous outcomes to compare treatment arms at the endpoint using the LOCF method. Treatment comparisons will be performed for the treatment difference in least squares means (LSMean). LSMean (standard error [SE]) by treatment group and visit (if applicable), the LSMean difference between treatment groups, along with 95% confidence limits of the treatment differences and the p-value for the treatment comparison will be displayed. For the change from baseline, p-value for the within-treatment difference will also be displayed.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated.

The changes on this SAP are based on the protocol amendment B5K-MC-IBHD(a) approved on 07 December 2016. Any other changes to the data analysis methods described in the protocol, and the justifications, will be described in the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

5.3. Adjustment for Multiplicity

This section explains the graphical approach in detail and illustrates how the graphical approach works in practice. As discussed by Bretz and colleagues (2009), this testing approach controls the family-wise type I error rate at alpha=0.05.

Figure IBHD.5.1 illustrates the graphical approach to adjust multiplicity for the primary and key secondary objectives. In Figure IBHD.5.1 and for the explanations of the scenarios, the **alternative** hypotheses H1 through H10 are defined as follows:

H1: CSII is noninferior to MDI in change in HbA1c using a NIM of 0.4%.

Key Secondary Objectives:

H2: CSII is superior to MDI in change in FPG.

H3: CSII is superior to MDI in proportions of subjects achieving HbA1c targets/values <7.0%.

H4: CSII is superior to MDI in change in HbA1c.

H5: CSII is superior to MDI in proportions of subjects achieving HbA1c targets/values <7.5%.

H6 through H10 are the same as H1 through H5 except that they are combined for the total study population Group A (without use of GLP-1 receptor agonists or SGLT2 inhibitors) and Group B (those who use GLP-1 receptor agonists or SGLT2 inhibitors).

As shown by Figure IBHD.5.1, the graphical approach begins with testing the noninferiority for the primary objective at alpha=0.05. The numbers (weights) on the arrows depict the proportion of alpha which is propagated to the next test if a null hypothesis is rejected. At each step, all hypotheses are tested based on the current alpha assigned to them by the approach. If, and only if, one of the null hypotheses is rejected, then the alpha flows based on the graph and the weights are updated based on the preset algorithms and rules as described by Bretz and colleagues (2009).

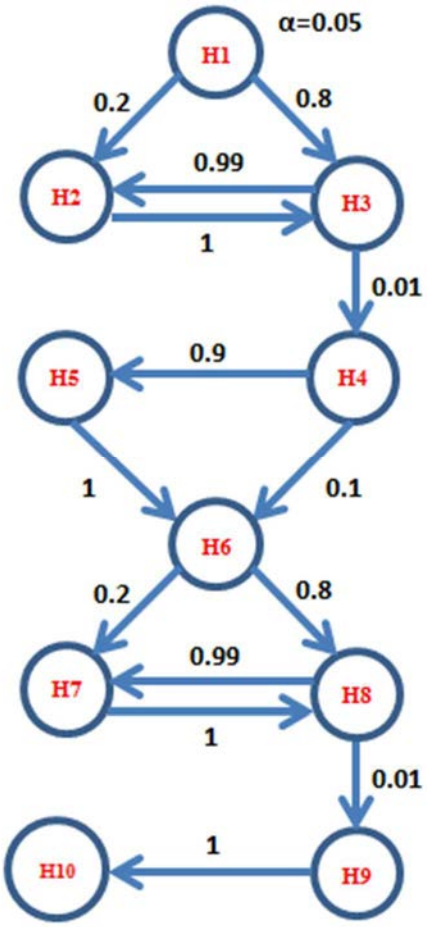


Figure IBHD.5.1. Graphical approach to adjust multiplicity.

5.4. Subject Disposition

All subjects who discontinue from the study will be listed, and the extent of their participation in the study (discontinuation visit) will be reported. The primary reasons for discontinuation will be listed for all subjects who have entered the study (signed informed consent). Reasons for discontinuation of study treatment and discontinuation of study will be summarized by treatment for the ARS, by visit and for overall study. All of the summaries will be broken down by "discontinue study treatment and device but still remain in the study" and "discontinue the study." All of the summaries will be done for Group A+B. The treatment comparison will be based on Fisher's exact test.

All entered subjects will be summarized including, but not limited to, total number of subjects screened, number of ineligible subjects, number of subjects who entered the lead-in period, total number of subjects randomized, and total number of subjects for each treatment. Within each treatment arm, the following will be summarized: number of subjects not treated by U-500R, number of subjects not treated by U-500R via the administration method to which they were assigned, number of subjects included in FAS, number of subjects who completed treatment, the

number of subjects who discontinued study treatment but remained in the study and completed the study, the number of subjects who discontinued study treatment but remained in the study and discontinued study at a later visit, and the number of subjects who discontinued study and study treatment at the same visit.

The number of randomized subjects per investigator for each treatment group and overall will be summarized. The listing of treatment assignment for all randomized subjects will be provided.

5.5. Subject Characteristics

Demographic and baseline characteristics will be summarized separately for Group A and Group A+B by each treatment group and overall for the ARS. For continuous measures, the treatment groups will be compared using an ANOVA. For categorical measures, treatment groups will be compared using Fisher's exact test.

The following baseline parameters will be included (but are not limited to) in the report:

- age (years)
- age class (≥65, <65 years)
- age class (≥75, <75 years)
- gender (male, female)
- race (White, American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander)
- ethnicity (Hispanic, Non-Hispanic)
- body weight (kilograms)
- height (centimeters)
- body mass index (BMI) (kilograms per meters squared)
- duration of diabetes (years)
- baseline TDD of insulin (units and units/kg body weight)
- TDD class (TDD ≤400U or >400U)
- TDD class (TDD≤2 U/kg or >2 U/kg)
- systolic blood pressure (mm Hg)
- diastolic blood pressure (mm Hg)
- pulse rate (beats per minute)
- baseline HbA1c value (%),
- baseline HbA1c stratification (HbA1c <8.5% or ≥8.5%)
- fasting plasma glucose (mg/dL)
- baseline estimated glomerular filtration rate (eGFR) (mL/min/1.73m^2)
- baseline eGFR class (chronic kidney disease [CKD] 1: ≥90 mL/min/1.73m^2; CKD 2: ≥60 and <90 mL/min/1.73m^2; CKD stage 3: ≥30 and <60 mL/min/1.73m^2)
- baseline AHA class: metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin, saxagliptin, linagliptin, and alogliptin), pioglitazone (Actos), GLP-1 receptor agonists

(albiglutide, dulaglutide, or liraglutide), and SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin)

- baseline insulin type (basal only, basal/bolus; human, analogues, premix)
    - basal only
        - human: neutral protamine Hagedorn (NPH) (Humulin N, Novolin N), Humulin U-500R (used as basal insulin only)
        - analogues: detemir (Levemir) or glargine (Lantus), glargine U-300 (Toujeo)
    - basal/bolus
        - human basal: NPH (Humulin N, Novolin N) plus Human insulin bolus: regular (Humulin R, Novolin R)
        - human basal/bolus: Humulin U-500R
        - analogue basal: detemir or glargine plus analogue bolus: lispro (Humalog) or glulisine (Apidra) or aspart (NovoLog, NovoRapid), lispro U-200 (Humalog U-200 KwikPen)
        - premix:
            - human: NPH/regular 70/30 (Humulin 70/30, Novolin 70/30)
            - analogues: insulin aspart 70/30 (NovoLog Mix 70/30), insulin lispro 75/25 (Humalog Mix 75/25), insulin lispro 50/50 (Humalog Mix50/50)
        - others
- baseline incidence of hypoglycemic event: documented (documented symptomatic, asymptomatic and unspecified), severe and nocturnal; defined as the incidence during the 2-week lead-in period prior to randomization (Visit 2 through Visit 4)
- baseline rate of hypoglycemic events (same categories as for baseline incidence) per 30 days during the 2-week lead-in period prior to randomization (Visit 2 through Visit 4)

5.6. Concomitant Therapy

Listings of concomitant medications will be provided. Concomitant medication use will be reported based on World Health Organization (WHO) dictionary. Medications will be ordered by decreasing frequency within Anatomical Therapeutic Chemical (ATC) level 4. For Group A and Group A+B, frequencies and percentages of concomitant medication for glycemic control used prior to and after randomization will be summarized and compared (using Fisher's exact test) by treatments for ARS. Frequencies and percentages of other general concomitant medication used after randomization will be summarized and compared (using Fisher's exact test) by treatments for ARS in Group A+B.

