Protocol F3Z-GH-IOQR

Comparison Between Basal Insulin Analog and Insulin AnaLog Mid Mixture AS Starter Insulin for Chinese Patients With Type 2 Diabetes Mellitus (CLASSIC Study)

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Confidential Information

Basal Insulin Analog and Insulin Analog Mid Mixture

Study F3Z-GH-IOQR is a multicenter, China-based, open label, 48-week, randomized, parallel-design pragmatic study in Chinese patients with T2DM who have failed to achieve adequate glycemic control with oral anti-hyperglycemic medications (OAMs) with the aim to compare the effectiveness of basal insulin analog once daily and insulin analog mid mixture twice daily treatments in real world setting

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1. Synopsis

Title of Study:

Comparison Between Basal Insulin Analog and Insulin Analog Mid Mixture As Starter Insulin for Chinese Patients With Type 2 Diabetes Mellitus (CLASSIC Study)

Rationale:

The purpose of Study is to compare basal insulin analog once daily(QD) and insulin analog mid mixture twice daily (BID) as starter insulin regimen in Chinese patients with type 2 diabetes mellitus (T2DM) who have inadequate glycemic control with oral antihyperglycemic medications (OAMs) in real world settings.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary	
1. To compare change in HbA1c from baseline to 24 weeks between insulin analog mid mixture BID and basal insulin analog QD treatments	1. The change in HbA1c from baseline to 24 weeks
Secondary	
2. To compare change in HbA1c from baseline to 48 weeks between insulin analog mid mixture BID and basal insulin analog QD treatments	2. The change in HbA1c from baseline to 48 weeks
3. To compare the proportion of patients who achieve HbA1c <7% at 24 and 48 weeks between insulin analog mid mixture BID and basal insulin analog QD treatments	3. Proportion of patients who achieve HbA1c <7% at 24 and 48 weeks
4. To compare the change in venous FPG from baseline to 24 and 48 weeks between insulin analog mid mixture BID and basal insulin analog QD treatments	4. Venous FPG change from baseline at 24 and 48 weeks
5. To compare the change in FSBG-based FBG and PPG from baseline to 24 and 48 weeks between insulin analog mid mixture BID and basal insulin analog QD treatments	5.FSBG-based FBG, PPG change from baseline at 24 and 48 weeks
6. To compare the daily insulin dose at 24 and 48 weeks between insulin analog mid mixture BID and basal insulin analog QD treatments	6. Daily insulin dose at 24 and 48 weeks
7. To compare the change in body weight from baseline to 24 and 48 weeks between insulin analog mid mixture BID and basal insulin analog QD treatments	7. Body weight change from baseline at 24 and 48 weeks
8. To compare the severe, nocturnal and total hypoglycemia incidences and rates during the 24-week and 48-week treatment period between insulin analog mid mixture BID and basal insulin analog QD treatments	8. The severe, nocturnal and total hypoglycemia incidences and rates during the 24-week and 48-week treatment period

Objectives	Endpoints
9. To compare time to insulin treatment change between insulin analog mid mixture BID and basal insulin analog QD treatments	9. Time to insulin treatment change: Defined as time to any of: insulin treatment discontinuation, switch, intensification or reduction in frequency Discontinuation: Defined as stopping insulin treatment for 30 days or more. Switch: Defined as stop the initial insulin therapy and started another insulin therapy of different class. Intensification: Defined as any of the following: adding meal time insulin in basal insulin analog QD group; changing from BID to TID in insulin analog mid mixture BID group Reduction in frequency: Defined as any of the following: changing from BID to QD; changing from TID to BID or QD
10. To compare the proportion of patients who achieve the HbA1c <7% without switching and discontinuing study insulin, and without using rescue therapy between insulin analog mid mixture BID and basal insulin analog QD treatments	10. Proportion of patients who achieve the HbA1c <7% without switching and discontinuing study insulin, and without using rescue therapy
11. To compare the patients-reported self-efficacy related to insulin therapy as assessed using SEITQ between insulin analog mid mixture BID and basal insulin analog QD treatments	11. The change in SEITQ score form baseline at 48 weeks

Abbreviations: BID = twice daily; FBG = fasting blood glucose; FPG = fasting plasma glucose; FSBG =finger stick blood glucose; HbA1c = hemoglobin A1c; PPG = post prandial glucose; QD = once daily; SEITQ = Self-efficacy about Insulin Therapy Questionnaire; TID = three times a day.

Summary of Study Design:

Study F3Z-GH-IOQR (IOQR) is a multicenter, open-label, randomized, 48-week, parallel, 2-arm pragmatic trial comparing the effectiveness of basal insulin analog QD and insulin analog mid mixture BID treatments in real world setting in adult Chinese patients (≥18 and ≤80 years) with T2DM who have failed to achieve adequate glycemic control with OAMs (hemoglobin A1c [HbA1c] ≥7.5%)

Treatment Arms and Duration:

There are 2 arms in this 48 week study: basal insulin analog QD arm and insulin analog mid mixture BID arm

Number of Patients:

Approximately 830 participants will be randomized 1:1 into the 2 treatment groups such that there will be approximately 664 evaluable participants for primary analyses at Week 24.

Statistical Analysis:

General Considerations: Both efficacy and safety analyses will be performed on randomized patients.

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

The baseline value for measurements will be defined as the last non-missing observation on or before the randomization visit. If no data are available, the baseline value will be treated as missing.

For continuous measures, summary statistics will include at least number of patients with data, mean, standard deviation (SD), median, minimum, and maximum. For categorical measures, summary statistics will include at least number of patients with data, frequency counts, and percentages. For comparisons based on analysis models, the differences will be reported using least squares (LS) means, along with 95% confidence intervals (CIs) and p-value. Sometimes, treatment-wise comparison on the summary statistics may be performed and p-values provided, and such p-values should be viewed as a descriptive measure only. Unless specified otherwise, a two-sample t-test will be used for continuous measurements and Fisher's exact test will be used for categorical measurements.

Primary Analysis: Missing measurements will not be imputed as HbA1c will be only measured once post-baseline at Week 24. In addition to common summary statistics for the change from baseline data, the comparison between 2 treatment arms will be conducted using an analysis of covariate (ANCOVA) model, with change from baseline in HbA1c as response, treatment as fixed effect and baseline HbA1c as a covariate. The 95% CI of LS means difference (insulin analog mid mixture BID – basal insulin analog QD) will be used to make conclusions for the comparison.

Secondary Analyses: For change from baseline in venous fasting plasma glucose (FPG), finger stick blood glucose (FSBG)-based fasting blood glucose (FBG), post prandial glucose (PPG) and blood glucose (BG) excursion, the analyses model will be similar to the primary analyses model, except that the comparison will be based on the treatment contrast p-value from the ANCOVA model.

