*These results are supplied for informational purposes only.*
*Prescribing decisions should be made based on the approved package insert in the country of prescription.*

| | |
|---|---|
| **Sponsor / Company:** Sanofi<br>**Drug substance(s):** Insulin Glargine (HOE901)<br>Insulin Glulisine (HMR1964) | **Study Identifiers:** NCT01212913, U1111-1117-2786<br>**Study code:** LANTU_L_04867 |
| **Title of the study:** Comparison of a Basal Plus (Insulin Glargine/Insulin Glulisine) Regimen to Premixed Insulin (Insulin Aspart/Insulin Aspart Protamine 30/70) in Type 2 Diabetes Mellitus patients, who require insulin intensification after basal insulin optimization (B to B) | |
| **Study center(s):** 12 sites in Republic of Korea | |
| **Study period:**<br>First subject enrolled date: 30 Aug 2010<br>Last subject completed date: 17 May 2012 | |
| **Phase of development:** Phase 4 | |

**Objectives:**

Primary objective:

The primary objective of this study was to demonstrate non-inferiority of Basal Plus (Lantus® added with 1~2 Apidra®) to Premixed Insulin (NovoMix® 30, twice per day) in the change of HbA1c from baseline to the end of treatment in a Korean population.

Secondary objectives:

To compare the following between treatment groups:

- Proportion (%) of subjects with HbA1c < 7% who did not experience hypoglycemia at the end of 24 weeks of treatment,
- Proportion (%) of subjects with HbA1c <7% and <6.5% at the end of 24 weeks of treatment, with or without hypoglycemia,
- Hypoglycemia occurrence frequency and proportion (symptomatic daytime and nocturnal hypoglycemia, asymptomatic hypoglycemia and severe hypoglycemia),
- Change in body weight from baseline to the end of 24 weeks of treatment,
- Total daily dose of insulin at the end of 24 weeks of treatment,
- Total daily dose of insulin in patients with HbA1c <7% who did not experience hypoglycemia at the end of 24 weeks of treatment,
- Total daily dose of insulin in patients with HbA1c <7% at the end of 24 weeks of treatment,
- Change in the Fasting Plasma Glucose (FPG) profile over 3 consecutive days,
- Change in the 7-point Plasma Glucose (PG) profile,
- Change in the 72-hr CGMS (Continuous Glucose Monitoring System) profile, (weeks 0, 24)
  - In the CGMS group, change in ROS (8-iso-PGF2) (Reactive Oxidative Stress) and MAGE (Mean Amplitude of Glycemic Excursions), SD (Standard Deviation), CONGA (Continuous Overlapping Net Glycemic Action), MODD (Mean Of Daily Glucose) measurements,
- Assessment of treatment satisfaction (DTSQs+c): DTSQs at screening visit and 12 weeks, 24 weeks; DTSQc at 24 weeks,
- Overall safety.

**Methodology:** This was a phase 4, multicenter, 1:1 randomized, open-label, controlled, 2-parallel group study consisting of 2 weeks of screening, followed by 24 weeks of treatment and up to 2 weeks of follow-up in a Korean population. During 2 weeks of screening, subjects maintained diet therapy, exercise therapy and their regimen at the time of screening visit (Insulin Glargine [Lantus®] with/without other oral hypoglycemic agents was/were taken at screening visit). Subjects determined as eligible for this study by satisfying all key selection criteria at the end of screening were randomized to be treated for 24 weeks in the Basal Plus or Premixed Insulin group. During treatment, subjects strictly controlled the insulin dose based on FPG and/or post-prandial PG. Additionally, randomized subjects who voluntarily expressed willingness for participation had a continuous glucose monitoring (CGMS) for 72 hours twice: at baseline and at completion of the study.

**Number of patients:** Planned: 160 (80 per treatment)
Randomized: 161 (Basal Plus 78, Premixed Insulin 83)
Treated: 160 (Basal Plus 78, Premixed Insulin 82)

**Evaluated**: Efficacy: Intent-To-Treat (ITT): 160 (Basal Plus 78, Premixed Insulin 82)
Per-Protocol (PP): 115 (Basal Plus 57, Premixed Insulin 58)
Safety: 160 (Basal Plus 78, Premixed Insulin 82)

**Key diagnosis and criteria for inclusion:**

1. Type 2 Diabetes Mellitus (DM) patients who have been on Insulin Glargine for at least 12 weeks,
2. If taking an Oral Anti-Diabetic (OAD), a patient who has been on a stable dose for at least 4 weeks based on screening,
3. Patients with 10%≥ HbA1c ≥7 % and FPG<130mg/dL.

**Study treatments**

Investigational products: Insulin Glargine (Lantus®), Insulin Glulisine (Apidra®), Insulin Aspart/Insulin Aspart Protamine 30/70 (NovoMix®30)

Formulations:

- Lantus®: 100 units/mL solution for injection using a Prefilled SoloStar® 3 mL pen
- Apidra®: 100 units/mL solution for injection using a Prefilled SoloStar® 3 mL pen
- NovoMix®30: 100 units/mL solution for injection using a Prefilled FlexPen®

Dosing route: Subcutaneous (SC) injection

Administration method:

Before randomization

During screening, subjects maintained the current therapy including diet therapy, exercise therapy and a stable dose of OAD and Insulin Glargine (Lantus®).

After randomization

The general principal insulin dose adjustment was as follows.

- Starting dose**:** Start at the dose used at randomization.
- PG monitoring and dose adjustment: Patients adjusted one's insulin dose under the investigator's strict supervision.
- The target was to reach 70 < FPG ≤ 100 mg/dL through dose adjustment.
- How to use insulin: To be conducted at baseline.
- Dose adjustment scheme: Patients used the last 3 daily morning FPG levels (including the level on the day of dose adjustment) for dose adjustment. Subjects adjusted one's insulin dose on a weekly basis.

The general principle was to use the median of the last 3 measurements of the FPG level used for dose adjustment, unless one of the 3 measurements was ≤ 70 mg/dL (in this case, this low level were to be used).