5.7. Treatment Compliance

The analyses described in this section will be done for both Group A and Group A+B. Compliance issues, as stated in study protocol Section 9.12, will be listed and summarized as protocol deviations and details can be found in this SAP (Section 5.8). Summaries of actual value and change from baseline (Visit 4) of TRIM-D compliance transformed score will include sample size, mean, SD, median, minimum, and maximum at each assessment at each visit for each treatment group and for the ARS population. The actual value and change from baseline in compliance scores will be analyzed using an MMRM approach.

For Group A, the MMRM model will include the following fixed effects: treatment (U-500R CSII, U-500R MDI), weeks on treatment, the interaction between treatment and weeks, and the stratification factors (U-500R at entry versus other insulins, entry HbA1c ≥8.5% or <8.5%). The model will also include the corresponding baseline of the response variable.

For Group A+B, the same MMRM model in Group A above will be used with the addition of the stratification factor (nonusers versus users of GLP-1 receptor agonists or SGLT2 inhibitors).

The proportion of subjects who have TRIM-D compliance score ≥80 at endpoint or ET will be analyzed using logistic regression including the similar fixed effects used in primary analysis.

5.8. Protocol Deviations

A listing and summary of important protocol deviations will be generated for ARS for Group A+B and Group A (summary only). Important protocol deviations are defined as deviations from the study protocol that may compromise the data integrity and subjects' safety. Important protocol deviations are included in Table IBHD.5.1 but these are not all-inclusive. Some situations not listed below may be decided on a case-by-case basis by the study team regarding whether to be considered as important and/or exclude subjects from the PP population. Subjects with one or more important protocol deviations that impact the primary efficacy outcome (per-protocol population exclusion flag [PPFLG]='Y' in Table IBHD.5.1) will be excluded from the PP population.

Table IBHD.5.1. Categorization of Important Protocol Deviations

Category	Sub-Category	Study Specific	Deviation Description	PPFLG	Methods of Identification
Informed Consent	Informed Consent Not Obtained	Lack of patient signature for main protocol	1. Issues with informed consent: lack of patient signature (main protocol)	Y	CRF data indicate the Study ICD date missing for main study.
Informed Consent	Improper Consent	NA	2. Issues with informed consent: lack of PI signature, date signed is after V1, lack of patient signature for CGM, revised ICD not signed (main protocol and CGM addendum)	N	Monitoring
Eligibility	Inclusion/ Exclusion	No T2DM	3. No confirmation of T2DM	Y	Medical history CRF data indicate missing record
Eligibility	Inclusion/ Exclusion	No T2DM	4. Not diagnosed with T2DM	Y	Monitoring
Eligibility	Inclusion/ Exclusion	TDD out of range at study entry	5. TDD is out of range (Inclusion range is >200U or ≤600U) at Visit 1	N	Data Management Reports and Monitoring
Eligibility	Inclusion/ Exclusion	TDD out of range at study entry	6. 4.TDD is out of range (Inclusion range is >200U or ≤600U) at Visit 4	Y	Data Management Reports and Monitoring
Eligibility	Inclusion/ Exclusion	HbA1c out of the range at study entry	7. HbA1c out of the range at study entry: (Inclusion range ≥7.5% and ≤12.0) at Visit 1	Y	GLS data
Eligibility	Inclusion/ Exclusion	Age out of range	8. Age out of range (>85 or <18 yrs)	N	Edits or monitoring
Eligibility	Inclusion/ Exclusion	BMI out of range at study entry	9. BMI out of range at study entry: (Inclusion range ≥25kg/m^2 and ≤50kg/m^2) at Visit 1	Y	Edits
Eligibility	Inclusion/ Exclusion	Unstable Body Weight at Visit 1	10. Unstable Body Weight at Visit 1	Y	Monitoring
Eligibility	Inclusion/ Exclusion	Took prohibited conmed at entry	11. Prohibited Conmed Therapy at study entry	N	Edits and Monitoring
Eligibility	Inclusion/ Exclusion	Took pioglitazone 45mg at entry	12. Took pioglitazone 45 mg at study entry	Y	Edits and Monitoring

Categorization of Important Protocol Deviations

Category	Sub-Category	Study Specific	Deviation Description	PPFLG	Methods of Identification
Study Procedures	Excluded Conmeds	Took prohibited conmed	13. Prohibited Conmed Therapy at any time during the trial	N	Edits and Monitoring
Study Procedures	Excluded Conmeds	Took pioglitzone 45 mg	14. Took Pioglitazone 45 mg at any time during the trial	Y	Edits and Monitoring
Eligibility	Inclusion/ Exclusion	AHA therapy not stable	15. AHA Therapy not stable per protocol requirements prior to Visit 1	N	Monitoring
Eligibility	Inclusion/ Exclusion	Diagnosed with other types of diabetes aside from T2DM	16. Diagnosed with T1DM or other types of diabetes aside from T2DM	Y	Monitoring
Eligibility	Inclusion/ Exclusion	Liver disease	17. Have obvious clinical or radiographic signs/symptoms of liver disease (except nonalchoholic fatty liver disease), cirrhosis, acute or chronic hepatitis, or alanine aminotransferase (ALT/SGPT) and/or aspartate aminotransferase (AST/SGOT) levels ≥2.5X upper limit of normal (ULN), alkaline phosphatase ≥2X ULN or total bilirubin ≥2X ULN (with the exception of known Gilbert syndrome) as defined by central laboratory.	N	Monitoring and GLS data
Eligibility	Inclusion/ Exclusion	Chronic kidney disease Stage 4 and higher	18. Have chronic kidney disease Stage 4 and higher (eGFR <30 mL/min/1.73 m^2) or history of renal transplantation.	N	GLS data and monitoring

Categorization of Important Protocol Deviations

Category	Sub-Category	Study Specific	Deviation Description	PPFLG	Methods of Identification
Eligibility	Inclusion/ Exclusion	History of more than 1 severe hypoglycemia episode	19. Have history of more than 1 episode of severe hypoglycemia requiring assistance of another person, resulting in coma, seizures, or disorientation within the 6 months prior to Visit 1.	N	CRF or monitoring
Eligibility	Inclusion/ Exclusion	Received U-500R insulin by CSII	20. Have received U-500R insulin by CSII in the 3 months prior to Visit 1.	Y	CRF or monitoring
Eligibility	Inclusion/ Exclusion	Had a blood transfusion or severe blood loss	21. Have had a blood transfusion or severe blood loss within 3 months prior to Visit 1or have known hemoglobinopathy, hemolytic anemia, or sickle cell anemia that is known to interfere with HbA1c measurement.	Y	CRF or monitoring
Eligibility	Inclusion/ Exclusion	Known allergy to human insulin preparations	22. Have known allergy to human insulin preparations or excipients contained in these products or prior history of suspected antibodies to human insulin.	N	Monitoring
Eligibility	Inclusion/ Exclusion	Taking chronic systemic glucocorticoid therapy	23. Are taking chronic (lasting longer than 14 consecutive days) systemic glucocorticoid therapy (excluding topical, intra-articular, intraocular, and inhaled prescriptions), or have received any systemic glucocorticoid therapy within the 4 weeks immediately prior to Visit 1.	Y	CRF or monitoring

