Synopsis

TITLE OF TRIAL

A FOUR-MONTH OPEN-LABEL RANDOMISED MULTI-CENTRE TWO-GROUP PARALLEL TRIAL COMPARING ADMINISTRATION OF INSULIN DETEMIR ONCE OR TWICE DAILY IN A BASAL-BOLUS REGIMEN WITH INSULIN ASPART IN PATIENTS WITH TYPE 1 DIABETES, FOLLOWED BY A THREE-MONTH EXTENSION PERIOD

INVESTIGATOR(S)

There were two investigators (in France and Belgium, respectively).

TRIAL SITE(S)

There were two trial sites (in France and Belgium, respectively).

PUBLICATIONS

Poster, 19th World International Diabetes Federation Congress, Cape Town, South Africa in 2006, December

Poster, ALFEDIAM-SFE Congress, Marseille, France in 2007, March

Poster, 43rd Annual Meeting of the European Association for the Study of Diabetes, Amsterdam, The Netherlands in 2007, September

Poster, ADA 67th Scientific Sessions, Chicago, USA in 2000, June

TRIAL PERIOD:	**DEVELOPMENT PHASE:**
Date of first enrolment: 27/06/2005 Date of last completed: 17/10/2006	IV

OBJECTIVES

The aim of the trial was to compare 2 basal bolus insulin regimens with detemir either once or twice daily in type 1 diabetes. The second objective was to evaluate insulin requirements during daytime and night-time in a large type 1 diabetic patients population.
The primary objective of this trial was to compare the glycaemic control of once-daily insulin detemir regimen with that of twice-daily insulin detemir regimen as measured by HbA1c in patients with type 1 diabetes on a basal-bolus regimen with insulin aspart as bolus insulin after 4 months of treatment (including a one-month titration period).

Secondary objectives of this trial was to analyse the two-treatment regimen (insulin detemir once daily versus twice daily) after 4 months of the treatment according to the criteria listed below.
In addition, secondary objectives of this trial was to describe and analyse changes during the 3 months extension period within the two treatment groups according to the criteria listed below.

The following criteria were evaluated at the 4-month visit and at the 7-month visit:

- Efficacy objectives

- Glycaemic control as measured by Fasting Blood Glucose (FBG),
- Glycaemic control as measured by Pre-prandial Blood Glucose (PreBG),
- Glycaemic control as measured by Post-prandial Blood Glucose (PostBG),
- HbA1c measurement (only 7-month visit),
- Percentage of patients with HbA1c ≤7%,
- Percentage of patients achieving Fasting Blood Glucose ≤6.7 mmol/L (1.2 g/L),
- Within–patient variation of blood glucose during the trial,
- Percentage of patients switching from twice daily to once daily and from once daily to twice daily (only 4-month visit), and percentage of patients with a once daily regimen at the 7-month visit,
- Incidence of hyperglycaemic episodes.

- Safety objectives

- Incidence of hypoglycaemic episodes,
- Weight change during the trial,
- Occurrence of adverse events during the trial.

- Insulin dose requirements (absolute and related to weight)

- Basal/bolus insulin doses ratio,
- Insulin needs day versus night (ratio evening dose/morning dose) in patients on twice daily detemir treatment (only 4-month visit),
- Number of snacks/day,
- Evaluation of "extra-injections"

METHODOLOGY

This was a randomised, multi-centre, bi-national, open-label; controlled 2 parallel groups treat to target trial. The patients were randomised to either once daily insulin detemir regimen or twice daily detemir regimen, mealtime insulin aspart being associated in both groups. The first month was a titration phase. The comparative period lasted 4 months. After that, the basal treatment was be re-evaluated and the patients were followed up during a 3-month extension period.

The control group was the "2 daily injections group" as this was the most usual mode of administration referred to in clinical trials involving Detemir. Randomisation allowed to get comparable population of patients in each group. The trial was open-label in order to avoid use of "double-dummy" techniques which required an undesirable increase in the number of injections and may affect compliance.

NUMBER OF SUBJECTS PLANNED AND ANALYZED

Planned: 750

Analysed: 527 (global population)

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Inclusion criteria:

1. Informed Consent obtained before any trial-related activities. (Trial-related activities are any procedure that would not were performed during normal management of the patient),
2. Type 1 diabetes for more than 1 year,
3. Patient between 18 and 70 years old,
4. Patient treated by any kind of insulin regimen and whatever the number of injections
5. Patients regularly followed up by the Investigator for at least 6 months,
6. HbA1c $\geq$ 7.5% and $\leq$10% (local dosage within the last 3 months).