For percentages of patients reaching treatment goals (<7%) at Week 24 and Week 48, no missing data will be imputed. Count and percentages of patients reaching treatment goals will be summarized, and also be analyzed by a logistic regression model, with logit link function, treatment as fixed effect and baseline HbA1c as continuous covariate.

Insulin dose at each visit will be descriptively summarized by treatment groups by total daily dose (IU and IU/kg).

Safety: The incidence rate of case report form (CRF) collected severe, nocturnal and total hypoglycemic events will be summarized by visit and for the overall study duration. Pairwise comparison between treatment arms will be performed by Fisher's exact test. The overall yearly rates (events/patient/year) of those hypoglycemic events, calculated as, for each patient, the number of episodes times 365.25 and then divided by the patient's treatment duration, will be summarized, and analyzed by a negative-binomial regression model with treatment as fixed effects and log of (patient's treatment duration/365.25) as an offset variable.

Other Analyses: For the medial resource utilization and patient-reported outcome measurements summary statistics will be provided and comparison will be performed by appropriate general test.

Subgroup analysis will be performed for baseline HbA1c, baseline morning PPG, BG excursion, gender, and persistence levels in 2 treatment groups.

2. Schedule of Activities

Table IOQR.1. Schedule of Activities for Prospective Cohorts

eCRF Visit No.:	**1**	**2**	**3**	**4**	**5**	**6**	**ET[a]**
Week of treatment	**0**	**4**	**12**	**24**	**36**	**48**	**ET**
Visit Window (days)	**–**	**±7**	**±7**	**±7**	**±14**	**±14**	**±14**
Informed consent (before procedures/tests)	X						
Demographics	X						
Weight	X	X	X	X	X	X	X
Height	X						
Local urine pregnancy test [b]	X						
Duration of diabetes	X						
Anti-hyperglycemic medications(Non-insulin)	X	X	X	X	X	X	X
Insulin treatment [c]	X	X	X	X	X	X	X
Insulin dose [d]	X	X	X	X	X	X	X
Preexisting conditions/Adverse events [e]	X	X	X	X	X	X	X
Severe, nocturnal and total hypoglycemia events [f]	X	X	X	X	X	X	X
Other categories of hypoglycemia events (if available) [g]	X	X	X	X	X	X	X
HbA1c	X[h]			X[i]		X[i]	X[i]
Venous FPG [j]	X			X		X	X
2-point FSBG (pre-breakfast FBG and post-breakfast PPG) [k]	X			X		X	X
Randomization	X						
SEITQ	X			X		X	X
ITSQ				X		X	X
Healthcare resource utilization	X		X	X	X	X	X
Patient training	X						
Dispense study diary and instruct to use	X	X	X	X	X		
Review study diary		X	X	X	X	X	X

Abbreviations: eCRF = electronic case report form; ET = early termination; FBG = fasting blood glucose; FPG = fasting plasma glucose; FSBG = finger stick blood glucose; HbA1c = hemoglobin A1c; ITSQ = Insulin Treatment Satisfaction Questionnaire; No. = number; PPG = post prandial glucose; SEITQ = Self-efficacy about Insulin Therapy Questionnaire.

[a] Early termination (ET) visit is conducted within 14 days after the decision of discontinuation. At ET visit, fasting laboratory samples will be collected if possible.

[b] A urine pregnancy test will be performed locally only for women of childbearing potential.

[c] The current insulin treatment regimen, insulin treatment pattern change from last visit including insulin discontinuation, switch, intensification and reduction in frequency, and reason for insulin treatment pattern change will be recorded

[d] For Visit 1, prescribed daily insulin dose by the physician will be recorded. For the following visits, actual daily insulin dose of day prior to the visit will be recorded. If the insulin treatment is temporarily suspended or discontinued before the visit, the actual daily insulin dose of the day in which the patient received his/her last insulin treatment will be recorded.

[e] After the informed consent form (ICF) is signed, study site personnel will record the occurrence and nature of each patient's preexisting conditions. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs.

[f] Severe, nocturnal and total hypoglycemia events will be collected and analyzed as secondary endpoints.

[g] Other categories of hypoglycemia (documented symptomatic, asymptomatic, unspecified, probable symptomatic and relative hypoglycemia) events will be collected if available and analyzed as exploratory objectives

[h] Blood draw is not required for patients who already have measurement prior to study entry (value within 12 weeks).

[i] HbA1c will be drawn locally +/- 4 weeks of visit date

[j] Venous FPG will be drawn locally after a fast of at least 8 hours without eating, drinking (except for water) or performing any significant physical activity +/- 2 weeks of visit date. Missing venous FPG measurement will not be considered as a protocol violation.

[k] Two-point FSBG [pre-breakfast (fasting) FBG and post-breakfast (approximately 2 hours after breakfast) PPG] should be measured on one day within 1 to 2 weeks before or at Visit 1 (Week 0), Visit 4 (Week 24), Visit 6 (Week 48)or the ET visit (if possible).

3. Introduction

The International Diabetes Federation (IDF) reports that the number of people with type 2 diabetes mellitus (T2DM) is going up in every country, particularly in Asian countries such as China due to multiple contributing factors, including diet, genes, and lifestyle (Hu 2011). By 2035, the prevalence of diabetes is estimated to be 592 million globally, with an estimation of 143 million in China alone (IDF Diabetes Atlas 2013). A recent national survey in China estimated that about 9.7% of Chinese adults might have had diabetes, suggesting that China has the largest population of individuals with type 2 diabetes in the world (Yang et al. 2010).

3.1. Background

Basal or premixed insulins are the recommended insulin starters following oral antihyperglycemic medication (OAM) failure in Chinese patients according to guidelines released by the Chinese Diabetes Society (CDS 2013). Premixed insulins contain rapid- and intermediate-acting insulin that control fasting (preprandial) and postprandial glucose (PPG) elevations, respectively. In many Asian countries, including China, patients initiate insulin therapy with premixed insulins (CDS 2013). In fact, over 50% of Chinese T2DM patients initiated insulin therapy with premixed insulin while less than 20% patients initiated with basal insulin (Ji et al. 2009; Ji et al. 2011). Two main causes may contribute for this phenomenon. Firstly, in patients with high PPG, which is a characteristic of Asian patient population, treatment with mixtures provides additional benefits by controlling PPG elevation (Kalra et al. 2010). Secondly, a great proportion of Chinese patients need more aggressive insulin regimen due to delay in diagnosis or insulin initiation. Patients who require intensive insulin treatment may prefer premixed insulin with a less number of injections per day to basal bolus regimen (Jia et al. 2015). Generally speaking, although some physicians believe that basal insulin once daily is more suitable for patients with mild or moderate hyperglycemia following OAM failure while premixed insulin twice daily is more suitable for patients with moderate or even more severe hyperglycemia, the perception about efficacy and safety profile between premixed insulin analog and basal insulin analog is comparable in China.

