Protocol 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

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Approval Date: 11-Jun-2015

1. Protocol 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 (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).

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 11-Jun-2015 GMT

2. Synopsis

Study Rationale

This prospective, randomized clinical trial will provide clinical information on the use of human regular U-500 insulin (Humulin® R U-500; U-500R) in high-dose insulin-requiring patients with type 2 diabetes mellitus (T2DM). Gaps in scientific and clinical knowledge for U-500R include initial dosing and transition from high-dose U-100 insulin therapy, dose titration including use of multiple daily injections (MDI) delivered three times daily (TID), administration safety in combination with antihyperglycemic agents (AHAs), and transition from U-500R MDI to continuous subcutaneous insulin infusion (CSII). Delivery of U-500R by CSII is used in patient care in United States (US) clinical practice (Reutrakul et al. 2011; Lane et al. 2013; Eby et al. 2014), but this mode of administration is not approved by the US Food and Drug Administration (FDA). A prospective, randomized clinical trial is needed to evaluate the efficacy and safety of U-500R delivered by CSII as compared to U-500R by MDI delivered TID, using a novel version of the OmniPod® Insulin Management System that is intended to deliver U-500 insulin with dosage in insulin units (U) without converting to U-100 "pump units" (Lane et al. 2009; Segal et al. 2010; Lane et al. 2010; Cochran et al. 2014), which is what would be required if U-500 insulin were to be used in a U-100 insulin system.

Clinical Protocol Synopsis: Study B5K-MC-IBHD

Name of Investigational Product:
Human regular U-500 insulin; Humulin® R U-500; U-500R (LY041001)

Title of Study: 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)

Number of Planned Subjects: Approximately 320 subjects requiring high dose insulin without use of glucagon-like peptide-1 (GLP-1) receptor agonists or sodium-glucose transporter protein (SGLT2) inhibitors (Group A) and approximately 64 to 96 additional subjects with use of GLP-1 receptor agonists or SGLT2 inhibitors (Group B), with or without other insulins/AHAs will be randomized based on a 1:1 ratio to two 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).
Entered: Approximately 586 subjects (450 in Group A plus an additional 90 to 136 in Group B)
Enrolled/Randomized: Approximately 416 subjects (320 in Group A plus an additional 64 to 96 in Group B)
Completed: Approximately 312 subjects (240 in Group A plus an additional 48 to 72 in Group B)

Phase of Development: 3b

Length of Study: 18 months
Estimated first patient visit: October 2015 Estimated last patient visit: December 2016

Objectives:
The primary objective is to demonstrate the change in glycated hemoglobin A1c (HbA1c) of U-500R administered by CSII is noninferior to U-500R administered by MDI therapy from baseline to the 26-week in high-dose insulin-requiring patients 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 high-dose U-500R insulin (MDI) without use of GLP-1 receptor agonists or SGLT2 inhibitors and with or without other insulins/AHAs. This population is referred to as Group A.

The following 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 two-sided 5% level by the graphical approach.

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]) 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]) that:
H6: CSII is noninferior to MDI in change in HbA1c using a NIM of 0.4%.
H7: CSII is superior to MDI in change in fasting plasma glucose (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%.

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 the total study population (Groups A and B), respectively (separately), with respect to the following:

- Proportions of subjects achieving HbA1c targets/values (≤6.5% and <8%);
- Mean change in 7-point self-monitored blood glucose (SMBG) including mean SMBG for each time point measurement;
- Change in 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;

Exploratory Objectives:

- 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 proportions 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 U, users of GLP-1 receptor agonists or SGLT2 inhibitors, and geriatric subjects (age ≥65 years and ≥75 years) for each of the primary and secondary objectives.
- Functionality and safe use of the OmniPod® U-500 system (Insulet Corporation; Bedford, MA).

Study Design: This 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 patients 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 a 1-week screening period, a 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).

Diagnosis and Main Criteria for Inclusion and Exclusions:
Planned subject population is men and women diagnosed with T2DM requiring high-dose insulin who have inadequate glycemic control.
Inclusion Criteria: Aged ≥18 to ≤85 years; are currently prescribed non U-500R insulin/analog by CSII or MDI or U-500R insulin by MDI with syringe and vial with or without AHAs for ≥3 months at a TDD >200 but ≤600 U; HbA1c ≥7.5% but ≤12.0%; body mass index ≥25 but ≤50 kg/m^2; history of stable body weight; concomitant AHA therapy may include metformin, dipeptidyl peptidase-4 inhibitors (sitagliptin, saxagliptin, linagliptin, and alogliptin), pioglitazone (doses ≤30 mg/day), GLP-1 receptor agonists (albiglutide, dulaglutide, or liraglutide [Group B only]), and SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin [Group B only]). Subjects' AHA therapy must have been stable for ≥3 months (except GLP-1 receptor agonists must have been stable for ≥4 months).
Exclusion Criteria: Type 1 diabetes mellitus or other types of diabetes; or alanine aminotransferase and/or aspartate aminotransferase (ALT/AST) ≥2.5x the upper limit of normal; chronic kidney disease Stage 4 and higher (estimated

glomerular filtration rate <30 mL/minute/1.73m^2 as measured by MDRD formula); history of >1 episode of severe hypoglycemia (defined as hypoglycemia requiring the assistance of a another person) within the prior 6 months; have received U-500R insulin by CSII in the 3 months prior to Visit 1; recent blood transfusion or severe blood loss within 3 months prior to Visit 1; known hemoglobinopathy, hemolytic anemia, sickle cell anemia; chronic systemic glucocorticoid therapy; use of weight loss drugs in 3 months prior to Visit 1; women who are pregnant, breastfeeding, or are sexually active and of childbearing potential but are not using appropriate contraception; men who intend to impregnate their partners; received sulfonylureas/glinides in the 3 months prior to Visit 1, or other injectable or oral AHA therapy not listed in the inclusion criteria in the prior 3 months; bariatric surgery; active or untreated malignancy; significant hearing loss or vision impairment; cardiac disease with functional status New York Heart Association Class III or IV; irregular sleep/wake cycle; use of nonapproved investigational drug within 1 month prior to trial.

Investigational Drug Product, Dosage, and Mode of Administration or Intervention:
Human regular U-500 insulin, per titration algorithm administered by CSII via OmniPod U-500 system

Planned Duration of Treatment:
Lead-in period: 2 weeks
Treatment period: 26 weeks

Reference Therapy, Dose, and Mode of Administration or Comparative Intervention:
Human regular U-500 insulin, per titration algorithm administered subcutaneously by MDI

Criteria for Evaluation:
Efficacy:
- HbA1c
- FPG
- 7-point SMBG
- TDD

Safety:
- Adverse events (AEs) and treatment-emergent adverse events (TEAEs)
- Incidence and rate of hypoglycemic episodes (documented [documented symptomatic, asymptomatic, and unspecified], severe, and nocturnal)
- Body weight
- Vital signs
- Study treatment exposure
- Clinical laboratory tests
- Product complaints

Exploratory:
- Functionality and safe use of the OmniPod U-500 system
- Patient reported outcomes: TRIM-D, TRIM-DD
- Pump-specific assessment: OmniPod U-500 System Exit Questionnaire

Statistical Methods:
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 two 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 a 2-sided alpha = 0.05.

Adjustment for Multiplicity: A graphical approach will be used to adjust multiplicity for the primary and key secondary objectives. This approach will control the family-wise Type 1 error rate at alpha=0.05.

Randomization Details: Stratify by entry HbA1c ≥8.5% or <8.5%, nonusers versus users of GLP-1 receptor agonists or SGLT2 inhibitors, and U-500-R at entry versus other insulins.

Safety Committee and Interim Analysis:
Trial level safety reviews (TLSRs) using selected blinded safety data will be conducted throughout the study by the study team. In addition, 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. Unblinding details are specified in the unblinding plan section of the Statistical Analysis Plan (SAP) and/or DMC Charter. The timing and frequency of these data reviews will be stated in the DMC charter. In the event of any patient safety concerns, the DMC will communicate to the study team so that the clinical research physician/clinical research scientist can inform the investigator of appropriate action. Study sites will receive information about interim results ONLY if they need to know for the safety of their subjects.

If an unplanned interim analysis is deemed necessary, the appropriate Lilly regulatory scientist will be consulted to determine whether it is necessary to amend the protocol.

Primary Efficacy:
The primary efficacy measure is change from baseline (last nonmissing value at or prior to the treatment starting at Visit 4) to the 26-week HbA1c value, which will be summarized and analyzed using a mixed-model repeated measures (MMRM) approach for the All Randomized Set (ARS) population. The baseline is selected to be the last value on or prior to the treatment starting visit: Visit 4 (Week 0). Neither last-observation-carried-forward (LOCF) method nor other imputation methods will be used for the outcome measures. However, LOCF method will be used for sensitivity analysis. The MMRM model adjusts for missing data through an observed-data-likelihood-based approach. 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 appropriate stratification factor (nonusers versus users of GLP-1 receptor agonists or SGLT2 inhibitors and U-500R at entry versus other insulins). The model will also include baseline HbA1c as a covariate. An unstructured covariance matrix will be first modeled for the repeated measures of each subject. If the analysis fails to converge, the following variance-covariance matrix will be used (in order) until one converges:

1. Heterogeneous compound symmetry;
2. Compound symmetry;
3. First-order autoregressive.

The test for the first primary objective of noninferiority will be performed at the 0.05 significance level using the least-squares (LS) mean estimate of the difference in change in HbA1c between the two treatments at Week 26. Noninferiority will be established if the upper limit of a 2-sided 95% confidence interval (CI) for the difference (U 500R CSII minus U-500R TID) is below the NIM of 0.4%.

Using the LS mean estimate of the difference in change in HbA1c between the 2 treatments, superiority will be established if the upper limit of a two-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 the ARS, then similar MMRM analyses will be done for the Full Analysis Set (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), and the Per-Protocol Population (subjects included in the ARS who have completed the study without significant protocol violations).
- An 'analysis of covariance' model with similar fixed effects as in the MMRM analysis using LOCF method for the ARS population.

Secondary Efficacy:
Similar MMRM models for the ARS population will be used to analyze the change from baseline for the following

values at week 26:

1) FPG (by laboratory measurement)
2) 7-point SMBG
3) Total Daily Insulin dose (TDD)

Baseline values will be the last value obtained for each subject at or prior to the randomization visit: Visit 4, unless otherwise stated. The MMRM model will include similar fixed effects as in the primary analysis, with the corresponding baseline measures included as a covariate. The model specifications will be carefully adjusted as appropriate.

For 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).

Treatment comparisons will be analyzed using a repeated-measure logistic regression model including subject to account for the repeated measurements and similar fixed effects as in the above MMRM models. The proportion of subjects achieving HbA1c targets with no documented symptomatic hypoglycemia (from baseline to corresponding visit) will be analyzed using a similar repeated-measure logistic regression model including the baseline documented symptomatic hypoglycemia event rate as a covariate.

Safety Analyses:

All of the secondary objectives related to safety will be analyzed for Group A and for the total study population (Groups A and B combined). All safety measures will be summarized for ARS by treatment and by visit for the 26-week treatment period. Safety measures will also be listed for those patients who discontinue study treatment but still remain in the study for safety monitoring purpose. These listings will contain data after the patients discontinue study treatment. For treatment comparisons of frequency and proportion of event variables (such as AEs and hypoglycemia events), the conventional Fisher's exact test or Pearson's chi-square test are appropriate to use.

Hypoglycemia: **(**documented [documented symptomatic, asymptomatic, and unspecified], severe, and nocturnal episodes): 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 (year). For documented (documented symptomatic, asymptomatic and unspecified), severe, and nocturnal hypoglycemic episodes, the following analyses will be conducted. The incidence and percentage of subjects with at least 1 hypoglycemic event will be analyzed using Fisher's exact test or Pearson's chi-square test, as appropriate. The rate of hypoglycemia events per 30 days and per 365 days will be analyzed using a repeated-measure negative binomial regression model with similar fixed effects as in the primary analysis model. Baseline hypoglycemia event rate for the corresponding category of the dependent hypoglycemia variable will be included as a covariate, as well as the stratification factors.

Body Weight: The body weight change will be analyzed separately by MMRM models similar to that which will be used in the primary analysis for the ARS population. The model specifications will be adjusted as appropriate.

TEAEs and serious adverse events (SAEs): Adverse events will be listed by subject, system organ class, preferred term, severity, and relationship to the study disease, drug, device, or procedure. Adverse events will be summarized as TEAEs during treatment period (defined as events that are newly reported after randomization Visit 4 or reported to be worsened in severity from randomization Visit 4) for ARS by treatment and visit. The frequency and proportion of subjects experiencing at least 1 of each reported TEAE will be summarized for treatment period. The frequency and proportion comparisons will be analyzed using Fisher's exact test or Pearson's chi-square test, as appropriate. The frequency and proportion of subjects experiencing at least 1 of each reported TEAE that are assessed as possibly related to the study disease, drug, device, or procedures will also be summarized. All SAEs (including severe hypoglycemic events) will be listed by subject with similar information as the AE listing. 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.

Vital Signs: Systolic and diastolic blood pressures and pulse will be summarized by visit and for endpoints (LOCF). Change from baseline to the last visit of each period for actual endpoint and endpoint (LOCF) will be summarized.

Study Treatment Exposure: Exposure to each treatment will be calculated for each subject and summarized by treatment. Total subject-years will be included in the summaries.

Laboratory Measures (chemistry, hematology, lipids): Treatment-emergent high, low, and abnormal values will be summarized for each lab measure.

Further details of analyses will be provided in the SAP.

Patient Reported Outcome Measures: As an exploratory objective, the TRIM-D and TRIM-DD measures will be used to compare the change in diabetes treatment and diabetes treatment device on patient's functioning, well-being and quality-of-life outcomes from baseline to the 26-week values between treatment groups. These analyses will be performed on the ARS using a MMRM model (similar to the primary/secondary analyses). Summaries of the continuous variables will include sample size, mean, SD, median, minimum, maximum, LS mean and standard error (SE) of LS mean.

