2 Synopsis

Trial Registration ID-number: NCT00789191	**IND Number: 51879** **EudraCT number: 2008-001050-40**
Title of Trial A 26 week randomised, open labelled, parallel group, multi-national, treat-to-target trial comparing efficacy and safety of insulin detemir once daily in combination with sitagliptin and metformin versus sitagliptin and metformin with or without sulphonylurea, in subjects with type 2 diabetes	
Investigator(s) The Principal investigator was [redacted], M.D., Ph. D., [redacted]	
Trial Site(s) 48 sites in 8 countries: Canada, Finland, France, Hungary, Slovakia, Republic of Korea, Turkey, USA	
Publications None	
Trial Period 12 Nov 2008 – 27 Aug 2009	**Development Phase** 3b

Objectives

Primary Objective:

- To compare glycaemic control, measured as HbA_{1c}, of insulin detemir given once daily in combination with sitagliptin and metformin versus sitagliptin and metformin ± SU after a 26-week treatment period in subjects with type 2 diabetes inadequately controlled on metformin treatment with or without other OADs

Secondary Objectives:

- To assess and compare efficacy and safety of insulin detemir given once daily in combination with sitagliptin and metformin versus sitagliptin and metformin ± SU after a 26-week treatment period in terms of:
- Proportion of subjects achieving $HbA_{1c} \leq 7.0\%$
- Proportion of subjects achieving $HbA_{1c} \leq 7.0\%$ without symptomatic hypoglycaemia with a plasma glucose value < 4.0 mmol/L (< 72 mg/dL) or any single plasma glucose value < 3.1 mmol/L (56 mg/dL) in the last three months of treatment
- Proportion of subjects achieving $HbA_{1c} \leq 6.5\%$
- Proportion of subjects achieving $HbA_{1c} \leq 6.5\%$ without symptomatic hypoglycaemia with a plasma glucose value < 4.0 mmol/L (< 72 mg/dL) or any single plasma glucose value < 3.1 mmol/L (56 mg/dL) in the last three months of treatment
- The glycaemic control as measured by fasting plasma glucose, FPG (central laboratory values)
- The glycaemic control as measured by 9-point plasma glucose profiles (self-measured)
- Incidence of hypoglycaemic episodes during the trial: nocturnal (23:00-05:59) and over 24 hours
- Incidence of adverse events (AEs)
- Change in clinical and laboratory safety parameters
- Change in body weight
- Change in waist:hip circumference ratio

Methodology

Subjects attended a screening visit, and if found eligible they were randomised within 2 weeks in a 1:1 manner into one of the two treatment arms. Subjects were randomised to receive either insulin detemir once daily plus sitagliptin (COMB arm) or sitagliptin (SITA arm) both as an add-on to their pre-study metformin dose (≥1000 mg), ± SU in the SITA arm. Current use of OADs, apart from metformin in the COMB arm and metformin ± SU in the SITA arm, was discontinued prior to initiation of trial product(s). Subjects were stratified based on previous metformin monotherapy or previous therapy with metformin in combination with other OADs. Insulin detemir treatment was administered in

the evening (from 1 hour before last main meal to bedtime). Sitagliptin 100 mg was administered once daily and metformin (± SU in the SITA arm) was continued at a stable pre-study dose. The SU dose could be reduced after randomisation at the discretion of the Investigator in case of hypoglycaemia. Subjects had weekly visits/phone contacts with the site after randomisation (Visit 2) and throughout the 26-week treatment period. Subjects receiving insulin detemir had their dose titrated weekly according to a titration guideline.

Number of Subjects Planned and Analysed

It was planned to screen 374 subjects in order to include 224 randomised subjects. This was expected to provide at least 200 subjects for the full analysis set (FAS) analysis and to achieve sufficient power for the analysis of the primary endpoint, HbA_{1c} The subject disposition is shown below:

	COMB N (%)	SITA N (%)	Total N (%)
Screened			344
Screening Failures			122
Randomised	111 (100.0)	111 (100.0)	222 (100.0)
Exposed	107 (96.4)	110 (99.1)	217 (97.7)
Withdrawals	14 (12.6)	19 (17.1)	33 (14.9)
Primary Reason for Discontinuation			
Adverse Event	2 (1.8)	4 (3.6)	6 (2.7)
Ineffective Therapy		5 (4.5)	5 (2.3)
Non-Compliance	5 (4.5)	3 (2.7)	8 (3.6)
Withdrawal Criteria	2 (1.8)	4 (3.6)	6 (2.7)
Other	5 (4.5)	3 (2.7)	8 (3.6)
Completed Trial	97 (87.4)	92 (82.9)	189 (85.1)
Full Analysis Set	107 (96.4)	110 (99.1)	217 (97.7)
Safety Analysis Set	107 (96.4)	110 (99.1)	217 (97.7)
PP Analysis Set	88 (79.3)	87 (78.4)	175 (78.8)