Currently, 2 classes of insulin analog mixtures are available in the China market based on different formulations: low mixtures with low ratio of rapid acting insulin like insulin lispro 75/25 and insulin aspart 70/30, or mid mixtures with equal ratio of rapid acting insulin and intermediate acting insulin like insulin lispro 50/50 and insulin aspart 50/50. Most of the physicians selected low mixtures analog as start insulin in their practice. The reasons probably are that insulin analog mid mixtures went on the market after low mixtures and physicians are more familiar with premixed human insulins which are more commonly provided as low mixed formulation and have been used for a long time in China. At the same time, basal insulin analogs, including levermir and glargine, are also widely used in China.

The F3Z-CR-IOQI (IOQI) (CLASSIFY) study is a Phase 4, randomized, open-label, multinational and multicenter trial (Watada et al. 2016). It showed that LM25 and LM50 were noninferior to each other in improving glycemic control in East Asian patients with T2DM. Additionally, LM50 was more efficacious than LM25 with respect to the percentage of subjects

reaching target hemoglobin A1c (HbA1c) levels. In China subgroup which accounts for around 40% of the whole study population, LM50 is superior to LM25 in HbA1c change (-2.03% versus -1.55%) from baseline, and a significantly higher percentage of patients achieved HbA1c levels of <7% (72.4% versus 45.0%; P=0.001) levels in the LM50 treatment group compared to the LM25 treatment group, while no increased hypoglycemia incidence or more weight gain is observed in LM50 group as trade-off (Su et al. 2015a). The better response to LM50 in the Chinese population is probably due to the pronounced high PPG which reflects Chinese patient's venerable beta cell function and high carbohydrate intake diet (Su et al. 2015b; Chen et al. 2016).

This evidence is of great value in helping physician's select insulin regimens, but it is the sole multicenter clinical trial supporting the use of insulin analog mid mixture as start insulin. More investigation is needed on mid mixtures as starter insulin in East-Asia patients.

3.2. Study Rationale

Given the results of the IOQI randomized clinical trial (Section 3.1), the proposed pragmatic study is designed to compare these insulin initiation regimens in more generalizable populations and clinical settings.

Pragmatic clinical trials (PCTs) may be characterized by selection of relevant alternative interventions (including "usual care") for comparison, inclusion of a diverse study population from heterogeneous practice settings, and/or collection of data on a broad range of health outcomes. Hence, PCTs address relative efficacy as well as provide a high degree of external validity. The concept of experimental versus pragmatic is not a dichotomy but a continuum, and any given trial may have experimental features (for example, narrow patient selection criteria) and pragmatic features (for example, liberal co-medication rules).

Premixed insulin analogs (including both insulin analog low mixture and mid mixture) and basal insulin analogs are both widely used in China. Many randomized clinical trials have compared efficacy and safety between insulin analog low mixture and basal insulin in Chinese population (Yang et al. 2013; Li et al. 2014; Qin et al. 2014).

Generally speaking, the low mixture analog is either inferior or superior to basal insulin in Chinese patients with inadequate control under oral agent treatment. The compliance rate between mixture and basal insulin also is comparable in some observational studies.

Nonetheless, little evidence is available to compare the insulin analog mid mixture and basal insulin analog as starter insulin in real world setting.

This study will provide information on whether the effectiveness of insulin analog mid mixture twice daily (BID) is comparable with basal insulin analog once daily (QD) as starter insulin in real world setting (Primary objective).

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks of study insulin treatments may be found in the package inserts of these insulin products.

4. Objectives and Endpoints

Table IOQR.2 shows the objectives and endpoints of the study.

Table IOQR.2. Objectives and Endpoints

Objectives	Endpoints
Primary	
1. To compare change in HbA1c from baseline to 24 weeks between insulin analog mid mixture BID and basal insulin analog QD treatments	1. The change in HbA1c from baseline to 24 weeks
Secondary	
2. To compare change in HbA1c from baseline to 48 weeks between insulin analog mid mixture BID and basal insulin analog QD treatments	2. The change in HbA1c from baseline to 48 weeks
3. To compare the proportion of patients who achieve HbA1c <7% at 24 and 48 weeks between insulin analog mid mixture BID and basal insulin analog QD treatments	3. Proportion of patients who achieve HbA1c <7% at 24 and 48 weeks
4. To compare the change in venous FPG from baseline to 24 and 48 weeks between insulin analog mid mixture BID and basal insulin analog QD treatments	4. Venous FPG change from baseline at 24 and 48 weeks
5. To compare the change in FSBG-based FBG and PPG from baseline to 24 and 48 weeks between insulin analog mid mixture BID and basal insulin analog QD treatments	5.FSBG-based FBG, PPG change from baseline at 24 and 48 weeks
6. To compare the daily insulin dose at 24 and 48 weeks between insulin analog mid mixture BID and basal insulin analog QD treatments	6. Daily insulin dose at 24 and 48 weeks
7. To compare the change in body weight from baseline to 24 and 48 weeks between insulin analog mid mixture BID and basal insulin analog QD treatments	7. Body weight change from baseline at 24 and 48 weeks
8. To compare the severe, nocturnal and total hypoglycemia incidences and rates during the 24-week and 48-week treatment period between insulin analog mid mixture BID and basal insulin analog QD treatments	8. The severe, nocturnal and total hypoglycemia incidences and rates during the 24-week and 48-week treatment period

Objectives and Endpoints

Objectives	Endpoints
9. To compare time to insulin treatment change between insulin analog mid mixture BID and basal insulin analog QD treatments	9. Time to insulin treatment change: Defined as time to any of: insulin treatment discontinuation, switch, intensification or reduction in frequency Discontinuation: Defined as stopping insulin treatment for 30 days or more. Switch: Defined as stop the initial insulin therapy and started another insulin therapy of different class. Intensification: Defined as any of the following: adding meal time insulin in basal insulin analog QD group; changing from BID to TID in insulin analog mid mixture BID group Reduction in frequency: Defined as any of the following: changing from BID to QD; changing from TID to BID or QD
10. To compare the proportion of patients who achieve the HbA1c <7% without switching and discontinuing study insulin, and without using rescue therapy between insulin analog mid mixture BID and basal insulin analog QD treatments	10. Proportion of patients who achieve the HbA1c <7% without switching and discontinuing study insulin, and without using rescue therapy
11. To compare the patients-reported self-efficacy related to insulin therapy as assessed using SEITQ between insulin analog mid mixture BID and basal insulin analog QD treatments	11. The change in SEITQ score form baseline at 48 weeks
Tertiary/Exploratory	
12. To compare the insulin treatment pattern for • discontinuation • switch • intensification • reduction in frequency between insulin analog mid mixture BID and basal insulin analog QD treatments	12. Time to insulin discontinuation, switch, intensification or reduction in frequency Proportion of patients who experience insulin discontinuation, switch, intensification or reduction in frequency during 48 weeks
13. To compare healthcare resource utilization (all-cause and T2DM-related; inpatient, outpatient and ER) between insulin analog mid mixture BID and basal insulin analog QD treatments	13. Healthcare resource utilization (all-cause and T2DM-related;inpatient, outpatient and ER) during 48 weeks
14. To compare patients' perception of insulin treatment satisfaction, as assessed using the ITSQ at 24 and 48 weeks between insulin analog mid mixture BID and basal insulin analog QD treatments	14. Domain and total ITSQ score at 24 and 48 weeks
15. To compare the patients-reported self-efficacy related to insulin therapy as assessed using SEITQ between insulin analog mid mixture BID and basal insulin analog QD treatments	15. The change in SEITQ score form baseline at 24 weeks