3. Table of Contents

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4. Abbreviations and Definitions

Term	Definition
Adverse event (AE)	Adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AHA	antihyperglycemic agent
ALT/SGPT	alanine aminotransferase (serum glutamic pyruvic transaminase)
ARS	All randomized set
AST/SGOT	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
AUC	Area under the curve
BG	blood glucose
BID	twice daily
CGM	continuous glucose monitoring
CHO	carbohydrate
CI	confidence interval
Complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
Compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
Consent	The act of obtaining informed consent for participation in a clinical trial from subjects deemed eligible or potentially eligible to participate in the clinical trial. Subjects entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
CRP/CRS	Clinical research physician/ Clinical research scientist: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CSII	continuous subcutaneous insulin infusion
DMC	Data monitoring committee
ECG	electrocardiogram

Term	Definition
eCRF	electronic clinical report form: An electronic form for recording study participants' data during a clinical study, as required by the protocol.
Efficacy	Efficacy is the ability of a treatment to achieve a beneficial intended result under controlled conditions.
End of trial (study)	End of trial is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last active subject in the study.
Enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the trial are those who have been assigned to a treatment.
Enter	Subjects entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ET	early termination
FAS	full analysis set
FDA	Food and Drug Administration
FPG	fasting plasma glucose (central laboratory value)
GCP	good clinical practice
GLP-1	glucagon-like peptide-1
HbA1c	glycated hemoglobin A1c
ICF	informed consent form
Informed consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
Institutional Review Board/ Ethical Review Board (IRB/ERB)	A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the subjects participating in a clinical study are protected.
IOB	Insulin-on-board: Active insulin circulating in the body from previous bolus doses
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
ITT	Intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (that is, planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.

Term	Definition
IWRS	interactive web response system
LOCF	last observation carried forward
LS mean	least-squares mean
MDI	multiple daily injections
MDRD	Modification of Diet in Renal Disease
MET	metformin
MMRM	mixed-model repeated measures
NIM	Noninferiority margin
PDM	Personal diabetes manager
PRO	patient-reported outcomes
Randomize	The act of assigning a subject to a treatment. Subjects who are randomized in the trial are those who have been assigned to a treatment.
SAE	serious adverse event
SAP	statistical analysis plan
Screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, diagnostic psychological tests, x-rays, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
SD	standard deviation
SE	standard error
SGLT2	sodium-glucose cotransporter 2
SMBG	self-monitored blood glucose
Subject	An individual who is or becomes a participant in clinical research, either as a recipient of the investigational product(s) or as a control. A subject may be either a healthy human or a patient.
SUSAR	suspected unexpected serious adverse reaction
TDD	total daily dose
TID	three times daily

Term	Definition
TPO	third party organization
Treatment-emergent adverse event (TEAE)	Treatment-emergent adverse event: Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
TRIM-D	treatment-related impact measure for diabetes
TRIM-DD	treatment-related impact measure for diabetes device
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
U-500R	human regular U-500 insulin; Humulin® R U-500 insulin
ULN	Upper limit of normal
US	United States
VAS	visual analog scale
WHO	World Health Organization

5. Introduction

Although human regular U-500 insulin (Humulin® R U-500; U-500R) has been available in the United States (US) market for more than 50 years, its clinical use has increased over the past 5 years due to the worsening epidemics of type 2 diabetes mellitus (T2DM) and obesity (Lane et al. 2009; Segal et al. 2010; Cochran et al. 2014).

According to published clinical reports and expert clinical reviews, high-dose insulin-treated insulin-resistant patients (requiring >200 units of U-100 insulin) have been treated successfully and safely with U-500R by injection, resulting in improved glycemic control (glycated hemoglobin A1c [HbA1c] reductions between 1% and 2%) with uncommon reports of severe hypoglycemia (Neal 2005; Ballani et al. 2006; Lane et al. 2009; Nayyar et al. 2010; Dailey et al. 2010; Quinn et al. 2011; Ziesmer et al. 2012; Boldo and Comi 2012; Reutrakul et al. 2012; Jones and Idris 2013; Hood et al. 2015). U-500R is typically dosed utilizing multiple-daily injections (MDI) with either twice daily (BID) or three times daily (TID) dosing (Humulin R U-500 package insert; de la Peña et al. 2011; Reutrakul et al. 2012). One small (N=28) randomized controlled trial of U-500R was recently published reporting a significant mean HbA1c reduction of 1.0% to 1.7% from baseline to 24-week endpoint (p=0.0001) with no reported episodes of severe hypoglycemia when combined with metformin and/or exenatide (Distiller et al. 2014).

The effect of U-500R begins within 30 minutes, has a peak similar to that observed with human regular U-100 insulin (U-100R), and has a relatively long duration of activity (up to 24 hours) following a single dose as compared with U-100R (de la Peña et al. 2011). Similarly, a U-500R pharmacokinetic/pharmacodynamics simulation modeling study indicated the steady-state basal pharmacokinetic/pharmacodynamics effect from both BID and TID dosing appears to support use of U-500R as insulin monotherapy (de la Peña. 2014). A recently completed randomized, controlled Phase 4 trial (B5K-US-IBHC) comparing TID versus BID U-500R monotherapy over 24 weeks in 325 subjects demonstrated that U-500R as insulin monotherapy is safe and efficacious (HbA1c reduction of 1.1% to 1.2% [Hood et al. 2015]).

Clinical expert reviews recommend MDI delivered TID injections for all dosage ranges of U-500R (Cochran et al. 2005; Lane et al. 2009; Segal et al. 2010; Reutrakul et al. 2012; Cochran et al. 2014). A number of clinical case series (Knee et al. 2003; Schwartz 2004; Lane 2006; Bulchandani et al. 2007; Lane et al. 2010; and Reutrakul et al. 2011) have also reported use of U-500R by continuous subcutaneous insulin infusion (CSII), a practice that may account for approximately one quarter of current U-500R therapy according to recent large retrospective real-world claims database analysis (Eby et al. 2014). These U-500 CSII therapy case series have shown improvements in HbA1c from 1.2% (Lane et al. 2010) to 3.5% (Knee et al. 2003), and a mean reduction of 1.64% in a review by Reutrakul et al. (2012) which reported severe hypoglycemia in 2 (n=55) subjects. The largest and longest case series (N=59; mean duration of follow up 49 months [range: 12 to 114 months]; Lane et al. 2013) reported 1.0% mean decrease in HbA1c (from 8.3% to 7.3%) sustained over 66 months of U-500 CSII therapy with severe hypoglycemia rate (defined by blood glucose [BG] ≤50 mg/dL or "blood glucose requiring treatment [regardless of value]") at 0.1 episodes per patient per year.

The aforementioned studies with U-500R in CSII therapy lacked controls, were predominately retrospective, and included a small number of subjects (<60 subjects per study; total: 114 subjects). Additionally, delivery by CSII in currently marketed insulin pumps requires dose transition to "U-100 insulin pump units" (one-fifth of actual U-500R dose per volume; Lane et al. 2006; Lane et al. 2009; Lane et al. 2010; Segal et al. 2010; and Cochran et al. 2014), which has the potential to result in dosing confusion and medication errors.

In summary, there is a clear clinical need to study the use of U-500 by CSII in a prospective, randomized clinical trial. Thus, Lilly has developed protocol B5K-MC-IBHD to evaluate the efficacy and safety of U-500R delivered by CSII as compared to U-500R MDI delivered TID. The CSII system uses a novel insulin pump device that is not commercially available with internal software appropriate for U-500 insulin dosage in U-500 insulin units.

Input obtained from T2DM patient interviews for this protocol development indicates a wide spectrum of knowledge and ability to utilize CSII features by patients. The current trial design was developed to meet the needs of high-dose insulin-requiring patients who could benefit from improved glycemic control with CSII. The unique properties of U-500R demonstrate that it can be used as both basal and bolus therapy in MDI or CSII regimens (CSII 50% basal and 50% bolus) (Hirsch 2010; de la Peña et al. 2011; Hood et al. 2015). The functionality of the OmniPod U-500 system in the trial allows for those patients requiring simpler interface, as well as those who would benefit from increased individualization. For example, the CSII treatment arm will initially utilize 2 basal rates for simplicity but allow for individualization up to 4 basal rates if needed. Additionally, a variety of bolus options will be available including boluses based on carbohydrate (CHO) counting, fixed meal doses, or doses based on meal sizes (small, medium, or large).

It is estimated that 10% to 18% of patients treated with U-500R are on concomitant noninsulin injectable therapy, including glucagon-like peptide-1 (GLP-1) receptor agonist therapy (Eby et al. 2013, 2014 and Data on File). Although the percentage of U-500R used in combination with sodium-glucose co-transporter 2 (SGLT2) inhibitors is unknown, combination of SGLT2 inhibitors with U-100 insulin has risen by 4-fold to 1.4% (July 2013 to April 2014 [IMS Data on File]). GLP-1 receptor agonists and SGLT2 inhibitors have been used in insulin-sparing and weight attenuating strategies and have shown clinical utility in combination with U-500R or U-100 insulin (Lane et al. 2011; Rosenstock et al. 2014). Two study population groups (Groups A and B) will be stratified by nonuse or use of these therapies. Subjects in each group will be randomly assigned equally between treatment arms. Study population Group A will include patients who are not using GLP-1 receptor agonists or SGLT2 inhibitors. The study population Group B will include patients who are using GLP-1 receptor agonists or SGLT2 inhibitors. Group A will be the primary analysis population. Combined Groups A and B will be included in the key and other secondary objectives. The use of GLP-1 receptor agonists or SGLT2 inhibitors is also intended for exploratory analyses.

Appropriate testing supporting use of the U-500R in the OmniPod U-500 Insulin Management System in clinical trials has been completed. More detailed information about the known and expected benefits and risks of U-500R may be found in the U-500R package insert. More

detailed information regarding the use of the OmniPod U-500 system may be found in the OmniPod U-500 Insulin Management System User Guide.

6. Objectives

6.1. Primary Objective

The primary objective is to demonstrate the change in HbA1c of U-500R administered by CSII is noninferior to U-500R administered by MDI therapy from baseline to the 26-week in high-dose insulin-requiring patients 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 high-dose U-500R insulin (MDI) without use of GLP-1 receptor agonists or SGLT2 inhibitors and with or without other insulins/antihyperglycemic agents (AHAs). This population is referred to as Group A.

The following 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 two-sided 5% level by the graphical approach, which will be discussed in detail in the Statistical Analysis Plan (SAP).

6.2. Secondary Objectives

6.2.1. 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 7.1]) 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 7.1]) 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%.

6.2.2. 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 the total study population (Groups A and B) 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 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.

6.3. Exploratory Objectives

- 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.

7. Investigational Plan

7.1. Summary of Study Design

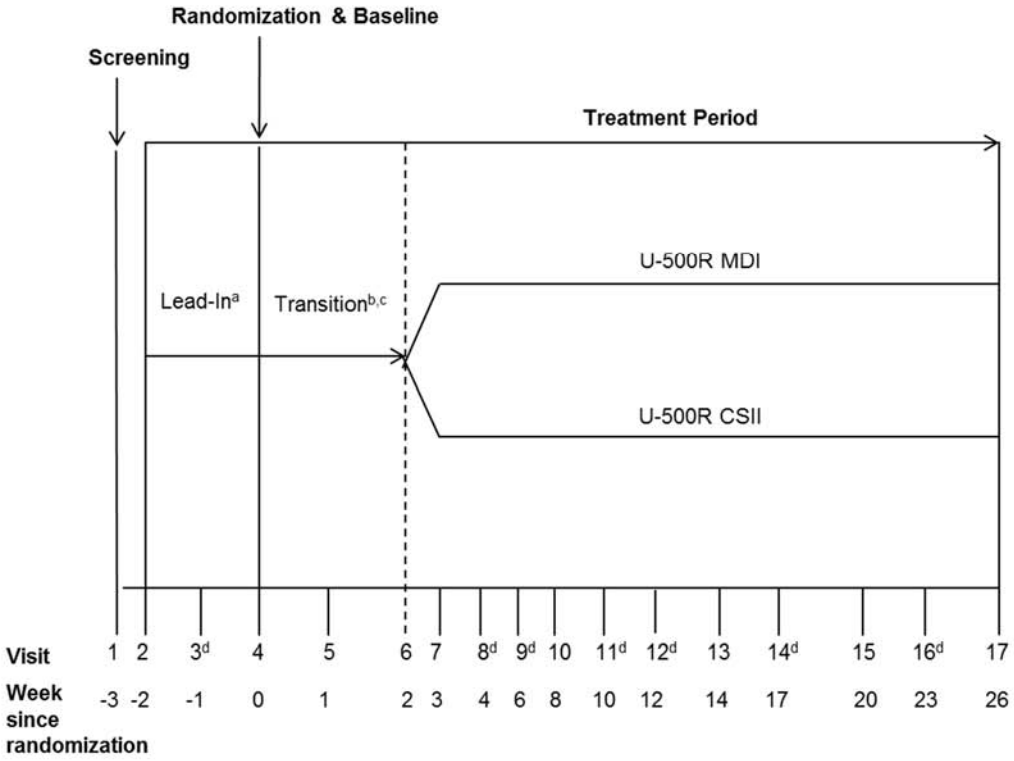
Study B5K-MC-IBHD is a Phase 3b, multicenter, randomized, open-label, parallel clinical trial comparing U-500R administered by CSII (OmniPod U-500 system) to U-500R administered MDI in high-dose insulin-requiring patients with T2DM who have inadequate glycemic control on high-dose non U-500R (>200 and ≤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.7.1), 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 two 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.7.1. 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.7.1 illustrates the study design.



Abbreviations: CSII = continuous subcutaneous insulin infusion; MDI = multiple daily injections.

[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.7.1. Illustration of study design for Clinical Protocol B5K-MC-IBHD.