**Basal Plus group**

- Insulin Glargine (Lantus®): SC administration using a SoloStar pen, once daily, at the same time at dinner or at bedtime
- Insulin Glulisine (Apidra®): SC administration using a SoloStar pen, once daily, within 15 min prior to a main meal (or twice per day, within 15 min prior to 2 main meals, in some cases)
- Dose adjustment schedule was as follows

1) Insulin Glargine (Lantus®)

| FPG mg/dL | Insulin dose |
|---|---|
| ≤ 70 or symptomatic hypoglycemia* | - 2 U |
| 70 < FPG ≤ 100 | Unchanged |
| 100 < FPG ≤ 140 | + 2 U |
| > 140 | + 4 U |

*symptomatic hypoglycemic : symptoms related hypoglycemia regardless FPG

2) Insulin Glulisine (Apidra®)

| Main/second main meal 2h-PPPG (2h-PPPG) mg/dL | Insulin dose |
|---|---|
| Symptomatic hypoglycemia* or ≤ 100 | - 1~-2 U |
| ≤ 140 | Unchanged |
| 140 < PPPG ≤ 150 | + 1 U |
| 150 < PPPG ≤ 180 | + 2 U |
| > 180 | + 3 U |

*symptomatic hypoglycemic : symptoms related hypoglycemia regardless 2h-PPPG

**Premixed Insulin group**

- Insulin Aspart/Insulin Aspart Protamine 30/70 (NovoMix® 30): SC administration using a FlexPen®, twice per day, within 15 min prior to breakfast and dinner
- Dose adjustment schedule was as follows

| FPG mg/dL | Insulin dose |
|---|---|
| ≤ 70 or symptomatic hypoglycemia* | - 2 U |
| 70 < FPG ≤ 100 | Unchanged |
| 100 < FPG ≤ 140 | + 2 U |
| > 140 | + 4 U |

*symptomatic hypoglycemic : symptoms related hypoglycemia regardless FPG

**Duration of treatment:** 24 weeks

**Duration of observation:** 28 weeks (2 weeks of screening, 24 weeks of treatment and 2 weeks of follow-up)

**Criteria for evaluation:**

Efficacy:

The primary efficacy endpoint was the mean change in HbA1c from baseline to the end of study treatment.

Secondary efficacy endpoints:

- Proportion (%) of subjects with HbA1c<7% who did not experience hypoglycemia at the end of 24 week treatment,
- Proportion (%) of subjects with HbA1c<7%, <6.5% at the end of 24 week treatment, with or without hypoglycemia
- Hypoglycemia occurrence frequency and proportion (%) (symptomatic daytime and nocturnal hypoglycemia, asymptomatic hypoglycemia and severe hypoglycemia),

**Criteria for evaluation** (cont'd)**:**

- Mean change in body weight from baseline to the end of 24 weeks of treatment,
- Total daily dose of insulin at the end of 24 weeks of treatment,
- Total daily dose of insulin in patients with HbA1c <7% who did not experience hypoglycemia at the end of 24 weeks of treatment,
- Total daily dose of insulin in patients with HbA1c <7% at the end of 24 weeks of treatment, with or without hypoglycemia
- Mean change in the FPG profile over 3 consecutive days,
- Mean change in the 7-point PG profile
- Mean change in the 72-hr CGMS profile (weeks 0, 24),
    - In the CGMS group, change in ROS (8-iso-PGF2) and MAGE, SD, CONGA, MODD measurements

Safety: Adverse events, laboratory findings and vital signs data.

Treatment satisfaction with DTSQs at screening visit and 12 weeks, 24 weeks; DTSQc at 24 weeks.

**Statistical methods:**

The intent-to-treat (ITT) set consisted of all randomized subjects who received the study drug. Subjects were to be analyzed according to the administered study drug. The per-protocol (PP) set was a sub-population of the ITT set, excluding all subjects with a major protocol violation (protocol violation that interferes with the primary efficacy endpoint assessment). The safety set consisted of all subjects who received at least one round of treatment. This was to be analyzed according to the administered study drug. Efficacy was analyzed based on the ITT set as the primary approach. Analysis of the PP set was considered using as the alternative approach on HbA1c. Safety was analyzed based on the safety set.

Analysis of the primary efficacy endpoint:

Non-inferiority of the Basal Plus (Lantus® added with 1~2 Apidra®) group to the Premixed Insulin (NovoMix® 30, BID) group was declared if the difference in HbA1c reduction is ≥ -0.4% by using 95% Confidence Interval (CI) using t-statistics.

Analysis of secondary efficacy endpoints:

- Proportion of subjects with HbA1c < 7% who did not experience hypoglycemia, frequency and proportion (%) of subjects with HbA1c < 7% and < 6.5% at the end of 24 week treatment were each presented and a between-group difference was compared using a Pearson's chi-square test or Fisher's exact test.

- Hypoglycemia was classified as follows:

. Asymptomatic hypoglycemia was defined as an event without clinical symptoms and the PG level is measured ≤ 70 mg/dL.

. Symptomatic hypoglycemia was defined as an event with clinical symptoms thought to be due to hypoglycemia (confirmed or unconfirmed by PG measurement ≤ 70 mg/dL).

. Daytime hypoglycemia was hypoglycemia occurring during waking hours, and nocturnal hypoglycemia was hypoglycemia that developed after bedtime and before waking up.

. Severe symptomatic hypoglycemia was defined as the event that was considered to be due to hypoglycemia, and the subject experienced clinical symptoms requiring other's help, in addition to one of the following criteria:
    - PG level measurement is <36 mg/dL,
    - Or is rapidly recovered after taking oral carbohydrate, dextrose IV injection or glucagon.

. Serious symptomatic hypoglycemia meant symptomatic hypoglycemia that was considered as a serious adverse event SAE

For all and each of hypoglycemia types, the number of events and occurrence proportion were presented by treatment, and the between-group difference was compared using a Pearson's chi-square test or Fisher's exact test.