Objectives and Endpoints

Objectives	Endpoints
16. To compare the incidences and rates of other categories of hypoglycemia (documented symptomatic, asymptomatic, unspecified, probable symptomatic and relative hypoglycemia), if available, during the 24-week and 48-week treatment period between insulin analog mid mixture BID and basal insulin analog QD treatments	16. The incidences and rates of other categories of hypoglycemia (documented symptomatic, asymptomatic, unspecified, probable symptomatic and relative hypoglycemia), if available, during the 24-week and 48-week treatment period

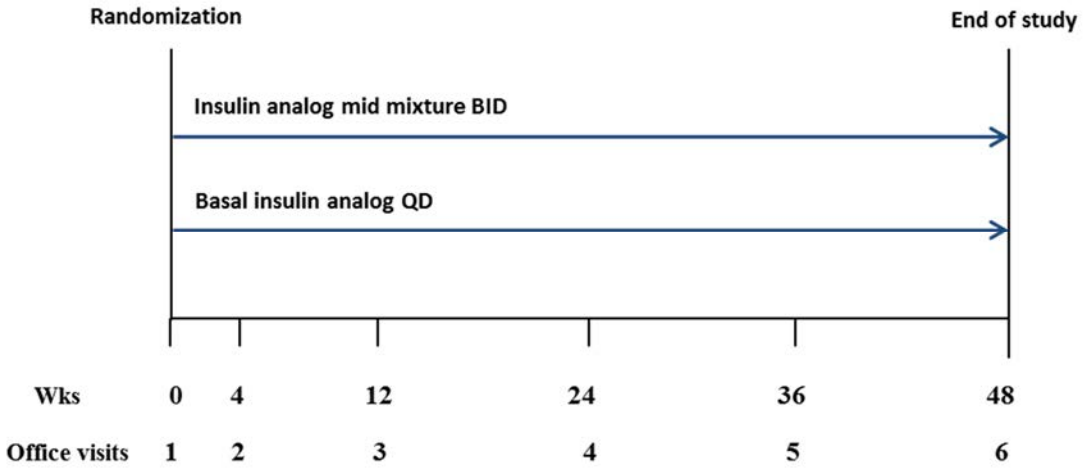
Abbreviations: BID = twice daily; FBG = fasting blood glucose; FPG = fasting plasma glucose; FSBG =finger stick blood glucose HbA1c = hemoglobin A1c; ITSQ = Insulin Treatment Satisfaction Questionnaire; PPG = post prandial glucose; QD = once daily; SEITQ = Self-efficacy about Insulin Therapy Questionnaire; T2DM = type 2 diabetes mellitus; TID = three times daily.

5. Study Design

5.1. Overall Design

Study F3Z-GH-IOQR (IOQR) is a multicenter, randomized, 48-week, parallel, 2-arm pragmatic trial in Chinese patients with T2DM who have failed to achieve adequate glycemic control with OAMs comparing the effectiveness of insulin analog mid mixture BID and basal insulin analog QD treatments in real world setting.

Figure IOQR.1 illustrates the study design.



Abbreviations: BID = twice daily; QD = once daily; wks = weeks.

Figure IOQR.1. Illustration of study design for Pragmatic Study F3Z-GH-IOQR.

5.2. Number of Participants

Approximately 830 participants will be randomized 1:1into the 2 treatment groups such that there will be approximately 664 evaluable participants for primary analyses at Week 24

5.3. End of Study Definition

End of the trial is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last patient.

5.4. Scientific Rationale for Study Design

Given the results of the previous IOQI randomized clinical trial, this pragmatic study is designed to demonstrate that the results drawn from the randomized clinical trial can be applied in more generalizable populations and real world settings.

According to the scientific questions raised, instead of a randomized clinical trial (RCT) or a prospective observational study, a PCT is selected because the study aims to compare effectiveness in real world settings with minimal intervention while randomization is required to remove selection bias and other confounding factors between arms.

Two arms including basal insulin analog, and insulin analog mid mixture will be compared in a Chinese general T2DM population. The following considerations have been incorporated into study design to ensure a robust study that represents real world situations:

- Restriction on inclusion and exclusion criteria for patients in this study is minimal compared with a typical RCT. Patients enrolled will represent a general T2DM population with uncontrolled HbA1c levels under OAM.
- There is also no restriction on insulin titration algorithm and OAM use. Also there is no restriction on switching or augmenting the initial insulin treatment. Physicians can pursue their general practice governed by local guideline.
- The schedule of visits is aimed to reflect real-world practice. In general, the frequency of visits to physician offices after insulin initiation is weekly or biweekly in a real world setting for dose titration and adjustment (CDS 2013). Therefore, the potential intervention brought by the scheduled monthly or every 3 month visits could be considered minimal.
- The duration of this study is 48 weeks which is relatively longer than a typical RCT with 24 or 26 weeks comparing 2 insulin regimens by measuring HbA1c. So adequate information from real world settings could be observed and collected.
- In China, the community based primary care health system is not well developed, and most of the patients go to see the endocrinologists to start insulin treatment instead of general practitioners. Therefore in this study, no community based clinical center will be selected as study sites.

In summary, the study design presented is intended to provide a better understanding of the real-world feasibility and performance of initiating insulin treatment with insulin analog mixtures.

5.5. Justification for Dose

No dose range assessment exists for this trial, therefore this is not applicable. This is a pragmatic trial and insulin titration will be determined by individual investigator as would occur in clinical practice setting.

6. Study Population

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

6.1. Inclusion Criteria

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

[1] have type 2 diabetes as defined by World Health Organization (WHO) criteria (Appendix 2)

[2] are ≥18 and ≤80 years of age at the time of Visit 1

[3] are taking OAMs and are judged as OAM failure by the investigator

[4] most recent HbA1c value ≥7.5% within 12 weeks of study entry

[5] in the opinion of the investigator, require to initiate premix analog or basal insulin analog treatment

[6] willing to start with insulin treatment

[7] are able and willing to give signed informed consent (Appendix 3)

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at enrollment:

[8] have a diagnosis of type 1 diabetes

[9] have received any type of insulin within 24 months of study entry (except for intermittent use of insulin of less than 1 month each time)

[10] have serious preexisting medical or other conditions that, in the judgment of the investigator, would preclude participation in this study.