Exclusion criteria:

1. Type 2 diabetes,
2. Treatment by OAD (within the last 6 months and/or during the trial),
3. Proliferative retinopathy,
4. Hypoglycaemia unawareness as judged by investigator,
5. Impaired hepatic function, renal function or cardiac function as judged by investigator
6. Pregnant, breast-feeding or the intention of becoming pregnant or not using adequate contraceptive measures as judged by the investigator,
7. History of alcoholism, drug abuse, or psychiatric disease or personality disorders likely to invalidate voluntary consent or to prevent good compliance with the trial protocol,
8. Mental incapacity, unwillingness or language barrier precluding adequate understanding or co-operation,
9. Legal incapacity or limited legal capacity,
10. Participation in another clinical trial less than one month before inclusion in this trial,
11. Illness requiring repeated hospitalisation,
12. Known or suspected allergy to the insulin or any compositional component,
13. Patient receiving concomitant medication known to interfere with glucose metabolism (corticoids, β-blockers, thyroid hormones),
14. Any other condition that the Investigator feels would interfere with trial participation or evaluation of results

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

-Insulin detemir 100 U/ml was supplied in 3 ml FlexPen®

-Insulin aspart 100 U/ml was supplied in 3 ml FlexPen®

Trial products were administered subcutaneously for insulin aspart and for insulin detemir using a FlexPen®

-Insulin Detemir 100 IU/mL - batch RP50752 - expiry date 29/01/2007
-Box of 5 3-mL Flexpen - batch RP51302 - expiry date 21/04/2007
-Insulin Aspart 100 IU/mL – batch RP50596 - expiry date 14/04/2007
-Box of 5 3-mL Flexpen - batch RP50961 – expiry date 25/05/2007

DURATION OF TREATMENT:

4 months (including a one-month titration period) with an extension period of 3 months

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Not applicable

CRITERIA FOR EVALUATION – EFFICACY

The main assessment criterion was glycaemic control, assessed by HbA1c after 4 months of treatment (V2).

The key secondary efficacy variables were glycaemic control assessed by HbA1c after 7 months of treatment (V3), mean Fasting, mean Preprandial and mean Postprandial Blood Glucose recorded the last 14 days before 4-month and 7-month evaluations (V2 and V3), percentage of patients achieving Fasting Blood Glucose ≤6.7 mmol/L (1.2 g/L), percentage of patients with HbA1c ≤7% after 4 and 7 months (V2 and V3) and with once daily and with twice daily insulin detemir, incidence of hyperglycaemic episodes.

Insulin dose requirements were assessed by mean daily dose of insulin detemir and insulin aspart between baseline evaluation and 4 months evaluation excluding the titration period (remaining 3 months duration, one month after V1 to V2) and from 4-month evaluation to 7-month evaluation (V2 to V3), basal/bolus insulin doses ratio, insulin needs day versus night (ratio evening dose/ morning dose) in patients on twice daily insulin detemir treatment, evaluation of "extra-injections", percentage of patients treated at 7 months (V3) by a once daily insulin detemir regimen.

CRITERIA FOR EVALUATION – SAFETY

The key safety variables were incidence of hypoglycaemic episodes (all, minor, major), weight at 4 and 7 months (V2 and V3) and adverse events.

STATISTICAL METHODS

The description of patients characteristics at baseline was performed by regimen group and in total on the global population, the ITT population and the ITT population excluding patients prematurely withdrawn from the trial.

Tests were performed for baseline characteristics in order to check the initial comparability of the 2 groups. Quantitative variables were compared using a Mann-Whitney-Wilcoxon test and qualitative variables were compared using a Chi-2 test or Fisher's exact test if the assumptions of Chi-2 were not met.

The HbA1c value after 4 months of treatments was compared between the 2 regimen groups using a covariance analysis with the HbA1c baseline value as covariate. 95% confidence interval of the adjusted means (Lsmeans corresponding to the covariate model) was calculated. Non-inferiority was achieved if the upper limit of the 95% confidence interval was less than 0.4% (absolute). The power of the test was calculated *a posteriori*.

Analysis of compliance was described by treatment group and in total after 4 months of treatment and after the 3 month extension period. Overall compliance in the investigator's opinion was described by repartition. Groups were compared using a Chi-2 test.

Group effect was studied at fixed time for evolution from V1 to the 4-month visit using a Wilcoxon test. Evolution from V2 to the 7-month visit within group was tested using a paired t-test.

For evolution of daily dose from V1 to the 4-month visit, group effect was studied for using a Wilcoxon test. Evolution from V2 to the 7-month visit within group was tested using a paired t-test.

DEMOGRAPHY OF TRIAL POPULATION

Not applicable

EFFICACY RESULTS

A total of 527 patients was recruited in 199 investigational centres in France and in Belgium. In these patients, 7 (1.3%) patients were not randomised. In all, 520 patients received the trial treatments. Patients were randomly allocated either to the group treated with 1 daily detemir injection (OD) or to the group treated with 2 daily detemir injections (BID).

