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Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Insulatard

insulin analogue human recombinant

Procedure no: EMEA/H/C/000441/P46/027

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On December the 1st 2016, the MAH submitted a paediatric study for Insulatard, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

The trial was considered a Post Authorisation Efficacy Study (PAES) and Post Authorisation Safety Study (PASS).

Insulin NPH (Insulatard) is a neutral suspension of isophane insulin human crystals formulated for long action. Insulin NPH is intended to cover the basal insulin requirements of people with T1DM and T2DM, and may be used alone or in combination with fast- or rapid-acting insulin.

Insulin NPH is an intermediate-acting insulin given to help control the blood glucose level of those with diabetes. In insulin NPH, protamine prolongs the dissociation time of the hexameric insulin molecules to the monomeric form. The absorption following the dissociation results in non-physiological insulin levels with initial hyper insulinaemia and thereby a risk of hypoglycaemia, mainly during the night. In addition, the currently available protracted formulations such as insulin NPH also have high intra-subject variation with regard to absorption. The day-to-day intra subject variation has previously been reported to be in the range 20–30%.

For further details please see the EU Summary of Product Characteristics (EU SmPC).

Currently an increased number of children and adolescents are diagnosed with T2DM, as a consequence of the global obesity epidemic. The treatment options for these patients are not fully explored, and an insulin analogue offering less weight gain and a reduced number of hypoglycaemic episodes could be a choice.

Trial NN304-4093 was conducted to evaluate the benefit and risks of IDet in combination with the maximum tolerated dose (MTD) of metformin, including complete metformin intolerance, administered to children and adolescents (aged 10–17 years) with type 2 diabetes inadequately controlled on the MTD of metformin ± other OAD(s) ± basal insulin at the time of enrolment in the trial.

Trial NN304-4093 (henceforth referred to as trial 4093) was terminated early due to a very slow recruitment rate. A total of 42 subjects were enrolled and randomised in this trial instead of 358 subjects as originally planned for enrolment. The decision to discontinue recruitment for the trial was not due to any safety concerns, and the trial did not reveal any safety issues. The study was not part of the paediatric development program for Insulatard.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study NN304-4093, a 26-week open label, randomised, 2-armed, parallel group, multi-centre trial investigating efficacy and safety of insulin detemir versus insulin neutral protamine Hagedorn in combination with the maximum tolerated dose of metformin and diet/exercise on glycaemic control in children and adolescents with type 2 diabetes insufficiently controlled on the

maximum tolerated dose of metformin ± other oral antidiabetic drug(s) ± basal insulin is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

Formulation in trial NN304-4093

IDet (Levemir) formulation contains 100 U/mL IDet (produced in Saccharomyces cerevisiae by recombinant DNA technology) and other excipients (glycerol, phenol, metacresol, zinc acetate, disodium phosphate dihydrate, sodium chloride, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections).

Insulin NPH (Insulatard, Protaphane, Novolin N) contains 100 IU/mL isophane (NPH) insulin (produced in Saccharomyces cerevisiae by recombinant DNA technology) and other excipients (zinc chloride, glycerol, metacresol, phenol, disodium phosphate dihydrate, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment), protamine sulfate and water for injections).

Device for subcutaneous injection in trial NN304-4093

IDet (Levemir) 100 U/mL was supplied in a 3 mL prefilled FlexPen. Levemir FlexPen is a pre-filled pen designed to be used with NovoFine disposable needles up to a length of 8 mm. FlexPen delivers 1−60 U in increments of 1 U.

Insulin NPH (Insulatard, Protaphane, Novolin N) 100 IU/mL was supplied in a 3 mL pre-filled FlexPen. One pre-filled pen contains 3 mL equivalent to 300 IU.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final abbreviated clinical trial report for:

- The MAH stated that study NN304-4093, a 26-week open label, randomised, 2-armed, parallel group, multi-centre trial investigating efficacy and safety of insulin detemir versus insulin neutral protamine Hagedorn in combination with the maximum tolerated dose of metformin and diet/exercise on glycaemic control in children and adolescents with type 2 diabetes insufficiently controlled on the maximum tolerated dose of metformin ± other oral antidiabetic drug(s) ± basal insulin

This was a multinational, multi-centre, randomised, open-label, parallel-group trial in subjects with type 2 diabetes aged 10–17 years, who were insufficiently treated with the MTD of metformin ± other OAD(s) ± basal insulin. The trial design is shown schematically in Figure 1.