[11] are pregnant or breastfeeding, or intend to become pregnant during the course of the study

[12] are currently enrolled or have participated, within the last 30 days in any other clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible

6.3. Lifestyle Restrictions

Not applicable.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

7. Treatments

7.1. Treatments Administered

This study involves a comparison of insulin analog mid mixture BID and basal insulin analog QD in routine care.

No drug will be provided, but drug treatments expected for this trial are:

- Insulin analog mid mixture: for example, Humalog Mix50, Novorapid 50
- Basal insulin analog: for example, insulin glargine, insulin detemir

After randomization to initial insulin treatment regimen, treatment decisions will be solely at the discretion of the physician and the patient, and anti-hyperglycemia treatment will be conducted within the construct of the standard care according to CDS guideline (CDS 2013).

Investigational products are defined as insulins being used in this study.

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

- explaining the correct use of the investigational products to the patient or care givers.
- verifying that instructions are followed properly

7.1.1. Packaging and Labelling

All study drugs are commercially available. Study drug will not be supplied to patients.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized to treatment/intervention at Visit 1. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive voice-response system (IVRS) or interactive web-response system (IWRS) and then the site will be responsible for providing the treatment/intervention to the patients.

7.2.1. Selection and Timing of Doses

The dose will be initiated, titrated and maintained at the discretion of the investigator following the usual standard of care according to CDS guideline (CDS 2013).

The timing of doses will follow product labels.

7.3. Blinding

This is an open-label study.

7.4. Dosage Modification

Dose adjustments are at the discretion of investigator following usual standard of care.

7.5. Preparation/Handling/Storage/Accountability

The healthcare professionals (HCPs) are responsible to ensure the safe handling and appropriate storage of the investigational products.

7.6. Treatment Compliance

No patient-reported and HCP-perceived compliance of the treatment will be assessed.

7.7. Concomitant Therapy

All concomitant therapies that are part of routine care are allowed and can be used during the study.

Only anti-hyperglycemic concomitant therapy will be collected at baseline and throughout the study (Section 2).

7.8. Treatment after the End of the Study

7.8.1. Study Extensions

Not applicable.

7.8.2. Continued Access

The insulin analogs used in this study are commercially available in China.

7.8.3. Special Treatment Considerations

Rescue therapy for hyperglycemia and hypoglycemia will be determined by the investigator following usual standard of care.

7.8.4. Patient Follow-Up in Pragmatic Trials

Patient follow-up is dictated only by usual care, no additional visit is required by the protocol.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

Not applicable due to the pragmatic nature of this trial.

8.1.2. Temporary Discontinuation from Study Treatment

Not applicable due to the pragmatic nature of this trial.

8.1.3. Discontinuation of Inadvertently Enrolled Patients

Not applicable due to the pragmatic nature of this trial.

8.2. Discontinuation from the Study

Patients will be discontinued from study in the following circumstances:

- Exclusion criteria: [10], [11] or [12] is/are observed or develop(s) after study entry or enrollment.

Some possible reasons that may lead to permanent discontinuation include:

- 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
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- investigator decision
    - the investigator decides that the patient should be discontinued from the study
- subject decision
    - the patient or the patient's designee, for example, parents or legal guardian requests to be withdrawn from the study

Patients who discontinue from the study early will have end-of-study procedures performed as shown in the Schedule of Activities (Section 2).

8.3. Lost to Follow-Up

A patient 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 patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, with the study procedures and their timing (including tolerance limits for timing).

9.1. Efficacy Assessments

9.1.1. Primary Effectiveness Assessments

The primary efficacy measure is the change in HbA1c from baseline to 24 weeks.

9.1.2. Secondary Effectiveness Assessments

The following secondary effectiveness measures will be collected at the time shown in the Schedule of Activities (Section 2):

- the change in HbA1c from baseline to 48 weeks
- proportion of patients who achieve HbA1c <7% at 24 and 48 weeks
- venous fasting plasma glucose (FPG) change from baseline at 24 and 48 weeks
- finger stick blood glucose (FSBG)-based fasting blood glucose (FBG), PPG change from baseline at 24 and 48 weeks
- daily insulin dose at 24 and 48 weeks
- body weight change from baseline at 24 and 48 weeks
- the severe, nocturnal and total hypoglycemia incidences and rates during the 24-week and 48-week treatment period
- time to insulin treatment change
- proportion of patients who achieve the HbA1c <7% without switching and discontinuing study insulin, and without using rescue therapy
- the change in Self-efficacy about Insulin Therapy Questionnaire (SEITQ) score from baseline at 48 weeks

9.1.3. Exploratory Effectiveness Assessments

- time to insulin discontinuation, switch, intensification or reduction in frequency
- proportion of patients who experience insulin discontinuation, switch, intensification or reduction in frequency during 48 weeks
- healthcare resource utilization (all-cause and T2DM-related; inpatient, outpatient and emergency room [ER]) during 48 weeks
- domain and total Insulin Treatment Satisfaction Questionnaire (ITSQ) score at 24 and 48 weeks
- the change in SEITQ score form baseline at 24 weeks

- the incidences and rates of other categories of hypoglycemia (documented symptomatic, asymptomatic, unspecified, probable symptomatic and relative hypoglycemia), if available, during the 24-week and 48-week treatment period

9.1.4. Appropriateness of Assessments

All effectiveness and safety measures assessed in this study are all well-established measures for insulin treatment.

Patient-reported outcomes measures (SEITQ, ITSQ) included in this study have been designed to provide information from the patient and the HCP perspective. Healthcare resource utilization assessments included in this study are acceptable methods for determining the impact of treatment/intervention from the payer perspective.

If a patient is unable to complete the questionnaire without assistance, someone not affiliated with the study may assist the patient in completing the questionnaire.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of patients 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 patient.

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

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, adverse events (AEs) that are serious or otherwise medically important, considered related to the investigational products or the study, or that caused the patient to discontinue the investigational products before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

After the informed consent form (ICF) is signed, study site personnel will record via case report form (CRF) the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure and/or investigational product, via CRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease and concomitant treatment or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between investigational products and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a patient's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via CRF, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

9.2.1. Serious Adverse Events

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

- death
- 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, based upon appropriate medical judgment.

Although all AEs occurring after signing the ICF are recorded in the CRF, serious adverse event (SAE) reporting begins after the patient has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, it needs to be reported ONLY if it is considered reasonably possibly related to study procedure.

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.

