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

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| Sponsor / Company: Sanofi<br>Drug substance(s): Insulin human | Study Identifiers: NCT01353469, U1111-1120-0701<br>Study code: EFC12059 |
| Title of the study: A multicenter, randomized, active-controlled, parallel-group study to assess the efficacy and safety of Insuman Comb 25 (insulin human) versus Novolin® 30R twice daily over 24 weeks in patients with type 2 diabetes mellitus who are under insulin therapy | |
| Study center(s): Multicenter (23 centers in China) | |
| Study period:<br>Date first patient enrolled: 10/May/2011<br>Date last patient completed: 09/Nov/2012 | |
| Phase of development: Phase 3 | |
| Objectives:<br>Primary: To compare the efficacy of Insuman Comb 25 versus Novolin® 30R on $HbA_{1c}$ reduction during a 24 weeks treatment period in patients with type 2 diabetes mellitus (T2DM).<br>Secondary:<br>• To assess the effects of Insuman Comb 25 versus Novolin® 30R in patients with T2DM on fasting plasma glucose (FPG)<br>• To assess the safety and tolerability of Insuman Comb 25 versus Novolin® 30R in patients with T2DM | |
| Methodology: The study was a randomized (2:1), open-label, active-controlled, 2-arm parallel-group, multicenter, single country, 24-week study. | |
| Number of patients: | Planned: 480<br>Randomized: 485<br>Treated: 484 (2 patients randomized but not treated, 1 patient treated but not randomized) |
| Evaluated: | Efficacy: 481<br>Safety: 483 |
| Diagnosis and criteria for inclusion: Type 2 diabetes mellitus patients, diagnosed for at least 1 year at the time of screening visit, who were under premix insulin therapy, with or without oral anti-diabetic drug (OAD); aged ≥18 and <75 years at screening; $HbA_{1c}$ ≥7% and ≤10% at screening. | |

Study treatments

Investigational medicinal product(s):

Tested drug: Insuman Comb 25 (a mixture containing 25% dissolved recombinant insulin of regular, human insulin and 75% human insulin isophane suspension)

Formulation: 300 IU/3 mL suspension (cartridge)

Route(s) of administration: Subcutaneous (SC) injection using ClikSTAR injection pen

Dose regimen: Self-injected twice daily, 30-45 minutes before breakfast and dinner

Control drug: Novolin® 30R (a mixture of 30% regular, human insulin and 70% human insulin isophane suspension)

Formulation: 300 IU/3 mL suspension (cartridge)

Route(s) of administration: SC injection using Novolin Pen® 4 injection pen

Dose regimen: Self-injected twice daily within 30 minutes before breakfast and dinner

Noninvestigational medicinal product(s): OADs

Formulation: The approved formulation in China

Route(s) of administration: Oral

Dose regimen: The type and dose, received prior to the study, were to remain unchanged during 24-week treatment period, unless identified safety concerns related to OADs necessitate a reduction in OAD dose.

Duration of treatment: 24 weeks

Duration of observation: Up to 27 weeks (up to 2 weeks screening + 24 weeks open-label treatment + 1 week follow-up)

Criteria for evaluation:

Efficacy:

Primary: Mean absolute change of $HbA_{1c}$ from baseline to the end of treatment

Secondary: Mean change in FPG from baseline to the end of treatment

Safety: Asymptomatic hypoglycemia, documented symptomatic hypoglycemia, severe hypoglycemia, probable symptomatic hypoglycemia, relative hypoglycemia, and nocturnal hypoglycemia; local tolerability at injection site; allergic or allergic-like reactions; other adverse events (AEs) and serious adverse events (SAEs); Vital signs; laboratory tests.

Statistical methods:

Efficacy: The efficacy analyses were based on the modified intent-to-treat (mITT) population, corresponding to all randomized patients who received at least one injection of investigational medicinal product (IMP) after randomization and had a baseline value and at least one post-baseline assessment of efficacy variables, irrespective of compliance with the study protocol and procedures.

The primary efficacy endpoint (mean absolute change from baseline to the end of treatment in $HbA_{1c}$) was analyzed using an analysis of covariance (ANCOVA) model with treatment, strata of $HbA_{1c}$ at screening (<8.5% and ≥8.5%) and strata of OAD use at screening (Yes, No) as fixed effects and using the baseline value as a covariate.

Non-inferiority of Insuman Comb 25 to Novolin® 30R was to be demonstrated if the upper bound of the 2-sided 95% confidence interval (CI) for the mean difference between Insuman Comb 25 and Novolin® 30R on mITT population was less than 0.4%.

The secondary endpoint (mean change in FPG from baseline to the end of treatment) was analyzed using the same ANCOVA model as described for the primary efficacy endpoint, which included fixed effect terms for treatment, randomization strata of $HbA_{1c}$ at screening (<8.5%, ≥8.5%) and randomization strata of OAD use at screening (Yes, No) with the corresponding baseline value as a covariate.