In the global population, 94/520 (18.1%) patients left the trial prematurely on the entire trial period, mainly for glycaemic imbalance and other reasons in group 1, and for discomfort related to the injections in group 2. Patients in G1 left significantly earlier i.e. after 56.62 days in mean (range: 5-184) while patients in G2 left after 93.13 days in mean (range: 10-198) as calculated for insulin detemir (p=0.015). Eight (1.5%) randomised patients were excluded from the intent to treat (ITT) population because they were not documented for the date of first insulin detemir injection or for the date of last detemir injection.

Description of patients characteristics was performed by regimen group on the ITT population (N=512) and on the "ITT population excluding patients prematurely withdrawn from V1 to V2" in order to make sure that the patients who stayed in the trial were not different from the initial ITT population.

The mean age of patients at baseline was 41.76 (±12.99) years. In the 512 trial patients, 52.1% of patients were male and 47.9% were female, with a repartition of 52.8% of males versus 47.2% of females in the 1-injection group, and 51.5% of males versus 48.5% females in the 2-injection group. The mean weight was 72.05 (±13.51) kg and the mean height was 169.51 (±9.27) cm. Mean BMI at

Visit 1 (inclusion) was 25.03 (±3.97) kg/m2 for the total ITT population, i.e. with a mean of 24.80 (±4.06) kg/m2 in the 1-injection group and of 25.24 (±3.88) kg/m2 in the 2-injection group. No significant difference was characterised between the groups.

The 2 randomised groups were not different for clinical examination, nor for vital signs. A total of 302 (59.0%) patients presented with medical/surgical history or concomitant diseases with a significant difference between groups (p=0.0251).

Trial patients were diagnosed for diabetes 16.62 (±10.72) years before initiation of the trial, with no difference between groups. A total of 216/512 (42.2%) patients presented with diabetes complications at baseline mainly dyslipidemia (50.0% of the patients in the ITT population), hypertension (43.5%), ocular complications (36.6%) and peripheral neuropathy (20.8%). Main complications related to diabetes were not different in the ITT population and ITT population excluding prematurely withdrawn patients. More patients had history of cardiac complications in G1 (11.0% vs. 4.3%) and more patients experienced dyslipidemia in G2 (45.0% vs. 54.3%). For hypoglycaemic episodes, results were similar in the ITT population and the ITT population excluding prematurely withdrawn patients, with a mean number of 3.44 (±3.80) episodes.

Combination of insulin therapies usually taken by patients over a 24-hour period at baseline was mainly basal insulin plus bolus insulin regimen. No significant difference was characterised between the groups. The total recommended dose of insulin per day at V1 in the ITT population was 51.16 (±18.99) IU in G1 and 49.83 (±18.04) IU in G2. No significant difference was characterised between the groups. The mean daily total dose of insulin detemir recommended for both groups was 26.77 (±12.17) IU. The mean daily total insulin aspart dose recommended for both groups was 23.71 (±11.74) IU. No significant difference was characterised between the groups.

Formal compliance with trial products was not assessed from V1 to V2 due to the variable doses used. Follow-up at V2 and V3 showed that compliance was "very good" or "good" as analysed in randomised patients.

The mean value of HbA1c at baseline was 8.48% (±0.90) for the total ITT population (range: 6.60%-13.50%) with a median of 8.30%. The 2 groups were not significantly different.

Primary objective

Mean HbA1c value after 4 months of insulin detemir treatment analysed in the ITT population (N=512) was 8.01 (±0.94)% (range: 6.60-11.20) with a median of 8.00%. There was no significant difference between the groups. The mean evolution of HbA1c within each group from V1 to V2 showed a significant decrease in HbA1c within each group by –0.40% in group 1, and –0.52% in G2 (p= <0.001). Yet evolution was more important in G2 and G2 patients were better-controlled after 4 months of treatment. In the PP population, similar results were found.

Non-inferiority of the 1-injection group was demonstrated using a model. The estimate of the difference of the adjusted means was 0.12 with a 95% CI of [-0.01;0.25]. As the upper limit of the 95% confidence interval was less than 0.4% (absolute), the analysis showed that the 1-injection group was non-inferior to the 2-injection group. The power of the test, estimated *a posteriori* was 95%. This was confirmed in the PP population, as the results were not different with an estimate of the difference of the adjusted means of 0.13 with a 95% CI of [-0.01;0.26].

Secondary objectives

Switch in treatment regimen

After 4 months of treatment (V2), 41.3% of the total ITT population patients switched regimen for insulin detemir injections. In the 2 groups, treatment with insulin aspart was maintained. Significantly more patients switched from 1 to 2 injections: In group 1, 172 (83.9%) patients switched from 1 daily to 2 daily injections. In group 2, 10 (4.2%) patients switched from 2 daily to 1 daily injection. The multivariate analysis showed that no predictive factor was retained for switching treatment after 4 months of insulin detemir regimen at significant level of 10%.

