Statistical Analysis Plan 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)

NCT03018938

Approval Date: 28-FEB-2017

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# Statistical Analysis Plan (SAP)

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**SIGNATURE PAGE STATISTICAL ANALYSIS PLAN**

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## REVISION HISTORY

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# 1. GLOSSARY OF ABBREVIATIONS

| Abbreviation or special term | Explanation |
|---|---|
| AE | Adverse Event |
| ANCOVA | Analysis of Covariance |
| BG | Blood glucose |
| D | Twice daily |
| BMI | Body Mass Index |
| CRF | Case Report Form |
| FBG | Fasting blood glucose |
| FPG | Fasting plasma glucose |
| FSBG | Finger stick blood glucose |
| HbA1c | Hemoglobin A1c |
| HCP | Healthcare processional |
| ITSQ | Insulin Treatment Satisfaction Questionnaire |
| MMRM | Mixed Model Repeated Measurements |
| NI | Non-inferiority |
| OAMs | Oral antihyperglycemic medications |
| PPG | Post prandial glucose |
| QD | Once daily |
| SAE | Serious adverse event |
| SEITQ | Self-efficacy about Insulin Therapy Questionnaire |
| TEAE | Treatment-emergent adverse event |
| TID | Three times a day |
| WHO | World health organization |
| T2DM | Type 2 diabetes mellitus |

## 2. INTRODUCTION

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. The table of contents and templates for the TFLs will be produced in a separate document.

## 3. STUDY OBJECTIVES AND ENDPOINTS

The objectives and endpoints of the study shows below：

| 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 | 6. Daily insulin dose at 24 and 48 weeks |

| | |
|---|---|
| basal insulin analog QD treatments | |
| 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 |
| 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<br><br>Discontinuation: Defined as stopping insulin treatment for 30 days or more.<br><br>Switch: Defined as stop the initial insulin therapy and started another insulin therapy of different class.<br><br>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<br><br>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<br>• discontinuation<br>• switch<br>• intensification<br>• reduction in frequency<br>between insulin analog mid mixture BID and basal insulin analog QD treatments | 12. Time to insulin discontinuation, switch, intensification or reduction in frequency<br>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 |
| 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 |

## 4. SUMMARY OF STUDY 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.

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

## 5. 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.

## 6. POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined:

### 6.1. Enrolled population

Enrolled population includes all participants who signed informed consent.

### 6.2. Randomized population

Randomized population includes all participants who were enrolled and who were randomized to any one of the treatment groups.

## 7. HANDLING OF MISSING DATA AND OUTLIERS

### 7.1. Handling of Missing Efficacy Data

The baseline value for efficacy measurements, which include HbA1c, FPG, FSBG-based FBG, PPG, BG excursion, daily insulin, body weight, SEITQ score, 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 last records within each window (Appendix 1) will be used for analyses for Week 24/Week 48.

### 7.2. Handing of Missing or Partial Date

**Partial Dates for Adverse Events**

- When only day is missing

- If it is the start date of an AE
    - If it occurs in a month before or after the month treatment started, the first day of the month will be used
    - If it occurs in the same month and year as the start of treatment
        - If the end date of the AE is prior to the start of study medication then the end date of the AE will be used
        - If the end date of the AE is missing or after the start of study medication then the date of the start of study medication will be used and the AE will be presumed to have started after the start of study medication
- If it is the end date of an AE, the last day of the month will be used.

- Only day and month are missing
    - If it is the start date of an AE
        - If it occurs in a year before or after the year treatment started then, January 1 of the year will be used
        - If it is occurred on the same year as the start of treatment, the date of the start of study medication will be used and the AE will be presumed to have started after the start of study medication.
    - If it is the end date of an AE, December 31 of the year will be used.

**Partial Dates for Prior and Concomitant Therapy**

- When only day is missing
    - If it is the start date of concomitant therapy then the first day of the month will be used
    - If it is the end date of concomitant therapy then the last day of the month will be used
- When day and month are missing
    - If it is the start date of concomitant therapy then January 1 of the year will be used
    - If it is the end date of concomitant therapy then December 31 of the year will be used

If the start date of concomitant therapy (including the imputed start date if applicable) is prior to the start of study medication or if the start date of concomitant therapy is missing then concomitant therapy will be classified as a prior medication.

