Clinical Trial Results Synopsis

Name of Sponsor/Company:
Medical University of Graz, Department of Internal Medicine, Division of Endocrinology and Metabolism, Austria

Name of Finished Product:
NovoRapid® (Novo Nordisk A/S, Bagsværd, Denmark)

Name of Active Ingredient:
Insulin aspart

Title of Study:
A single-centre, randomised, controlled, 2-period cross-over, open-labelled trial to evaluate the impact of different application volumes on pharmacokinetic and pharmacodynamic properties of insulin aspart in subjects with type 1 diabetes

Investigators:
Principal Investigator: Thomas R. Pieber, MD, Medical University of Graz, Austria

Study Centre(s):
The single-centre study was conducted at the Clinical Research Centre at the Medical University of Graz, Austria.

Publication (reference):
Mader JK, Birngruber T, Korsatko S, Deller S, Köhler G, Boysen S, Augustin T, Mautner SI, Sinner F, Pieber TR, on behalf of the AP@home consortium. Enhanced Absorption of Insulin Aspart as the Result of a Dispersed Injection Strategy Tested in a Randomized Trial in Type 1 Diabetic Patients. Diabetes Care 2013;36(4):780-785

Study Period:
The study has been conducted between April 2011 and June 2011.

Phase of Development:
Phase IV

Objectives:
The primary objective of the study was to compare the pharmacokinetic response (based on the time to maximum observed serum insulin concentration) of rapid-acting insulin aspart after s.c. injection of a defined dose (volume) at one versus nine injection sites in patients with type 1 diabetes.

The secondary objectives of the study were to characterise and compare the pharmacokinetic and pharmacodynamic profiles, and to assess the safety and tolerability of rapid-acting insulin aspart after s.c. injection of a defined dose (volume) at one versus nine injection sites in patients with type 1 diabetes.

Methodology:

This study was a single-centre, randomised, controlled, two-period crossover euglycaemic clamp study conducted in patients with type 1 diabetes. The study consisted of four visits: one screening visit, two clamp visits that were separated by a washout phase of 5 – 21 days, and one follow-up visit. At the clamp visits, rapid-acting insulin aspart was administered s.c. (adipose tissue of the abdominal wall) either as a single bolus of 18 IU or as nine boluses of 2 IU each in a predefined 10 mm grid pattern. Participants were randomly assigned to one of the injection strategies at their first clamp visit. The other injection strategy was then administered on the second clamp visit.

Euglycaemia was maintained during the clamps by a variable glucose infusion. The clamps were continued for 8 hours after dosing, but were terminated earlier if plasma glucose reached >200 mg/dL. Plasma glucose was measured in 5 to 10-min intervals throughout the clamp. Serum samples for insulin analysis were taken at baseline, in 5-min intervals up to 120 min, in 15-min intervals from 120 to 180 min, in 30-min intervals from 180 to 240 min, followed by 60-min intervals from 240 min to 480 min.

Number of Subjects (planned and analysed):

A total of 12 participants were planned, 13 were screened and 12 were enrolled and randomly allocated to one treatment sequence. All participants completed both clamp visits and were included in the analysis.

Diagnosis and Main Criteria for Inclusion:

People with type 1 diabetes that fulfilled all of the following inclusion criteria and gave written informed consent were included in the study:

- Male or female aged 18 – 60 years (both inclusive)
- Type 1 diabetes treated with multiple daily insulin injection or continuous subcutaneous insulin infusion for ≥ 12 months
- Fasting C-peptide <0.3 nmol/L
- Body mass index 20.0 – 28.0 kg/m² (both inclusive)
- HbA1c <10%

Individuals were excluded from the study if any of the following criteria applied:

- Female of childbearing potential who is pregnant or breast-feeding, or who intend to become pregnant or is not using adequate contraceptive methods
- Skin pathology or condition prohibiting needle insertion/insulin administration as judged by the investigator
- History of bleeding disorder
- Current participation in another clinical study
- Significant acute or chronic illness that might interfere with subject safety or integrity of results as judged by the investigator
- Smoker (defined as >5 cigarettes/d)
- Lipodystrophy
- Current treatment with systemic (oral or i.v.) corticosteroids, monoamine oxidase inhibitors, non-selective beta-blockers, growth hormone, herbal products or non-routine vitamins, or thyroid hormones (the latter are not allowed unless their use has been stable during the past 3 months).
- Significant history of alcoholism or drug abuse or a positive result in urine drug/alcohol screen.