**Statistical methods** (cont'd)**:**

- For body weight measured at screening, Week 12 and Week 24 and the change, descriptive statistics (mean, SD, median, minimum, maximum) were presented by treatment and the between-group difference at each time point was compared using an ANCOVA or rank ANCOVA with the screening level as a covariate.
- For total daily dose of insulin at the end of 24 week treatment, total daily insulin dose in subjects with HbA1c < 7%, with or without hypoglycemia, and total daily insulin dose in subjects with HbA1c < 7% with no hypoglycemia, descriptive statistics (mean, SD, median, minimum, maximum) were presented by treatment and a between-group difference was analyzed using a student's *t*-test or Wilcoxon's rank sum test.
- For the FPG profile over 3 consecutive days (72 hr), the mean FPG for 3 consecutive days prior to Week 0 (baseline), Week 12, Week 24 visits was calculated and presented with descriptive statistics (mean, SD, median, minimum, maximum) by treatment, and the between-group difference at each time point was compared using an ANCOVA or rank ANCOVA with the baseline level as a covariate.
- For the 7-point mean PG profile and daily PG, the mean over 2 days within 1 week prior to Week 0 (baseline), Week 12, Week 24 visits was calculated and presented with descriptive statistics (mean, SD, median, minimum, maximum) by treatment, and the between-group difference at each time point was compared using an ANCOVA or rank ANCOVA with the baseline level as a covariate.
- Changes in the 72-hr CGMS/MAGE profile and ROS were separately analyzed in Samsung Medical Center.

Safety

- Adverse events: summarized and analyzed adverse events included all treatment-emergent adverse events (TEAEs) that occurred or worsened from the first dose of the investigational product to 24 hr after the last dose. The incidence of all adverse events, incidence of events related to the investigational product, and incidence of serious adverse events were presented and compared between treatment groups. Between-group difference was tested using a Pearson's chi-square test or Fisher's exact test.
- For all laboratory test and vital sing findings, within-group and between-group comparisons were performed.

Treatment satisfaction

For DTSQ status assessment, DTSQs total score for treatment satisfaction (sum of items 1, 4, 5, 6, 7, 8) at screening, Week 12, Week 24 was calculated and descriptive statistics (mean, SD, median, minimum, maximum) were presented by treatment; change from screening to the end of treatment was compared using an ANCOVA or rank ANCOVA with treatment as a fixed effect and baseline level as a covariate.

For DTSQ change assessment, DTSQc total score for treatment satisfaction (sum of items 1, 4, 5, 6, 7, 8) at the end of treatment was calculated and descriptive statistics (mean, SD, median, minimum, maximum) were presented by treatment and compared using an ANCOVA or rank ANCOVA with treatment as a fixed effect and screening DTSQs score as a covariate.

**Summary:**

Of 161 randomized subjects (Basal Plus 78, Premixed Insulin 83), 160 subjects (Basal Plus 78, Premixed Insulin 82) were included in the safety set, after excluding 1 subject who withdrew consent prior to investigational product administration. ITT population was the same as the safety population and 115 of these patients (Basal Plus 57, Premixed Insulin 58) were included in the PP set. Of the randomized subjects, a total of 128 subjects (Basal Plus 63, Premixed Insulin 65) completed the study whereas 33 subjects (Basal Plus 15, Premixed Insulin 18) were withdrawn from the study.