If the end date of concomitant therapy (including the imputed end date, if applicable) is after the start of study medication or if the end date of concomitant therapy is missing then concomitant therapy will be classified as a concomitant medication.

Concomitant therapy may be classified as a prior medication, or a concomitant medication.

## 8. GENERAL STATISTICAL CONSIDERATIONS

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.
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.
Mean and median will be presented with one more decimal place than the precision of the data. Standard deviation will be presented with two more decimal places than the precision of the data. Minimum and maximum will be presented with the same precision as the original data.

### 8.1. Treatment Group Comparability

#### 8.1.1. 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. The data summary will at least contain the following information:

- Number of subjects screened and reason for that

- Number of subjects randomized
- Number and percent of subjects who completed treatment
- Number and percent of subjects who discontinued study and reason for that

Listing will be prepared to present data concerning subject disposition. Listing for screen failure subjects will also be provided along with their screen failure reason. Subjects with study protocol violations summarized by type of violation and listed by treatment and investigative site.

### 8.1.2. 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. Demographics and baseline characteristics will be listed for all enrolled subjects.

Demographic characteristics will be summarized by treatment groups. For continuous variables such as age, height, weight, income and BMI, the descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be reported. For categorical variables such as sex, education, the number and percentage of subjects in each category will be reported.

The Baseline characteristics of include HbA1C, FPG, FSBG,SEITQ and ITSQ,

For continuous variables, the descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be reported. For categorical variables, the number and percentage of subjects in each category will be reported.

Medical history findings will be summarized by reporting the incidence of subjects with reported MedDRA SOC and preferred terms. Medical history findings will be listed for all enrolled subjects.

### 8.1.3. Concomitant Therapy

Anti-hyperglycemic concomitant therapy will be summarized at baseline and throughout the study by treatment arm and overall population with coded using the most recent version of the WHO Drug Dictionary. The numbers of subjects using concomitant therapy will be categorized by drug classification (ATC1) and preferred term, and presented by treatment group. By-patient listing will be presented.General concomitant therapy will not be collected or summarized. Anti-hyperglycemic concomitant therapy will be listed for all enrolled subjects.

### 8.1.4. Treatment Compliance

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

## 8.2. Efficacy Analyses

Efficacy analyses will be performed on randomized patients.

### 8.2.1. Primary Analyses

The primary outcome of the study is the change from baseline in HbA1c at Week 24. The null and alternative hypotheses to be tested are as follows:

$H_0$: $\hat{\mu}_{arm1} = \hat{\mu}_{arm2}$

$H_a$: $\hat{\mu}_{arm1} \neq \hat{\mu}_{arm2}$

where μ is the mean change from baseline at Week 24 for HbA1c (primary endpoint).
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;

The summary statistics for the change from baseline data includes the number of subjects in each treatment group, mean, SD, median, min and max.
The primary analyses will at least contain n, raw mean, raw SD, adjusted mean. The least-square means (LSmeans) of change from baseline for each treatment group and difference in LSmeans between treatment groups will be presented along with the associated SE and 95% CI.

As a sensitivity analyses, the primary analyses will be repeated by censoring all efficacy data after patients changed the randomized treatment regimen. These analyses will also utilize an ANCOVA model with treatment as factors and the baseline as a covariate. Related plots will also be reported. The primary efficacy endpoints will be listed for each subject at each planned visit.

### 8.2.2. Secondary Analyses

Missing efficacy values which are HbA1c, FPG, FSBG-based FBG, PPG, BG excursion daily insulin, body weight, SEITQ score will do LOCF. Those missing values will be the last non-missing post-baseline observation up to date of missing values of measurement.
All secondary efficacy endpoints will be listed separately for each subject at each planned visit.