7.1.1. Diaries

As indicated in the study schedule (Attachment 1), starting at Visit 1 (Week -3) subjects will be given a study diary at each office visit and instructed to record 4- point, and 7-point SMBG values, insulin doses, hypoglycemic episodes, adverse events (AEs), illnesses, concomitant medications, infusion site changes, and reasons for nonroutine infusion site changes (post-randomization and transition to U-500R) through the end of participation in the study or at ET, if applicable. Investigators should encourage subjects to measure BG values during the symptoms of hypoglycemia and record BG values in their study diaries. Investigative staff will review the study diaries and transfer data to electronic case report forms (eCRFs) at each office visit beginning at Visit 2 (Week -2), with the exception of 4-point SMBG values. Investigative staff will also record any additional AEs and episodes of hypoglycemia that are reported by subjects and that have occurred since the previous entry on the eCRFs, even when the event was initially not entered into the study diary. Study diaries are considered source information and are to be returned to the investigator (or designee) at each office visit.

7.1.2. Type 2 Diabetes Lifestyle Counseling

Per the study schedule (Attachment 1), qualified medical staff will provide diabetes management counseling including diet, exercise, and education about the signs, symptoms, and treatment of hypoglycemia, should it occur. Subjects should continue their usual exercise habits and generally follow stable meal plans (consistent meal size and time of day) throughout the course of the study. Instruction on how to assess CHO content and caloric content of meals may be incorporated into the counseling. Dietary counseling may be reviewed throughout the study as needed. Subjects are not to initiate a weight loss program during the trial.

7.1.3. Blood Glucose Monitoring

The U-500R dosage will be based on subjects' individual needs, as assessed by SMBG results obtained from monitoring at home. Site personnel may request additional BG monitoring from subjects and/or assess BG values at other times during the study in order to make dose adjustment decisions. Subjects should record both 4- and 7-point SMBG measurements, as well as insulin doses, in the subject diary provided.

7.1.3.1. 4-Point SMBG

Subjects will be instructed to record 4-point SMBGs daily beginning with the screening period. The 4-point SMBG consists of BG measurements at:

- Pre-morning meal (fasting)
- Pre-midday meal
- Pre-evening meal
- Bedtime (at least 2 hours after the evening meal)

7.1.3.2. 7-Point SMBG

All subjects will be instructed to record 7-point SMBG profiles on any 2 nonconsecutive days in the 2 weeks prior to visits as outlined in the study schedule (Attachment 1); profiles should include weekend day(s), if possible. The timing of the 7-point SMBG measurement over a 24-hour period is as follows:

- Pre-morning meal (fasting)
- 2 hours after the morning meal
- Pre-midday meal
- 2 hours after the midday meal
- Pre-evening meal
- 2 hours after the evening meal
- 0300 hours

7.1.3.3. 0300 Hours SMBG

Subjects will also be instructed to record their 0300 hours BG within 48 hours of each increase in insulin dose titration at telephone and office visits (preferably the first night after the dosage adjustment). The investigator or site personnel will ask the subjects about these BG measurements and the **investigator** will recommend dosage titrations based on glucose targets within the CSII (Section 9.8.1.1) and MDI (Section 9.8.2.1) algorithms during telephone and office visits.

7.1.4. Screening Period

This study contains a 1-week screening period between Visit 1 (Week -3) and Visit 2 (Week -2), which allows for the evaluation and assessment of potential subjects' eligibility against the inclusion and exclusion criteria (Sections 8.1 and 8.2, respectively). Subjects may be prescreened for inclusion/exclusion criteria that are available from their subject files, including any laboratory values on file collected within the previous 30 days, in compliance with local privacy regulations. Subjects will continue their pre-study insulin and AHA regimens and doses (per inclusion/exclusion criteria in Sections 8.1 and 8.2). Refer to Attachment 1 for the study schedule of screening period activities.

7.1.5. Lead-In Period

Eligible subjects will begin a 2-week lead-in period at Visit 2 (Week -2) according to the Study Schedule (Attachment 1). The lead-in period is intended to stabilize HbA1c related to study effect (Gale et al. 2007) and verify insulin dose. Subjects entering the trial at Visit 1 will continue their pre-study insulin regimen. Subjects will also continue taking pre-study AHA regimens and doses (per inclusion/exclusion criteria in Sections 8.1 and 8.2) and should not discontinue or change doses during the study, apart from specific instructions provided in Section 9.11.

7.1.6. Randomization

Study subjects who have completed all screening procedures will be randomized at a 1:1 ratio to the two treatment arms (U-500R CSII or MDI) using interactive web-response system (IWRS) at Visit 4 (Section 9.6).

A review of subjects' understanding of daily glucose monitoring and emphasis on adherence, 4-point and 7-point SMBG profile, use of glucose meters, hypo- and hyperglycemia, and completion of subjects' diary will be conducted.

7.1.7. Treatment Period

At Visit 4 through Visit 17 or ET, subjects will be treated with U-500R based on titration algorithms. The total treatment period for this study will be 26 weeks (2 week transition to U-500R MDI administered TID, 12 weeks titration and 12 weeks maintenance U-500R CSII or MDI).

During the Treatment Period, Visits 8, 9, 11, 12, 14, and 16 will be telephone visits only and subjects will not be required to return to the study site. At office visits (Visits 5, 6, 7, 10, 13, 15,

and 17), clinical assessments and required procedures should occur as outlined in the Study Schedule (Attachment 1). Adverse event and product complaint collection should occur at each office and telephone visit.

Apart from scheduled telephone visits, per the Study Schedule (Attachment 1), subjects will be instructed to call the study site office if a serious adverse event (SAE) or device-related event occurs, or for any concern at any time. Specific reasons may include but are not limited to: hospital admission for any reason, persistent or severe hypoglycemia, recommendations for changes of medication from another provider, injection device or study glucose meter malfunction, questions about study treatment and dose changes, or scheduled surgical or dental procedures.

Subjects will continue taking noninsulin pre-study AHAs (per inclusion/exclusion criteria in Sections 8.1 and 8.2 and allowed concomitant therapies in Section 9.11) and should not discontinue or change doses during the study.

7.1.7.1. Transition to U-500R MDI

A 2-week transition period is included in the 26-week treatment period and will follow randomization. The transition period is intended to transition all subjects safely from their current insulin regimen to U-500R TID 40:30:30 (Section 9.5), and to titrate U-500R according to the TID algorithm (Section 9.8.2.1). The highest 24-hour TDD from the past 3 days will be utilized for calculation of the U-500R TID dose and the dose split into the ratio of 40:30:30. Those subjects already on U-500R TID at entry can continue their pre-entry U-500R TID proportions at the discretion of the investigator. At Visit 6 through Visit 17 or ET, subjects will be treated with either U-500R CSII (Section 9.8.1.1) or U-500R MDI delivered TID (Section 9.8.2.1) based on titration algorithms and the treatment to which they are randomized.

7.1.7.2. U-100 Insulin Syringe for Administering U-500R MDI

All subjects will receive training on the appropriate use of U-100 insulin syringes for drawing up and administering correct doses of U-500R, including the conversion of insulin units of U-500R to the unit markings (one-fifth of actual volume) on the U-100 insulin syringe (Section 9.7.1).

7.1.7.3. CSII Pump Training

Subjects assigned to U-500R CSII treatment will receive training on the OmniPod U-500 system at 2 visits (Visit 5 [Week 1] and Visit 6 (Week 2). At Visit 5, subjects will be introduced to the basics of pump usage (ie, basal rates, boluses, and filling Pods). At Visit 6, subjects will receive hands-on training on the U-500 OmniPod System. Additional subject training can be considered at the investigator's discretion after consulting with Lilly clinical research physician (CRP)/clinical research scientist (CRS) (Section 9.7.2).

7.2. Discussion of Design and Control

This is a randomized, open-label, parallel study comparing U-500R administered by CSII (OmniPod U-500 system) to U-500R administered by MDI in high-dose insulin-requiring patients with T2DM who have inadequate glycemic control on existing 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. Delivery of U-500R insulin by CSII in currently marketed insulin pumps requires dose conversion to "U-100 pump units" (one-fifth of U-500R insulin dose per volume), which potentially could result in dosing confusion. The OmniPod Insulin Management System for use with U-500 insulin (OmniPod U-500 system) software has been developed so that 1 unit of insulin is delivered with every 4 pulses of the drive mechanism (for example, the OmniPod U-500 system would deliver 0.25 units per pulse compared to 0.05 units per pulse in the conventional U-100 OmniPod insulin pump). The volume delivered in 1 pulse is the same for the U-100 and U-500 insulin pumps; thus due to higher concentration, fewer pulses are required by the U-500 pump to deliver the same insulin dose (4 pulses for 1-unit for U-500 insulin versus 20 pulses for 1-unit for U-100 insulin).

The majority (86%) of patients currently using U-500R have T2DM (Eby et al. 2013). Because patients with type 1 diabetes mellitus (T1DM) constitute a small proportion of U-500R users and could have a different response to the algorithms and/or CSII delivery system, they are excluded from this study.

The total treatment period for this study will be 26 weeks. The 26-week duration of treatment in this study was selected because it allows enough time for insulin therapy to be intensified, and permits sufficient time to show glycemic improvement and stabilization as measured by HbA1c, FPG, SMBG values, and TDD.

After Visit 1 (screening), subjects who meet all of the inclusion criteria (Section 8.1) and none of the exclusion criteria (Section 8.2) will remain on their pre-study treatment for a 2 week lead-in period at Visit 2 (Week -2). This lead-in period is intended to stabilize HbA1c related to study effect (Gale et al. 2007) and verify actual insulin dose. Following the lead-in, subjects will be randomized at Visit 4 (Week 0) in an open-label fashion based on a 1:1 ratio to U-500R treatment by MDI or U-500R treatment by CSII. A 2-week transition to U-500R by MDI administered TID, regardless of insulin or combination thereof at Visit 2 (Week -2) (Section 9.5) will begin after randomization (Visit 4 [Week 0]) utilizing the TID algorithm with weekly titrations (Section 9.8.2.1). The transition period is to ensure safe transition to U-500R insulin from entry insulin (as applicable). After completion of the 2-week transition period, 24-weeks of U-500R delivered by MDI versus CSII will begin.

The primary and key secondary objectives will be assessed in subjects from Group A (without use of GLP-1 receptor agonists or SGLT2 inhibitors) and combined for the total study population Group A and Group B (those who use GLP-1 receptor agonists or SGLT2 inhibitors).

The study will be performed open-label since blinding of the investigators, subjects, and study site personnel could not be accomplished given the differing modes of delivery of U-500R (CSII versus MDI). To minimize bias, aggregate review of summary data by the study team (that is, CRP/CRS overseeing the global conduct of the study, statisticians, and statistical analysts) will remain blinded until after the final database is locked (Section 9.10).

8. Study Population

Individuals who do not meet the inclusion criteria for participation in this study (screen failure) may be re-screened once. The interval between screen and re-screen should be at least 2 weeks. When re-screening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number.

Entered subjects who meet all inclusion criteria ([1] through [7]) and are not excluded by exclusion criteria ([8] through [28]) will initiate the lead-in period at Visit 2 (Week -2).

Prior to randomization at Visit 4, all subjects will be re-confirmed for inclusion criteria [1], [2] and [7] and exclusion criteria [18].

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

8.1. Inclusion Criteria

Subjects are eligible to be included in the study only if they meet all of the following criteria:

[1] Diagnosed with T2DM (World Health Organization [WHO] Classification of Diabetes [Attachment 3]).

[2] Current TDD >200 but ≤600 units of non U-500R insulin/analog (basal; premixed; or basal/bolus by any injection device [MDI; pens and/or syringe/vial or CSII]) and/or U-500R by MDI with syringe and vial for ≥3 months at entry.

- If TDD of U-500R and other insulins are combined, then insulin other than U-500R not to exceed 25% of TDD.

[3] HbA1c ≥7.5% and ≤12.0% as measured by the central laboratory at Visit 1.

[4] Aged ≥18 to ≤85 years.

[5] Body mass index ≥25 but ≤50 kg/m^2.

[6] Have a history of stable body weight (not varying by greater than 5% for at least 3 months prior to study entry).

[7] Concomitant AHA therapy may include metformin (MET), dipeptidyl peptidase-4 inhibitors (sitagliptin, saxagliptin, linagliptin, and alogliptin), and/or pioglitazone (doses ≤30 mg/day). Subjects' AHA therapy must have been stable for ≥3 months See exclusion criteria [18] and [19] for excluded medications.

- Approximately 64 to 96 subjects using GLP-1 receptor agonists (albiglutide, dulaglutide, or liraglutide) or SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin) will be enrolled in Study Group B. (GLP-1 receptor agonists must have been stable for ≥4 months). After the enrollment of this group is completed, subjects using GLP-1 receptor agonists or SGLT2 inhibitors will no longer be enrolled in the study. 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.

8.2. Exclusion Criteria

Subjects will be excluded from study if they meet any of the following criteria:

[8] Diagnosed with T1DM or other types of diabetes apart from T2DM (WHO Classification of Diabetes Attachment 3; ADA 2014).

[9] Have obvious clinical or radiographic signs or symptoms of liver disease (except nonalcoholic 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.

[10] Have chronic kidney disease Stage 4 and higher (estimated glomerular filtration rate <30 mL/minute/1.73m^2 as measured by Modification of Diet in Renal Disease [MDRD] formula) (NKF 2007) or history of renal transplantation.

[11] 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.

[12] Have received U-500R insulin by CSII in the 3 months prior to Visit 1.

[13] Have had a blood transfusion or severe blood loss within 3 months prior to Visit 1 or have known hemoglobinopathy, hemolytic anemia, or sickle cell anemia that is known to interfere with HbA1c measurement.

[14] Have known allergy to human insulin preparations or excipients contained in these products or prior history of suspected antibodies to human insulin.

[15] 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.

[16] Have an irregular sleep/wake cycle (for example, subjects who sleep during the day and work during the night), in the investigator's opinion.

[17] Intend to participate in an extended period of fasting during the study period (for religious or other purposes).

[18] 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 (for example, for MET: serum creatinine ≥1.4 mg/dL in women or ≥1.5 mg/dL in men).

[19] Have used any weight loss drugs (for example, prescription drugs; lorcaserin, orlistat, phentermine, phentermine/topiramate, naltrexone/bupropion, or over-the-counter weight loss medications) in the 3 months prior to Visit 1.