Diagnosis and Main Criteria for Inclusion

Male and female subjects with type 2 diabetes aged ≥ 18years, with a BMI ≤ 45kg/m^2, and an $HbA_{1c} \geq 7.5\%$ and ≤ 10.0%. Subjects must have been treated with a minimum of 1000 mg metformin daily for at least 3 month. Subjects were to be insulin naïve and DPP-4 inhibitor naïve. Subjects were not to have been treated with thiazolidinedione (TZD) or GLP-1 analogues within 2 months of screening or have severe hypertension, cardiac disease, renal disorders, hepatic disorders, proliferative retinopathy or maculopathy requiring acute treatment, or any other disease or medication known to interfere with the trial.

Test Product, Dose and Mode of Administration, Batch Number

Insulin detemir (Levemir®) 100 U/mL, 3 mL FlexPen®, batch number VP5092 to be injected s.c.

Duration of Treatment

2-week screening period followed by a 26-week treatment period.

Reference Therapy, Dose and Mode of Administration, Batch Number

Sitagliptin (Januvia®) 100 mg tablets for oral administration batch number T5699

Criteria for Evaluation – Efficacy

- HbA_{1c}, percentage of subjects achieving the treatment targets of: $HbA_{1c} \leq 6.5\%$, $HbA_{1c} \leq 7.0\%$, percentage of subjects achieving $HbA_{1c} \leq 6.5\%$ and $HbA_{1c} \leq 7.0\%$ without hypoglycaemia, 9-point plasma glucose profiles, fasting plasma glucose (FPG), body weight, body mass index (BMI), waist-hip ratio

Criteria for Evaluation – Safety

- Adverse events, hypoglycaemia, physical examination, vital signs, electrocardiogram (ECG) 12 lead, fundoscopy/fundusphotography, β-cell function, laboratory assessments.

Statistical Methods

Primary Endpoint

The primary endpoint, HbA_{1c} after 26 weeks of treatment, was analysed by means of an ANCOVA model with treatment (COMB, SITA), stratification factor (metformin monotherapy, metformin in combination with other OADs) and country (Canada, Finland, France, Hungary, Slovakia, Republic of Korea, Turkey and USA) as fixed effects and the corresponding baseline value as a covariate. A two-sided 95 % confidence interval was constructed for the difference (d) between the means of COMB and SITA. Superiority of COMB against SITA was to be concluded if the upper limit of the confidence interval for the difference is less than 0 (zero), corresponding to hypothesis H_A and having a negative estimate of the treatment difference (d). The primary analysis was performed using the full analysis set (FAS). This analysis was repeated for the per protocol set (PP) as a secondary analysis.

Secondary Endpoints

The proportion of subjects reaching $HbA_{1c} \leq 7.0$ % after 26 weeks of treatment was compared between treatment groups by applying a logistic regression model. Each subject was classified according to having $HbA_{1c} \leq 7.0$ % or not after 26 weeks of treatment. This was modelled within a logistic regression model with treatment, stratification factor and country as fixed effects and baseline HbA_{1c} as covariate. Likewise, the proportion of subjects reaching $HbA_{1c} \leq 7.0$ % who during the last 3 months of treatment did not experience any symptomatic hypoglycaemia confirmed by plasma glucose value < 4.0 mmol/L (< 72 mg/dL) nor a single plasma glucose value < 3.1 mmol/L (< 56 mg/dL) nor any major hypoglycaemia was compared between treatment groups with a similar model. The above two analyses were repeated using an HbA_{1c} threshold of ≤6.5 %.

FPG (central laboratory) after 26 weeks of treatment was analysed by means of an ANCOVA model with treatment, stratification factor and country as fixed effects and the corresponding baseline value as a covariate.