HbA1c levels

HbA1c levels were analysed according to defined classes (≤6.5%,]6.5%;7.5%],]7.5%;8.5%], >8.5%), baseline HbA1c quartiles, responders/non-responders patients (HbA1c <=7%), stable levels or increase/decrease (increase <0.4% or >=0.4%, decrease <0.4% or >=0.4%).

The mean evolution of HbA1c from baseline to V2 showed a decrease in both groups, by -0.40% in G1 and -0.52% in G2. The difference between the groups was non-significant (p=0.0943). No difference was characterised as for the evolution in classes.

The total number of responder patients (patients with HbA1c ≤7%) at V2 was 71 (14.9%) patients. No significant difference was characterised between the groups.

When analysing the probability to have HbA1c<=7% at V2, the results of the multivariate analyses showed that probability was higher in patients with low HbA1c levels at baseline, less insulin injections administered before inclusion, a high total dose of insulin aspart recommended per day at baseline, and minor episodes of hypoglycaemia reported before inclusion.

When analysing the potential predictive factors for controlled HbA1c at V2, the results of the multivariate analyses showed that gender was involved (female patients had a lower HbA1c level), high HbA1c at baseline resulted in high HbA1c levels at V2, patient with no bolus insulin before inclusion had lower HbA1c levels at V2, high number of insulin injections before inclusion resulted in high HbA1c levels at V2, a higher total dose of insulin aspart per day recommended at V1 resulted in lower HbA1c levels at V2. and when the patient had no symptomatic episodes of hypoglycaemia before inclusion, HbA1c levels at V2 were high.

Mean HbA1c level after 7 months of treatment for the total ITT population was 7.92% (±0.96) with 7.87 (±0.84) in G1 and 7.96% (±1.06) in G2. No significant difference was characterised between the groups.

The evolution of HbA1c from V2 to V3 was -0.16 (±0.58)% in mean in G1 and 0.00 (±0.56) in mean in G2. Evolution within groups was significant in G1 ($p<0.001$). No significant evolution was shown in G2.

When considering defined classes (≤6.5%,]6.5%;7.5%],]7.5%;8.5%], >8.5%), the evolution of HbA1c within group from V2 to V3 was significant in G1 ($p<0.001$) and not significant in G2.

When considering the defined classes from V2-V3, transition for HbA1c was found significant in G1 ($p<0.0001$) but not significant in G2. In G 1, most patients remained stable or improved their control of HbA1c levels. In G2, most patients remained stable or improved their control of HbA1c levels except in class Q1<HbA1c <= median. The evolution within group was significant in G1 ($p=0.0055$) and not in G2.

Responder patients (patients with HbA1c ≤7%) at V3 in the ITT population were 14.1% in G1 and 17.8% in G2. The evolution was not characterised as significant in any group. The mean evolution of HbA1c from V1-V3 was -0.55%. No significant difference was characterised between the groups.

Hyperglycaemic episodes

The mean number of hyperglycaemic episodes reported by the patients in the total ITT population was 30.16 (±9.83) episodes. The 2 treatment groups show no significant difference. The mean number of hyperglycaemic episodes reported during the last 14 days preceding V3 in the ITT population was 29.42 (10.20) in G1 and 29.46 (8.95) in G2. No significant difference was shown between groups. After 7 months of treatment, the evolution of the number of hyperglycaemic episodes was -1.47 (±9.82) episodes in mean in group 1, and–0.77 (±8.49) episodes in mean in G2. The evolution of the number of hyperglycaemic episodes from V2 to V3 was calculated in the PP population and was -1.78 (±9.95) episodes in mean in group 1, and -0.56 (±8.32) episodes in mean in G2. A significant difference was characterised in G1 ($p=0.020$) with less episodes after 7 months of treatment. No difference was shown in G2 ($p=0.347$).

Hypoglycaemia

Hypoglycaemia was analysed on the ITT population. In the last 14 days before V2, the mean number of hypoglycaemic episodes was 1.25 episodes. At V2, the mean number of hypoglycaemic episodes was 22.91 (±20.62) episodes.

In the last 14 days before V2 and V3, it was 2.52 episodes in mean for the total ITT population. Over the entire trial, the mean total number of hypoglycaemic episodes was 38.92. The 2 groups showed no significant difference. The same was observed in the PP population.

Glycaemic control after treatment was assessed by self-measured fasting blood glucose (FBG), pre-prandial blood glucose (preBG), post-prandial blood glucose (postBG), within patient variation of blood glucose and biological determination of HbA1c in blood samples at V1, V2 and V3 on the ITT population.

Blood Glucose: After 4 months of treatment, the analysis of the covariance showed that patients were significantly better-controlled in the 1-injection group for FBG and after breakfast BG. In contrast, patients in the 2-injection group were significantly better-controlled for before/after lunch, before/after dinner and bedtime BG.

After 7 months of treatment, the mean evolution of BG from V2 to V3 was characterised as significant in G1 for before/after lunch, before/after dinner and bedtime BG, except for after breakfast BG. All evolutions were characterised as non-significant in G2.