[20] Have a history of bariatric surgery including Roux-en-Y gastric bypass surgery, gastric banding, and/or gastric sleeve.

[21] Have a history of an active or untreated malignancy, or in remission from a clinically significant 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 a malignancy occurred >5 years ago, subject is eligible with documentation of disease-free state since treatment).

[22] Significant hearing loss and/or vision impairment deemed by the investigator to interfere with the safe use of OmniPod U-500 system.

[23] Have cardiac disease with functional status that is New York Heart Association (NYHA) Class III or IV per New York Heart Association Cardiac Disease Functional Classification [Attachment 4] or have congestive heart failure requiring pharmacologic treatment.

[24] 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.

[25] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[26] Are Lilly or Insulet employees, or are employees of third party organizations (TPOs) involved in study that require exclusion of their employees.

[27] Are currently enrolled in, or discontinued within the last 30 days, from a clinical trial involving an investigational product or nonapproved 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.

[28] 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.

8.2.1. Rationale for Exclusion of Certain Study Candidates

Exclusion criterion [8] ensures that subjects with T1DM or other types of diabetes (except T2DM) will be excluded from the study due to the potentially different response to the algorithms and/or device. Exclusion criteria [9], [10], [13], [14], [16], [17], [21], and [23] represent clinical situations that may prevent subjects from completing the protocol, or may influence the efficacy or safety of study regimens, or are serious conditions that pose a risk for morbidity and mortality. Exclusion criterion [11] addresses the potential difficulty of distinguishing if severe hypoglycemia is related to study drugs, or to counter-regulatory deficiencies, or to the natural history of the disease in subjects with recurring episodes. Exclusion criterion [12] relates to the potential of sub-optimal glycemic control and possible changes in quality of life when changing from U-500R CSII therapy. Exclusion criterion [15] relates to the negative effect of steroid therapy on the management of diabetes and need for altered dosing titration of insulin. Exclusion criterion [18] excludes medications that are restricted by product label (exenatide), may cause HbA1c-lowering not attributable to the study insulin regimens or the combination of AHAs being studied, or which could confound interpretation of the results, or may influence the safety of study regimens. Exclusion criteria [19], [20] and [27] prevent a situation in which positive or negative outcomes may not be clearly attributable to the regimens in this study. Exclusion criterion [22] would prevent the subject from safely using the OmniPod U-500 system. Exclusion criterion [24] ensures the safety of unborn or newborn children. Exclusion criteria [25] and [26] reduce potential bias due to conflict of interest. Exclusion criterion [28] excludes subjects who may be unwilling or unable to perform study procedures per protocol instructions for their safety.

8.3. Discontinuations

8.3.1. Discontinuation of Inadvertently Enrolled Subjects

The criteria for enrollment must be followed explicitly. If the investigator site identifies a subject who did not meet enrollment criteria and who was inadvertently enrolled, the sponsor must be notified. If the sponsor identifies a subject who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the sponsor CRP/CRS and the investigator to determine whether the subject may continue in the study, with or without study treatment. Inadvertently enrolled subjects may be maintained in the study and on study treatment when the Lilly CRP/CRS agrees with the investigator that it is medically appropriate for that subject. The subject may not continue in the study with or without study treatment if the Lilly CRP/CRS does not agree with the

investigator's determination it is medically appropriate for the subject to continue. The investigator must obtain documented approval from the Lilly CRP/CRS to allow the inadvertently enrolled subject to continue in the study with or without study treatment.

8.3.2. Discontinuation of Study Treatment

Subjects will be discontinued from the study treatment in the following circumstances:

- If Exclusion Criteria [9] (with the exception of the hepatic laboratory values; Section 10.4.5), [11] to [15], [18] to [21], [23] and [24] are observed or develop after study enrollment, the subject will be discontinued from the study treatment at the next visit or sooner.
- If in the investigators judgment, the subject is not at least 80% compliant with study treatment (i.e.; investigator recommended dose adjustments based on algorithms)
- If the subject is off study medication for more than 7 consecutive days during the study treatment period.

In the event that the subject is discontinued from the study treatment, the investigator should encourage the subject to remain in the study for continued safety monitoring.

8.3.3. Subject Discontinuation from the Study

If exclusion criterion [25] through [28] is observed or develops after entry or enrollment, the subject will be discontinued from the study at the next site visit or sooner in the event of a safety exclusion criterion.

Subjects who discontinue the study early will have ET procedures performed as shown in the Study Schedule (Attachment 1). For information as to how efficacy and safety analyses will be conducted for subjects who are discontinued from study treatment, see Sections 12.2.3 and 12.2.10, respectively.

The subject may be discontinued from the study if:

- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Investigator decision
    - The investigator decides that the subject should be discontinued from the study (this can be for safety reasons, such as for recurrent hypoglycemia, or it can be for any reason).
    - If the subject, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent.
- Subject decision
    - The subject requests to be withdrawn from the study.

- Sponsor decision
    - Lilly or its designee stops the study or stops the subject's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).
- Adverse event
    - If the investigator decides that the subject should be withdrawn because of a SAE, treatment emergent adverse event (TEAE), or a clinically significant laboratory value, study treatment is to be discontinued and appropriate measures are to be taken. Lilly or its designee is to be alerted immediately. Refer to Safety Evaluations Section 10.4.

8.3.4. Subjects Lost to Follow-Up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact subjects who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Site personnel, or an independent third party, will attempt to collect the vital status of the subject within legal and ethical boundaries for all subjects randomized, including those who did not get study treatment. Public sources may be searched for vital status information. If vital status is determined, this will be documented and the subject will not be considered lost to follow up.

Lilly personnel will not be involved in any attempts to collect vital status information.

8.3.5. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ethical review board (ERB) of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

8.3.6. Discontinuation of the Study

The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

9. Treatment

9.1. Treatments Administered

This study involves a comparison of U-500R administered by CSII with U-500R administered by MDI. Table IBHD.9.1 shows the treatment regimens.

Table IBHD.9.1. Treatment Regimens

Regimen	Dose
U-500R CSII	Per titration algorithm (continuous infusion, injectable solution)
U-500R MDI	Per titration algorithm (TID, injectable solution)

Abbreviations: CSII = continuous subcutaneous insulin infusion; MDI = multiple daily injections; TID = three times daily.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the investigational agent(s) to the subject/site personnel,
- verifying that subject clearly understands instructions and is able to demonstrate understanding, maintaining accurate records of study treatment dispensing and collection, and returning all unused medication or devices to Lilly or its designee at the end of the study.

Note: In some cases, sites may destroy the material if, during the investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical trial materials. In all other cases, the site has to return used or unused material to Lilly or designee.

Subjects will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with study treatment or drug delivery system so that the situation can be assessed.

9.2. Materials and Supplies

Subjects should continue taking their noninsulin pre-study AHA doses throughout the study, as applicable. Pre-study AHAs must be used as described in their respective product labeling.

Supplies and appropriate instructions for use will be provided for both treatment groups beginning at screening Visit 1 (Week -3). Study drug and additional supplies will be provided at Visits 4, 5, and as needed thereafter per the Study Schedule (Attachment 1).

Subjects will be assigned to treatment arm at randomization Visit 4 (Week 0). Appropriate pump training will be provided for the CSII group (Section 9.7.2). The OmniPod U-500 system

supplies for infusion including PDM and Pod with fill syringe will be provided at Visit 6 (Week -2) and as needed thereafter per the study schedule.

U-500R will be provided in 20-mL vials (10,000 U) for use by CSII or MDI. Unopened U-500R vials or U-500R vials not in-use should be stored in a refrigerator (2° to 8°C [36° to 46°F]), but not in the freezer. Once opened, the U-500R vial can be kept unrefrigerated as long as it is kept as cool as possible (below 30°C [86°F]) and away from heat and light. In-use vials must be used within 40 days or be discarded, even if they still contain U-500R.

The respective labeling information will be provided with the insulin pump and supplies, the disposable syringes, and the study drug as applicable. In addition, a commercially available BG meter will be provided with necessary supplies and instructions at Visit 1 (Week -3). Clinical trial materials will be labeled according to the respective country's regulatory requirements.

Table IBHD.9.2. Study Devices

Regimen	Device	Device Details
U-500R CSII	OmniPod U-500 system[a]	CSII
U-500R MDI	BD U-100 insulin syringe and needle	0.5 mL syringe for ≤250-U dose; or 1.0 mL syringe for >250-U dose; 31 gauge; 6 mm length needle

Abbreviations: BD = Becton Dickinson; CSII = continuous subcutaneous insulin infusion; MDI = multiple daily injections; U = unit.

[a] The OmniPod U-500 system is an investigational device.

9.3. Method of Assignment to Treatment

Subjects will continue on their pre-study insulin regimens until Visit 4 (Week 0). After re-confirmation of eligibility, subjects who meet specific criteria (Section 8) for enrollment will be randomized at Visit 4 (Week 0) to open-label treatment with U-500R administered by one of two treatment regimens: MDI or CSII. However, subjects randomized to CSII will not initiate U-500R administered by CSII until transition to U-500R is complete (Section 9.7). Assignment to treatment arms will be determined by a computer-generated random sequence using an IWRS.

9.4. Rationale for Selection of Doses in the Study

Protocol IBHD dosing transition to U-500R MDI and titration regimens for the CSII and MDI treatment groups are guided by initial insulin TDD (based on the highest TDD recorded in the 3 days before Visit 2), screening HbA1c (Visit 1), subsequent glucose monitoring, literature expert reviews (Lane 2006; Lane et al. 2009; Hirsch 2010, Lane et al. 2010; Segal et al. 2010; Reutrakul et al. 2012), efficacy and safety results from one Phase 4 clinical study (B5K-US-IBHC [Hood et al, 2015]), results from simulations performed using a systems physiology model of diabetes (Entelos PhysioLab® Modeler) based on data from previous pharmacodynamics/pharmacokinetics studies (de la Peña et al. 2011) of U-500R and U-100 Humulin regular insulin) and on expert protocol consultant advice.

Fasting and bolus for CSII and MDI therapy plasma-equivalent glucose target ranges are 80 to 140 mg/dL. Recommended administration of U-500R bolus doses, within approximately

30 minutes before meals by CSII or MDI dosing, is based on label advice and recent pharmacodynamics/pharmacokinetics study results in obese, healthy subjects that demonstrate both prandial and basal activity of U-500R (de la Peña et al. 2011). Administration of U-500R bolus doses 15 minutes before meals will be assessed in a subset of subjects participating in the continuous glucose monitoring (CGM) addendum to demonstrate glycemic impact. If the shorter bolus time period is found to be equally efficacious, there may be a potential benefit on adherence.

9.5. Lead-in Period

The 2-week lead-in period of the trial includes the interval between Visit 2 and Visit 4.

Subjects' current diet (particularly caloric intake) and exercise levels will be reviewed during lead-in and at subsequent visits throughout the study, as needed, to assess adherence to the lifestyle advice discussed at Visit 2 (Week -2) as part of subject training and education. Subjects should be encouraged to eat 3 meals a day plus a snack before bedtime (21 grams CHO Extend Bar®, Extend Nutrition, St. Louis, MO or equivalent) to support U-500R dosing per CSII or MDI during the study.

Subjects will continue taking prestudy AHAs and doses (per inclusion/exclusion criteria in Sections 8.1 and 8.2 and allowed concomitant therapies in Section 9.11) and should not discontinue or change doses during the study. Refer to Study Schedule for details of events (Attachment 1).

9.6. Randomization

At Visit 4 (Week 0), if subjects have been re-confirmed for trial eligibility (Section 8), they will be randomized at a 1:1 ratio to the two treatment arms (CSII or MDI) using IWRS (Section 9.3). Subjects will be stratified by entry HbA1c ≥8.5% or <8.5%, nonusers versus users of GLP-1 receptor agonists or SGLT2 inhibitors, and U-500R at entry versus other insulins.

Subjects in the study will continue taking noninsulin pre-study AHA regimens (per inclusion/exclusion criteria in Sections 8.1and 8.2) and allowed concomitant therapies. Subjects should not discontinue or change doses during the study (Section 9.11). Subjects will transition to U-500R MDI for 2 weeks and then initiate 24 weeks of CSII or MDI treatment (Section 9.7).

Subjects who discontinue prior to randomization will be considered screen failures. No ET activities will be applicable.

9.7. Transition to U-500R MDI

All subjects will administer U-500R MDI delivered TID (40:30:30 unless otherwise noted) during the transition period (Weeks 0-2). Transition to U-500R MDI will follow the criteria below in Table IBHC.9.3. Subjects will have their insulin adjusted weekly by the investigator using the algorithm from Section 9.8.2.1.

Table IBHC.9.3. Transition from entry insulin to U-500R MDI

Insulin Regimen (Screening)	HbA1c (Screening)	Mean SMBG (Screening to Week -2)	Conversion from Screening TDD to U-500R TID Dose
Insulin with or without U-500R	>8%	>183 mg/dL	1:1
Insulin with or without U-500R	>8%	≤183 mg/dL	Reduce TDD by 20%
Insulin with or without U-500R	≤8%	--	Reduce TDD by 20%
U-500R only	--	--	1:1

Abbreviations: HbA1c = hemoglobin A1c; SMBG=self-monitored blood glucose; MDI = multiple daily injections; TID= three times daily; TDD=total daily dose.

Subjects treated with U-100 and/or other concentrated insulin (with or without U-500R) at screening Visit 1 (Week -3) with HbA1c levels >8% and a mean SMBG (recorded prior to Visit 4 [Week 0]) value >183 mg/dL (corresponding to HbA1c value of >8.0% [estimated average glucose; Nathan et al. 2008]) at Visit 4 should be transitioned to U-500R using 1:1 dosage conversion.

Subjects treated with U-100 and/or other concentrated insulin (with or without U-500R) at screening Visit 1 (Week -3) with HbA1c levels >8% and a mean SMBG (recorded prior to Visit 4 [Week 0]) value ≤183 mg/dL (corresponding to HbA1c value of ≤8.0%) at Visit 4, should transition by reducing their U-500R TDD by 20%.