Categorization of Important Protocol Deviations

Category	Sub-Category	Study Specific	Deviation Description	PPFLG	Methods of Identification
Eligibility	Inclusion/ Exclusion	Have an irregular sleep/wake cycle	24. Have an irregular sleep/wake cycle (for example, subjects who sleep during the day and work during the night), in the investigator's opinion.	N	Monitoring
Eligibility	Inclusion/ Exclusion	Intention to fasting	25. Intend to participate in an extended period of fasting during the study period (for religious or other purposes.)	N	Medical History; Monitoring
Eligibility	Inclusion/ Exclusion	Took prohibited conmed at entry	26. Have used rosiglitazone, sulfonylurea/glinides, pramlintide, once-weekly or twice-daily exenatide, or other AHAs not listed in the inclusion criteria in the 3 months prior to Visit 1 are taking AHA doses exceeding the respective product labels, or have a contraindication to current AHA usage per respective product labels.	N	CRF or monitoring
Eligibility	Inclusion/ Exclusion	Took weight loss drugs	27. Have used any weight loss drugs (for example, prescription drugs: lorcaserin, orlistat, phentermine, phentermine/topiramate, naltrexone/bupropion, or over-the-counter weight loss medications and herbal supplements) in the 3 months prior to Visit 1.	N	CRF or monitoring
Eligibility	Inclusion/ Exclusion	History of bariatric surgery	28. Have a history of bariatric surgery including Roux-en-Y gastric bypass surgery, gastric banding, and/or gastric sleeve.	Y	CRF or monitoring

Categorization of Important Protocol Deviations

Category	Sub-Category	Study Specific	Deviation Description	PPFLG	Methods of Identification
Eligibility	Inclusion/ Exclusion	History of malignancy	29. Have a history or an active or untreated malignancy, or in remission from a clinically important malignancy (other than basal cell or squamous cell skin cancer, in situ carcinomas of the cervix, colon or prostate that is considered cured) during the last 5 years before Visit 1 (if malignancy occurred >5 years ago, subject is eligible with documentation of disease-free state since treatment.)	N	CRF or monitoring
Eligibility	Inclusion/ Exclusion	Hearing loss and/or vision impairment	30. Important hearing loss and/or vision impairment deemed by the investigator to interfere with the safe use of the OmniPod U-500 System.	N	Monitoring
Eligibility	Inclusion/ Exclusion	Cardiac disease	31. Have cardiac disease with functional status that is Class III or IV according to the New York Heart Association Cardiac Disease Classification.	N	Monitoring

Categorization of Important Protocol Deviations

Category	Sub-Category	Study Specific	Deviation Description	PPFLG	Methods of Identification
Eligibility	Inclusion/ Exclusion	Breastfeeding or pregnant	32. Are women breastfeeding or pregnant or intend to become pregnant during the course of the study; are men who intend to impregnate their partners; or are sexually active of procreation potential not actively practicing birth control by a method determined by the investigator to be medically acceptable.	N	CRF or monitoring
Eligibility	Inclusion/ Exclusion	Investigator-site personnel and family	33. Are investigator-site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as spouse, parent, child, or sibling, whether biological or legally adopted.	N	Monitoring Source Documentation – should catch that all I/E were checked
Eligibility	Inclusion/ Exclusion	Lilly, Insulet, or TPO employee	34. Are Lilly or Insulet employees or are employees of third-party organizations (TPOs) involved in study who require exclusion of their employees.	N	Monitoring Source Documentation – should catch that all I/E were checked

Categorization of Important Protocol Deviations

Category	Sub-Category	Study Specific	Deviation Description	PPFLG	Methods of Identification
Eligibility	Inclusion/ Exclusion	Currently in any other clinical trials	35. Are currently enrolled in, or discontinued within the last 30 days, from a clinical trial involving an investigational product or non-approved use of a drug or device (other than the study treatment used in this study), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study, and any subjects who have previously completed or withdrawn from this study.	Y	Summary or Monitoring Source Documentation – should catch that all I/E were checked
Eligibility	Inclusion/ Exclusion	Unwilling or unable to independently perform study procedures	36. Are unwilling or unable to independently perform study procedures, such as monitoring SMBG levels, recording diary data, and/or administering medication via syringe or CSII as applicable, or have any illness or condition (including known drug or alcohol abuse or psychiatric disorder) within the 6 months prior to Visit 1, that precludes subject from following and completing the protocol according to the investigator's judgment. Subjects may not use a proxy to perform collection procedures, administer medication or record data.	N	Monitoring Source Documentation – should catch that all I/E were checked

Categorization of Important Protocol Deviations

Category	Sub-Category	Study Specific	Deviation Description	PPFLG	Methods of Identification
Study Procedures	Other	Missing HbA1c at V4 and/or V17	37. Missing primary efficacy measures at primary time point: specifically, missing HbA1c values at Visit 4 and/or Visit 17.	Y	GLS data and monitoring
Study Procedures	Other	Missing fasting plasma glucose (by laboratory measurement) at V4 and/or V17	38. Missing secondary efficacy measures at primary time point: specifically, missing fasting plasma glucose (FPG) values by laboratory measurement at Visit 4 and/or Visit 17.	N	GLS data
Study Procedures	Other	Random (as opposed to fasting) plasma glucose at V4 and/or V17	39. Fasting plasma glucose (by laboratory measurement) later determined to be a random draw at Visit 4 and/or Visit 17.	N	GLS data
Study Procedures	Visit Schedule Criteria	Missed office visit or visit window exceeds 3 weeks	40. Any missed office visit during the entire study or visit window intervals exceed 3 weeks outside of expected visit dates for in-office visits that significantly impacted the accuracy or reliability of the study data (does not include the allowable deviation time per study schedule).	N	Monitoring – Source Documentation
Study Procedures	Other	Subject continues study after pregnant	41. If the subject continues in the study after becoming pregnant post study enrollment.	N	Monitoring
Study Procedures	Violation of Discontinuation Criteria	Subject continues treatment after meeting DC criteria	42. Subject does not DC the study treatment or study while he/she should have DCd based on protocol criteria: Section 8.3.2 and Section 8.3.3 in study protocol.	Y	Monitoring
Study Procedures	Other	Subjects change AHA dose	43. Subject changes their dose of noninsulin pre-study AHA medications.	Y	InForm or Monitoring

Categorization of Important Protocol Deviations

Category	Sub-Category	Study Specific	Deviation Description	PPFLG	Methods of Identification
Investigational Product	Treatment Assignment/ Randomization error	IWRS data entry errors that impact patient stratification	44. IWRS data entry errors that impact patient stratification (data entry error into IWRS- prior to randomization)	N	Check to match IWRS to visits
Safety	SAE	Failure to report SAE	45. Failure to report an SAE as required by protocol/GCP standards	N	Monitoring - Make sure SAEs are listed; Source documentation
Investigational Product	Other	Incorrect study treatment	46. Incorrect study treatment (post randomization) will be reviewed on a case by case basis (includes drug dispensing errors and failure to maintain their randomization treatment – CSII or MDI).	Y	Monitoring
Administrative/ Oversight	Suspected Misconduct	Suspected Fraud	47. Suspected Fraud	N	Monitoring
Administrative/ Oversight	Suspected Misconduct	Suspected Fraud	48. Confirmed Fraud	Y	Monitoring
Investigational Product	Other	Use of expired CT Material <7 days	49. Use of expired CT Material less than 7 consecutive days	N	Monitoring
Investigational Product	Other	Use of expired CT Material ≥7 days	50. Use of expired CT Material for at least 7 consecutive days	Y	Monitoring
Investigational Product	Patient took study drug not fit for use	Received drug that was declared “Not Fit for Use” <7 consecutive days	51. Subject received drug that was declared “Not Fit For Use” for less than 7 days	N	Monitoring
Investigational Product	Patient took study drug not fit for use	Received drug that was declared “Not Fit for Use” ≥7 consecutive days	52. Subject received drug that was declared “Not Fit for Use” for at least 7 consecutive days	Y	Monitoring
Administrative/ Oversight	Suspected Misconduct	Suspected scientific misconduct	53. Suspected Scientific misconduct	N	Monitoring