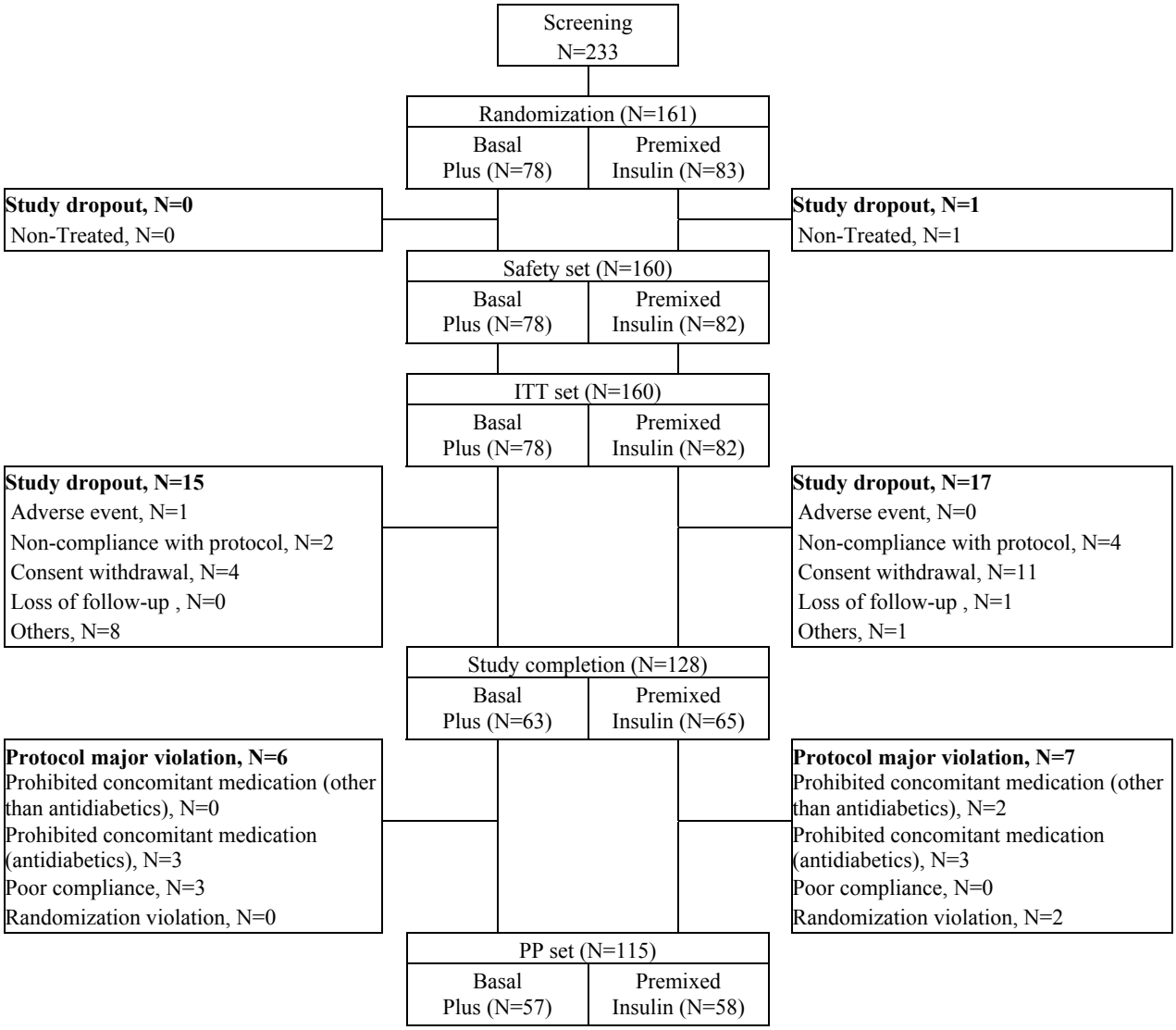



**Figure 1.** Subject Disposition

**Demographics:**

Mean age of randomized subjects was 59.5 years with those in their 50s~60s accounting for 75%. There was no difference in gender between the two treatment groups and mean height, body weight, and Body Mass Index (BMI) were 162 cm, 64 kg, and 24.5 kg/m$^2$, respectively. There was no demographic parameter showing a statistically significant difference between two groups. Regarding investigational medicinal product (IMP) exposure, total subject was 65.91 pt-year, Basal Plus group was 33.69 pt-year and Premixed Insulin group was 32.22 pt-year.

**Table 1** Demographic Information

| | | Total N=160 n (%) | Basal Plus N=78 n (%) | Premixed Insulin N=82 n (%) | *p*-value |
|---|---|---|---|---|---|
| Age (years) | Mean±SD | 59.48±9.35 | 59.45±10.03 | 59.50±8.72 | 0.8590+ |
| | Median | 59.50 | 59.00 | 60.00 | |
| | Min, Max | 22.00,80.00 | 22.00,80.00 | 36.00,78.00 | |
| | ≤ 29 | 1 (0.63) | 1 (1.28) | 0 (0.00) | 0.8029‡ |
| | 30~39 | 4 (2.50) | 2 (2.56) | 2 (2.44) | |
| | 40~49 | 12 (7.50) | 4 (5.13) | 8 (9.76) | |
| | 50~59 | 63 (39.38) | 33 (42.31) | 30 (36.59) | |
| | 60~69 | 56 (35.00) | 26 (33.33) | 30 (36.59) | |
| | ≥ 70 | 24 (15.00) | 12 (15.38) | 12 (14.63) | |
| Sex | M | 78 (48.75) | 39 (50.00) | 39 (47.56) | 0.7577† |
| | F | 82 (51.25) | 39 (50.00) | 43 (52.44) | |
| Duration of DM (year) | Mean±SD | 15.69±6.59 | 15.17±6.77 | 16.19±6.42 | 0.2954+ |
| | Median | 15.21 | 14.21 | 15.53 | |
| | Min, Max | 4.40,29.92 | 4.40,29.42 | 4.66,29.92 | |
| BMI (kg/m$^2$) | Mean±SD | 24.53±2.69 | 24.71±2.71 | 24.35±2.67 | 0.4304+ |
| | Median | 24.34 | 24.47 | 24.05 | |
| | Min, Max | 18.44,32.59 | 20.08,29.95 | 18.44,32.59 | |
| | <18.5 | 1 (0.63) | 0 (0.00) | 1 (1.22) | 0.4653‡ |
| | 18.5~<23 | 49 (30.63) | 23 (29.49) | 26 (31.71) | |
| | 23~<25 | 44 (27.50) | 20 (25.64) | 24 (29.27) | |
| | 25~<30 | 64 (40.00) | 35 (44.87) | 29 (35.37) | |
| | ≥30 | 2 (1.25) | 0 (0.00) | 2 (2.44) | |
| Height (cm) | Mean±SD | 161.88±8.31 | 161.97±8.37 | 161.79±8.29 | 0.7122+ |
| | Median | 161.70 | 162.00 | 161.00 | |
| | Min, Max | 146.00,181.00 | 146.00,180.00 | 146.00,181.00 | |
| Body weight(kg) | Mean±SD | 64.41±9.57 | 64.94±9.39 | 63.90±9.77 | 0.3090+ |
| | Median | 64.00 | 65.00 | 63.05 | |
| | Min, Max | 44.70,90.60 | 46.80,86.20 | 44.70,90.60 | |

+: Wilcoxon's rank sum test
†: Pearson's chi-square test
‡: Fisher's exact test

In Basal plus group, Apidra was given as once daily injection in 39 subjects (50%) and twice daily injection in 39 subjects (50%).
Chronic complications of diabetes, disease/surgery history and frequency of concomitant medications were comparable across groups.

**Efficacy results**:
In the ITT set, HbA1c reduction (Mean±SD) after 24 weeks of treatment was 0.91±0.80% for Basal Plus and 1.07±0.95% for Premixed Insulin with a between-group difference of -0.16% and 95% CI of [-0.45, 0.12]; as the lower limit of CI was < -0.4%, a non-inferior margin, non-inferiority was not demonstrated. Similar results were shown in the PP set.