Subjects treated with U-100 and/or other concentrated insulin (with or without U-500R) at screening Visit 1 (Week -3) with HbA1c ≤8% should transition to U-500R at Visit 4 (Week 0) by reducing their U-500R TDD by 20%, regardless of SMBG value.

Subjects treated with U-500R insulin only at screening Visit 1 (Week -3) should transition to U-500R TID with proportion 40:30:30 using a 1:1 dosage conversion at Visit 4 (Week 0), regardless of HbA1c and/or SMBG. Those subjects already on U-500R TID at entry can continue their pre-entry U-500R TID proportions at the discretion of the investigator. Investigators may also deviate from the proportion, if deemed necessary, for the safety or well-being of the subject (that is, due to a safety concern). Any major deviation from the recommended proportion must be discussed with Lilly CRP/CRS.

9.7.1. Dosing Using U-100 Insulin Syringes

The units marked on a U-100 insulin syringe do not accurately reflect the unit dose of U-500R insulin because U-500R is 5 times more concentrated than U-100 insulin, and thus only one-fifth of the volume is needed to give an equivalent dose to U-100 insulin. Site personnel should instruct subjects on the dose conversion of calculated U-500R to the U-100 insulin syringe unit markings (examples below and conversion charts are also provided in the U-500R package insert and Subject Information on U-500R).

The U-100 insulin 0.5 mL syringes should be used for administration for all U-500R doses ≤250 U. All U-500R doses >250 units should be administered using 1.0 mL U-100 insulin syringes.

For example:

- 155 units of U-500R has a volume equivalent to 31 units markings on a 0.5 mL U-100 insulin syringe (155 divided by 5=31).
- 100 units of U-500R has a volume equivalent to 20 units markings on a 0.5 mL U-100 insulin syringe (100 divided by 5=20).
- 300 units of U-500R has a volume equivalent to 60 units markings on a 1.0 mL U-100 insulin syringe (300 divided by 5=60).

9.7.2. CSII Training

Subjects randomized to the CSII treatment arm will be trained on the use of the OmniPod U-500 system after randomization at Visits 5 and 6 (Weeks 1 and 2). CSII training will include but not be limited to pre-pump training regarding basal rates and bolus dosing, initial PDM and Pod setup, setting basal rates (including temporary basal rate) and boluses (CHO counting, fixed dosages or meal sizes), and responding to hazard alarms. The OmniPod U-500 system basics of pump usage (ie, basal rates, boluses, and filling Pods) will be introduced to subjects at Visit 5 (Week 1) and the hands on training will occur at Visit 6 (Week 2) (Section 7.1.7.3.).

9.7.3. Intensified Dose Titration Period

The 12-week intensified dose titration period of the trial will extend from Visit 6 (Week 2) to Visit 13 (Week 14) and will include **investigator-driven** dosage titration according to the titration algorithms (Sections 9.8.1.1 and 9.8.2.1) at weekly intervals starting on Visit 6 through 8 (Weeks 2 through 4) and biweekly starting at Visit 9 through 13 (Weeks 6 through 14) (Attachment 1). Additional dosage titrations per algorithms may be made more frequently if needed per investigator's judgment during this period.

9.7.4. Maintenance Dose Titration Period

The 12-week maintenance dose titration period of the trial will extend from Visit 13 (Week 14) to the final visit, Visit 17 (Week 26) or ET visit. Dose titrations by the **investigator** will be completed in an identical manner to those during the intensified dose titration period (Sections 9.8.1.1 and 9.8.2.1) but will be at 3-week intervals (Attachment 1). Additional dosage titrations per algorithms may also be made more frequently if needed per investigator's judgment during this period.

9.8. Treatment Periods

9.8.1. CSII

The OmniPod U-500 system is designed to deliver U-500 insulin in insulin units without converting to U-100 insulin 'pump units' (Section 7.2). Beginning at Visit 6 (Week 2), all CSII subjects will be instructed to change their OmniPod U-500 system Pod every 2 to 3 days (depending on TDD) during the treatment period. Subjects will be instructed to inspect Pod cannula insertion sites for signs of redness, swelling, or leakage and to respond to any CSII alarms (Bolderman et al. 2013).

For subjects randomized to CSII:

- The OmniPod U-500 system Pod should be filled in the clinic with U-500R during Visit 6.
- The highest 24-hour TDD from the past 3 days will be utilized for calculation of the CSII doses.
- 50% of the TDD will be basal split into 2 rates:
    - 2100 to 0600 hours 10% basal rate reduction
    - 0600 to 2100 hours for the calculated basal rate
- 50% of the TDD will be bolus split into the following ratio:
    - 40:30:30 (Section 9.8.1.3) for fixed bolus doses.
    - Suggested initial setting for insulin: CHO ratio should be programmed between 1:3 and 1:5.

9.8.1.1. CSII Treatment Group Algorithms

Subjects in the CSII group will have their basal rates (Table IBHD.9.4) and bolus doses (Table IBHD.9.5) adjusted at each study visit (office and telephone) **by the investigator** according to the CSII titration algorithms. Investigators may deviate from the algorithms, if deemed necessary, for the safety or well-being of the subject (that is, due to illness or other safety concern). Any major deviation from the algorithm must be discussed with Lilly. The CSII bolus titration scheme (Table IBHD.9.5) will be divided into 2 dosing bins: TDD <400 units and TDD ≥400 units. Subjects will have their U-500R adjusted according to the TDD at the time of adjustment.

Subjects taking <400 units TDD at Visit 6 (Week 2) should use a 1:10 correction factor with a target of 100 mg/dL starting at 25 mg/dL above target for all mealtime boluses. Subjects taking ≥400 units TDD at Visit 6 (Week 2) should use a 1:5 correction factor with a target of 100 mg/dL starting at 25 mg/dL above target for all mealtime boluses. If, in the opinion of the investigator, the subject would benefit from a different correction factor, the investigator should discuss this with the Sponsor.

Note: Subjects should be instructed to hold their U-500R bolus dose if a meal is skipped.

Table IBHD.9.4. Basal Titration Scheme for CSII

Median SMBG (mg/dL)	Titration of Corresponding Basal Rate for All Dose Ranges[a]
<80	-5%
80-140	0
141-190	+5%
191-230	+10%
>230	+15%
3-day median SMBG measure	**Dose adjusted**
Pre-Morning Meal, 0300 hours[b]	Overnight infusion
Pre-Evening Meal	Daytime infusion

Abbreviations: CSII = continuous subcutaneous insulin infusion; SMBG = self-monitored blood glucose.

a Any plasma glucose (SMBG or lab) measurement <50 mg/dL or ≤70 mg/dL at 0300 hours during the week, investigator should reduce corresponding basal dose by 10-20% as soon as it occurs or notification of the reading occurs.

b If subject acquires more than the 2 initial basal rates, adjusted basal doses will continue to be based on the pre-morning meal and 0300 hours, and pre-evening meal SMBG.

Table IBHD.9.5. Bolus Titration Scheme for CSII

Median SMBG[a,b,c] (mg/dL)	Dosing Bin for TDD <400 U Titration (U)	Dosing Bin for TDD ≥400 U Titration (U)
<80	-5	-10
80-140	0	0
141-190	+2.5	+5
191-230	+5	+10
>230	+7.5	+15
3 Day Median SMBG[d]		**Adjusted Dose**
Pre-midday meal		Pre-morning meal
Pre-evening meal		Pre-midday meal
Bedtime[e]		Pre-evening meal

Abbreviations: CSII = continuous subcutaneous insulin infusion; CHO = carbohydrate; SMBG = self-monitored blood glucose; TDD = total daily dose; U = units.

a Each of the 3 bolus doses is adjusted independently based on the median of 3 corresponding SMBG values (preferably most recent 3 days).

b Any plasma glucose (SMBG or lab) measurement <50 mg/dL, investigator should reduce corresponding bolus dose by 10-20% as soon as it occurs or notification of the reading occurs.

c If the algorithm adjustment leads to overlapping basal and bolus adjustments, the investigator has the discretion to reduce the bolus adjustment for safety.

d If the subject is using CHO meal sizes or CHO counting for boluses and their SMBGs are not in the target range for the corresponding meal at the visits (telephone or office) for algorithm titrations, then the principal investigator should adjust (increase or decrease) the insulin CHO ratio by approximately 10% to 15%.

e In the event that nocturnal hypoglycemia occurs requiring a reduction in the overnight basal rate, the investigator may reduce the pre-dinner dose even if the bedtime SMBG median is in the target range of 80-140 mg/dL.

Note: All CSII basal and bolus doses will be rounded to the nearest 0.25 units.

9.8.1.2. CSII Basal Rate

The overnight basal rate from 2100 to 0600 hours is adjusted based on the median fasting pre-breakfast SMBG from the past 3 values (most recent 3 days recommended) and the basal rate from 0600 to 2100 hours is adjusted based on pre-dinner SMBG (most recent 3 days recommended). The principal investigator may increase the number of basal rates up to 4 basal rates during the trial, if in the investigator's opinion the subject needs further individualization of basal rates based on blood sugar trends, such as nocturnal hypoglycemia or the dawn phenomenon indicating a need for the change(s).

9.8.1.2.1. Adding a Basal Rate for Nocturnal Hypoglycemia

If a subject has persistent nocturnal hypoglycemia, an additional basal rate reduction can be added. For example, if a subject has persistent nocturnal hypoglycemia between 2100 hours and midnight after the initial 10% reduction in the basal rate between 2100 and 0600 hours, an additional basal rate reduction can be added in the time period from 2000 hours to midnight (that is, 20% reduction between 2000 hours and midnight with 10% reduction continuing between midnight and 0600 hours). Alternatively, the investigator may decide to suspend the basal rate overnight.

9.8.1.2.2. Adding a Basal Rate for Dawn Phenomenon

If a subject has significant dawn phenomenon leading to persistent hyperglycemia, an additional basal rate increase can be added based on investigator discretion. For example, if a subject has persistent hyperglycemia from 0600 to 1000 hours, an additional basal rate increase of 10% can be added from 0600 to 1000 hours.

9.8.1.3. CSII Bolus Dosing

Subjects should bolus 30 minutes prior to meals except for a subset of the subjects in the CGM addendum who will be assigned to bolus 15 minutes prior to meals.

Subjects should be encouraged to eat a bedtime snack (Extend Bar 21 gm CHO or equivalent) without administering a bolus for the snack. **Note:** If the subject has an allergy or intolerance to the Extend Bar, then the subject may substitute a bedtime snack between 15 and 25 grams CHO.

9.8.1.3.1. CSII Bolus Settings

The **investigator** has the option of prescribing 3 bolus options. Table IBHD.9.5 should be followed for dosage adjustments. The U500 OmniPod system bolus calculator should be set to one of the following bolus options (according to principal investigator discretion):

- Use fixed bolus regimen based on previous mealtime insulin requirements. Bolus dose will be imputed manually (that is, the user would enter their BG value and answer 'use for bolus calcs?' with 'yes'; answer 'are you going to eat now' with 'no' and then override the suggested bolus based on the fixed bolus dose size).
- A mealtime bolus utilizing CHO meal sizes. Adjust dose based on a preset CHO meal size (for example: small = 30 gram CHO; medium = 60 gram CHO; and large = 90 gram CHO).
- A mealtime bolus for the corresponding meal if the subject is using CHO counting.

Note: Subjects should be encouraged to maintain the bolus option throughout the study.

All subjects should have the insulin-on-board (IOB) setting programmed at 6 hours except for a subset of the subjects participating in the CGM Addendum who will have the IOB set at 8 hours. The clinical protocol addendum will assess alternative IOB based on U-500R time action profile.

9.8.2. MDI

For MDI subjects, initial doses of U-500R will be determined according to Section 9.7; dosage titrations per bolus titration schedule (Table IBHD.9.6) will occur at the same visits (telephone or office) as for CSII subjects.

MDI subjects should also bolus U-500R 30 minutes prior to meals except for a subset of the subjects participating in the CGM addendum who will bolus 15 minutes prior to meals.

Subjects should be instructed to eat a bedtime snack (Extend Bar 21 gm CHO or equivalent).

Subjects should be instructed to use a U-100 insulin syringe to draw up the U-500R dose (Section 9.7.1). All bolus doses will be rounded to the nearest 5 units.

9.8.2.1. MDI Treatment Group Algorithms

Subjects in the MDI group will have their insulin dosages adjusted at each study visit (office and telephone) by the **investigator** according to the TID titration algorithm (Table IBHD.9.6). The MDI bolus titration scheme will be divided into 2 dosing bins; TDD <400 units and TDD ≥400 units. Subjects will have their U-500R adjusted according to the TDD at the time of adjustment.

Note: Subjects should be instructed to reduce their U-500R dose by 50% if a meal is skipped.

Table IBHD.9.6. Bolus Titration Scheme for MDI Delivered TID

Median SMBG[a,b] (mg/dL)	Dosing Bin for TDD <400 U Titration (U)	Dosing Bin for TDD ≥400 U Titration (U)
<80	-10	-20
80-140	0	0
141-190	+5	+10
191-230	+10	+20
>230	+15	+30
3 Day Median SMBG		**Dose Adjusted**
Pre-midday meal		Pre-morning meal
Pre-evening meal		Pre-midday meal
Pre-morning meal, 0300 hours		Pre-evening meal

Abbreviations: MDI = multiple daily injections; SMBG = self-monitored blood glucose; TDD = total daily dose; TID = three times daily; U = units.

[a] Each of the 3 bolus doses are adjusted independently based on the median of 3 corresponding SMBG values (preferably most recent 3 days).

[b] Any plasma glucose (SMBG or lab) measurement below 50 mg/dL or ≤70 mg/dL at 0300 hours, investigator should reduce corresponding bolus dose by 10%-20% as soon as it occurs or notification of the reading occurs.

9.9. Special Treatment Considerations

9.9.1. Rescue Therapy

Rescue therapy should be initiated in the following circumstances:

- If median of 3 fasting SMBG >300 mg/dL over a 3-day period is unexplained from previous week, starting at Visit 10 through Visit 13 (Weeks 8 through 14).
- If HbA1c value at Visit 13 (Week 14) is ≥10.0% and decreased by <0.4% compared to Visit 10 (Week 8) HbA1c.
- If HbA1c value at Visit 15 (Week 20) is ≥10.0% and decreased by <0.4% compared to Visit 13 (Week 14) HbA1c.