Categorization of Important Protocol Deviations

Category	Sub-Category	Study Specific	Deviation Description	PPFLG	Methods of Identification
Administrative/ Oversight	Suspected Misconduct	Confirmed scientific misconduct	54. Only confirmed scientific misconduct will lead to exclusion from per-protocol population.	Y	Monitoring
Investigational Product	Compliance	Off study drug for >7 consecutive days	55. Subject off study drug for more than 7 consecutive days	Y	Monitoring
Investigational Product	Compliance	Subject <80% compliant with algorithm	56. If the investigator determines that that patient is noncompliant (<80% compliant with algorithm) and should be discontinued.	Y	Monitoring
Study Procedures	Other	Lack of initiation of rescue therapy	57. Lack of initiation of rescue therapy despite meeting rescue criteria.	N	Monitoring
Study Procedures	Other	Inappropriate rescue	58. Inappropriate rescue despite not meeting rescue criteria.	Y	Monitoring; Source Documents
Investigational Product	Compliance	Took more than the prescribed study treatment	59. Is judged by the investigator to have intentionally or repeatedly taken more or less than the prescribed amount of medication that may cause patient safety concerns.	N	Monitoring
Study Procedures	Other	Other, Not specified	60. Other, not specified (i.e. delay in randomization, investigator used PI discretion vs. titration tools, staff member not listed on 1572, site did not use IWRS to dispense medication or Pod, dosing error)	N	Monitoring
Eligibility	Inclusion/Exclusion	Subject switched to U-500R prior to V4	61. Subject did not continue their pre-study insulin regimen until Visit 4; subject switched from their baseline insulin to U-500R at Visit 1	Y	Monitoring

Categorization of Important Protocol Deviations (Abbreviations)

Abbreviations: AHA = antihyperglycemic agents; BMI = body mass index; Conmed = concomitant medication; CGM = continuous glucose monitoring; CRF = case report form; CSII = continuous subcutaneous insulin infusion; DC = discontinue; DCd = discontinued; GLS = Generic Laboratory System; HbA1c = hemoglobin A1c; ICD = informed consent document; I/E = inclusion/exclusion; IWRS = Interactive Web Response System; MDI = multiple daily injections; N = no; NA = not applicable; PPFLG = per-protocol population exclusion flag; SAE = serious adverse event; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; SMBG = self-monitored blood glucose; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; TDD = total daily dose; ULN = upper limit of normal; V = visit; Y = yes.

5.9. Primary Outcome and Methodology

The primary efficacy measure is change from baseline to the 26-week HbA1c value. The primary analysis will be conducted for the ARS population in Group A. There will be 2 primary analysis methods for different purposes as follows.

1. Per FDA's request, the analysis method will use the copy reference approach to impute missing data based on multiple imputations with a pattern mixture model (later referred to as 'copy reference multiple imputation analysis'). This analysis will include post study treatment discontinuation data. The reference is all observed data from all randomized subjects in the U-500R MDI arm who discontinued study treatment but completed the study without missing data. After imputation, an ANCOVA with baseline HbA1c as a covariate, treatment (U-500R CSII, U-500R MDI) and the stratification factor (U-500R at entry versus other insulins) as fixed effects will be used to analyze the 26-week HbA1c including imputed values.

   If in the reference group mentioned above there is only a limited number of subjects and this leads to a failure in performing the proposed multiple imputation analysis, the reference will be changed to include all observed data from all randomized subjects in the U-500R MDI arm who do not have missing data.

2. For manuscripts and other non-FDA submission purposes, an MMRM model that does not include post study treatment discontinuation data and adjusts for missing data through an observed-data-likelihood-based approach will be used. The model will include the following fixed effects: treatment (U-500R CSII, U-500R MDI), weeks on treatment, the interaction between treatment and weeks, and the stratification factor (U-500R at entry versus other insulins). The model will also include baseline HbA1c as a covariate.

   As a sensitivity analysis to the missing at random assumption of MMRM model, a stress test will be performed. The missing data are first imputed with the missing at random assumption. Prior to multiple-imputation analysis, in the CSII arm the imputed values will be replaced by the imputed value plus delta. Multiple values of delta within a clinically reasonable and meaningful range will be tested (delta=0.1, 0.2, 0.3, 0.4) to assess if the conclusion from the MMRM primary analysis changes.

For the MMRM model, the Kenward-Roger approximation will be used to estimate denominator degrees of freedom. An unstructured covariance matrix will be used to model the within-subject errors. If the unstructured covariance configuration results in a lack of convergence, then the following variance-covariance matrix will be used (in order) until one converges: Heterogeneous Toeplitz; Heterogeneous First Order Autoregressive; Heterogeneous Compound Symmetry; Toeplitz; First Order Autoregressive; Compound Symmetry. If all variance-covariance matrices selected fail to converge, Variance Components will be used as the next attempt at convergence.

The test for the primary objective of non-inferiority will be performed at the 0.05 significance level using the LSMean estimate of the difference in change in HbA1c between the 2 treatments

at Week 26. Non-inferiority will be established if the upper limit of a 2-sided 95% confidence interval (CI) for the difference (U-500R CSII minus U-500R MDI) is below the NIM of 0.4%.

Using the LSMean estimate of the difference in change in HbA1c between the 2 treatments, superiority will be established if the upper limit of a 2-sided 95% CI for the difference (U-500R CSII minus U-500R MDI) is below 0.

The following supportive and sensitivity analyses will also be conducted:

- If the following sets are different from ARS, then similar copy reference multiple imputation and MMRM analyses will be done for the FAS (subjects who were randomized and received at least 1 dose of the study insulin through the administration method they were assigned to), all completer set (subjects who complete the study treatment), and the per-protocol population (subjects included in the ARS who have completed the study without important protocol deviations that will impact the primary outcome).
- An ANCOVA model with similar fixed effects as in the copy reference multiple imputation analysis using LOCF method for the ARS will also be performed.
- For the analysis performed for the ARS population for Groups A+B, the analysis model will include an additional stratification factor (nonusers versus users of GLP-1 receptor agonists or SGLT2 inhibitors) as a fixed effect.

5.10. Secondary Outcomes and Analyses

For Group A and Group A+B in the ARS population, similar to the primary analysis, 2 sets of analysis approaches (copy reference multiple imputation and MMRM) will be used to analyze the change from baseline for the following key secondary endpoints 1 and 2 at Week 26. For endpoint 3, only MMRM analysis will be performed.

1) FPG (by laboratory measurement)
2) 7-point SMBG
3) total daily insulin dose (TDD)

For Group A, the MMRM model will include the following fixed effects: treatment (U-500R CSII, U-500R MDI), weeks on treatment, the interaction between treatment and weeks, and the stratification factors (U-500R at entry versus other insulins, entry HbA1c ≥8.5% or <8.5%). The model will also include the corresponding baseline of the response variable. For the copy reference approach, the ANCOVA model will include the following fixed effects: treatment (U-500R CSII, U-500R MDI), the stratification factors (U-500R at entry versus other insulins, entry HbA1c ≥8.5% or <8.5%) and the corresponding baseline measures.

For Group A+B, the same MMRM model and ANCOVA models in Group A above will be used with the addition of the stratification factor (nonusers versus users of GLP-1 receptor agonists or SGLT2 inhibitors).

For SMBG, the average of the 2 non-consecutive-day values for scheduled visits will be used.

Total daily dose will be calculated as the sum of maximum total bolus dose and basal dose at each visit. The maximum total bolus dose of the 3 days prior to each scheduled visit for each subject will be used to calculate the TDD value for data summary and statistical analysis to avoid the underestimated TDD due to missed meal(s). The basal dose will be only collected for 1 day prior to each visit and used to calculate TDD for each visit. Body weight at each visit will be used for TDD (units/kg) calculation. Summary statistics will be done for both actual values and change from baseline (CFBL) values. The percentages of bolus and basal doses from TDD in the U-500R CSII group will be summarized by visit.