**Table 2** HbA1c reduction after 12 week, 24 week treatment

| | | Total | Basal Plus | Premixed Insulin | Difference [95% C.I.] | *p*-value |
|---|---|---|---|---|---|---|
| **ITT set** | | **N=160** | **N=78** | **N=82** | | |
| Baseline | n | 160 | 78 | 82 | | 0.1501* |
| | Mean±SD | 8.40±0.74 | 8.31±0.74 | 8.48±0.74 | | |
| | Median | 8.26 | 8.20 | 8.35 | | |
| | Min, Max | 7.04 ,9.99 | 7.04 ,9.99 | 7.04 ,9.92 | | |
| Week 12 | n | 151 | 76 | 75 | | |
| | Mean±SD | 7.56±0.80 | 7.50±0.74 | 7.62±0.85 | | |
| | Median | 7.53 | 7.49 | 7.63 | | |
| | Min, Max | 5.67 ,9.30 | 6.00 ,9.30 | 5.67 ,9.16 | | |
| Week 24 | n | 151 | 76 | 75 | | |
| | Mean±SD | 7.39±0.86 | 7.41±0.85 | 7.37±0.87 | | |
| | Median | 7.27 | 7.22 | 7.36 | | |
| | Min, Max | 5.49 ,10.47 | 6.04 ,10.47 | 5.49 ,9.88 | | |
| Change1 | n | 151 | 76 | 75 | | |
| | Mean±SD | 0.82±0.74 | 0.81±0.61 | 0.82±0.86 | -0.01[-0.25,0.23] | 0.9447* |
| | Median | 0.86 | 0.88 | 0.84 | | |
| | Min, Max | -0.99 ,3.92 | -0.77 ,1.93 | -0.99 ,3.92 | | |
| Change2 | n | 151 | 76 | 75 | | |
| | Mean±SD | 0.99±0.88 | 0.91±0.80 | 1.07±0.95 | -0.16[-0.45,0.12] | 0.2571* |
| | Median | 0.94 | 0.87 | 1.19 | | |
| | Min, Max | -1.31 ,3.99 | -1.01 ,3.10 | -1.31 ,3.99 | | |
| **PP set** | | **N=115** | **N=57** | **N=58** | | |
| Baseline | Mean±SD | 8.41±0.73 | 8.36±0.73 | 8.46±0.74 | | 0.4945* |
| | Median | 8.33 | 8.43 | 8.32 | | |
| | Min, Max | 7.04 ,9.99 | 7.12 ,9.99 | 7.04 ,9.92 | | |
| Week 12 | Mean±SD | 7.55±0.81 | 7.53±0.75 | 7.58±0.87 | | |
| | Median | 7.54 | 7.53 | 7.61 | | |
| | Min, Max | 5.67 ,9.30 | 6.00 ,9.30 | 5.67 ,9.16 | | |
| Week 24 | Mean±SD | 7.31±0.85 | 7.34±0.84 | 7.28±0.86 | | |
| | Median | 7.19 | 7.13 | 7.26 | | |
| | Min, Max | 5.49 ,9.88 | 6.04 ,9.48 | 5.49 ,9.88 | | |
| Change1 | Mean±SD | 0.86±0.79 | 0.84±0.66 | 0.87±0.90 | -0.04[-0.33,0.26] | 0.8021* |
| | Median | 0.87 | 0.92 | 0.85 | | |
| | Min, Max | -0.88 ,3.92 | -0.77 ,1.93 | -0.88 ,3.92 | | |
| Change2 | Mean±SD | 1.10±0.89 | 1.02±0.81 | 1.18±0.96 | -0.15[-0.48,0.18] | 0.3580* |
| | Median | 1.18 | 1.05 | 1.28 | | |
| | Min, Max | -1.31 ,3.99 | -0.29 ,3.10 | -1.31 ,3.99 | | |

Change1=Baseline - Week 12
Change2=Baseline - Week 24
*: Student's *t*-test

Additionally, HbA1c reduction (LS Mean±SE) after 24 weeks of treatment was analyzed after adjustment with baseline HbA1c; it was 0.94±0.09% for Basal Plus and 1.04±0.09% for Premixed Insulin with a between-group difference of -0.09% and 95% CI of [-0.35, 0.16]. As the lower limit of CI was higher than a non-inferior margin of -0.4%, non-inferiority was demonstrated. Non-inferiority was also proven in the PP set, after adjustment.

**Table 3** Baseline-adjusted HbA1c reduction after 12 week, 24 week treatment

| | | Total | Basal Plus | Premixed Insulin | Difference [95% C.I.] | *p*-value |
|---|---|---|---|---|---|---|
| **ITT set** | | **N=160** | **N=78** | **N=82** | | |
| Baseline | n | 160 | 78 | 82 | | |
| | Mean±SD | 8.40±0.74 | 8.31±0.74 | 8.48±0.74 | | 0.1501* |
| | Median | 8.26 | 8.20 | 8.35 | | |
| | Min, Max | 7.04,9.99 | 7.04,9.99 | 7.04,9.92 | | |
| Week 12 | n | 151 | 76 | 75 | | |
| | Mean±SD | 7.56±0.80 | 7.50±0.74 | 7.62±0.85 | | |
| | Median | 7.53 | 7.49 | 7.63 | | |
| | Min, Max | 5.67,9.30 | 6.00,9.30 | 5.67,9.16 | | |
| Week 24 | n | 151 | 76 | 75 | | |
| | Mean±SD | 7.39±0.86 | 7.41±0.85 | 7.37±0.87 | | |
| | Median | 7.27 | 7.22 | 7.36 | | |
| | Min, Max | 5.49,10.47 | 6.04,10.47 | 5.49,9.88 | | |
| Change1 | n | 151 | 76 | 75 | | |
| | Mean±SD | 0.82±0.74 | 0.81±0.61 | 0.82±0.86 | | |
| | LS Mean±SE | | 0.84±0.08 | 0.79±0.08 | -0.05[-0.17,0.26] | 0.6783∫ |
| | Median | 0.86 | 0.88 | 0.84 | | |
| | Min, Max | -0.99,3.92 | -0.77,1.93 | -0.99,3.92 | | |
| Change2 | n | 151 | 76 | 75 | | |
| | Mean±SD | 0.99±0.88 | 0.91±0.80 | 1.07±0.95 | | |
| | LS Mean±SE | | 0.94±0.09 | 1.04±0.09 | -0.09[-0.35,0.16] | 0.4630∫ |
| | Median | 0.94 | 0.87 | 1.19 | | |
| | Min, Max | -1.31,3.99 | -1.01,3.10 | -1.31,3.99 | | |
| **PP set** | | **N=115** | **N=57** | **N=58** | | |
| Baseline | Mean±SD | 8.41±0.73 | 8.36±0.73 | 8.46±0.74 | | 0.4945* |
| | Median | 8.33 | 8.43 | 8.32 | | |
| | Min, Max | 7.04,9.99 | 7.12,9.99 | 7.04,9.92 | | |
| Week 12 | Mean±SD | 7.55±0.81 | 7.53±0.75 | 7.58±0.87 | | |
| | Median | 7.54 | 7.53 | 7.61 | | |
| | Min, Max | 5.67,9.30 | 6.00,9.30 | 5.67,9.16 | | |
| Week 24 | Mean±SD | 7.31±0.85 | 7.34±0.84 | 7.28±0.86 | | |
| | Median | 7.19 | 7.13 | 7.26 | | |
| | Min, Max | 5.49,9.88 | 6.04,9.48 | 5.49,9.88 | | |
| Change1 | Mean±SD | 0.86±0.79 | 0.84±0.66 | 0.87±0.90 | | |
| | LS Mean±SE | | 0.86±0.09 | 0.85±0.09 | 0.01[-0.26,0.27] | 0.9607∫ |
| | Median | 0.87 | 0.92 | 0.85 | | |
| | Min, Max | -0.88,3.92 | -0.77,1.93 | -0.88,3.92 | | |
| Change2 | Mean±SD | 1.10±0.89 | 1.02±0.81 | 1.18±0.96 | | |
| | LS Mean±SE | | 1.05±0.10 | 1.15±0.10 | -0.10[-0.39,0.19] | 0.4993∫ |
| | Median | 1.18 | 1.05 | 1.28 | | |
| | Min, Max | -1.31,3.99 | -0.29,3.10 | -1.31,3.99 | | |