Over the entire trial, no significant difference was characterised between the groups as regard all BG measurements, due to the imbalance of the switch.

Fasting Blood Glucose: After 4 months of treatment, mean self-measured FBG was higher in G2 than in G1 (1.46 (±0.42) g/L in G1 and 1.61 (±0.42) g/L in G2). There was significantly more patients achieving the target FBG ≤6.7 mmol/L (1.20 g/L) at V2 in the 1-injection group (30.8% vs. 12.0%). More patients reached target FBG in G1 in all baseline quartiles.

After 7 months of treatment (V3), mean self-measured FBG was not different between groups, with 1.55 (±0.42) g/L in G1 and 1.56 (±0.37) g/L in G2. The evolution of mean self-measured FBG from V2 to V3 showed an increase by +0.11 (±0.40) g/L in G1 and a

decrease by –0.04 (±0.37) g/L in G2. It was characterised as significant in G1 (p<0.001) while not significant in G2. Transition for patients achieving self-measured fasting Blood Glucose <=6.7 mmol/L (1.2 g/L) at visit V3 compared to V2 and was significant in both groups.

Over the entire trial, the target value for FBG was achieved in 78 (19.0%) patients after 7 months of treatment in the total ITT population.

Pre-prandial Blood Glucose: After 4 months of treatment, mean pre-prandial Blood Glucose was significantly better-controlled in the 2-injection group at V2.

The target value for pre-dinner Blood Glucose was <=6.7 mmol/L (1.20 g/L) and was achieved by similar proportions of patients in both groups: 18 (8.1%) patients in G1 and 21 (8.6%) patients in G2. No significant difference was characterised.

After 7 months of treatment, mean pre-prandial BG was not significantly different between groups with 1.57 (±0.30) g/L in G1 and 1.54 (±0.28) g/L in G2. The evolution of mean PreBG showed a decrease in G1 and stable results in G2, with -0.06 (±0.27) g/L in G1 and –0.00 (±0.24) g/L in G2. A significant evolution was characterised in G1 (p=0.002). No significant evolution was shown in G2.

No significant difference was characterised between the groups as for proportions of patients achieving target preBG <=6.7 mmol/L (1.2 g/L) at V3: 19 (9.8%) patients in G1 and 20 (9.0%) in G2. Compared to V2, this change within each group was not significant in G1 nor in G2.

Post-prandial blood glucose: After 4 months of treatment, mean post-prandial Blood Glucose was significantly lower in G2 with 1.71 (±0.42) g/L in G1 and 1.63 (±0.36) g/L in G2.

The target value for post-prandial blood glucose was <=10 mmol/L (1.80 g/L), measured between 1 h and 1 h 30 after meals as defined in the protocol. At V2, the percentage of patients achieving post-prandial FBG<=10 mmol/L (1.8 g/L) was more important in G2 (59.2% vs. 71.6%). The results showed that PostBG was significantly better-controlled in the 2-injection group.

After 7 months of treatment, mean post-prandial BG value was similar in both groups, (1.55 vs. 1.59 g/L). Most patients achieved target PostBG in both groups (76.6% vs. 74.1%). No significant difference was characterised. The evolution of mean PostBG from V2-V3 showed a tendency to decrease: by -0.11 (±0.47) g/L in G1 and -0.03 (±0.35) g/L in G2. The evolution was characterised as significant in G1 (p=0.004) and not in G2. In G1, slightly more patients achieved target postBG at V3 than in G2 (76.6% vs. 74.1%). Compared to V2, the change was significant in G1 and not significant in G2.

Mean self-measured Blood Glucose at all times: Mean Blood Glucose measured at all times at V2 was significantly higher in G1 (1.71 vs. 1.60 g/L) after 4 months of treatment. The results showed that mean BG was better-controlled in the 2-injection group at all times for all predefined classes. The variance of the mean showed that there was a significant difference between the 2 treatment groups (p= 0.0003) while the coefficient of variation of the mean (p=0.1364) showed a non-significant difference.

After 7 months of treatment (V3), it was similar between groups, with 1.58 (±0.28) g/L in G1 with a significant decrease from V2 to V3 by -0.10 (±0.27) and 1.59 (±0.27) g/L in G2 with a non-significant evolution from V2 to V3 of 0.00 (±0.24) g/L. The evolution of the variance of BG at all times from V2 to V3 was significant in G1 (p<0.001) while not in G2.

The evolution of the coefficient of variation from V2-V3 was significant in G1 (p=0.006) with -0.02 (±0.08). In contrast, it was characterised as non-significant in G2 with an evolution of -0.01 (±0.09).

When considering predefined classes, no significant difference was characterised between the groups from V2-V3. Yet transition was characterised as significant (p=0.0002) in G1 and non-significant in G2.