Similar to the primary analysis, 2 sets of analysis approaches (repeated-measure [or longitudinal] logistic regression excluding post study treatment discontinuation data and the multiple imputations based logistic regression including post study treatment discontinuation data) will be applied to assess the following secondary objectives in the following values at Week 26:

- proportions of subjects achieving HbA1c targets/values (≤6.5%, <7.0%, <7.5%, and <8.0%)
- proportions of subjects achieving HbA1c targets/values (≤6.5%, <7.0%, <7.5%, and <8.0%) without documented symptomatic hypoglycemia (SMBG <50 mg/dL)

The logistic regression model will include similar fixed effects as in the above ANCOVA and MMRM models. The proportion of subjects achieving HbA1c targets with no documented symptomatic hypoglycemia (from baseline to the corresponding visit) will be analyzed using similar logistic regression models including the baseline documented symptomatic hypoglycemia event rate as a covariate.

Analyses to assess the following 2 secondary objectives are presented in Section 5.13 since those are considered safety measures:

- rate and incidence of hypoglycemia (documented [documented symptomatic, asymptomatic, and unspecified], severe, and nocturnal)
- change in body weight between treatment groups and as a function of change in HbA1c

5.11. Exploratory Efficacy Analysis

As mentioned in Section 5.2, exploratory objectives will be analyzed for Group A+B. Summary statistics for both actual values and CFBL values will be reported for each treatment by visit for the following parameters related to 7-point SMBG:

- within-day glucose variability measured by the SD of 7-point SMBG
- between-day glucose variability measured by the SD of the SMBG during the 2-nonconsecutive-day measurement within the same scheduled visit
- within-day and between-day glucose coefficient of variation (CV) of 7-point SMBG (Clarke and Kovatchev 2009)
- average daily risk range (ADRR) defined by (Kovatchev et al. 2006)

- mean of daily differences (MODD) calculated as the average of the difference between values on different days within the same scheduled visit but at the same time

Each of the parameters above will be analyzed using an MMRM model which includes the following fixed effects: treatment (U-500R CSII, U-500R MDI), weeks on treatment, the interaction between treatment and weeks, and the stratification factors (U-500R at entry versus other insulins, entry HbA1c ≥8.5% or <8.5%, and nonusers versus users of GLP-1 receptor agonists or SGLT2 inhibitors). The model will also include the corresponding baseline of the response variable. An ANCOVA will also be used to compare treatment arms at endpoint using the LOCF method. The ANCOVA model will include the same fixed effects in the MMRM model but without the terms involving weeks

The postprandial contribution to total hyperglycemia will be further explored (Riddle et al. 2011). The daily blood glucose (BG) response to meals will be estimated by calculating the incremental AUC of daytime BG from the overall glucose profile. Four areas were calculated geometrically from the seven-point curve as follows:

1) normal glycemic exposure (AUC_N): 100 mg/dLx24 h = 2,400 mg/dL per hour of exposure
2) basal hyperglycemia (BHG) (AUC_B): the area between 100 mg/dL and a line projected rightward for 24 hours from the fasting (before breakfast) glucose value in the profile (the area is taken to represent the daily abnormal glycemic exposure resulting from BHG)
3) postprandial hyperglycemia (PPHG) (AUC_P): the area above the line projected rightward from the fasting sample before breakfast and below the line connecting the 6 remaining points, minus any area below the line projected from the basal value, if applicable (this area is considered a reflection of the postprandial glycemic responses to breakfast, lunch, and dinner)
4) total glucose (AUC_G): the total area under the glucose curve is the sum of the other 3 areas [$AUC_G = AUC_N + AUC_B + AUC_P$]. As a result, the relative contributions of postprandial and fasting BG to the total BG increment were calculated, respectively, by using the following equations: [$AUC_P/(AUC_B + AUC_P)$] x100% for the postprandial contribution and [$AUC_B/(AUC_B + AUC_P)$] x 100% for the basal contribution. Negative values were set to zero.

Analyses include Mean (SD) of and Pearson correlation (p-value) between HbA1c CFBL at Week 26 (LOCF) and each of CFBL of: AUC_B, AUC_P, AUC_G, BHG contribution and PHG contribution at Week 26 (LOCF). The AUC_B and AUC_P will be analyzed separately by fitting ANCOVA model with baseline corresponding parameter as a covariate, treatment as fixed effect to compare the treatment effect.

Total hyperglycemia (%) separated by BHG and PPHG will be plotted for each treatment in bar chart format with x-axis for different HbA1c category (<6.5%, 6.5% to <7%, 7% to <7.5%, 7.5 to <8%, ≥8%, and overall).

Proportions of subjects with HbA1c ≥9% or <9% at Week 26 will be reported and will be analyzed using the same logistic regression model used in the analysis of the proportions of subjects achieving different HbA1c targets in Section 5.10.

5.12. Exploratory Objectives Analyses

As mentioned in Section 5.2, exploratory objectives will be analyzed for ARS in Group A+B unless otherwise specified.

The plan of analysis for the exploratory pharmacogenetic objective is in Section 5.15 of this document.

5.12.1. Patient Reported Outcome

The TRIM-D and TRIM-DD will be administered at Visit 4 (Week 0, prior to randomization), at Visit 13 (Week 14) and at Visit 17 (Week 26) or ET if subjects do not complete the full 26 weeks of the study.

If a respondent answers at least half of the items in a multi-item domain (or half plus one in the case of domains with an odd number of items) then a domain score should be calculated. The average score (across completed items in the same domain) for that respondent will be used to estimate any missing item in that domain. For example, if a respondent leaves 1 item in the 5-item Diabetes Management domain blank, substitute the respondent's average score (across the 4 answered Diabetes Management items) for the missing score for that item.

For both TRIM-D and TRIM-DD, the domain score and overall score will be transformed to a 0-100 scales by Domain = (raw score – lowest possible raw score)/possible raw score range *100. The transformed score will be used for the analysis purpose.

5.12.1.1. TRIM-D

The TRIM-D consists of 28 items which are measured on a 5-point scale, where a higher score indicates a better health state. In addition to an overall score, the TRIM-D items make up the 5 domains of impact: treatment burden (6 items), daily life (5 items), diabetes management (5 items), compliance (4 items) (see Section 5.7), and psychological health (8 items). The domains of daily life, compliance, and psychological health need to be reverse coded for scoring.

Summaries of domain and overall transformed scores will include sample size, mean, SD, median, minimum, and maximum at each assessment at each visit for each treatment group and for the ARS population. The actual value and change from baseline (Visit 4) will be summarized for the overall analysis population. The actual value and change from baseline in domain transformed scores and total transformed scores of TRIM-D will be analyzed using an MMRM approach. The MMRM model will include the following fixed effects: treatment (U-500R CSII, U-500R MDI), weeks on treatment, the interaction between treatment and weeks, and the stratification factors (U-500R at entry versus other insulins, entry HbA1c ≥8.5% or <8.5% and nonusers versus users of GLP-1 receptor agonists or SGLT2 inhibitors). The model will also include the corresponding baseline measures as a covariate. The covariance matrix will be chosen in the same order as the primary analysis.

The proportion of subjects who have TRIM-D compliance transformed score ≥80 at endpoint or ET will be analyzed using logistic regression with the following fixed effects: treatment (U-500R CSII, U-500R MDI) and the stratification factors (U-500R at entry versus other insulins, entry HbA1c ≥8.5% or <8.5%, and nonusers versus users of GLP-1 receptor agonists or SGLT2 inhibitors).

5.12.1.2. TRIM-DD

The TRIM-DD consists of 8 items which are measured on a 5-point scale, where a higher score indicates a better health state. In addition to an overall score, the TRIM-DD items make up the 2 domains of impact: device function (5 items) and bother of device (3 items). The bother of device domain need to be reverse coded for scoring.

Summaries of domain and overall transformed scores will include sample size, mean, SD, median, minimum, and maximum at each assessment at each visit for each treatment group and for the ARS population. The actual value and change from baseline (Visit 4) in domain and total transformed scores of TRIM-DD will be summarized and analyzed using an MMRM approach. The MMRM model will include the following fixed effects: treatment (U-500R CSII, U-500R MDI), weeks on treatment, the interaction between treatment and weeks, and the stratification factors (U-500R at entry versus other insulins, entry HbA1c ≥8.5% or <8.5%, and nonusers versus users of GLP-1 receptor agonists or SGLT2 inhibitors). The model will also include the corresponding baseline values as a covariate. The covariance matrix will be chosen in the same order as the primary analysis.