Change1=Baseline - Week 12
Change2=Baseline - Week 24
*: Student's *t*-test
∫: ANCOVA using covariates as baseline

The proportion of subjects with HbA1c < 7% who did not experience hypoglycemia at the end of 24 week treatment was 1.32% (1/76 subjects) for Basal Plus and 4.00% (3/75 subjects) for Premixed Insulin; the difference between the two groups was not statistically significant.

The proportion of subjects with HbA1c < 7% was 34.21% (26/76 subjects) for Basal Plus and 32.00% (24/75 subjects) for Premixed Insulin; the proportion of subjects with HbA1c < 6.5% was 14.47% (11/76 subjects) for Basal Plus and 16.00% (12/75 subjects) for Premixed Insulin; the difference between two groups was not statistically significant.

**Table 4** Proportion of patients reaching HbA1c targets (ITT)

| | | Total N=160 n (%) | Basal Plus N=78 n (%) | Premixed Insulin N=82 n (%) | *p*-value |
|---|---|---|---|---|---|
| HbA1c<7% and no experience of hypoglycemia | n | 151 | 76 | 75 | 0.3666‡ |
| | Yes | 4 (2.65) | 1 (1.32) | 3 (4.00) | |
| | No | 147 (97.35) | 75 (98.68) | 72 (96.00) | |
| HbA1c<7% | n | 151 | 76 | 75 | 0.7729† |
| | Yes | 50 (33.11) | 26 (34.21) | 24 (32.00) | |
| | No | 101 (66.89) | 50 (65.79) | 51 (68.00) | |
| HbA1c<6.5% | n | 151 | 76 | 75 | 0.7941† |
| | Yes | 23 (15.23) | 11 (14.47) | 12 (16.00) | |
| | No | 128 (84.77) | 65 (85.53) | 63 (84.00) | |

†: Pearson's chi-square test

‡: Fisher's exact test

The proportion of subjects who experienced hypoglycemia was 91.03% (71/78 subjects, 1054 events) for Basal Plus and 81.71% (67/82 subjects, 571 events) for Premixed Insulin (*p*=0.0871). Of these, the proportion of subjects with symptomatic daytime hypoglycemia was 80.77% (63/78 subjects, 407 events) for Basal Plus and 68.29% (56/82 subjects, 296 events) for Premixed Insulin (*p*=0.0708); the proportion of subjects with symptomatic nocturnal hypoglycemia was 41.03% (32/78 subjects, 126 events) for Basal Plus and 40.24% (33/82 subjects, 118 events) for Premixed Insulin (*p*=0.9198). The proportion of subjects with asymptomatic hypoglycemia was 85.90% (67/78 subjects, 828 events) for Basal Plus and 64.63% (53/82 subjects, 347 events) for Premixed Insulin and the statistical difference between the two groups was significant (*p*=0.0019). The proportion of subjects with severe symptomatic hypoglycemia was 2.56% (2/78 subjects, 2 events) for Basal Plus and 1.22% (1/82 subjects, 1 event) for Premixed Insulin (*p*=0.6133).

**Table 5** Proportion of subjects experiencing hypoglycemia (ITT)

| | Total N=160 | | Basal Plus N=78 | | Premixed Insulin N=82 | | *p*-value |
|---|---|---|---|---|---|---|---|
| | n (%) | [No. of events] | n (%) | [No. of events] | n (%) | [No. of events] | |
| All hypoglycemia | 138 (86.25) | [1625] | 71 (91.03) | [1054] | 67 (81.71) | [571] | 0.0871† |
| Symptomatic daytime hypoglycemia | 119 (74.38) | [703] | 63 (80.77) | [407] | 56 (68.29) | [296] | 0.0708† |
| Symptomatic nocturnal hypoglycemia | 65 (40.63) | [244] | 32 (41.03) | [126] | 33 (40.24) | [118] | 0.9198† |
| Asymptomatic hypoglycemia | 120 (75.00) | [1175] | 67 (85.90) | [828] | 53 (64.63) | [347] | 0.0019† |
| Severe symptomatic hypoglycemia | 3 (1.88) | [3] | 2 (2.56) | [2] | 1 (1.22) | [1] | 0.6133‡ |

†: Pearson's chi-square test

‡: Fisher's exact test

The mean ±SD change in body weight from baseline to the end of 24-week treatment was 1.22±0.37 kg for Basal Plus and 1.05±0.36 kg for Premixed Insulin with no statistically significant difference between the two groups ($p$=0.5366).

The mean ±SD total daily insulin dose at the end of 24-week treatment, which was calculated to sum total injected daily dose of insulin regardless basal or short acting insulin, was 45.35±21.81 U for Basal Plus and 45.68±20.41 U for Premixed Insulin with no statistically significant difference between two groups ($p$=0.6448).

The mean ±SD total daily insulin dose in the subgroup of subjects with HbA1c < 7% with or without hypoglycemia at the end of 24-week treatment was 41.77±21.44 U for Basal Plus and 39.92±15.73 U for Premixed Insulin ($p$=0.9845); whereas in the subgroup of subjects with HbA1c < 7% who did not experience hypoglycemia, it was 18.00±18.00 U for Basal Plus and 38.00±13.11 U for Premixed Insulin.