Pregnancy (during maternal or paternal exposure to investigational products) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the patient summary CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

Investigators or other study personnel are requested to report adverse reactions in temporal association with Lilly drugs not under evaluation and with any non-Lilly drugs to the appropriate

party (for example, regulators or local market authorization holder) as they would in normal practice as required by applicable laws, regulations, and practices.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the investigator's brochure (IB) and that the investigator identifies as related to investigational products or procedure. 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 guidances.

9.2.2. Complaint Handling

Lilly collects product complaints on investigational products 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.

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

Investigators are instructed to report product complaints related to marketed products directly to the manufacturer following package inserts.

9.3. Treatment of Overdose

Refer to the product label of study insulins for advice on overdose.

9.4. Safety

9.4.1. Hypoglycemia

Patients will be trained about signs and symptoms of hypoglycemia, how to treat hypoglycemia, and how to collect appropriate information in the study diary according to the Schedule of Activities (Section 2). Hypoglycemia will be classified as follows (ADA 2005) (Note: the blood glucose (BG) concentrations listed below refer to values reported by a laboratory or obtained with FSBG meter):

- **Documented symptomatic hypoglycemia:** An event during which typical symptoms of hypoglycemia are accompanied by BG ≤70 mg/dL (≤3.9 mmol/L).
- **Asymptomatic hypoglycemia:** An event not accompanied by typical symptoms of hypoglycemia but with BG ≤70 mg/dL (≤3.9 mmol/L).
- **Unspecified hypoglycemia:** An event during which BG ≤70 mg/dL (≤3.9 mmol/L) but no information relative to symptoms of hypoglycemia was recorded
- **Severe hypoglycemia:** An event requiring assistance of another person to actively administer carbohydrate, glucagon, or 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 BG concentration to normal is considered sufficient evidence that the event was induced by a low BG concentration (BG ≤70 mg/dL [≤3.9 mmol/L]).

- **Nocturnal hypoglycemia:** Any hypoglycemic event (documented hypoglycemia or probable symptomatic hypoglycemia, including severe hypoglycemia) that occurs between bedtime and waking. This is consistent with the ADA recommendations of reporting events that occur during sleep (ADA 2005). It is also important to collect the actual time when a hypoglycemic event occurred to allow further characterization of hypoglycemia timing (for example, to qualify the hypoglycemic events that are occurring between midnight to 6 AM or to look at frequency of events occurring across a 24-hour clock).
- **Probable symptomatic hypoglycemia:** An event during which symptoms indicative of hypoglycemia are not accompanied by a BG determination (but that was presumably caused by BG ≤70 mg/dL [≤3.9 mmol/L]).
- **Relative hypoglycemia:** An event during which typical symptoms of hypoglycemia, that do not require the assistance of another person, are accompanied by BG >70 mg/dL (>3.9 mmol/L), but these levels may be quickly approaching the 70 mg/dL (3.9 mmol/L) threshold. The BG level of patients with chronically poor glycemic control can decrease so rapidly that patients may report symptoms of hypoglycemia before their BG concentration is <70 mg/dL (<3.9 mmol/L). The evaluation of this category is optional. However, if a patient reports a relative hypoglycemia event where assistance from another person was received or the patient experienced significant symptoms, the study team should clarify the circumstances to ensure the event is not a severe hypoglycemia event, and report it appropriately.
- **Total hypoglycemia:** This optional category combines all cases of hypoglycemia (documented hypoglycemia or probable symptomatic hypoglycemia, including severe hypoglycemia) excluding the events of relative hypoglycemia. Nocturnal and severe hypoglycemia are special cases of documented or probable hypoglycemia. If an event of hypoglycemia falls into multiple subcategories, that event should only be counted once in this category.

All episodes of hypoglycemia should be recorded in the "Hypoglycemic Episodes" section of the electronic case report form (eCRF). If a hypoglycemic event meets the criteria of SAE (Section 9.2.1), it should also be recorded on "Serious Adverse Events" section of the eCRF (that is, recorded as an SAE).

Severe, nocturnal and total hypoglycemia events will be collected and analyzed as secondary endpoints. Other categories of hypoglycemia (documented symptomatic, asymptomatic, unspecified, probable symptomatic and relative hypoglycemia) events will be collected if available and analyzed as exploratory objectives.

9.4.2. Electrocardiograms

Not applicable.

9.4.3. Vital Signs

For each patient, height and weight should be conducted according to the Schedule of Activities (Section 2).

9.4.4. Clinical Laboratory Tests

For each patient, HbA1c and FBG should be obtained locally according to the Schedule of Activities (Section 2).

Two-point FSBG [pre-breakfast (fasting) and post-breakfast (approximately 2 hours after breakfast)] should be measured on one day within 1 to 2 weeks before or at Visit 1 (Week 0), Visit 4 (Week 24), Visit 6 (Week 48), or the ET visit (if possible).

For each woman of childbearing potential (as assessed by the HCP), a urine pregnancy test should be obtained locally according to the Schedule of Activities (Section 2).

9.4.5. Other Tests

Not applicable.

9.4.6. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

9.5. Pharmacokinetics

Not applicable.

9.6. Pharmacodynamics

Not applicable.

9.7. Pharmacogenomics

Not applicable.

9.8. Biomarkers

Not applicable.

9.9. Medical Resource Utilization and Health Economics

9.9.1. Insulin Treatment Pattern

The insulin treatment patterns of interest during the 48-week period were defined as follows:

- **Discontinuation:** Defined as stopping insulin treatment for 30 days or more. Time to discontinuation will be calculated as the number of days from initiation of insulin to insulin discontinuation or censoring. Time to insulin discontinuation and proportion of patient discontinued insulin will be compared.
- **Switch:** Defined as stop the initial insulin therapy and started another insulin therapy of different class. Proportion of patient switching and time to switching will be compared.

  Note: Switching to a different brand of the same class will not be considered as an insulin treatment pattern switch.
- **Intensification:** Defined as any of the following: adding meal time insulin in basal insulin analog QD group; changing from BID to TID in insulin analog mid mixture BID group. Time to insulin treatment intensification and proportion of patient undergone insulin treatment intensification will be compared.
- **Reduction in frequency**: Defined as any of the following: changing from BID to QD; changing from TID to BID or QD. Time to insulin treatment reduction in frequency and proportion of patient undergone insulin treatment reduction in frequency will be compared.
- **Time to insulin treatment change:** Defined as time to any of: insulin treatment discontinuation, switch, intensification, or reduction in frequency.

  Insulin treatment change and reason for insulin treatment change will be collected in the CRF by investigator and study-site personnel for all participants throughout the study.

9.9.2. Patient-Reported Outcomes

The self-reported questionnaires will be administered according to the Schedule of Activities (Section 2). These questionnaires have been translated into Chinese and linguistically validated.