1. 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 24 and Week 48. This MMRM model will have all post-baseline HbA1c as responses, baseline HbA1c as a continuous covariate, treatment group, Visits (Week 24 or Visit 48), and treatment by visit interaction as fixed effects and patient as a random effect. An unstructured covariance structure will be used to model the correlation within subjects. In case of failure of convergence using unstructured covariance structure, the first-order autoregressive [AR(1)] covariance structure will be used. Missing data will be assumed to be missing at random and therefore maintained as missing. The difference between each of treatment will be assessed by the least-squares means (LSM) difference at Week 24 and Week 48 (alpha=0.05, 2-sided).
   A plot of least-squares means for change from baseline by visit for each treatment will be used to display the results of this endpoint.
   As sensitivity analyses, the endpoint analyses will be repeated by censoring all efficacy data after patients changed the randomized treatment regimen at Week 48, Ancova analyses for row data and LOCF data at Week 48 separately.
2. 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 24 and Week 48), except for comparison will be based on the treatment contrast p-value from the corresponding analyses model. The sensitivity analyses will also be performed.

Plots of least-squares means for change from baseline by visit for each treatment will be used to display the results of endpoints.

As sensitivity analyses, the endpoint analyses will be repeated by censoring all efficacy data after patients changed the randomized treatment regimen at Week 24 and Week 48, Ancova analyses for row data and LOCF data at Week 24 and Week 48 separately.

3. 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. Adjusted odds ratio, 95% CI and P-value will be presented. Related plot will be reported.

   Plots of percentages of patients reaching treatment goals by visit for each treatment will be used to display the results of endpoints.

   As sensitivity analyses, the endpoint analyses will be repeated by censoring all efficacy data after patients changed the randomized treatment regimen at Week 24 and Week 48, Ancova analyses for row data and LOCF data at Week 24 and Week 48 separately.
4. Same analyses strategy (refer to above 3) 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. Those patients should be without switching or discontinuing study insulin, and without using rescue therapy which will be determined by the investigator following usual standard of care between insulin analog mid mixture BID and basal insulin analog QD treatments.
5. Insulin dose at each visit will be descriptively summarized by treatment groups by total daily dose (IU and IU/kg). The descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) and P-value of a two-sample t-test will be reported.
6. Time to insulin treatment change will be compared between treatment arms by a log rank test. Table and related plot will be reported. 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. Time to insulin treatment change: Defined as time to any of: insulin treatment

discontinuation, switch, intensification or reduction in frequency. ((date of event/censored - (date of first dose of study drug) + 1.)

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.

Plots of time to event by weeks will be used to display the results of endpoints.

### 8.3. Exploratory Analyses

All exploratory endpoints will be listed for each subject at each planned visit.

#### 8.3.1. Adherence and Insulin Treatment Pattern

For these measurements which are the insulin treatment pattern for insulin discontinuation, switch, intensification or reduction in frequency, summary statistics will be provided, and comparison will be performed by appropriate general test (Fisher's exact test). Proportion of patients who experience insulin discontinuation, switch, intensification or reduction in frequency during 48 weeks and P value should be in summary statistics.

#### 8.3.2. Resource Utilization

Utilization data will be summarized descriptively by category across arms (for example, surgery, hospitalization type, reason for hospitalization, T2DM-related and hospitalization days) for a treatment arm, including a frequency table with tabular statistics. Fisher's exact test for differences in proportions between treatment arms will be performed.

#### 8.3.3. Insulin Treatment Satisfaction Questionnaire (ITSQ)

Overall and domain will be summarized and tabulated for ITSQ score at 24 and 48 weeks for each treatment group. Table should contain the number of subjects in each treatment group, mean, SD, median, min and max. A two-sample t-test for differences between treatment arms will be performed.

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

Categorical responses for the each question will be summarized at baseline and endpoint (24 weeks). The change in SEITQ score form baseline at 24 weeks for each treatment group will be presented and P-value will be show in tables. The descriptive statistics (n, mean, median,

standard deviation, minimum, and maximum) and P-value of a two-sample t-test will be reported also.

### 8.3.5. The Incidences and Rates of Other Categories of Hypoglycemia

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 will be presented for each treatment group. Tests for differences between treatment arms will be performed. P-value of fish's exact test will be reported also.

## 8.4. Safety Analyses

All safety analyses specified in this subsection will be performed on the randomized population unless otherwise specified. All safety endpoints will be listed for each subject at each planned visit.