The trial period consisted of a 2-week screening period and a 26-week treatment period.

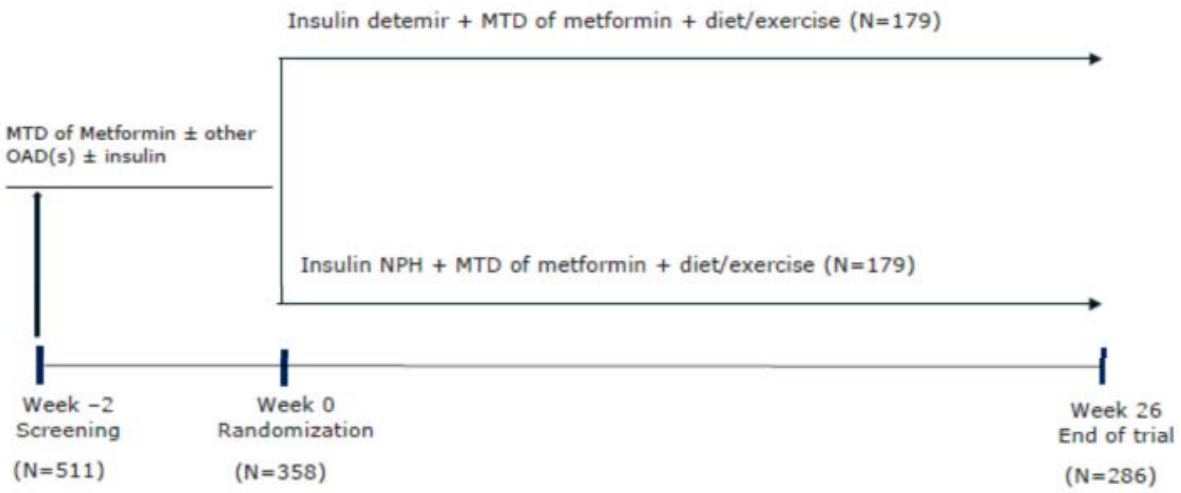

Figure 1 Trial design

2.3.2. Clinical study

Clinical study number and title

NN304-4093: A 26-week open label, randomised, 2-armed, parallel group, multi-centre trial investigating efficacy and safety of insulin detemir versus insulin neutral protamine Hagedorn in combination with the maximum tolerated dose of metformin and diet/exercise on glycaemic control in children and adolescents with type 2 diabetes insufficiently controlled on the maximum tolerated dose of metformin ± other oral antidiabetic drug(s) ± basal insulin.

Methods

Objective(s)

Primary objective:

- To compare the efficacy of insulin detemir (IDet) in combination with the maximum tolerated dose (MTD) of metformin and diet/exercise versus insulin neutral protamine Hagedorn (NPH) in combination with the MTD of metformin and diet/exercise in controlling glycaemia, after 26 weeks of treatment, in children and adolescents (aged 10–17 years) with type 2 diabetes, who are insufficiently treated with the MTD of metformin ± other oral anti-diabetic drugs (OAD(s)) ± basal insulin.

Secondary objectives:

- To compare the efficacy of insulin detemir in combination with the MTD of metformin and diet/exercise versus insulin NPH in combination with the MTD of metformin and diet/exercise on body weight, after 26 weeks of treatment, in children and adolescents (aged 10–17 years) with type 2 diabetes, who are insufficiently treated with the MTD of metformin ± other OAD(s) ± basal insulin.

- To compare the proportion of subjects achieving glycaemic control without experiencing severe hypoglycaemia, after 26 weeks of treatment, for insulin detemir in combination with the MTD of metformin and diet/exercise versus insulin NPH in combination with the MTD of metformin and diet/exercise, in children and adolescents (aged 10-17 years) with type 2 diabetes, who are insufficiently treated with the MTD of metformin ± other OAD(s) ± basal insulin.
- To assess and compare the safety and tolerability of insulin detemir in combination with the MTD of metformin and diet/exercise versus insulin NPH in combination with the MTD of metformin and diet/exercise, during 26 weeks of treatment, in children and adolescents (aged 10−17 years) with type 2 diabetes, who are insufficiently treated with the MTD of metformin ± other OAD(s) ± basal insulin.