Safety: The safety population was defined as all randomized patients who receive at least one injection of the IMP after randomization, regardless of the amount of treatment administered, according to the treatment actually received. The review of safety and tolerance were performed on the safety population. The safety analyses were based on the reported hypoglycemia, AEs and other safety information (clinical laboratory evaluations and vital signs). The summaries of safety results were presented for each treatment group (Insuman Comb 25 and Novolin® 30R).


Summary:

Population characteristics:

A total of 485 patients were randomized in 23 centers in China to 1 of the 2 treatment groups (322 patients and 163 patients in the Insuman and Novolin treatment groups, respectively). Of the 485 randomized patients, 483 patients were exposed to the study treatment and included in the analyses. During the on-treatment period, 10 patients (3.1%) in the Insuman treatment group and 1 patient (0.6%) in the Novolin treatment group prematurely discontinued the study treatment.

Of the 485 randomized patients, 481 patients (318 patients and 163 patients in the Insuman and Novolin treatment groups, respectively) were included in the mITT efficacy population; 483 patients (320 patients and 163 patients in the Insuman and Novolin treatment groups, respectively) were included in the safety population.

The demographic and patient baseline characteristics were generally similar between the 2 treatment groups for the safety population. Disease characteristics, including diabetic history, were generally comparable between the 2 treatment groups. The use of background OAD treatment at screening and at baseline was generally similar between the 2 treatment groups. Baseline efficacy variables ($HbA_{1c}$ and FPG) were generally comparable between the 2 treatment groups for the safety population.

Efficacy results:

For the primary efficacy endpoint, the least squares (LS) mean change in $HbA_{1c}$ from baseline to Week 24 (last observation carried forward [LOCF]) was -0.33% (mean value of 8.10% at baseline, 7.78% at Week 24) in the Insuman treatment group compared with -0.65% (mean value of 8.09% at baseline, 7.46% at week 24) in the Novolin treatment group (LS mean difference for Insuman versus Novolin was 0.32%; 95% CI: 0.149, 0.486). Based on the pre-specified analysis of ANCOVA model, non-inferiority of Insuman versus Novolin was not demonstrated because the upper bound of the 2-sided 95% CI for the LS mean difference was greater than the predefined non-inferiority margin of 0.4%.

For the secondary efficacy endpoint, the LS mean change in FPG from baseline to Week 24 (LOCF) was -0.60 mmol/L (mean value of 8.87 mmol/L at baseline, 8.24 mmol/L at Week 24) in the Insuman treatment group compared with -0.84 mmol/L (mean value of 8.65 mmol/L at baseline, 7.94 mmol/L at Week 24) in the Novolin treatment group (LS mean difference for Insuman versus Novolin was 0.25 mmol/L; 95% CI: -0.177, 0.671).

Safety results:

The number of any hypoglycemia events that occurred during the on-treatment period was 435 in the Insuman treatment group (320 patients) and 276 in the Novolin treatment group (163 patients). The mean event rate of any hypoglycemia (events/patient-years) was lower in the Insuman treatment group (2.94) compared with the Novolin treatment group (3.64). The ratio of the mean event rates of any hypoglycemia between the Insuman and Novolin treatment groups was 0.82 (95% CI: 0.53, 1.28). The incidence rate of any hypoglycemia was lower in the Insuman treatment group (34.4%) compared with the Novolin treatment group (42.9%). The incidence rate of documented symptomatic hypoglycemia was also lower in the Insuman treatment group (20.3%) compared with the Novolin treatment group (30.7%). No severe hypoglycemia occurred during the on-treatment period, ie, no treatment-emergent adverse event (TEAE) of severe symptomatic hypoglycemia was reported during the on-treatment period.

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| The incidence of TEAEs was 33.8% in the Insuman treatment group compared with 41.1% in the Novolin treatment group. The most frequently reported TEAE by system organ class (SOC) was infections and infestations in the 2 treatment groups (14.1% and 14.7% in the Insuman and Novolin treatment groups, respectively). Overall, 7 patients (2.2%) in the Insuman treatment group and 1 patient (0.6%) in the Novolin treatment group had TEAEs of local intolerability or allergic/allergic-like reactions. All patients with these TEAEs recovered from the events. Two patients (0.6%) in the Insuman treatment group had TEAEs that led to permanent discontinuation of study treatment.<br><br>A total of 16 patients had 17 SAEs during the on-treatment period: 11 patients (3.4%) in the Insuman treatment group compared with 5 patients (3.1%) in the Novolin treatment group. None of these SAEs led to permanent treatment discontinuation. All patients with these SAEs recovered from the events without sequelae after corrective treatments were given. There was no death during the study. |
| Issue date: 13-Feb-2014 |