**Table 6** Total daily insulin dose at the end of 24 week treatment (ITT)

| | | Total N=160 | Basal Plus N=78 | Premixed Insulin N=82 | *p*-value |
|---|---|---|---|---|---|
| Total daily insulin dose at the end of 24 week treatment | n | 158 | 78 | 80 | 0.6448+ |
| | Mean±SD | 45.51 ±21.05 | 45.35 ±21.81 | 45.68 ±20.41 | |
| | Median | 42.00 | 42.50 | 42.00 | |
| | Min, Max | 8.00 ,134.00 | 8.00 ,112.00 | 8.00 ,134.00 | |
| Total daily insulin dose at the end of 24 week treatment in subjects with HbA1c<7% | n | 50 | 26 | 24 | 0.9845+ |
| | Mean±SD | 40.88 ±18.75 | 41.77 ±21.44 | 39.92 ±15.73 | |
| | Median | 39.50 | 39.50 | 39.00 | |
| | Min, Max | 16.00 ,112.00 | 16.00 ,112.00 | 22.00 ,74.00 | |
| Total daily insulin dose at the end of 24 week treatment in subjects with HbA1c<7% and no hypoglycemia | n | 4 | 1 | 3 | |
| | Mean±SD | 33.00 ±14.65 | 18.00 ±. | 38.00 ±13.11 | |
| | Median | 32.00 | 18.00 | 40.00 | |
| | Min, Max | 18.00 ,50.00 | 18.00 ,18.00 | 24.00 ,50.00 | |

+: Wilcoxon's rank sum test

Change (LS Mean±SE) of mean FPG on 3 consecutive days at Week 12 was 1.93±4.02 mg/dL (mean FPG [Mean±SD] at Week 12: 107.32±26.73 mg/dL) for Basal Plus and 22.86±3.94 mg/dL (mean FPG [Mean±SD] at Week 12: 129.25±40.70 mg/dL) for Premixed Insulin; at Week 24, it was 3.11±3.61 mg/dL (mean FPG [Mean±SD] at Week 24: 108.33±24.68 mg/dL) for Basal Plus and 24.44±3.51 mg/dL (mean FPG [Mean±SD] at Week 24: 130.95±36.00 mg/dL) for Premixed Insulin; the mean FPG increase was higher for Premixed Insulin than Basal Plus both at Week 12 and Week 24 and the between-group difference in the change was statistically significant (Week 12: $p$=0.0005, Week 24: $p$=0.0001).

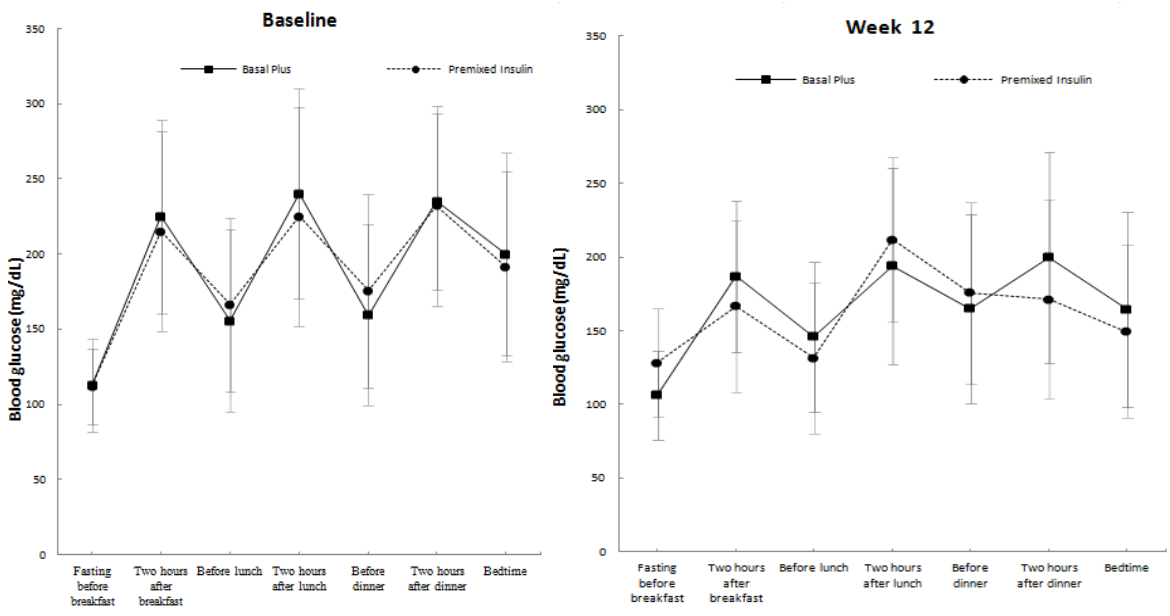
**Table 7** FPG profile over 3 consecutive days prior to a visit (ITT)

| | | Total N=160 | Basal Plus N=78 | Premixed Insulin N=82 | *p*-value |
|---|---|---|---|---|---|
| Baseline | n | 159 | 77 | 82 | 0.7136+ |
| | Mean±SD | 106.50 ±21.61 | 105.10 ±20.26 | 107.82 ±22.84 | |
| Week 12 | n | 148 | 73 | 75 | 0.0001+ |
| | Mean±SD | 118.44 ±36.12 | 107.32 ±26.73 | 129.25 ±40.70 | |
| Week 24 | n | 149 | 73 | 76 | <.0001+ |
| | Mean±SD | 119.86 ±32.89 | 108.33 ±24.68 | 130.95 ±36.00 | |

| | | | | | |
|---|---|---|---|---|---|
| Change1 | n | 147 | 72 | 75 | |
| | Mean±SD | 12.61 ±37.95 | 3.07 ±28.45 | 21.76 ±43.49 | |
| | LS Mean±SE | | 1.93 ±4.02 | 22.86 ±3.94 | 0.0005 ∬ |
| | Median | 7.33 | 1.33 | 20.00 | |
| | Min, Max | -61.33 ,175.33 | -56.67 ,113.33 | -61.33 ,175.33 | |
| Change2 | n | 148 | 72 | 76 | |
| | Mean±SD | 14.06 ±35.33 | 4.44 ±28.61 | 23.18 ±38.72 | |
| | LS Mean±SE | | 3.11 ±3.61 | 24.44 ±3.51 | 0.0001 ∬ |
| | Median | 11.17 | 1.83 | 22.00 | |
| | Min, Max | -68.00 ,132.17 | -48.33 ,90.33 | -68.00 ,132.17 | |

Change1=Week 12 - Baseline
Change2=Week 24 - Baseline
+: Wilcoxon's rank sum test
∫: ANCOVA using covariates as baseline
∬ : Rank ANCOVA using covariates as baseline