Subjects receiving U-500R MDI will be rescued by the addition of a bedtime U-500R dose (increase injections to 4-times daily therapy). A suggested starting dose for the rescue dose would be 10% of TDD, but this may be modified based on investigator judgment.

Subjects receiving CSII U-500R will be rescued by the addition of a bedtime U-500R dose delivered by CSII. A suggested starting dose for the rescue dose would be 5% to 10% of TDD, but this may be modified based on investigator judgment.

Subjects should be instructed to record their 0300-hour BG within 24 hours after adding a rescue dose and subjects should also be encouraged to record their 0300-hour BG 2 to 3 times the first 2 weeks after adding a rescue dose.

Every attempt should be made to keep these subjects in the study. Change in treatment regimen should be recorded in the eCRF.

9.9.2. Continued Access to Study Treatment

The U-500R insulin used in this study is commercially available in the US and is therefore available for subjects after the conclusion of this study.

9.10. Blinding

This is an open-label study. 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, CRP/CRS overseeing the global conduct of the study, statisticians, and statistical analysts) will remain blinded 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.

9.11. Concomitant Therapy

All concomitant therapies that are part of routine care are allowed and may be used during the study with the exception of those specifically outlined in Sections 8.1 and 8.2. Subjects who take any excluded concomitant therapy will be discontinued from the study treatment at the next visit or sooner. In emergency/urgent situations, subjects may cease taking study medication for 7 consecutive days and may be treated instead with nonstudy insulin during that time. If a subject takes nonstudy insulin for more than 7 consecutive days, then discontinuation criteria apply (Section 8.3.2).

9.11.1. Concomitant Medications Including Antihyperglycemic Agents

Subjects will be allowed to continue to use any concomitant medications with the exception of those listed in the exclusion criteria. A list of selected concomitant medications that have an effect on glucose metabolism, and their conditions for use, is presented in Table IBHD.9.7. The subject should be encouraged to report any new concomitant medications after initiating the medication. Please check with the study team if you have any concerns or questions about a medication the subject is taking.

Table IBHD.9.7. Concomitant Medications and Conditions for Use

Drug Class	As Needed	Chronic Use	Conditions for Use
Metformin	N	Y	
DPP-4 inhibitors	N	Y	
Pioglitazone	N	Y	Dosages ≤30 mg daily
SGLT2 inhibitors	N	Y[a]	
Rosiglitazone	N	N	
Alpha glucosidase inhibitors	N	N	
Bromocriptine	N	N	
Sulfonylureas/glinides	N	N	
GLP-1 receptor agonists (except exenatide)	N	Y[a]	
Pramlintide	N	N	
Niacin[b]	N	Y/N	
Bile acid resin binders[b]	N	Y/N	
Systemic glucocorticoids (excluding ocular topical, other topical, or inhaled preparations)	Y if ≤2 weeks	N	

Abbreviations: DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; N = No; SGLT2 = Sodium-glucose transporter protein; Y = Yes.

[a] Allowed for study population Group B only.

[b] Low doses are acceptable.

9.12. Treatment Compliance

Subject compliance with study medication will be assessed at each applicable study visit. Compliance will be based on adherence to the Study Schedule (Attachment 1), compliance with appropriate assigned injection method (CSII versus MDI), completion of the subject's diary, and any other parameters the investigator deems necessary. Compliance will be assessed by direct questioning and returned study materials.

Subjects who are deemed significantly noncompliant will be discontinued from the study treatment. A subject will be considered significantly noncompliant if he or she:

- misses more than 7 consecutive days of study medication during the study.
- is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication that may cause patient safety concerns.
- is not at least 80% compliant with study treatment (ie, PI recommended doses adjustments based on algorithms).

10. Efficacy, Patient Reported Outcomes, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Study procedures and their timing (including tolerance limits for timing) are summarized in the Study Schedule (Attachment 1).

10.1. Efficacy Measures

10.1.1. Primary Efficacy Measure

The primary efficacy measure for this study is change in HbA1c from baseline (last nonmissing value at or prior to the treatment starting Visit 4) to the 26-week value.

10.1.2. Secondary Efficacy Measures

The following secondary efficacy measures will be collected at the times shown in the Study Schedule (Attachment 1). The secondary objectives are summarized in Section 6.2.

10.1.2.1. Fasting Plasma Glucose

Change in mean FPG levels will be compared between treatments.

10.1.2.2. 7-point SMBG

Mean plasma glucose will be analyzed for each individual time point using the 7-point SMBG. The 7-point SMBG is a subject self-administered plasma glucose test that utilizes measurements at specific time points over a 24-hour period. The timing of the 7-point SMBG measurement is described in Section 7.1.3.2.

10.1.2.3. Total Daily Insulin Dose

Change in TDD (unit and unit/kg) as basal/bolus for the CSII arm and by bolus dosing for the MDI arm from baseline to 26-week value will be calculated and analyzed.

10.2. Patient Reported Outcomes

The self-reported questionnaires will be administered, according to the Study Schedule (Attachment 1).

10.2.1. TRIM-D and TRIM-D Device

The TRIM-D and TRIM-DD scales are valid and reliable patient-reported outcome (PRO) measures, which capture the full range of impact of diabetes treatment on subject functioning and well-being across T1DM and T2DM subjects, as well as across all currently available delivery systems and treatments (oral agents, GLP-1 receptor agonist pens, inhaled- or pump-delivered insulin, and insulin delivered with syringe/pens) (Brod et al. 2009). The TRIM-D consists of 28 items, and the TRIM-DD consists of 8 items. In both of these PROs, items are measured on a 5-point scale, where the 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), and

Psychological Health (8 items). In addition to an overall score, the TRIM-DD items include the domain's device function (5 items) and bother of device (3 items).

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.

10.3. OmniPod U-500 System Exit Questionnaire

An OmniPod U-500 system exit questionnaire will be administered to subjects in the CSII group at Visit 17 (Week 26) or at ET if subjects terminate.

10.4. Safety Evaluations

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject.

The investigator is responsible for the appropriate medical care of subjects during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to the study treatment or the study, related to the study device (U-500 OmniPod system), or that caused the subject to discontinue before completing the study. The subject should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

Safety evaluations include the following:

- Frequency and incidence of AEs and TEAEs
- Incidence/rate of hypoglycemia (documented [documented symptomatic, asymptomatic, and unspecified], severe, and nocturnal)
- Body weight
- Vital signs
- Study treatment exposure
- Clinical laboratory tests abnormalities
- Product complaints

10.4.1. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent.

Lack of drug effect is not an AE in clinical studies because the purpose of the clinical study is to establish drug effect.

Cases of pregnancy that occur during maternal or paternal exposures to study treatment or drug delivery system should be reported. Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation.

Study site personnel will record the occurrence and nature of each subject's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

After the ICF is signed, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs. All AEs related to protocol procedures are reported to Lilly or designee.

In addition, all AEs occurring after the subject receives the first dose of study treatment must be reported to Lilly or its designee via the eCRF.

Any clinically significant findings (vital sign measurements, laboratory measures, and treatment exposure) that result in a diagnosis should be reported to Lilly or its designee.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure, study treatment, and/or drug delivery system via eCRF.

The investigator decides whether he or she interprets the observed AEs as either related to disease, to the study medication, study procedure, study device, or other concomitant treatment or pathologies. To assess the relationship of the AE to study treatment, the following terminologies are defined:

Related: a direct cause and effect relationship between the study treatment and the AE is likely

Possibly related: a cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible

Unrelated: without question, the AE is definitely not associated with the study treatment.

As per Lilly's standard operating procedures, all "related" and "possibly related" AEs and SAEs will be defined as related to study treatment.

If a subject's dosage is reduced, or treatment is discontinued as a result of an AE, study site personnel must clearly report to Lilly or its designee via eCRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

10.4.1.1. Serious Adverse Events

Serious adverse event collection begins after the subject has signed informed consent and has received study treatment. If a subject experiences an SAE after signing informed consent, but prior to receiving study treatment, the event will NOT be reported as serious unless the investigator feels the event may have been caused by a protocol procedure.

Planned surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a Sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

An SAE is any AE from this study that results in one of the following outcomes:

- Death
- Severe hypoglycemia (as defined in Section 10.4.2)
- Initial or prolonged inpatient hospitalization
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Considered significant by the investigator for any other reason

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

When a condition related to the U-500 OmniPod system necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned.

Serious adverse events occurring up to and including the subject's last study visit will be collected, regardless of the investigator's opinion of causation, in the clinical data collection database and the pharmacovigilance system at the sponsor.

The investigator does not need to actively monitor subjects for AEs once the trial has ended, unless provided otherwise in the protocol. However, if an investigator becomes aware of SAEs occurring to a subject after the subject's participation in the trial has ended, the investigator should report the SAEs to the Sponsor, regardless of the investigator's opinion of causation; the SAEs will be entered in the pharmacovigilance system by the sponsor.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the Sponsor in aggregate periodically during the course of the trial may be found in the USPI.

10.4.1.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the USPI and that the investigator identifies as related to study treatment or procedure. United

States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC, and the associated detailed guidance or national regulatory requirements in participating countries, require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidance.

10.4.2. Hypoglycemia

As a secondary objective, the rate/incidence of hypoglycemia will be analyzed and compared between treatment groups. Subjects are encouraged to perform SMBG whenever hypoglycemia may be suspected, either by symptoms experienced or perceived increased risk as related to dietary intake, physical activity, or inadvertent or atypical insulin dosing. All subjects will be instructed to treat a SMBG ≤70 mg/dL as hypoglycemia by ingesting 15 gram of CHO (for example, 4 ounces of juice or 3 to 5 gram glucose tabs). All subjects will be advised to contact the site if they experience severe hypoglycemia or SMBG <50 mg/dL.

Hypoglycemia is defined as ≤70 mg/dL (Seaquist et al. 2013) and categorized as follows:

- **Documented hypoglycemia**
    - **Documented symptomatic** – an event that:
        1. is accompanied by with signs/symptoms of hypoglycemia, and
        2. is accompanied by a measured SMBG concentrations of ≤70 mg/dL.
    - **Asymptomatic hypoglycemia** an event that:
        1. is not accompanied with signs/symptoms of hypoglycemia, and
        2. is accompanied with a measured SMBG concentration of ≤70 mg/dL.
    - **Unspecified hypoglycemia** an event during that:
        1. no relative signs/symptoms of hypoglycemia are recorded, and
        2. is accompanied with a measured SMBG concentration of ≤70 mg/dL.
- **Severe hypoglycemia**: An event accompanied by neuroglycopenic symptoms that result in cognitive impairment such that the patient requires assistance of another person to actively administer CHO, 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 (≤70 mg/dL).
- **Nocturnal hypoglycemia**: Any hypoglycemic event (documented hypoglycemia or severe hypoglycemia) that occurs between bedtime and waking.

10.4.3. Body Weight

The scale should be zeroed out before the subject is weighed. Subjects should remove their shoes and any additional layers of clothing (such as sweaters or coats) and empty their pockets before being weighed. If possible, subjects should also be given the opportunity to empty bladder/bowel before being weighed. The weight value should be recorded in the source documentation and the eCRF.

10.4.4. Other Safety Measures

10.4.4.1. Vital signs

Blood pressure and pulse, as well as height and weight, will be measured and recorded at the indicated visits per the Study Schedule (Attachment 1). Blood pressure will be measured using a standard blood pressure meter to obtain the systolic and diastolic pressures with the subject sitting for at least 5 minutes prior to the measurement.

10.4.4.2. Physical Examinations

Complete physical examinations will be performed at Visit 1 according to the Study Schedule (Attachment 1).

10.4.4.3. Electrocardiograms

For each subject, 12-lead digital electrocardiograms (ECGs) will be performed locally at Visit 1 according to the Study Schedule (Attachment 1). Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

The ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the subject is still present, to determine whether the subject meets entry criteria at the relevant visit(s) and for immediate subject management, should any clinically relevant findings be identified. Investigators must document their review of ECG reports.

10.4.4.4. Clinical Laboratory Tests

Clinical laboratory tests will be conducted at the indicated visits per the Study Schedule (Attachment 1) and Clinical Laboratory Tests (Attachment 2).

10.4.4.5. Concomitant Medications

Concomitant medication usage will be assessed at office visits, per the Study Schedule (Attachment 1). Concomitant medications allowed in this study are discussed in Section 9.11 and Table IBHD.9.7.

10.4.4.6. Functionality and Safe Use of OmniPod U-500 System

The functionality issues, hazards alarms, and safe use of the OmniPod U-500 system will be evaluated at study visits and/or by an assessment of device complaint data.

10.4.5. Safety Monitoring

The Lilly CRP or CRS will monitor safety data throughout the course of the study.

Lilly will review SAEs within timeframes mandated by company procedures. The Lilly CRP/CRS will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist, and periodically review:

- Trends in safety data
- Laboratory analytes
- AEs
- Product complaints

If a study subject experiences elevated ALT or AST ≥3X ULN, elevated total bilirubin ≥2X ULN, or alkaline phosphatase ≥2X ULN, clinical and laboratory monitoring should be initiated by the investigator. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure subject safety and comply with regulatory guidance, the investigator is to consult with the Lilly designated medical monitor regarding collection of specific recommended clinical information and follow-up laboratory tests.

10.4.6. Complaint Handling

Lilly collects product complaints on study treatment and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Complaints related to unblinded drug delivery systems (with exception of U-500 OmniPod system) are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- Recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose.
- The completed product complaint form must be faxed within 24 hours to Lilly or its designee.

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

10.5. Sample Collection and Testing

The Study Schedule (Attachment 1) lists the schedule for sample collections in this study. The Clinical Laboratory Tests (Attachment 2) lists the laboratory tests that will be performed for this study.