Self-efficacy about Insulin Therapy Questionnaire (SEITQ). The SEITQ is designed to measure an individual's self-efficacy related to insulin therapy. The SEITQ consists of 5 items (that is, statements). The first 4 statements imply confidence in completing the tasks needed to take insulin correctly and avoid both hyperglycemia and hypoglycemia, whereas the last statement is an outcome expectation and implies that performance of these tasks will lead to avoidance of complications. The items are preceded by the stem "I am confident that I will be able to..." The directions ask respondents to indicate their level of agreement with each statement on a 7-point scale ranging from "1" (Strongly disagree) to "7" (Strongly Agree). The directions do not include a recall period nor do they refer to a specific insulin therapy or delivery system.

Insulin Treatment Satisfaction Questionnaire (ITSQ). The ITSQ is a validated measure consisting of 22 items that comprehensively assess treatment satisfaction for persons with

diabetes taking insulin. Items are measured on a 7-point scale, where lower scores reflect better outcomes. In addition to an overall score, the items that make up the 5 domains of satisfaction are categorized as: ·Inconvenience of Regimen (5 items), Lifestyle Flexibility (3 items), Glycemic Control (3 items), Hypoglycemic Control (5 items), and Insulin Delivery Device (6 items).

9.9.3. Healthcare Resource Utilization

Medical resource utilization data, associated with medical encounters, will be collected in the CRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

Healthcare resource utilization will be examined as all-cause and T2DM-related, and categorized as inpatient, outpatient, and ER utilizations:

- Inpatient hospital utilization will be identified using medical encounters where the place of service is an inpatient hospital facility.
- Outpatient utilization will be identified using medical encounters where the place of service is outpatient facility.
- Emergency room utilization will be identified using medical encounters where the place of service is an ER. Emergency room claims that have the same service date as a hospitalization will not be counted as an ER visit. Emergency room visits adjacent to a hospitalization will be considered a hospitalization and will not be counted as an ER visit.

The data collected may be used to conduct exploratory economic analyses and will include:

- number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- reason and duration of hospitalization (total days length of stay, including duration by wards; for example, intensive care unit)
- number and character of diagnostic and therapeutic tests and procedures

10. Statistical Considerations

10.1. Sample Size Determination

The primary objective of the study will be evaluated using the classification method as proposed by Qu and colleagues (2011). With no prior hypothesis specified, the study will be considered a success if a conclusion may be reached by the classification method. With a 1:1 randomization ratio between insulin analog mid mixture BID and basal insulin analog QD, and assuming a non-inferiority margin of 0.4%, no treatment difference between mid mixture BID and basal insulin analog QD, and a common SD of 1.5% for the change from baseline in HbA1c at Week 24, 332 evaluable patients per arm will provide greater than 99% possibility for the study to reach a conclusion for primary analyses with 2-sided alpha level of 0.05. If we assume 20% of the patients will drop out without providing an evaluable post-baseline HbA1c), 415 patients per arm need to be randomized.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who signed informed consent.
Randomized	All participants who were enrolled and who were randomized to any one of the treatment groups.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. Any change 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 change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan (SAP) or the clinical study report (CSR). Additional exploratory analyses of data will be conducted, as deemed appropriate.

Given the nature of this pragmatic study, both efficacy and safety analyses will be performed on randomized patients. As sensitivity analyses, certain efficacy analyses may be repeated by censoring all efficacy data after patients changed the randomized treatment regimen.

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

The baseline value for measurements will be defined as the last non-missing observation on or before the randomization visit. If no data are available, the baseline value will be treated as missing. The Week 24 value for measurements will be the last non-missing post-baseline observation up to 24 weeks, and the Week 48 value for measurements will be the last non-missing post-baseline observation up to 48 weeks.

For continuous measures, summary statistics will include at least the number of patients with data, mean, SD, median, minimum, and maximum. For categorical measures, summary statistics will include at least the number of patients with data, frequency counts, and percentages. For comparisons based on analysis models, the differences will be reported using LS means, along with 95% CIs and p-value. Sometimes, comparison on the summary statistics may be performed and p-values be provided, and such p-values should be viewed as a descriptive measure only. Unless specified otherwise, a two-sample t-test will be used for continuous measurements and Fisher's exact test will be used for categorical measurements.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

The overall study disposition status will be summarized over all enrolled patients. Reasons for screen failures and study discontinuations will be tabulated for each treatment arm and overall population.

10.3.2.2. Patient Characteristics

Patient characteristics at baseline (for example, demographics, diabetes history, and comorbidity) will be summarized by treatment arm and overall population. No formal statistical comparisons will be performed.

10.3.2.3. Concomitant Therapy

Anti-hyperglycemic concomitant therapy will be summarized at baseline and throughout the study by treatment arm and overall population. General concomitant therapy will not be collected or summarized.

10.3.2.4. Treatment Compliance

No patient-reported and HCP-perceived compliance of the treatment will be collected and summarized.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary outcome of the study is the change from baseline in HbA1c at Week 24. In this study, HbA1c will be only measured once post-baseline at Week 24, so missing measurements will not be imputed. In addition to common summary statistics for the change from baseline data, the comparison between 2 treatment arms will be conducted using an analysis of covariate (ANCOVA) model, with change from baseline in HbA1c as response, treatment as fixed effect and baseline HbA1c as a covariate. The 95% CI of LS means difference (insulin analog mid mixture BID – basal insulin analog QD) will be used to make conclusions for the comparison. Specifically, let L and U be the lower and upper limit of this CI. Then,

- If L>-0.4%, the Non-inferiority (NI) of basal insulin analog QD to insulin analog mid mixture BID is established;
- If L>0%, the superiority of basal insulin analog QD to insulin analog mid mixture BID is established;

- If U<0.4%, the NI of insulin analog mid mixture BID to basal insulin analog QD is established;
- If U<0%, the superiority of insulin analog mid mixture BID to basal insulin analog QD is established;

For more details, refer to the SAP and Qu and colleagues (2011). P-value for the treatment contrast from the ANCOVA may still be displayed, but should not be used to make a conclusion.

As a sensitivity analyses, the primary analyses will be repeated by censoring all efficacy data after patients changed the randomized treatment regimen.

10.3.3.2. Secondary Analyses

For change from baseline in HbA1c at Week 48, the analyses model will be similar to the primary analyses model, and the sensitivity analyses will also be performed. Also, a mixed-model repeated measures (MMRM) model will be employed to analyze the HbA1c change from baseline at Week 48. This MMRM model will have all post-baseline HbA1c as responses, baseline HbA1c as a continuous covariate, treatment group, Visit (Week 24 or Visit 48), and treatment by visit interaction as fixed effects and patient as a random effect. Treatment contrast at Week 48 will be used for making the inference.

For change from baseline in venous FPG, FSBG-based FBG, PPG, BG excursion and bodyweight at Week 24 and Week 48, the analyses will be done similarly to the primary analyses model (ANCOVA for Week 24 and Week 48, and MMRM for Week 48), except for the comparison will be based on the treatment contrast p-value from the corresponding analyses model.