Within-patient variation

Within-patient variation during the last 14 days before visit V2 was more important in G1 (1.48 vs. 1.33 g/L) and the difference was significantly characterised between the groups. During the last 14 days before visit V3, it was not significantly different between groups (1.30 vs. 1.27 g/L).

The evolution of the within-patient variation from V2 to V3 was more important in G1 (-0.14 vs. -0.04 g/L). Change from V2 to V3 within each treatment group change was significant (p<0.001 and p=0.032 respectively).

Weight and BMI

The evolution of weight from V1 to V2 was 0.54 (±2.44) kg in mean in G1 (range: 6.00-10.00 kg), and 0.49 (±2.99) kg in mean in G2 (range: –15.00 to 10.00 kg) No significant difference was characterised between the 2 groups. No difference was characterised as for the evolution in weight (p=0.8422). From V2 to V3, evolution of weight was 0.40 (±1.86) kg in mean in G1 (range: –5.0 to 5.00 kg) and 0.54 (±2.05) kg in mean in G2 (range: –4.00 to 10.00 kg). A significant increase was characterised in G1 (p=0.003) and in G2

(p<0.001). Weight increase was significantly higher in G2 however.

For the entire trial (V1-V3), the evolution of weight was observed as 1.01 (±3.13) kg in mean (range: –9.0 to 16.0 kg), that is an increase of 1.49% after 7 months of detemir treatment. In all, 44.7% of patients tended to loose weight and 55.3% to gain weight. No significant difference was characterised between the treatment regimen. The results of the multivariate analysis for evolution of weight from V1 to V3 showed that weight tended to increase after 7 months of treatment when: the total dose of insulin aspart administered per day at V3 increased and when the evolution of HbA1c from V1 to V3 decreased.

The multivariate analysis for positive evolution of weight from V1 to V3 showed that weight tended to increase after 7 months of treatment when HbA1c tended to decrease from V1-V3 and when the total dose of insulin aspart administered per day at V3 tended to rise.

The evolution of BMI from V1 and V2 was 0.19 (±0.83) kg/m2 in mean in G1 ranging from –1.88 to 3.91 kg/m2 and 0.17 (±1.04) kg/m2 in mean in G2 ranging from -5.19 kg to 3.52 kg/m2. No significant difference was characterised between the groups (p=0.8584). No difference was characterised as for the evolution in BMI within each group.

The mean evolution of BMI from V2 to V3 was 0.15 (±0.64) kg/m2 in G1 (range: -2.05 to 1.93 kg/m2) and 0.19 (±0.73) kg/m2 in G2 (range: –1.43 to 4.11 kg/m2). A significant difference was characterised in BMI evolution in G1 (p=0.002) and also in G2 (p<0.001). BMI increase was significantly more important in G2. For the entire trial (V1-V3), evolution of BMI for the total ITT population was 0.35 (±1.09) kg/m2 in mean ranging from –13.04 kg/m2 to 24.24 kg/m2, that is an increase of 1.51% in mean after 7 months of treatment. In all, 44.7% of the ITT population had a BMI progress <= 0 and 55.3% a progress >0 kg. In group 1, the mean evolution of BMI was 0.35 (±1.06) kg/m2, and 0.36 (±1.13) kg/m2. The median of both groups was 0.31 and 0.33 respectively. No significant difference was evidenced between the treatment groups.

The multivariate analysis for evolution of BMI from V1 to V3 showed that BMI tended to increase after 7 months of treatment when the total dose of insulin aspart administered per day at V3 increased and when HbA1c levels from V1 to V3 decreased.

The multivariate analysis for positive evolution of BMI from V1 to V3 showed that BMI tended to increase after 7 months of treatment when HbA1c tended to decrease from V1 to V3 and the total dose of insulin aspart administered per day at V3 rose.

SAFETY RESULTS

Trial patients were exposed to the trial products for a median duration of 198.00 treatment days. For the 4-month comparative period (V1-V2), duration of treatment was 113 days for detemir and aspart insulins. Duration of treatment was not significantly different in both groups.

Adverse events

Adverse events were evaluated in the global population. There was no death during the trial.

<u>During the entire trial</u>, 182/527 patients (34.5%) reported with at least one adverse event. A total of 181/527 (34.4%) patients had at least one emergent adverse event. Two patients in G1 experienced up to 5 AEs and 5 patients had up to 4 events in G2. 3.2% of patients had to discontinue insulin detemir permanently due to the emergent event, and 3.0% insulin aspart. 8.6% of patients had at least one emergent adverse event related to insulin detemir and 4.8% of patients related to insulin aspart. There was no significant difference between the groups.

The most frequently reported SOC for emergent AEs were (by descending order) infections and infestations system, metabolism and nutrition disorders system, general disorders and administration site conditions, gastrointestinal system disorders. There was no comparison calculated between the groups. No emergent AEs were reported in G1 as regard blood and lymphatic system disorders, cardiac disorders and hepatobiliary disorders.