The 9-point plasma glucose profiles were tested for parallelism using a linear mixed effect model with treatment, time, country and time-by-treatment interaction as explanatory variables and subject as a random factor. The residual variance structure was modelled as 'unstructured' for each subject. Complete independence was assumed across subjects. If the time by treatment interaction was statistically significant, the 9-point plasma glucose profiles would be assumed parallel and the estimated overall treatment difference from the model was reported. In the case of non-parallel profiles, the interpretation of the overall treatment difference would be not applicable and the two treatments will also be compared at each time point in the same model.

Body weight measurements, waist-hip ratio and change in BMI at the end of the treatment were analysed for treatment differences with an ANCOVA model including treatment, stratification factor and country as fixed effects and body weight at baseline as a covariate.

The incidence of hypoglycaemic episodes was evaluated by estimating the relative risk of having a hypoglycaemic episode between the two treatment arms. The number of hypoglycaemic episodes per subject occurring during treatment was analysed by means of a negative binomial regression including treatment, baseline HbA_{1c}, stratification and country as independent variables. Data was collected for all, major, minor, symptoms only nocturnal and diurnal hypoglycaemic episodes. Analyses were made for all and minor hypoglycaemic episodes

Demography of Trial Population

Demographic characteristics were generally similar between the treatment groups, except that mean body weight was 5 kg greater in the COMB group but mean BMI was similar in the two treatment groups, probably due to the larger number of males in the COMB group (64% of subjects were male) compared to the SITA group (46% of subjects were male), please see the table below Other baseline characteristics were similar across treatment groups.

	COMB	SITA	Total
Number exposed (n)	107	110	217
Males, n (%)	68 (63.6)	50 (45.5)	118 (54.4)
Females, n (%)	39 (36.4)	60 (54.5)	99 (45.6)
Race n (%)	107	110	217
Asian	13 (13.1)	17 (16.3)	30 (14.8)
Black or African American	3 (3.0)	2 (1.9)	5 (2.5)
Other		1 (1.0)	1 (0.5)
White	83 (83.8)	84 (80.8)	167 (82.3)
Weight (kg) Mean (SD)	93.1 (20.2)	88.2 (19.2)	90.6 (19.8)
BMI (kg/m^2) Mean (SD)	31.8 (5.2)	31.9 (5.9)	31.9 (5.6)
Age (yrs) Mean (SD)	56.7 (9.96)	57.1 (8.41)	56.9 (9.19)
Diabetes (yrs) Mean (SD)	9.6 (5.6)	9.9 (5.7)	9.7 (5.6)
HbA_{1c} % Mean (SD)	8.52 (0.7)	8.52 (0.7)	8.52 (0.7)

Efficacy Results

Primary endpoint

- Analysis of HbA_{1c} after 26 weeks of treatment showed that the reduction in HbA_{1c} was significantly larger in the COMB group compared to SITA with a difference of -0.55%, CI [-0.77; -0.33] ($p < 0.001$). As the confidence interval did not include a zero COMB was found to be superior to SITA with respect to HbA_{1c}.
- Estimated mean HbA_{1c} after 26 weeks was 7.08% with COMB and 7.64% with SITA.

Secondary endpoints

- The odds for reaching the $HbA_{1c} \leq 7.0\%$ target at end of trial with or without hypoglycaemic episodes were significantly higher for COMB than for SITA. The COMB/SITA odds ratios were 3.20, CI [1.65, 6.19], p= 0.001 and 2.47 [1.26, 4.81], p= 0.008, respectively, for reaching the target with and without hypoglycaemic episodes.
- The odds for reaching the $HbA_{1c} \leq 6.5$ % target at end of trial with or without hypoglycaemic episodes were not significantly different for COMB and SITA. The COMB/SITA odds ratios were 2.23, CI [0.96, 5.20], P= 0.063 and 2.07, CI [0.80, 5.37], .p= 0.135, respectively, for reaching the target with and without hypoglycaemic episodes.
- At end of trial, the number of subjects who met the target of $HbA_{1c} \leq 7.0\%$ was 46 (47%) with COMB and 25 (27%) with SITA. HbA_{1c} of $\leq 6.5\%$ was achieved in 20 (21%) and 11(12%) subjects with COMB and SITA respectively. Of those meeting the $HbA_{1c} \leq 7.0\%$ target, 37 (COMB) and 21 (SITA) subjects did not experience any symptomatic hypoglycaemic episodes in the last 3 months of treatment. Of those meeting the $HbA_{1c} \leq 6.5.0\%$ target, 15 (COMB) and 8 (SITA) subjects did not experience any symptomatic hypoglycaemic episodes in the last 3 months of treatment.
- At end of trial, FPG (lab and self-measured) was significantly lower in the COMB group compared to the SITA group with a difference of -2.45 mmol/L, CI [-3.01; -1.88], $p < 0.001$
- After 26 weeks, 9-point PG was significantly lower for all time points in the COMB group compared to the SITA group, except before dinner. Differences and confidence intervals ranged from -2.01 mmol/L, CI [-2.50, -1.51] (before breakfast) to -0.77mmol/L CI [-1.58, 0.05] (before dinner).
- After 26 weeks, there was a small reduction in body weight in both groups. No significant differences in weight,