5.12.1.3. OmniPod U-500 System Exit Questionnaire

The percentage of subjects giving each answer to each question on the OmniPod U-500 System Exit Questionnaire will be summarized. The percentage will also be broken down by gender, and age ranges (18 to <25, 25 to <35, 35 to <45, 45 to <55, 55 to <65, 65 to <75, and ≥75 years).

5.12.2. Functionality and Safe Use of the OmniPod U-500 System

The functionality and safe use of the OmniPod U-500 system will be evaluated by an assessment of device complaint data, subject reported hazard alarms, and clinically relevant hyperglycemia possibly related to site occlusion. A listing of reported hazard alarms associated with routine and non-routine site changes as well as a listing of non-routine site changes with no alarms associated with hyperglycemia will be provided.

5.12.3. Subgroup Analysis

For the primary objective (Section 4.1 of the SAP), the following subgroup analyses will be performed for Group A if at least 20 subjects in each treatment group are in each of the subgroups: baseline TDD >2 and ≤2 units/kg, baseline TDD >400 and ≤400 units, TDD >200 units at baseline that fall below TDD 200 units during the study and TDD >200 units at baseline that stay 200 units or above during the study, and geriatric subjects (age <65 and ≥65 years; and age< 75 and ≥75 years). Within each strata of the specific subgroup, analysis will be performed using the similar model for the primary efficacy analysis using MMRM. To assess treatment by subgroup interaction, analysis will be conducted by adding subgroup as a main

effect and interaction term between treatment and subgroup, the 3-way interaction of the primary treatment arms, visit, and the subgroup variable will also be added for the MMRM analysis model. The interaction effects will be tested at significance level of 0.10.

5.13. Safety Analyses

Safety measures will include hypoglycemic events, AEs/treatment-emergent adverse events (TEAEs), body weight, vital signs (systolic and diastolic blood pressures and pulse rate), treatment exposure, and laboratory measures. In general, safety summary analyses will be done for Group A+B. However, hypoglycemic event and weight analyses assessing secondary objectives will be done for both Group A and Group A+B. All safety measures will be summarized for ARS by treatment for the 26-week treatment period. If listings are provided, they will contain data after the subjects discontinue the study treatment. For treatment comparisons of frequency and proportion of event variables (such as AEs and hypoglycemia events), Fisher's exact test will be used, unless otherwise specified.

5.13.1. Study Treatment Exposure

Exposure to each treatment during the treatment period of the study will be calculated for each subject and summarized by treatment group for ARS using first dosing and last dosing information. If a subject's first dosing date/time is missing, it will be replaced by the randomization date/time. If a subject's last dosing date/time is missing, it will be replaced by the last visit date/time up to discontinuation of study treatment or completion date/time (whichever is earlier). Total subject-years will be included in the summaries. The mean of exposure will be compared between treatment groups using a two-sample t-test.

5.13.2. Hypoglycemic Episodes

Hypoglycemia is defined and categorized as follows:

Documented hypoglycemia:

- **Documented symptomatic hypoglycemia:** an event during which typical symptoms of hypoglycemia are accompanied by SMBG ≤70 mg/dL.
- **Asymptomatic hypoglycemia:** an event not accompanied by typical symptoms of hypoglycemia but with SMBG ≤70 mg/dL.
- **Unspecified or unclassifiable hypoglycemia:** an event during which SMBG ≤70 mg/dL but no information relative to symptoms of hypoglycemia was recorded.
- **Severe hypoglycemia:** an event accompanied by neuroglycopenic symptoms that results in cognitive impairment such that the patient requires assistance of another person to actively administer carbohydrates, glucagon, or perform other resuscitative actions. During these episodes, the patient has an altered mental status, and cannot assist in their care, is semiconscious or unconscious, or experienced coma with or without seizures, and may require parenteral therapy. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of SMBG concentration to normal is considered sufficient evidence that the event was induced by a

low SMBG concentration (SMBG ≤70 mg/dL). The determination of a hypoglycemic event as an episode of severe hypoglycemia is made by the investigator.

- **Nocturnal hypoglycemia:** any hypoglycemic event (documented hypoglycemia or severe hypoglycemia) that occurs between bedtime and waking.

5.13.2.1. Hypoglycemic Analyses

Hypoglycemic analyses will be conducted on the ARS population. The same categories and subcategories defined in Section 5.13.2 will be used for summary and modeling purposes.

The hypoglycemic event rate (per 30 days and per 1 year), incidence (number) and percent of subjects reporting at least 1 hypoglycemic episode for a given treatment at certain week intervals will be summarized. The week intervals include: lead-in period (-2, 0], treatment period including (0, 2], (2 to 8], (8 to 26], (0 to 26] weeks. Note that the closed brackets will indicate to include a value/week; whereas, parentheses will indicate not to include the corresponding value/week. For example, (0 to 2] means all values between Week 0 and Week 2, including Week 2, but not including Week 0.

Treatment comparison of the incidence of hypoglycemia (documented [documented symptomatic, asymptomatic, and unspecified], severe, and nocturnal) will be done using logistic regression for each week interval, excluding poststudy treatment discontinuation data. For the analysis in Group A, the logistic model will include baseline hypoglycemia event rate for week interval (-2, 0] of the corresponding category of the dependent hypoglycemia variable standardized by 30 days (or 1 year) as covariates, treatment (U-500R CSII, U-500R MDI), and the stratification factors (U-500R at entry versus other insulins, entry HbA1c ≥8.5% or <8.5%) as fixed effects. For the analysis in Group A+B, the stratification factor (and nonusers versus users of GLP-1 receptor agonists or SGLT2 inhibitors) will be added into the model.

For summary purpose, the rate per 30 days calculated between 2 visits is defined as the total number of episodes for all subjects between the visits divided by the total actual number of exposure days between the visits, and then multiplied by 30 days. A similar definition will be used to calculate the rate per subject per 365 days (1 year).

The analysis approach for the rate of hypoglycemia is based on a negative binomial model with log link function, excluding post study treatment discontinuation data. The response variable is the hypoglycemic event count per visit per subject. For Group A, the model will include baseline hypoglycemia event rate for week interval (-2, 0] of the corresponding category of the dependent hypoglycemia variable standardized by 30 days as covariates, treatment (U-500R CSII, U-500R MDI), and the stratification factors (U-500R at entry versus other insulins, entry HbA1c ≥8.5% or <8.5%) as fixed effects. For the analysis in Group A+B, the stratification factor (nonusers versus users of GLP-1 receptor agonists or SGLT2 inhibitors) will be added into the model. The logarithm of exposure days (standardized by 30 days) between visits will be used as the offset variable. In LSMeans statement, Observed Margin (OM) option will be added to specify weighting scheme for LSMean computation as determined by the input data set. The LSMean of hypoglycemia rate per 30-days by treatment for each week interval will be reported,

and the rate ratio between treatments will also be presented. Wilcoxon signed-rank test may be performed as sensitivity analysis.

The 1-year rate of documented symptomatic and severe hypoglycemia (with BG ≤70 mg/dL) for every 2-hour interval (0:00-1:59, 2:00-3:59, 22:00-23:59) over the 26 week post-randomization period will be summarized. The rate of hypoglycemia will also be analyzed using a negative binomial model. The response variable is the hypoglycemic event count per 2-hour interval per subject. The analysis approach will be similar to the hypoglycemia rate analysis approach above for Group A and Group A+B.

5.13.3. Treatment Emergent Adverse Events and Serious Adverse Events

Adverse events will be summarized as TEAEs (defined as events that are newly reported after randomization Visit 4 or reported to worsen in severity from randomization Visit 4) for ARS by treatment. The frequency and proportion of subjects experiencing at least 1 of each reported TEAE will be summarized by System Organ Class (SOC), Preferred Term (PT), and treatment group. Events will be ordered by decreasing frequency within SOC. The frequency and proportion comparisons will be analyzed using Fisher's exact test. The frequency and proportion of subjects experiencing at least 1 of each reported TEAE that are assessed as possibly related to the study drug, device, procedures will also be summarized, separately.