An emergent adverse event was related to the treatment if its relation with the insulin detemir/aspart treatment was probable or doubtful. A total of 45 patients experienced emergent AEs related to insulin detemir and 25 patients related to insulin aspart. Emergent AEs were mainly of mild and moderate intensity.

A total of 41 (7.8%) patients reported with at least one SAE, with no significant difference characterised between groups.

<u>During the comparative period</u> (V1-V2), a total of 127/527 patients (24.1%) reported with at least one adverse event. No significant difference was characterised between the groups as to AEs, except for the number of emergent adverse events by patient.

In all, 24.0% of patients had at least one emergent AE. The maximum number of emergent events experienced by patients was 5 events in G1 (1 patient) and 3 events in G2 (9 patients). The 2 treatment groups were significantly different (p=0.0417) with more emergent AEs occurring in G1 between V1-V2.

Insulin detemir had to be discontinued permanently due to the emergent event in 2.3% of patients and insulin aspart in 2.1% of patients. In all, 6.3% of patients had at least one emergent AE related to insulin detemir and 3.0% of patients related to insulin aspart. There was no significant difference between the groups.

The most frequently reported SOC for emergent AEs were the same as for the entire trial.

A total of 22 (4.2%) patients had at least one SAE, with no significant difference characterised between groups.

During the extension period (V2-V3), 91/527 patients (17.3%) reported with at least one AE. No significant difference was characterised between the 2 groups as to AEs during this period.

In all, 17.3% of patients reported at least one emergent AE. No patients had to discontinue any of the insulin products permanently due to the emergent event in G1 while 5 (1.9%) patients had to discontinue insulin detemir and insulin aspart due to an emergent AE.

2.7% of patients had at least one emergent AE related to insulin detemir 1.9% of patients related to insulin aspart. There was no significant difference between the groups.

The most frequently reported SOC for emergent adverse events (by descending order) were not the same as in period V1-V2: musculoskeletal and connective tissue disorders were reported more often than gastrointestinal system disorders.

A total of 19 (3.6%) patients reported with at least one SAE, with no significant difference between groups. At V2-V3, the 2 groups were not significantly different, but there were slightly less SAEs reported in both groups

Vital signs

Vital signs were analysed on the ITT population and PP population at V2 and V3. Mean DBP, SBP and heart rate values were within the normal range during the trial.

After 4 months of treatment, mean SBP at V2 was 127.31 (±14.10) mmHg. No significant difference was characterised between the groups. No abnormal value was observed after 4 months of treatment in G1 patients. Only 1 (0.4%) patient in G2 reported with abnormal values. At V3, mean SBP was 127.08 (±14.76) mmHg. A significant difference was characterised between the groups at V3 with a more elevated SBP in G1 (ITT and PP populations).

The evolution of SBP from V2 to V3 was +1.10 (±11.39) mmHg in mean in G1 and -1.60 (±12.82) mmHg in mean in G2. In the PP population, it was +0.79 in mean in G1 and -1.49 in mean in G2. It was shown that no significant evolution was characterised in any group. Yet, it is interesting to note that SBP tended to rise in G1 and decreased in G2 at V3.

Mean DBP measured at V2 was 74.62 (±8.18) mmHg in G1 and 75.38 (±8.66) mmHg in G2. At V3 it was 76.03 (±8.51) mmHg in G1 and 74.52 (±8.31) mmHg in group 2.

The evolution of DBP from V2 to V3 in the ITT population was +1.15 (±8.77) mmHg in mean in G1 and -0.79 (±8.59) mmHg in mean in G2. No significant evolution was characterised within G1 nor in G2. No abnormal values were reported in G1 nor in G2 after 7 months treatment in the ITT population or in the PP population. In group 1, 1 patient reported abnormal values at V2 but recovered normal DBP at V3, in group 2, 1 (0.4%) patient also reported DBP abnormal values at V2 but recovered normal DBP at V3.

In the global population, heart rate at V2 was 75.05 bpm in mean in G1 and 75.47 bpm in mean in G2. The evolution of heart rate from V1 to V2 was 1.38 bpm in G1 and 1.64 bpm in G2. No significant difference was characterised between the groups.

CONCLUSIONS:

Detemir insulin is a long-acting analogue developed for basal insulin therapy in basal-bolus regimen. Although pharmacological studies showed that it can be used once daily, most clinical trials have been conducted with detemir twice daily. This was the first controlled trial addressing the question of its use either once or twice daily in type 1 diabetic patients.