10.5.1. Samples for Study Qualification and Health Monitoring

Standard laboratory tests including chemistry, hematology, and urinalysis panels will be performed. The Clinical Laboratory Tests (Attachment 2) lists the specific tests that will be performed for this study. Clinical laboratory tests will be analyzed by a central laboratory selected by Lilly.

Blood and urine samples will be collected per standard procedures at the times specified in the Study Schedule (Attachment 1). Blood will be collected by venipuncture.

Investigators must document their review of each laboratory safety report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

10.5.2. Pharmacogenetic Samples for Biomarker Research

Samples will be stored and analysis may be performed on genetic variants thought to play a role in insulin sensitivity, efficacy, beta cell function, hypoglycemia risk, and TDD requirements (Section 6.3) including, but not limited to, Insulin receptor, Insulin like Growth Factor-1, Melatonin Receptor 1B1, adiponectin and transcription factor 7-like 2, Phosphoinositide-3-Kinase, Regulatory Subunit 1 and B-Cell CLL/Lymphoma 11A to evaluate their association with observed clinical outcomes to U-500R (a one-time collection, as noted in the Study Schedule [Attachment 1]).

There is growing evidence that genetic variation may impact a subject's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology and/or the molecular subtype of the disease being treated. Therefore, where local regulations and ERBs allow, a blood sample will be collected for pharmacogenetic analysis.

In the event of an unexpected AE or the observation of unusual response, the pharmacogenetic samples may be genotyped and analysis may be performed to evaluate a genetic association with response to U-500R. These investigations may be limited to a focused candidate gene study or, if appropriate, genome-wide analysis may be performed to identify regions of the genome associated with the variability observed in drug response. The pharmacogenetic samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

The samples will be coded with the subject number and stored for up to a maximum 15 years after the last subject visit for the study at a facility selected by the Sponsor. The samples and any data generated from them can only be linked back to the subject by investigator site personnel. The duration allows the Sponsor to respond to regulatory requests related to study treatment.

Pharmacogenetic data will not be provided to the investigators nor will it be shared with patients in the trial. Samples will be destroyed according to a process consistent with local regulation.

10.5.3. Nonpharmacogenetic Biomarker Stored Samples

Collection of samples for nonpharmacogenetic biomarker research is a required part of this study. Urine and blood (serum and plasma) samples will be collected as specified in the Study Schedule (Attachment 1).

Samples may be used for research to understand the pathophysiology of T2DM or its complications, the mechanism of action, efficacy, and/or adverse effects related to U-500R. In addition, samples may be used to develop research methods and/or validate diagnostic tools or assays. Nonpharmacogenetic biomarker data from stored samples will not be provided to the investigators nor will it be shared with patients in the trial.

Samples will be identified by the subject number (coded) and stored for up for a maximum of 15 years after the last subject visit for the study at a facility selected by the Sponsor.

10.6. Appropriateness of Measurements

All efficacy and safety assessments included in this study are generally regarded as reliable and accurate with respect to management of T2DM.

11. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate.
- Provide start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- Make periodic visits to the study site.
- Be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax.
- Review and evaluate eCRF data and use standard computer edits to detect errors in data collection.
- Conduct a quality review of the database.

To reduce missing data in the study, subjects who are discontinued from study treatment before study completion will be encouraged to remain in the study for continued safety monitoring (see Section 8.3.2). In addition, study site investigators will be trained on the importance of complete data collection.

Lilly or its representatives will periodically check a sample of the subject data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and subject medical records in the subject files as original source documents for the study. If requested, the investigator will provide the Sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

11.1. Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the Sponsor-provided electronic data capture system. Case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly generic labs system.

Any data for which paper documentation provided by the subject will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the subject may include, for example, a paper diary to collect PRO measures (for example, a rating scale), a daily dosing schedule, or an event diary.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

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 two 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.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

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

Unless otherwise specified, both safety and efficacy analyses will be conducted on the ARS, including those rescued. This set includes all randomized patients and is defined based on the intention-to-treat (ITT) principle. Sensitivity analysis may be done for the Full Analysis Set (FAS) that includes ARS subjects who received at least 1 dose of the U-500R via the administration method to which they were assigned.

In general, missing data will not be imputed, unless otherwise specified, eg, where the LOCF method is mentioned.

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

Separate listings for safety data will also be done for those patients who discontinue study treatment but still remain in the study for safety monitoring purpose. These listings will contain data after the patients discontinue the study treatment.

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

Changes to the data analysis methods described in the protocol will require an amendment **only** if it changes a principal feature of the protocol. Any other changes to the data analysis methods described in the protocol, and the justifications, will be described in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

12.2.2. Adjustment for Multiplicity

This section explains the graphical approach in detail and illustrates how the graphical approach works in practice. As discussed in Bretz et al. 2009, this testing approach controls the

family-wise type I error rate at alpha=0.05. More details of this method will be documented in the SAP.

Figure IBHD.12.1 illustrates the graphical approach to adjust multiplicity for the primary and key secondary objectives. In Figure IBHD.12.1 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 the Figure IBHD.12.1, 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 in Bretz et al. 2009.

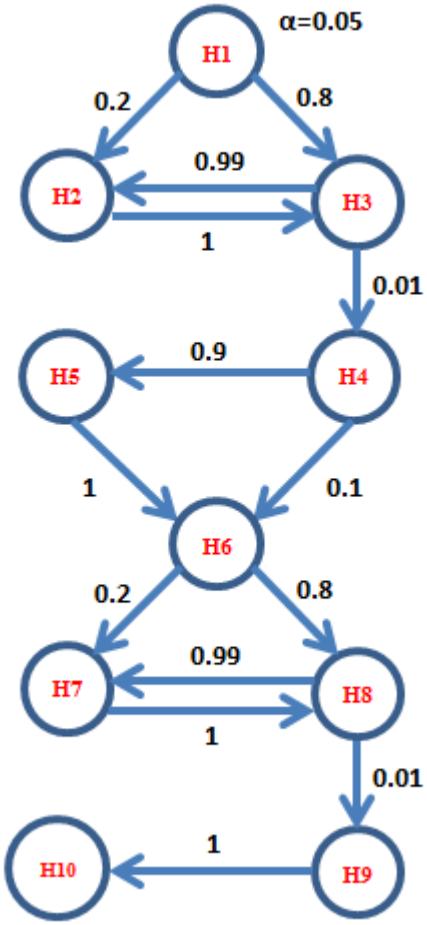


Figure IBHD.12.1. Graphical approach to adjust multiplicity.

One of the possible scenarios for the graphical approach is given below (step by step) for illustration only:

- The null hypothesis for H1 is rejected at alpha=0.05, so H2 will be tested at alpha=0.01 and H3 will be tested at alpha=0.04.
- The null hypothesis for H3 is rejected at alpha=0.04, so based on the graph (Figure IBHD.12.1), 99% of the alpha (0.0396) from H3 will flow to H2 and 1% of the alpha (0.0004) from H3 will flow to H4. Therefore, H2 will be tested at alpha=0.01+0.0396=0.0496 and H4 will be tested at alpha=0+0.0004=0.0004.
- The null hypothesis for H2 is rejected at alpha=0.0496, so based on the updated graph and weights, 100% of its alpha will flow to H4 and H4 will be tested at alpha=0.0004+0.0496=0.05.
- The null hypothesis for H4 cannot be rejected at alpha=0.05, so the graphical approach stops here.

12.2.3. Subject Disposition

All subjects who discontinue from the study will be identified, and the extent of their participation in the study (discontinuation visit; whether remain in the study after discontinuation of study treatment for safety monitoring) will be reported. If known, a reason for their discontinuation will be given. The primary reasons for discontinuation will be listed for all subjects who have entered the study (signed informed consent) and will be summarized for the lead-in period. Reasons for discontinuation of study treatment and study will also 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 but remain for safety monitoring" and "discontinue both study treatment and the study". The treatment comparison will be based on Fisher's exact test or Pearson's chi-square test, as appropriate.

12.2.4. Subject Characteristics

The subject characteristics and demographic variables will be recorded at Screening (Visit 1; Week -3) and will be listed and summarized by treatments. The summaries will include descriptive statistics such as: mean, SD, sample size, median, minimum, and maximum for continuous variables; and frequency, percentage, and number of subjects for categorical variables. The treatment groups will be compared using an analysis of variance model for continuous measurements and Fisher's exact test for categorical measurements. In addition, these analyses will be conducted for baseline hypoglycemic episodes collected from Visit 2 to Visit 4.

12.2.5. Concomitant Therapy

Frequencies and percentages of concomitant medication used prior to and after randomization (by visit), will be summarized by treatments. Antihyperglycemic agents will be summarized by treatment at entry, randomization, and the end of study. AHA usage change and AHA mean daily-dose change from baseline to the end of study will be summarized by treatment. Treatment comparisons will be conducted.

12.2.6. Treatment Compliance

No specific study data will be collected for analysis for treatment compliance except as it is collected in Patient Reported Outcomes Questionnaires.

12.2.7. Primary Outcome and Methodology

The primary efficacy measure is change from baseline (last nonmissing value at or prior to the treatment starting at randomization) to the 26-week HbA1c value, which will be summarized and analyzed using a MMRM approach for the ARS. The baseline is selected to be the last value on or prior to the randomization visit: Visit 4 (Week 0). Neither LOCF method nor other imputation methods will be used for the outcome measures. However, LOCF method will be used for sensitivity analysis. The MMRM model adjusts for missing data through an observed-data-likelihood-based approach. 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 appropriate stratification factor (nonusers versus users of GLP-1 receptor agonists or SGLT2 inhibitors and U-500R at entry versus other insulins). The model will also include baseline HbA1c as a covariate. An unstructured covariance matrix will be first modeled for the repeated measures of each subject. If the analysis fails to converge, the following variance-covariance matrix will be used (in order) until one converges:

1. Heterogeneous compound symmetry;
2. Compound symmetry;
3. First-order autoregressive.

The test for the first primary objective of noninferiority will be performed at the 0.05 significance level using the LS mean estimate of the difference in change in HbA1c between the two treatments at Week 26. Noninferiority 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 LS mean estimate of the difference in change in HbA1c between the 2 treatments, superiority will be established if the upper limit of a two-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 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), and the per-protocol population (subjects included in the ARS who have completed the study without significant protocol violations).
- An "analysis of covariance" model with similar fixed effects as in the MMRM analysis using LOCF method for the ARS.

12.2.8. Secondary Efficacy Analyses

Similar MMRM models for the ARS will be used to analyze the change from baseline for the following values at week 26:

1) FPG (by laboratory measurement)
2) 7-point SMBG
3) Total Daily Insulin dose (TDD)

Baseline values will be the last value obtained for each subject at or prior to the randomization visit: Visit 4, unless otherwise stated. The MMRM model will include similar fixed effects as in the primary analysis, with the corresponding baseline measures included as a covariate. The model specifications will be carefully adjusted as appropriate.

For 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).

Treatment comparisons will be analyzed using a repeated-measure logistic regression model including subject to account for the repeated measurements and similar fixed effects as in the above MMRM models. The proportion of subjects achieving HbA1c targets with no documented symptomatic hypoglycemia (from baseline to the corresponding visit) will be analyzed using a similar repeated-measure logistic regression model including the baseline documented symptomatic hypoglycemia event rate as a covariate.

12.2.9. Exploratory Analyses

12.2.9.1. Patient Reported Outcomes Analyses

As an exploratory objective, the TRIM-D and TRIM-DD measures will be used to compare the change in diabetes treatment and diabetes treatment device on patient's functioning, well-being, and quality-of-life outcomes from baseline to the 26-week values between treatment groups.

12.2.9.1.1. TRIM-D and TRIM-DD

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.

Summaries of the domain and overall scores will include sample size, mean, SD, median, minimum, maximum, LS mean and standard error (SE) of LS mean. The changes from baseline in domain scores and total scores of TRIM-D and TRIM-DD will be analyzed using MMRM model (similar to the primary/secondary analyses). For change from baseline, LS means and SE of LS means will be reported by treatment group. For treatment difference of change, LS means, SE of LS means, 95% CI, and p-value will be reported.

12.2.9.2. OmniPod U-500 System Exit Questionnaire

An OmniPod U-500 System Exit Questionnaire will be administered to CSII subjects at Visit 17 (Week 26) or at ET if subjects do not complete the full 26 weeks of the study.

Descriptive statistics will be provided to summarize the results from the U-500 System Exit Questionnaire.

12.2.9.3. 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 and subject reported hazard alarms and clinically relevant hyperglycemia possibly related to site occlusion. Lilly should be contacted for CSII device complaints and will provide the data to be listed. The reported hazard alarms as well as the "Infusion Site Change" from the diary will be listed also.

12.2.10. Safety Analyses

As stated in Section 6.2, all of the secondary objectives will be analyzed for Group A and for the total study population (Groups A and B combined). Safety measures will include hypoglycemic events, body weight, AEs and TEAEs, vital signs (systolic and diastolic blood pressures and pulse), study treatment exposure, and laboratory measures. As stated in Section 12.2.1, all safety measures will be summarized for ARS by treatment and by visit for the 26-week treatment period. Safety measures will also be listed for those patients who discontinue study treatment but still remain in the study for safety monitoring purpose. These listings will contain data after the patients discontinue the study treatment. For treatment comparisons of frequency and proportion of event variables (such as AEs and hypoglycemia events), the conventional Fisher's exact test or Pearson's chi-square test are appropriate to use. Further details of analyses will be provided in the SAP.

12.2.10.1. Hypoglycemia

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 (year).

For documented (documented symptomatic, asymptomatic and unspecified), severe and nocturnal hypoglycemic episodes, the following analyses will be conducted. The incidence and percentage of subjects with at least 1 hypoglycemic event will be analyzed using Fisher's exact test or Pearson's chi-square test, as appropriate. The rate of hypoglycemic events per 30 days and per 365 days will be analyzed using a repeated-measure negative binomial regression model with similar fixed effects as in the primary analysis model. Baseline hypoglycemic event rate for the corresponding category of the dependent hypoglycemia variable will be included as a covariate, as well as the stratification factors.