BMI and waist-hip ratio could be detected between treatment groups.

Safety Results

- A total of 63 treatment emergent hypoglycaemic episodes were reported in 31(29%) subjects in the COMB group and 83 episodes in 25 (23%) subjects in the SITA group. No major hypoglycaemic episodes were reported in either treatment group. No differences were found between rates of hypoglycaemia in the treatment groups.
- In all, 76 subjects in the COMB group and 73 subjects in the SITA group reported AEs. The overall proportion of subjects with treatment emergent SAEs and non-serious AEs was comparable between the treatment groups although the rate (events per 100 exposure years) was greater for the SITA group due to a larger number of mild AEs in this group.
- In the COMB group, there were 12 AEs in 9 subjects possibly or probably related to insulin detemir There were 6 SAEs, 2 (COMB) and 4 (SITA), none were considered related to trial products.
- There were 2 subjects in the COMB group and 4 subjects in the SITA group with AEs leading to withdrawal. Both subjects in the COMB group were withdrawn due to injection site reactions ('hypersensitivity' and 'injection site hypersensitivity') which were probably related to insulin detemir. One (1) subject in the SITA group suffered 2 AEs of dyspnoea and oedema peripheral and was withdrawn as a result. The remaining 3 subjects were withdrawn due to 'optic ischemic neuropathy', 'atrial fibrillation' and 'generalised erythema', the latter was considered probably related to sitagliptin.
- After 26 weeks of treatment, the mean total daily insulin detemir dose in the COMB group was 0.59U/Kg.
- No clinically relevant differences between treatment groups were observed in standard laboratory parameters or cardiovascular risk markers after 26 weeks.
- No clinically significant changes were observed in vital signs and physical examination.

Conclusions

In a population of insulin naïve subjects with type 2 diabetes inadequately controlled with metformin (as mono therapy or in combination with OADs) once daily treatment for 26 weeks with insulin detemir in combination with sitagliptin (COMB) versus sitagliptin ± SU (SITA) both in combination with metformin resulted in the following:

- COMB was shown to be superior to SITA with respect to reduction in HbA_{1c}.
- The odds for reaching target HbA_{1c} of ≤7.0% at end of trial with or without hypoglycaemic episodes, were higher in the COMB group and the COMB/SITA odds ratio was significantly higher than 1
- The odds for reaching target HbA_{1c} of ≤6.5.0% at end of trial with or without hypoglycaemic episodes, were not statistically significantly higher in the COMB group than in the SITA group
- At end of trial, FPG was significantly lower in the COMB group compared to the SITA group and the 9 point SMPG were significantly lower for all time points in the COMB group compared to the SITA group, except before dinner.
- After 26 weeks, there were no significant differences in body weight, BMI and waist-hip ratio between treatment groups
- No subjects experienced severe hypoglycaemia. There was no difference in the rates of hypoglycaemia in the COMB versus SITA groups.
- The overall proportion of subjects experiencing AEs and the AE profile was generally comparable in the two groups although the rate of AEs was higher in the SITA group due to a larger number of mild AEs per subject. There were few SAEs and AE withdrawals in both groups.
- There were no safety issues raised during this trial

The trial was conducted in accordance with the World Medical Association. Declaration of Helsinki (. Ethical Principles for Medical Research Involving Human Subjects. 52nd WMA General Assembly, Edinburgh, Scotland, October 2000. Last amended with Note of Clarification on Paragraph 29 by the WMA General Assembly, Washington 2002, and Note of Clarification on Paragraph 30 by the WMA General assembly, Tokyo 2004) and ICH Harmonised Tripartite Guideline. Good Clinical Practice (01-May-1996).

The results presented reflect data available in the clinical database as of 21-June-2010.