All SAEs (including severe hypoglycemic events) will be listed by subject including SOC, Medical Dictionary for Regulatory Activities (MedDRA) PT, severity, and relationship to the study disease, drug, device, or procedure for all subjects. The listing will contain data after the subjects discontinue the study treatment.

If a sufficient number of SAEs are reported, then a frequency and proportion summary, similar to the summary for TEAEs, will be included for the ARS.

Discontinuations due to AEs and SAEs will be listed separately, by subject (including specific AE and SAE information and whether they discontinue only the study treatment or study treatment and the study), and summarized (if a sufficient number of events are reported) by SOC, PT, and treatment group.

5.13.4. Body Weight

The body weight actual value and CFBL based on actual value at visits will be analyzed by MMRM models similar to that which will be used in the primary analysis for the ARS population. An ANCOVA model will also be used as a sensitivity analysis. A scatter plot that includes a regression line of LOCF weight CFBL by LOCF HbA1c CFBL will be presented.

For Group A, the MMRM model will include the following fixed effects: treatment (U-500R CSII, U-500R MDI), weeks on treatment, the interaction between treatment and weeks, and the stratification factors (U-500R at entry versus other insulins, entry HbA1c ≥8.5% or <8.5%). The model will also include the corresponding baseline of the response variable. The ANCOVA model will include the following fixed effects: treatment (U-500R CSII, U-500R MDI), the

stratification factors (U-500R at entry versus other insulins, entry HbA1c ≥8.5% or <8.5%), and the baseline weight as covariate.

For Group A+B, the same MMRM model and ANCOVA models in Group A above will be used with the addition of the stratification factor (nonusers versus users of GLP-1 receptor agonists or SGLT2 inhibitors).

5.13.5. Vital Signs

Systolic blood pressure, diastolic blood pressure, and pulse rate will be summarized at each scheduled visit including baseline for the ARS in Group A+B. Additionally, CFBL for all postrandomization visits will be summarized. The CFBL and actual value at visits will be analyzed using a MMRM model with the following fixed effects: treatment (U-500R CSII, U-500R MDI), weeks on treatment, the interaction between treatment and weeks, and the stratification factors (U-500R at entry versus other insulins, entry HbA1c ≥8.5% or <8.5%, nonusers versus users of GLP-1 receptor agonists or SGLT2 inhibitors). The model will also include the corresponding baseline measures as a covariate. The actual value and CFBL based on LOCF endpoint will be analyzed using ANCOVA model, as a sensitivity analysis. The ANCOVA model will include the same fixed effects in the MMRM model but without the terms involving weeks.

5.13.6. Laboratory Measures

As applicable per protocol, measures within the following panels will be summarized at Screening (Visit 1), Visit 4 (Week 0), Visit 13 (Week 14), and Visit 17 (Week 26) or endpoint (LOCF):

- chemistry (creatinine, uric acid)
- c-peptide
- eGFR
- lipids (total cholesterol, calculated low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], triglycerides [TG], and free fatty acids [FFAs])
- liver test panel (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transferase, alkaline phosphatase)

Treatment-emergent high, low, and abnormal values will be summarized for each lab measure listed above. A treatment-emergent **high value** is defined as a value that was normal or low at baseline and subsequently found to be above the normal range at any post-baseline visit. A treatment-emergent **low value** is defined as a value that was normal or high at baseline and subsequently found to be below the normal range at any post-baseline visit. A treatment-emergent **abnormal value** is defined as a value that was normal at baseline and subsequently found to be abnormal at any post-baseline visit; however, for ALT/serum glutamic pyruvic transaminase (SGPT) or AST/serum glutamic oxaloacetic transaminase (SGOT) ≥2.5X upper limit of normal (ULN) will be used as the abnormal threshold. The proportion comparisons between 2 treatment groups will be analyzed using Fisher's exact test.

Actual value, percentage CFBL in lipids panel (total cholesterol, calculated LDL-C, HDL-C, TG, FFAs), and CFBL in other measures will be summarized and analyzed. If only one post-baseline measurement is scheduled, then an ANCOVA model will be used; if more than one post-baseline measurement is scheduled, then an MMRM model will be used. The MMRM model will include the following fixed effects: treatment (U-500R CSII, U-500R MDI), weeks on treatment, the interaction between treatment and weeks, and the stratification factors (U-500R at entry versus other insulins, entry HbA1c ≥8.5% or <8.5%, nonusers versus users of GLP-1 receptor agonists or SGLT2 inhibitors). The model will also include the corresponding baseline measures as a covariate. The ANCOVA model will include the same fixed effects in the MMRM model but without the terms involving weeks.

5.14. Rescue Therapy

A listing of all subjects receiving rescue therapy will be provided. The listing will include, but not be limited to, subject ID, treatment group, rescue therapy date, and dose.

5.15. Exploratory Pharmacogenetic Analysis

Pharmacogenetic analyses will be documented in a stand-alone PGx SAP and conducted by Lilly diabetes PGx statistics group or its designees.

5.16. Interim Analyses

A DMC (Data Monitoring Committee) will have access to unblinded data for their review(s). Only the DMC is authorized to evaluate unblinded interim safety analyses. The DMC will be composed of individuals internal and external to Lilly who are not part of the study team and will monitor the safety of U-500R administered CSII or MDI and may recommend changes to the protocol, including termination. The analysis plans for the DMC are specified in the DMC Charter.

6. Unblinding Plan

The purpose of this blinding and unblinding plan is to detail procedures in place to minimize bias while preparing for or conducting any summary or analysis of Study IBHD's data for DMC reports, trial level safety reports (TLSR), or CSRs. Additionally, this plan identifies who will be unblinded for the interim data analysis in support of the DMC meetings.

6.1. Creating the Blind: General Blinding Requirements

Study IBHD is a Phase 3b, multicenter, randomized, open-label, parallel clinical trial comparing U-500R administered by CSII (OmniPod U-500 system) to U-500R administered MDI in high-dose insulin-requiring subjects with T2DM. Treatment blinding of the investigators, subjects, and study site personnel is not feasible due to differences in the appearance and functionality of the delivery devices. To minimize bias, aggregate review of summary data by the study team (that is, clinical research physician/clinical research scientist (CRP/CRS) overseeing the global conduct of the study, statisticians, and statistical analysts) will remain blinded with respect to treatment assignment until after the final database is locked. Unblinding of the subject study treatment assignment may occur in the course of individual subject consultation between the investigator and the study team (principally between the investigator and the CRP/CRS) or during review of SAEs. No systematic unblinding of study treatment assignments will be solicited by the study team.

Besides the above discussion about treatment assignment, the following 5 case report forms (CRFs) will be blinded/scrambled to the study team (that is, CRP/CRS overseeing the global conduct of the study, statisticians, and statistical analysts) at an individual level, because they contain information which will lead to unblinding of treatment assignment:

- QS_OMNI (OMNI1001)
- DE_HAZ (OPHA1001)
- EX_BASAL (EX1001_F3)
- EX_BOLUS (EX1001_F4)
- EX_RESCUE (EX1001_F5)

6.2. Details of Maintaining the Blind

For TLSR and DMC and the final data: treatment assignments and the 5 CRF forms will remain blinded to study team as defined in Section 6.1.

- treatment assignments will be scrambled by data management group before raw data transfer
- the unblinded raw data for the 5 CRF forms together with other raw data will be transferred to: CLUWE/lillyce/qa/ly041001/b5k_mc_ibhd/prelock/data/raw/dm/edc

The study team as defined in Section 6.1 does not have access to this folder.

The DMC Statistical Analysis Center (SAC) statistician, who is outside of the study team, will scramble the QS_OMNI (OMNI1001) and DE_HAZ (OPHA1001) by reassigning the patient

IDs using a random patient list generated from all study patient IDs. The DMC SAC statistician will blind EX_BASAL, by removing basal dose records (PAGE="EX1001_F3"), which are the only information specific to CSII-arm subjects in this dataset. The bolus doses (EX_BOLUS [EX1001_F4]) and rescue doses (EX_RESCUE [EX1001_F5]) will be rounded to the nearest increment of 5.