12.2.10.2. Body Weight

Baseline values used for the weight analysis will be obtained for each subject at or prior to randomization. The body weight change will be analyzed by MMRM models similar to that which will be used in the primary analysis for the ARS population. The MMRM model will include similar fixed and random effects, as in the primary analysis, with the corresponding baseline measures included as a covariate. The model specifications will be adjusted as appropriate.

12.2.10.3. Treatment-Emergent Adverse Events and Serious Adverse Events

Adverse events will be listed by subject, system organ class, preferred term, severity, and relationship to the study disease, drug, device, or procedure. Adverse events will be summarized as TEAEs during treatment period (defined as events that are newly reported after randomization Visit 4 or reported to be worsened in severity from randomization Visit 4) for ARS by treatment and visit. Similar listings will be done for subjects who discontinued study treatment but still remain in the study for safety monitoring purpose. These listings will contain data after the patients discontinue the study treatment.

The frequency and proportion of subjects experiencing at least 1 of each reported TEAE will be summarized by system organ class, preferred term, and treatment group for treatment period. The frequency and proportion comparisons will be analyzed using Fisher's exact test or Pearson's chi-square test, as appropriate. The frequency and proportion of subjects experiencing at least 1 of each reported TEAE that are assessed as possibly related to the study disease, drug, device, or procedures will also be summarized.

All SAEs (including severe hypoglycemic events) will be listed by subject with similar information as the AE listing. 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 TEAEs and SAEs will be listed separately, by subject (including information about whether they discontinue only the study treatment or study treatment and the study), and summarized (if a sufficient number of events are reported) by treatment. All of the summaries will be broken down by "discontinue study treatment but remain for safety monitoring" and "discontinue both study treatment and the study."

12.2.10.4. Vital Signs

Systolic and diastolic blood pressures and pulse will be summarized by visit and additionally for endpoints (LOCF). Additionally, change from baseline to the last visit of each period for actual value and endpoint (LOCF) will be summarized.

12.2.10.5. Study Treatment Exposure

Exposure to each treatment will be calculated for each subject and summarized by treatment. Total subject-years will be included in the summaries.

12.2.10.6. 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
- Hematology
- Lipids

Treatment-emergent high, low, and abnormal values will be summarized for each lab measure.

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.

12.2.11. Safety Committee

Trial level safety reviews using selected blinded safety data will be conducted throughout the study by the study team.

12.2.12. 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. Unblinding details are specified in the unblinding plan section of the SAP and/or DMC Charter. The timing and frequency of these data reviews will be stated in the DMC charter. In the event of any patient safety concerns, the DMC will communicate to the study team so that the CRP/CRS can inform the investigator of appropriate action. Study sites will receive information about interim results ONLY if they need to know for the safety of their subjects.

If an unplanned interim analysis is deemed necessary, the appropriate Lilly regulatory scientist will be consulted to determine whether it is necessary to amend the protocol.

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

The investigator is responsible for ensuring that the subject understands the potential risks and benefits of participating in the study, including answering any questions the subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject's willingness to continue his or her participation in the trial.

The ICF will be used to explain the potential risks and benefits of study participation to the subject in simple terms before the subject is entered into the study, and to document that the subject is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each subject or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of study treatment.

As used in this protocol, the term "informed consent" includes all consent and assent given by subjects or their legal representatives.

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are used at investigative sites. All ICFs must be compliant with the International Conference on Harmonisation (ICH) guideline on GCP.

The investigator must give assurance that the ERB was properly constituted and convened as required by ICH guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative sites. The ERB(s) will review the protocol as required.

The study site's ERB(s) should be provided with the following:

- IBHD Subject Information, Humulin R U-500 USPI, OmniPod U-500 Insulin Management System User Guide, and updates during the course of the study
- ICF
- Relevant curricula vitae

13.3. Regulatory Considerations

This study will be conducted in accordance with:

- Consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.

- The ICH GCP Guideline [E6].
- Applicable laws and regulations.

The investigator or designee will promptly submit the protocol to applicable ERB(s).

Some of the obligations of the Sponsor will be assigned to a TPO.

An identification code assigned to each subject will be used in lieu of the subject's name to protect the subject's identity when reporting AEs and/or other trial-related data.

13.3.1. Investigator Information

Physicians with a specialty in internal medicine or endocrinology with extensive experience in intensive insulin therapy including CSII therapy may participate as investigators in this clinical trial.

13.3.2. Protocol Signatures

The Sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

13.3.3. Final Report Signature

The clinical study report-coordinating investigator will sign the final clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The Sponsor's responsible medical officer and statistician will approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

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Attachment 1. Protocol IBHD Study Schedule

Study Schedule, Protocol B5K-MC-IBHD

Perform procedure as indicated.

↓ **Visit 6: CSII Treatment Arm Begins**

	S	Lead- In		R	Transition		Treatment Period											ET[a]
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	
Week of Study (week prior to visit)	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**17**	**20**	**23**	**26**	
Allowable Range (± d=days, w=weeks)	**-**	**1w**	**3d**	**1w**	**3d**	**3d**	**3d**	**3d**	**3d**	**3d**	**3d**	**3d**	**3d**	**3d**	**3d**	**3d**	**1w**	
Telephone (T) or Office (O) Visit	**O**	**O**	**T**	**O**	**O**	**O**	**O**	**T**	**T**	**O**	**T**	**T**	**O**	**T**	**O**	**T**	**O**	
Informed consent	X																	
Confirm eligibility	X			X[b]														
Demographic data	X																	
Randomization				X														
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[c]																		
Subjects fast prior to visit				X									X				X	X
Clinical chemistry/hematology	X			X									X				X	X
Estimated glomerular filtration rate (eGFR)	X			X									X				X	X
Lipid panel				X									X				X	X
Urinalysis	X																X	X
Pregnancy test[d]	X																	
HbA1c	X			X						X			X		X		X	X
Fasting plasma glucose				X									X				X	X
C-peptide				X													X	X
Pharmacogenetic sample for storage				X														
Nonpharmacogenetic biomarkers sample storage (plasma, serum, urine)	X			X						X			X		X		X	X
Clinical Assessments																		
ECG	X																	
Medical history	X																	
Preexisting conditions	X																	
Physical examination	X																	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

↓ **Visit 6: CSII Treatment Arm Begins**

	S	Lead- In		R	Transition		Treatment Period											ET[a]
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	
Week of Study (week prior to visit)	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**17**	**20**	**23**	**26**	
Allowable Range (± d=days, w=weeks)	**-**	**1w**	**3d**	**1w**	**3d**	**3d**	**3d**	**3d**	**3d**	**3d**	**3d**	**3d**	**3d**	**3d**	**3d**	**3d**	**1w**	
Telephone (T) or Office (O) Visit	**O**	**O**	**T**	**O**	**O**	**O**	**O**	**T**	**T**	**O**	**T**	**T**	**O**	**T**	**O**	**T**	**O**	
Clinical Assessments, Cont.																		
Assess/record BG and hypoglycemic events[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X		X	X	X	X			X			X		X		X	X
Weight	X	X		X	X	X	X			X			X		X		X	X
Height	X																	
Training on 7-point SMBG profiles		X																
Subject records 7-point SMBG profiles[f]				X									X				X	
Health Outcomes Questionnaires																		
TRIM-D				X[g]									X				X	X
TRIM-DD				X[g]									X				X	X
Pump Specific Endpoint Assessment																		
OmniPod U-500 Exit Questionnaire for CSII subjects																	X	X[h]
Study Drug/Devices/Diaries																		
Dispense and training of glucose meter	X																	
Education on diabetes lifestyle and diet		X		X														
Training on OmniPod U-500 (CSII treatment arm only)					X[i]	X[j]												
Dispense study diary	X	X		X	X	X	X			X			X		X			
Collect study diary		X		X	X	X	X			X			X		X		X	X
Dispense study drug				X	X[k]	X[k]	X[k]			X[k]			X[k]		X[k]			
Collect study drug					X	X	X			X			X		X		X	X
Dispense subject supplies	X	X		X	X	X	X			X			X		X			
Dispense OmniPod U-500 supplies (CSII treatment arm only)						X	X			X			X		X			

Study Schedule, Protocol B5K-MC-IBHD

↓ **Visit 6: CSII Treatment Arm Begins**

	S	Lead- In		R	Transition		Treatment Period											ET[a]
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	
Week of Study (week prior to visit)	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**17**	**20**	**23**	**26**	
Allowable Range (± d=days, w=weeks)	**-**	**1w**	**3d**	**1w**	**3d**	**3d**	**3d**	**3d**	**3d**	**3d**	**3d**	**3d**	**3d**	**3d**	**3d**	**3d**	**1w**	
Telephone (T) or Office (O) Visit	**O**	**O**	**T**	**O**	**O**	**O**	**O**	**T**	**T**	**O**	**T**	**T**	**O**	**T**	**O**	**T**	**O**	
Study Drug/Devices/Diaries, Cont																		
Dispense nutrition bars		X		X	X	X	X			X			X		X			
Adjust/record insulin dose		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Product complaints					X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; BG = blood glucose; CRF = case report form; d = day; ET = early termination; HbA1c = Hemoglobin A1c; IWRS = interactive web response system; O = office, R = randomization, S = screening; SAE = serious adverse event; SMBG = self-monitored blood glucose; T = telephone; TRIM-D = treatment-related impact measure for diabetes; TRIM-DD = treatment-related impact measure for diabetes device; w = week.

a Early termination visit only performed on subjects who did not complete the full 26 weeks of the study.

b Prior to randomization at Visit 4, all subjects will be re-confirmed for inclusion criteria [1], [2], and [7] and exclusion criteria [18].

c Central laboratory unless otherwise specified. Laboratory tests may be performed at any time at the investigator's discretion in the event of an adverse event.

d Serum screening pregnancy test will be performed at Visit 1 for women of childbearing potential by a Lilly-designated central laboratory. A urine pregnancy test may be repeated locally for any follow-up visits.

e Hypoglycemic and AEs should be collected in the subject's diary and will be discussed during telephone visits and at the next onsite visit for each subject unless a severe hypoglycemic event occurs (SAE that needs to be reported immediately).

f Subjects will be instructed to record 7-point SMBG profiles on 2 nonconsecutive days (including a weekend day if possible) in the 2 weeks prior to Visits 4, 13, and 17.

g Health outcomes questionnaires will be administered prior to randomization during this office visit.

h OmniPod U-500 System Exit Questionnaire will be administered to CSII subjects at ET if subjects terminate during treatment period.

i Subjects will be introduced to the basics of the OmniPod U-500 system at investigator site before beginning CSII treatment but will not be given the device.

j Subjects will receive hands-on training of the OmniPod U-500 system at investigator site using study drug and will be given device to begin CSII treatment.

k Study drug assessed and dispensed based on need and expiration.

Attachment 2. Protocol IBHD Clinical Laboratory Tests

Clinical Laboratory Tests[a]

Hematology	**Clinical Chemistry**	**Urinalysis**
Hemoglobin	BUN	Bilirubin
Hematocrit	Creatinine	Blood
MCH	Uric acid	Glucose
MCHC	LDH	Ketones
MCV	Albumin	Urine leukocyte esterase
Platelets	Total Protein	Nitrite
Erythrocyte count (RBC)	Calcium	pH
RBC Morphology	Magnesium	Protein
Leukocytes (WBC)	Chloride	Specific gravity
WBC Differential	Potassium	Urobilinogen
Neutrophils, segmented	Sodium	[b] Microscopic
Lymphocytes	Phosphorus	
Monocytes	Bicarbonate	eGFR (MDRD equation)
Eosinophils	CK	
Basophils	Total bilirubin	
	Direct bilirubin	
HbA1c	Alkaline phosphatase	
Glucose, fasting plasma	Alanine aminotransferase (ALT)	
C-peptide	Aspartate aminotransferase (AST)	
	Gamma-Glutamyl Transferase (GGT)	
CDC Lipid Panel	**Pregnancy Test** (females only)	
Cholesterol		
Triglycerides		**Storage Samples**
HDL		Non-PGx Biomarkers: Urine, Serum, Plasma
LDL (calculated)		PGx: DNA Whole Blood
FFA		

Abbreviations: BUN = blood urea nitrogen; CDC = Centers for Disease Control and Prevention; CK = creatine kinase; DNA = deoxyribonucleic acid; FFA= free fatty acids; HbA1c = hemoglobin A1c; HDL = high density lipoprotein; LDH = lactic acid dehydrogenase; LDL = low-density lipoprotein; MCH = mean cell hemoglobin; MCHC = mean cell hemoglobin concentration; MCV = mean corpuscular volume; PGx = pharmacogenetics; RBC = red blood cells; WBC = white blood cells; eGFR = estimated glomerular filtration rate; MDRD = Modification of Diet in Renal Disease.

[a] Assayed by Lilly-designated central laboratory.

[b] Microscopic evaluation if any listed urinalysis analyte is positive.

Attachment 3. World Health Organization (WHO) Classification of Diabetes

Type 1 Diabetes Mellitus: Type 1 diabetes mellitus is judged to be present when the classical symptoms of diabetes (thirst, polyuria, wasting and stupor, or coma) are associated with readily detectable concentrations of glucose and ketone bodies in the blood and urine. Insulin treatment is necessary not only to control hyperglycemia but also to prevent spontaneous ketosis and death (Alberti and Zimmet 1998).

Type 2 Diabetes Mellitus: Type 2 diabetes mellitus, although often asymptomatic, may also present with classical hyperglycemic symptoms (thirst, polyuria, weight loss), but despite hyperglycemia, ketone bodies are present in only low concentrations in the blood and urine. Coma is rare in type 2 diabetes but may result from extreme hyperglycemia and hyperosmolarity; lactic acidosis or ketoacidosis can also occur in fulminating illness (for example, severe infection or mesenteric artery thrombosis) due to an acute increase in insulin requirements, but spontaneous ketosis does not occur. Some patients with type 2 diabetes later progress to a state of absolute insulin deficiency (Alberti and Zimmet 1998).

Attachment 4. New York Heart Association (NYHA) Cardiac Disease Classifications

Functional Capacity (CCNYHA 1994):

Class I.
Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.

Class II.
Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.

Class III.
Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.

Class IV.
Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

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