This was an open, multicenter, randomised trial which was conducted in a large sample of type 1 diabetic patients from two countries, France and Belgium, to compare basal-bolus insulin regimen with detemir administered once daily or twice daily. Because detemir once daily was more convenient for the patients, and because detemir administered twice daily should result in a better or at least equal glucose control than detemir administered once daily, a non-inferiority analysis was decided. Prior to the trial, non-inferiority was clinically defined as a difference in HbA1c lower than 0.4%. The observed result was 0.12%, with a 95% confidence interval [-0.01; 0.25]. Thus, non-inferiority of detemir administered once daily was accepted. A specific bias of this kind of analysis was the risk of accepting non-inferiority because of large fluctuations of data due to interfering factors and leading to wide individual variability. In our trial, the 95% confidence interval of the difference in HbA1c levels did not support that hypothesis. In addition, the true power of the test, estimated *a posteriori*, was 95%.

A particular aspect dealt with patients lost for follow-up, which, in the intent-to-treat analysis, had the same HbA1c value at end-point than at inclusion. Some patients withdrew from the trial before end-point, because either of poor metabolic control (mainly in group 1) or discomfort (mainly in group 2). That was an important point to consider, because these patients might induce wrong conclusions of non-inferiority. Here, the per-protocol analysis, excluding these patients, was especially interesting, showing a similar result (difference 0.13%; [-0.01; 0.26]), then suggesting the strength of the conclusion of non-inferiority. Finally, we could conclude that, in type 1 diabetic patients not withdrawing because of short-term poor metabolic control (mainly detemir administered once daily) or discomfort (mainly detemir administered twice daily), basal-bolus insulin regimen with detemir administered once daily was not inferior to regimen with detemir administered twice daily.

However some differences in glucose profiles could be observed: better fasting results were observed with detemir administered once daily, whereas better results were observed before and after lunch and dinner with detemir administered twice daily. This was likely related to a short duration of detemir action in some patients, leading to an increase in blood glucose level before the next detemir injection in patients treated once daily.

Total insulin doses were quite similar in both groups. However, detemir doses were higher when detemir was used twice daily and aspart doses were higher when associated with detemir administered once daily. This suggested two different strategies in the management of glucose levels. With detemir administered once daily, increasing detemir doses was restricted by fasting glucose value and the risk of hypoglycaemia during the second part of the night. Glucose levels before lunch and dinner could only be managed using short-acting aspart. It appeared to be difficult, probably because of the risk of hypoglycaemia between meals, and results in elevated glucose levels before meals. With detemir administered twice daily, good glucose levels are easily reached before and after lunch and dinner, using quite similar detemir doses injected before breakfast and at bedtime. However it seemed difficult to increase detemir dose at bedtime, because of the risk of hypoglycaemia during the first part of the night. Thus, hyperglycaemia occurred during the second part of the night as shown by elevated fasting glucose level. Lower aspart doses were requested, compared to detemir administered once daily, and management of post-prandial hyperglycemias appeared easier with a low frequency of hypoglycaemia between meals.

After the switch at 4 months, most patients were treated with detemir administered twice daily, not necessarily in respect with switching proposed rules: although 28% of the patients had HbA1c <7.5%, only 13% of them stayed on detemir administered once daily. That was probably because most patients and investigators considered a priori that detemir administered twice daily should induce a better glucose control than detemir administered once daily. Interestingly, switching did not improve dramatically their HbA1c, especially in those patients switching from detemir administered once daily to twice daily. On the other hand, patients remaining with 1 daily detemir injection still showed good glucose control. That supported that one regimen (detemir administered twice daily) did not necessarily induce a better glucose control that the other (detemir administered once daily) in all patients, but that patients' insulin requirements and results depended mainly on individual factors. Thus, for one defined patient the choice of the best regimen should be based on his glucose profile and estimated insulin duration of action: patients previously known to have forenoon and afternoon hypoglycaemia, or with a long duration of insulin action could be treated with detemir administered once daily. The same for patients with an important dawn phenomenon. On the contrary, patients with a short duration of insulin action, or with hyperglycemias before dinner should better used detemir twice daily. Intermediary situations could occur, such as elevated glycaemia before breakfast and dinner, as observed in some patients switching from detemir administered once to twice daily, leading to prefer detemir twice daily but with higher doses at bedtime.

Regarding weight, over 6 months, weight increased by 1.0 ±3.1 kg and BMI increased by 0.4 ±1.1 kg/m², with 55% of patients gaining weight. Similar results were shown in groups receiving either once- or twice-daily detemir injections (1.0 ±3.0 versus 1.0 ±3.2 kg, 0.4 ±1.1 versus 0.4 ±1.1 kg/m², respectively, NS). Weight gain was significantly associated with the absence of diabetes complications (1.9 ±0.3 versus 1.0 ±0.3; $p<0.05$), improvement in HbA1c ($r=0.22$; $p<0.001$), the aspart dose ($r=0.13$; $p<0.01$) and the total insulin

dose (r=0.10; p<0.05), but not with the frequency of hypoglycaemia or with the detemir dose. The multivariate analyses showed that the improvement in HbA1c and the aspart dose were explanatory factors for weight gain (multiple regression: R^2=0.08; logistic: R^2=0.02; p<0.001). Similar results were found with BMI.
The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.