For percentages of patients reaching treatment goals (<7%) at Week 24 and Week 48, no missing data will be imputed. Count and percentages of patients reaching treatment goals will be summarized (when calculating percentages, the denominator will be the patients with non-missing HbA1c data at Week 24 or Week 48), and also be analyzed by a logistic regression model, with logit link function, treatment as fixed effect and baseline HbA1c as continuous covariate. Same analyses strategy will be used for the composite endpoint of patients reaching treatment goals (<7%) and did not switch from or discontinue study treatment, and did not take rescue medication.

Insulin dose at each visit will be descriptively summarized by treatment groups by total daily dose (IU and IU/kg).

Time to insulin treatment change (as defined in Section 9.9.1) will be compared between treatment arms by a log rank test at Week 48. Patients who did not have any insulin treatment change up to Week 48 (or up to early discontinuation) will be considered as censored at Week 48 (or time of early discontinuation) with no event.

10.3.4. Safety Analyses

General AEs will be collected in this study. Count and frequency of AEs will be summarized for overall study population and by treatment arm. Also, AEs as a cause for insulin treatment change will be collected, and summarized by treatment arm.

Serious adverse events will be collected and reported per Lilly standard operating procedure (SOP) and local regulatory requirement. Count and frequency of SAEs will be summarized by treatment arm.

The incidence rate of CRF-collected severe, nocturnal and total hypoglycemic events will be summarized by visit and for the overall study duration. Comparison between treatment arms will be performed by Fisher's exact test. The overall yearly rates (events/patient/year) of those hypoglycemic events, calculated as, for each patient, the number of episodes times 365.25 and then divided by the patient's treatment duration, will be summarized, and analyzed by a Negative-binomial regression model with treatment as fixed effects and log of (patient's treatment duration/365.25) as an offset variable.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

No pharmacokinetic/pharmacodynamics (PK/PD) analyses will be performed in this study.

10.3.6. Other Analyses

10.3.6.1. Medical Resource Utilization and Health Economics

10.3.6.1.1. Adherence and Insulin Treatment Pattern

For these measurements, summary statistics will be provided, and comparison will be performed by appropriate general test (see Section 10.3.1).

10.3.6.1.2. Resource Utilization

Utilization data will be summarized descriptively by category across arms (for example, surgery, and hospitalization days) for a treatment arm, including a frequency table with tabular statistics. Tests for differences in proportions between treatment arms will be performed.

10.3.6.1.3. Insulin Treatment Satisfaction Questionnaire (ITSQ)

Overall and domain scores will be summarized and tabulated for ITSQ score at endpoint.

10.3.6.1.4. SEITQ = Self-efficacy about Insulin Therapy Questionnaire (SEITQ)

Categorical responses for the each question will be summarized at baseline and endpoint. Comparisons will also be performed.

10.3.6.2. Subgroup Analyses

Subgroup analyses may be performed on selected outcomes in subgroups of interest. All subgroup analyses will be exploratory in nature. As the interest will be on how different treatment regimens work in a specific subgroup, instead of whether the treatment differences are the same across different subgroups, the subgroup analyses will be performed by analyzing the outcome data in different subgroups, instead of analyzing the outcome data in the whole population with subgroup factors included in the analyses model.

The following subgroups will be explored, and additional subgroups may be further explored if needed:

- baseline HbA1c (<8.4% and ≥8.4%)
- baseline morning PPG (<13.5 mmol/L and ≥13.5 mmol/L)
- baseline morning BG excursion (<4.4 mmol/L and ≥4.4 mmol/L)
- baseline body mass index (BMI) (<25 and ≥25)
- gender (male and female)
- 3-month persistence (discontinued insulin in the first 3 months of treatment or not)

10.3.7. Interim Analyses

An interim analysis may be conducted after all patients complete Visit 4. The analysis will include the primary objective and key secondary objectives to be described in more detail in the SAP. Although the study is open label, in order to avoid influencing study conduct in any way results will not be publicly disclosed until the last patient completes Visit 6.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
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.
ANCOVA	analysis of covariance
BG	blood glucose
BID	bwice daily
BMI	body mass index
CIOMS	Council for International Organizations of Medical Sciences
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.
CRF/eCRF	case report form/electronic case report from
CSR	clinical study report
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ER	emergency room
ERB	ethical review board
FBG	fasting blood glucose
FPG	fasting plasma glucose
FSBG	finger stick blood glucose
GCP	good clinical practice

HbA1c	hemoglobin A1c
HCP	healthcare professional
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDF	International Diabetes Federation
Investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
ITSQ	Insulin Treatment Satisfaction Questionnaire
IVRS/	interactive voice-response system
IWRS	interactive web-response system
MMRM	mixed-model repeated measures
NI	Non-inferiority
OAMs	oral antihyperglycemic medications
PCT	pragmatic clinical trial
PD	pharmacodynamic
PK	pharmacokinetic
PPG	post prandial glucose
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
QD	once daily
RCT	randomized clinical trial
SAE	serious adverse event
SAP	statistical analysis plan
SEITQ	Self-efficacy about Insulin Therapy Questionnaire
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. BG measured by Self-Monitoring Blood Glucose Device

SUSARs	suspected unexpected serious adverse reactions
WHO	World Health Organization
T2DM	type 2 diabetes mellitus


CCI

Appendix 3. Study Governance Considerations

Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 3.1.1. Informed Consent

The investigator is responsible for ensuring:

- that the patient understands the potential risks and benefits of participating in the study
- that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational products.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

Appendix 3.1.2. Ethical Review

The investigator or an appropriate local representative must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Conference on Harmonisation (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 site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on Good Clinical Practice (GCP).

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

- the current package inserts and updates during the course of the study
- informed consent form
- relevant curricula vitae

Appendix 3.1.3. 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 (CIOMS) International Ethical Guidelines
- applicable ICH GCP Guidelines
- applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third-party.

Appendix 3.1.4. Investigator Information

Physicians who work in teaching or nonteaching hospitals with a specialty in in endocrinology or internal medicine and over three years' experience initiating premix or basal insulin in type 2 diabetes mellitus (T2DM) patients, will be qualified to participate as investigators in this clinical trial.

Appendix 3.1.5. 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.

Appendix 3.1.6. Final Report Signature

The clinical study report (CSR) coordinating investigator will sign the final CSR 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 CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Appendix 3.2. 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
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the case report forms (CRFs), 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 CRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the patient 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.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Appendix 3.2.1. 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 electronic data capture system.

Any data for which paper documentation provided by the patient 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 patient may include, for example, a paper diary to collect patient-reported outcome (PRO) measures (for example, a rating scale), a daily dosing schedule, or an event diary.

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

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

Appendix 3.3.2. 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.

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