### 8.4.1. Adverse Event

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.
Adverse events (AEs) and treatment-emergent adverse events (TEAEs) will be coded using the MedDRA dictionary. AEs and TEAEs will be categorized by system organ class and preferred term and will be presented. TEAEs are defined as AEs occurring during or after the initial dose of study drug. AEs documented prior to initial dose cannot be classified as TEAEs unless there is a worsening in severity during or after the initial dose of study drug.
The overall incidence of TEAEs with all causalities will be summarized as the number and percentage subjects in each of the categories: TEAE, TEAEs leading to insulin treatment change, SAE.
The following summaries will be presented at both the subject (number [%] of subjects) and event (number of events) level:

- AEs by SOC, PT, and treatment
- Treatment-emergent AEs by SOC, PT, and treatment
- Treatment-emergent AEs by SOC, PT, maximum severity, and treatment
- SAE by SOC, PT, and treatment
- SAE related to study drug by SOC, PT, and treatment

- Treatment-emergent AEs leading to treatment insulin treatment change by SOC, PT, and treatment
- Treatment-emergent AEs related to study drug by SOC, PT, and treatment

For the incidence at the subject level by SOC and PT, if a subject experiences more than one event within the same SOC and PT, only one occurrence will be included in the incidence.
For the incidence at the subject level by SOC, PT, and severity, if a subject experiences more than one event within the same SOC and PT, only the most severe occurrence will be included in the incidence.
For the incidence at the subject level by SOC, PT, and relationship to investigational product, if a subject experiences more than one event within the same SOC and PT, only the most related occurrence will be included in the incidence.
For the summary of number of events, if a subject experiences more than one event within the same SOC and PT, all events will be counted.
All adverse events will be listed. Additional listings will include adverse events reported as reasons for insulin treatment change.

### 8.4.2. Laboratory Evaluation

For the treatment period of the study, descriptive statistics by treatment group will be provided at each scheduled visit with laboratory assessment. For laboratory test with quantitative value, descriptive statistics (number, mean, median, SD, minimum, and maximum) of the observed values and changes from baseline at each scheduled visit will be reported. For laboratory test with categorical value, the number and percentage of subjects in each category will be summarized by treatment group at each scheduled visit. Shift tables (abnormal low, normal, abnormal high) of baseline against each post-baseline visit will be provided for laboratory tests.
By subject listing for laboratory tests will be presented and record with abnormal value will be flagged.

### 8.4.3. Vital Signs

Vital signs will be summarized similar to those described for the laboratory analyses.
By subject listing for vital sign data will be presented and record with abnormal value will be flagged.

### 8.4.4. Severe, Nocturnal and Total Hypoglycemic Events

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.

### 8.5. 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.

Subgroup analyses will be performed for the primary endpoint and the secondary endpoints to determine whether significant differences exist in primary and secondary endpoint results between subgroups.

These subgroup analyses will be carried out using the subjects from the randomized population.

The list of potential subgroups (with applicable definitions in parentheses) includes, but is not necessarily limited to, the following:

- 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)

### 8.6. 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. Although the study is open label, in order to avoid influencing study conduct in any way, should the interim analyses be performed, results will not be publicly disclosed until the last patient completes Visit 6.

## 9. REFERENCES

1. Medical Dictionary for Regulatory Activities (MedDRA), Version 6.1. IFPMA, International Committee on Harmonization.

2. WHO Drug Dictionary. WHO Collaborating Centre for International Drug Monitoring. Uppsala, Sweden, (Box 26, S-751-03), 1993.

3. Qu Y, Liu R, Dmitriento A, Offen W. A new classification approach for comparing two active treatments when there is no prior projection on which one is better. *Stat Med*. 2011;30(30):3488-3495.

## 10. APPENDICES

### Appendix 1: Definition of Exposure Interval

| Analysis Visit No. | | Analysis Visit Label | Target Day | Visit Window |
|---|---|---|---|---|
| 1 | | Baseline | 0 | relDay<=0 |
| 2 | | Week 24 | 24 | 1<=relDay and date<=date of visit 4 |
| 3 | | Week 48 | 48 | date of visit 4< date<=date of visit 6 |

*Baseline: the last non-missing observation on or before the randomization visit. Last records within each window will be used for analyses.