Regarding the change in the 7-point PG profile at 12 weeks, a statistically significant difference between the two groups was observed before breakfast (Basal Plus -6.03±3.64 mg/dL, Premixed Insulin 12.82±3.78 mg/dL, *p*=0.0001), 2 hr after breakfast (Basal Plus -38.73±6.59 mg/dL, Premixed Insulin -58.88±7.36 mg/dL, *p*=0.0225), and 2 hr after dinner (Basal Plus -41.39±8.10 mg/dL, Premixed Insulin -70.23±9.12 mg/dL, *p*=0.0151). Whereas for the change at 24 weeks, a statistically significant between-group difference was observed before breakfast (Basal Plus -4.27±3.58 mg/dL, Premixed Insulin 16.24±3.71, *p*=0.0001) and 2 hr after lunch (Basal Plus -59.42±7.12 mg/dL, Premixed Insulin -32.01±7.71 mg/dL, *p*=0.0104).



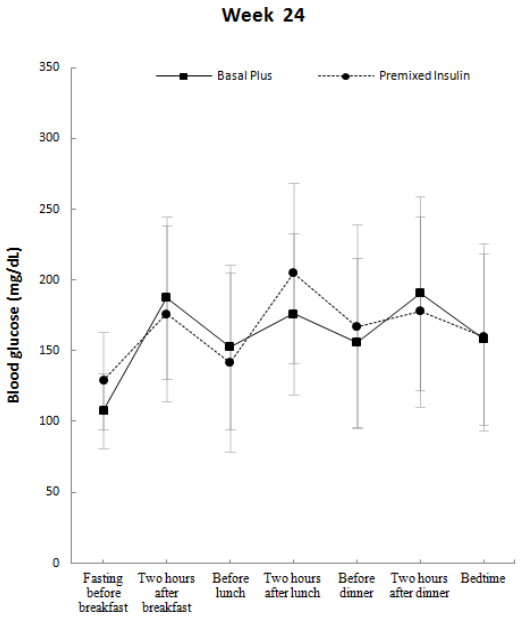



**Figure 2** 7-point PG profile (ITT)

The change in the 72 hr CGMS profile from baseline to the end of 24 week treatment was assessed in 12 randomized subjects (Basal Plus 5, Premixed Insulin 7); mean ±SD PG change was -28.58±22.42 mg/dL for Basal Plus and -20.52±41.93 mg/dL for Premixed Insulin with no statistically significant between-group difference. The mean ±SD change in MAGE was -4.73±54.82 for Basal Plus and 21.15±72.04 for Premixed Insulin, SD mean ±SD change was -3.16±11.84 and -2.38±27.45, respectively, $CONGA_1$ mean ±SD change was -3.61 ±8.07 and 0.00±22.75, respectively, and MODD mean ±SD change was -6.38±12.59 and 1.12±19.14, respectively; the statistical difference between the two groups was not significant in all cases.
Change in ROS (reactive oxygen species) from baseline to the end of 24 week treatment was assessed by random urine 8-OH PGF2a; the mean ±SD change was 15.70±96.45 pg/mg Cr for Basal plus and -38.68±122.39 pg/mg Cr for Premixed with no statistically significant difference between two groups.

**Safety results:**

Unless classified as a serious adverse event in this study, hypoglycemia was not considered as an adverse event but collected independently from adverse events and analyzed as a secondary efficacy endpoint.
The proportion of subjects who experienced at least 1 adverse event after investigational product administration was 33.33% (26/78 subjects, 45 events) for Basal Plus and 45.12% (37/82 subjects, 62 events) for Premixed Insulin. Of these, the incidence of adverse drug reactions for which the relationship with the investigational product could not be excluded was 1.28% (1/78 subjects, 1 event) for Basal Plus and 3.66% (3/82 subjects, 4 events) for Premixed Insulin. Serious adverse events were reported at 3.85% (3/78 subjects, 3 events) for Basal Plus and 1.22% (1/82 subjects, 1 event) for Premixed Insulin. In the Basal Plus group, 1 subject (1.28%) was withdrawn due to an adverse event. In both groups, events were classified by System Organ Class (SOC) with the most frequent being 'infections and infestations', followed by 'musculoskeletal and connective tissue disorders'. The most frequently observed adverse event when classified according to preferred term (PT) was 'nasopharyngitis' in both groups.

**Table 8** Adverse event summary

| | Total N=160 | | Basal Plus N=78 | | Premixed Insulin N=82 | |
|---|---|---|---|---|---|---|
| | n (%) | [No. of events] | n (%) | [No. of events] | n (%) | [No. of events] |
| Adverse event(AE) | 63 (39.38) | [107] | 26 (33.33) | [45] | 37 (45.12) | [62] |
| Adverse drug reaction(ADR) | 4 (2.50) | [5] | 1 (1.28) | [1] | 3 (3.66) | [4] |
| Serious adverse event(SAE) | 4 (2.50) | [4] | 3 (3.85) | [3] | 1 (1.22) | [1] |
| Adverse event resulting in withdrawal | 1 (0.63) | [1] | 1 (1.28) | [1] | 0 (0.00) | [0] |
| Death | 0 (0.00) | [0] | 0 (0.00) | [0] | 0 (0.00) | [0] |

Regarding laboratory test and vital sign parameters, there was no statistically significant between-group difference at Week 24.

**Treatment satisfaction results:**

The mean ±SD change in treatment satisfaction of subjects assessed with DTSQs after 12-week treatment was 1.04±0.80 points for Basal Plus and 0.36±0.82 points for Premixed Insulin, indicating slightly increased satisfaction in both groups; after 24 weeks of treatment, it was -1.86±0.94 points for Basal Plus and -1.45±0.98 points for Premixed Insulin showing lowered satisfaction in both groups. No statistically significant between-group difference was observed in treatment satisfaction (Week 12: p=0.9625, Week 24: p=0.4074). When assessed with DTSQc after 24 weeks, the mean ±SD change in satisfaction at the end of treatment was 9.00±0.96 points for Basal Plus and 7.90±1.01 points for Premixed Insulin, indicating improved satisfaction in both groups and no statistically significant between-group difference (p=0.8610).

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