Test Product, Dose and Mode of Administration:

NovoRapid® (100 IU/mL, FlexPen), 1 X 18 IU s.c Bolus or 9 X 2 IU s.c. injection,

Duration of Treatment:

The trial consisted of four visits (one screening visit, two clamp visits and one follow-up visit). The clamp visits were separated by 5 – 21 days. The participants were involved in the study for up to 65 days.

Reference Product, Dose and Mode of Administration, Batch number:

N.A.

Criteria for Evaluation:

Efficacy:

Primary pharmacokinetic endpoint:

- Insulin t_{max}: time to reach maximum serum insulin aspart concentration

Secondary pharmacokinetic endpoints:

- Insulin t_{max10}: time to reach 10% of maximum serum insulin aspart concentration
- Insulin t_{max50}: time to reach 50% of maximum serum insulin aspart concentration
- C-INS_{max}: maximum serum insulin aspart concentration
- AUC-INS_{t30}, AUC-INS_{t60}, AUC-INS_{t120}, AUC-INS_{t240}, AUC-INS_{t360}, AUC-INS_{t480}: area under the serum insulin aspart concentration-time curve for different time frames (0 – 30 min, 0 – 60 min, 0 – 120 min, 0 – 240 min, 0 – 360 min, 0 – 480 min)
- AUC-INS_{tmax}: area under the serum insulin aspart concentration-time curve from 0 to timepoint of C-INS_{max}
- AUC-$INS_{t\infty}$: area under the serum insulin aspart concentration-time curve from 0 to infinity
- Onset of appearance: time from trial product administration until the first time serum insulin aspart concentration is >30 pmol/L

Secondary pharmacodynamic endpoints:

- GIR t_{max}: time to reach maximum glucose infusion rate
- GIR t_{max10}: time to reach 10% of maximum glucose infusion rate
- GIR t_{max50}: time to reach 50% of maximum glucose infusion rate
- C-GIR_{max}: maximum glucose infusion rate
- AUC-GIR_{t30}, AUC-GIR_{t60}, AUC-GIR_{t120}, AUC-GIR_{t240}, AUC-GIR_{t360}, AUC-GIR_{t480}: area under the glucose infusion rate curve for different time frames (0 – 30 min, 0 – 60 min, 0 – 120 min, 0 – 240 min, 0 – 360 min, 0 – 480 min)
- AUC-GIR_{tmax}: area under the glucose infusion rate curve from 0 to timepoint of C-GIR_{max}
- AUC-$GIR_{t\infty}$: area under the glucose infusion rate curve from 0 to infinity
- Onset of action: time from trial product administration until plasma glucose concentration has decreased at least 5mg/dL from the baseline value
- Duration of action: time from onset of action until plasma glucose exceeds 150mg/dL without any glucose infusion

Safety:
Secondary safety endpoints included adverse events, laboratory safety parameters and onset of appearance.

Statistical Methods:
All data were tested for normal distribution using a Shapiro-Wilk test. The paired measurements were analysed with paired *t*-tests or Wilcoxon signed rank tests, depending on whether the paired differences were normally distributed. Area under the curves were estimated with the trapezoidal rule for defined time points. $P<0.05$ was considered to indicate a significant difference. Bonferroni corrections were used to correct for multiple testing of the pharmacokinetic and pharmacodynamic results. All statistical analyses were performed with the software package R (v.2.10.1).

SUMMARY OF RESULTS AND CONCLUSIONS:

Baseline Demographics and Characteristics:
All participants (6 male and 6 female) were C-peptide-negative type 1 diabetic patients with a mean ± SD age of 32 ± 9 years and a mean diabetes duration of 19 ± 10 years. The mean body mass index was 23.9 ± 2.5 kg/m^2 and mean HbA1c was 7.3 ± 0.6%.

Subject Disposition:
A total of 12 participants were enrolled into the study and received the study drug. All participants completed the study.

Efficacy Results:
Results on primary and secondary endpoints are summarised in Table 1.