Then the blinded data for each data transfer will be saved to:

- TLSR1: CLUWE/lillyce/qa/ly041001/b5k_mc_ibhd/safety_review1/data/raw/shared
- TLSR2: CLUWE/lillyce/qa/ly041001/b5k_mc_ibhd/safety_review2/data/raw/shared
- DMC: CLUWE/lillyce/qa/ly041001/b5k_mc_ibhd/dmc_blinded1/data/raw/shared
- FINAL TEST DATA:
  CLUWE/lillyce/qa/ly041001/b5k_mc_ibhd/final/data/raw/shared

The study team statistician and analysts have access to this folder that contains blinded data

For DMC: summary of treatment assignments and the 5 CRF forms will be unblinded to the following who are all external to the study team:

- LRL Senior Management Designee
- SAC Statistician and DMC Secretary
- DMC Chairperson
- DMC Voting Members

The DMC SAC statistician will use the unblinded SDTM and ADaM data to generate TFL outputs, at the following locations respectively.

- SDTM folder:
  CLUWE/lillyce/qa/ly041001/b5k_mc_ibhd/dmc_unblinded1/data/observed/restricted
- ADaM folder:
  CLUWE/lillyce/qa/ly041001/b5k_mc_ibhd/dmc_unblinded1/data/analysis/restricted
- TFL folder:
  CLUWE/lillyce/qa/ly041001/b5k_mc_ibhd/dmc_unblinded1/output/restricted

The study team does not have access to these folders.

7. CGM Addendum

Unless otherwise specified, all discussions in this section are within the context of the CGM addendum only. Subjects who choose to participate in Protocol Addendum IBHD(1) will sign an addendum-specific informed consent form (ICF). The commercial CGM device (Dexcom G4 Platinum) that will be used for this addendum is labeled to collect data for 7 consecutive days. These subjects will be asked to perform CGM on 3 occasions for up to 7 days per occasion as indicated in the Study Schedule. Continuous glucose monitoring should occur during the week prior to Visit 4 (Week 0), Visit 13 (Week 14), and Visit 17 (Week 26).

7.1. Addendum Objectives

7.1.1. Primary Objective

The primary objective of this addendum is to compare glycemic control change from baseline to end of treatment period of within-day glucose variability as measured by mean daily SD of the interstitial glucose measurements between CSII and MDI.

7.1.2. Secondary Objectives

The secondary objectives for the CGM addendum are:

1) To compare glycemic control change from baseline to endpoint of the treatment period between CSII and MDI as assessed by CGM based on mean daily AUC and percentage of time:
   - ≤70 mg/dL
   - ≤50 mg/dL
   - ≥180 mg/dL
   - ≤70 mg/dL during the nocturnal period between midnight and 0600 hours
   - ≤50 mg/dL during the nocturnal period between midnight and 0600 hours
   - >70 mg/dL to ≤120 mg/dL
2) To compare the low blood glucose index (LBGI) and high blood glucose index (HBGI) during the nocturnal period defined as midnight to 0600 hours and during a 24-hour period between CSII and MDI at end of treatment period
3) To compare the combined BG risk index (sum of the LBGI and HBGI) during the nocturnal period defined as midnight to 0600 hours and during a 24-hour period between CSII and MDI at end of treatment period
4) To evaluate the insulin-on-board (IOB, 6- or 8-hour) pump settings by analysis of mean glucose AUC between bolus doses at breakfast and lunch and between bolus doses at lunch and dinner, respectively, for CSII treatment at end of treatment period
5) To evaluate optimal bolus timing (15 or 30 minutes prior to meal) response by analysis of mean glucose AUC for 4 hours after the start of the meal at end of treatment period

7.2. Determination of Sample Size

The CGM data collected in this addendum will be for exploratory purposes; therefore, the sample size is not based on power consideration. Assuming 25% dropout rate, 27 subjects in each treatment arm (54 total) are needed to have 20 completers in each treatment arm (40 total).

7.3. Analytic Variables

A third party organization (TPO) will collect and compile the CGM data. Besides the CGM raw data, the TPO will also provide the analytic variables for each patient as follows:

- daily SD of the CGM glucose measures
- daily amplitude of glycemic excursion (MAGE) index and continuous overall net glycemic action (CONGA)
- daily AUC and percentage of time when glucose measures are:
  - ≤70 mg/dL
  - ≤50 mg/dL
  - ≥180 mg/dL
  - ≤70 mg/dL during the nocturnal period between midnight and 0600 hours
  - ≤50 mg/dL during the nocturnal period between midnight and 0600 hours
  - >70 mg/dL to ≤120 mg/dL
- daily LBGI, HBGI, and the combined BG risk index (sum of the LBGI and HBGI) during the nocturnal period (defined as midnight to 0600 hours) and during a 24-hour period
- daily AUC between bolus doses at breakfast and lunch and daily AUC between bolus doses at lunch and dinner, respectively
- daily AUC for 4 hours after the start of each meal

MAGE is the mean of the differences between consecutive peaks and nadirs in BG, provided that the absolute value of difference was greater than the SD (Service et al. 1970). CONGA is the SD of the difference between the current and previous observations and measures the overall intra-day variation of glucose recorded by CGM (McDonnell et al. 2005).

The LBGI (Kovatchev et al. 2005) has been developed to quantitate both frequency and severity of hypoglycemia. The LBGI has been validated as a predictor of severe hypoglycemia (Kovatchev et al. 2003; Kovatchev et al. 1998), which is a SAE and could result in coma or death if unrecognized and untreated. The HBGI quantifies both frequency and severity of hyperglycemia (Kovatchev et al. 2005) and has been related to HbA1c and risk for hyperglycemia (Kovatchev et al. 2003). Additionally, the LBGI and HBGI both have a high sensitivity to changes in glycemic profiles and control (Kovatchev et al. 2002). The LBGI and HBGI will be derived values.

7.4. A Priori Statistical Methods

Baseline characteristics will be summarized by treatment arm. Means will be analyzed using an analysis of variance model. Proportions will be analyzed using Fisher's exact test.

The primary objective measure is mean daily SD calculated as the mean of the optimal values for each visit. An MMRM model will be used to analyze the actual measurements and change from baseline of the continuous dependent variables. The model will include fixed effects such as treatment, weeks on treatment (considered as categorical variable), the interaction between treatment and weeks, and the stratification factors. Subject will be considered as a random effect. The corresponding baseline values will be included as a covariate.

For the MMRM model, the Kenward-Roger approximation will be used to estimate denominator degrees of freedom. An unstructured covariance matrix will be used to model the within-subject errors. If the unstructured covariance configuration results in a lack of convergence, then the following variance-covariance matrix will be used (in order) until one converges: Heterogeneous Toeplitz; Heterogeneous First Order Autoregressive; Heterogeneous Compound Symmetry; Toeplitz; First Order Autoregressive; Compound Symmetry. If all variance-covariance matrices selected fail to converge, Variance Components will be used as the next attempt at convergence.

If the model still does not converge after changing to different covariance structures, then the stratification factors will be removed from the model. If the model still does not converge, then an ANCOVA analysis which only includes baseline and the 26-week values will be performed.

The similar variable calculation method and MMRM approach will be used for all other secondary objectives. Model specifications, such as fixed effects, covariates, and repeated measurement structures need to be carefully adjusted according to the specific objectives and measurements. For Secondary Objective 4, only those subjects assigned to CSII arm will be analyzed; therefore, the treatment effect and its interactions with other effects will be removed from the model. For Secondary Objective 5, the interaction between optimal bolus timing (15 or 30 minutes prior to meal) and treatment will be added into the MMRM model; the interaction between optimal bolus timing and weeks will also be added. Depending on the model convergence situation, the interaction between treatment and weeks may be removed.

Other measures of variability of the interstitial glucose measurements may be analyzed as sensitivity analyses (for example, MAGE index and CONGA).

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