Maximum insulin concentrations were similar for both injection strategies. Time to reach maximum insulin concentration was shorter for the dispersed injection strategy (9 X 2 IU) although the differences were only significant for time to reach 10% and 50% of the maximum insulin concentration. The areas under the insulin concentration-time curve were significantly enhanced for the dispersed injection strategy within the first 30 and 60 minutes, whereas for all other time frames no differences between the injection strategies were observed.

Times taken to reach 10% and 50% of maximum glucose infusion rate were also significantly lower for the dispersed injection strategy (9 X 2 IU), whereas the concentrations at maximum insulin action were similar for both injection strategies. The area under the glucose infusion rate curve of the first 60 minutes was significantly larger for the dispersed injection strategy, whereas the area under the curve until time of maximum glucose infusion rate was significantly smaller. The area under the glucose infusion rate curve for all other time frames were similar for both injection strategies.

Table 1. Pharmacokinetic and pharmacodynamic parameters for the two injection strategies.

	1 × 18 IU	9 × 2 IU	*P* value
Pharmacokinetics			
Insulin t_{max10} (min)	14.2 ± 5.6	9.2 ± 4.2	0.03
Insulin t_{max50} (min)	35.0 ± 8.3	24.6 ± 7.5	0.001
Insulin t_{max} (min)	66.3 ± 38	56.3 ± 14	0.3
C-INS_{max} (mU/L)	526.0 ± 275	546.0 ± 243	0.7
AUC-$INS_{t_{max}}$	13,279 ± 7,220	16,507 ± 8,575	0.2
AUC-INS_{t30}	3,044 ± 1,982	5,595 ± 4,432	0.04
AUC-INS_{t60}	13,042 ± 7,635	18,866 ± 11,476	0.01
AUC-INS_{t120}	31,817 ± 16,759	37,443 ± 9,843	0.1
AUC-INS_{t240}	52,288 ± 27,458	51,824 ± 27,240	0.9
AUC-INS_{t360}	61,024 ± 33,138	57,417 ± 30,145	0.4
AUC-INS_{t480}	66,202 ± 36,516	60,312 ± 31,699	0.2
Pharmacodynamics			
GIR t_{max10} (min)	29.6 ± 9.9	22.5 ± 6.2	0.05
GIR t_{max50} (min)	48.8 ± 15.7	37.5 ± 8.7	0.001
GIR t_{max} (min)	126.7 ± 92.8	68.3 ± 33.3	0.01
C-GIR_{max} ($mg \cdot kg^{-1} \cdot min^{-1}$)	8.8 ± 3.5	10.0 ± 3.9	0.5
AUC-$GIR_{t_{max}}$	501 ± 396	242 ± 183	0.007
AUC-GIR_{t30}	10 ± 10	21 ± 15	0.07
AUC-GIR_{t60}	137 ± 75	219 ± 89	0.001
AUC-GIR_{t120}	571 ± 249	678 ± 216	0.1
AUC-GIR_{t240}	1,275 ± 510	1,258 ± 394	0.9
AUC-GIR_{t360}	1,494 ± 524	1,351 ± 448	0.2
AUC-GIR_{t480}	1,565 ± 527	1,361 ± 469	0.08

AUC-GIR, area under the curve for GIR; AUC-INS, area under the curve for insulin; C-GIR_{max}, maximum glucose infusion rate; C-INS_{max}, maximum insulin concentration; t_{30}–t_{480}, times 130–480 min; t_{max}, time to reach maximum concentration or rate; t_{max10}, time to reach 10% of maximum concentration or rate; t_{max50}, time to reach 50% of maximum concentration or rate.

Safety Results:

No clinically relevant adverse events were observed during the study.

Conclusion:

The present study demonstrates that insulin absorption can be accelerated by using a dispersed insulin bolus injection strategy. Time to reach maximum glucose infusion rate was almost halved when the insulin bolus was evenly dispersed among nine injection sites compared with a single injection site, indicating a much faster onset of insulin action. In combination with fast-acting insulin analogues, a clinically feasible dispersed injection strategy might better mimic physiological insulin profiles. To evaluate the implications for clinical outcomes, such as a reduction of late postprandial hypoglycaemia, both reduction of glucose fluctuations and improvement in glycaemic control need to be addressed in further clinical studies.

Additional registrations:

This trial was additionally registered at ClinicalTrials.gov (www.clinicaltrials.gov; clinical trial reg. no. NCT01399346).

Date of the report: 08 June 2020