Rapporteur's comments

The objectives are stated clearly and considered relevant.

Study design

This was a multinational, multi-centre, randomised, open-label, parallel-group trial in subjects with type 2 diabetes aged 10–17 years, who were insufficiently treated with the MTD of metformin ± other OAD(s) ± basal insulin.

An open labelled trial design was chosen as it was not possible to blind the 2 formulations (insulin NPH is a suspension while IDet is a solution).

For both treatment arms, a diet/exercise intervention was introduced, which was expected to further improve glycaemic control for the children and adolescents. Also, providing diet/exercise intervention to these patients may improve their motivation and be an added benefit as they are likely to put on weight when receiving insulin.

Twenty-six (26) weeks of treatment was chosen as this period was sufficient for the evaluation of the primary endpoint and the safety profile.

Stratification was included to secure an equal distribution of age groups and subjects, who had previously been treated with metformin in combination with other OAD(s) within the two treatment arms.

The trial was designed in accordance with requirements for adequate and well-controlled trials.

Rapporteur's comments

The design is acceptable.

Study population /Sample size

A total of 358 subjects were planned for enrolment. Subjects were children and adolescents aged 10−17 years with T2DM.

Subject selection was based on the inclusion and exclusion, see below. Subjects who met all of the inclusion criteria and none of the exclusion criteria were eligible to participate in the trial.

Inclusion criteria:

1. Informed consent from the subject or a legally acceptable representative and child assent from the subject obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial

2. Male or female, 10 years ≤ age ≤ 17 years at the time of signing informed consent/assent

3. Diagnosis of type 2 diabetes mellitus at least 3 months prior to screening

4. Treated with the maximum tolerated stable dose of metformin for at least 3 months prior to screening or have documented complete metformin intolerance

5. HbA_{1c} (glycosylated haemoglobin) ≥ 7.0% and ≤ 10.5% (≥ 53 mmol/mol and ≤ 91 mmol/mol) at screening

Exclusion criteria:

1. Maturity onset diabetes of the young

2. Fasting C-peptide at screening below 0.6 ng/mL

3. Impaired liver function defined as alanine aminotransferase above or equal to 2.5 times upper normal limit

4. Known proliferative retinopathy or maculopathy requiring acute treatment as judged by the investigator

5. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 3 months before the day of screening

Rapporteur's comments

Inclusion and exclusion criteria are acceptable.

Treatments

Eligible subjects were randomised to receive either IDet or insulin NPH, both administered subcutaneously. During the treatment period, the basal insulin dose was determined by a 2-4-6-8 titration algorithm (titration of insulin dose by 2, 4, 6 or 8 units based on average pre-breakfast or pre-dinner self-measured plasma glucose values). The treatment with metformin was continued unchanged during the treatment period, while treatment with other OAD(s) and basal insulin were discontinued.

The diet/exercise intervention was performed through changes in eating and activity behaviours.

The randomisation was stratified according to age and prior antidiabetic therapy.

A DMC was established to independently review and evaluate accumulating safety data from the trial in order to protect the safety of the subjects and to evaluate the benefit and risk assessment.

Rapporteur's comments

Acceptable

Outcomes/endpoints

Primary endpoint:

- Change in HbA_{1c} from baseline to week 26

Key secondary endpoints:

- Change in body weight standard deviation score (SDS) from baseline to week 26
- Proportion of subjects achieving HbA_{1c} <7.0% at week 26, who have not experienced any treatment-emergent severe hypoglycaemic episodes within the last 14 weeks of treatment
- Proportion of subjects achieving HbA_{1c} <7.5% at week 26, who have not experienced any treatment-emergent severe hypoglycaemic episodes within the last 14 weeks of treatment
- Incidence of adverse events (AEs) during 26 weeks of treatment
- Total number of treatment-emergent nocturnal (23:00-06:59) severe or blood glucose (BG) confirmed symptomatic
- hypoglycaemic episodes during 26 weeks of treatment
- Total number of treatment-emergent severe or BG confirmed symptomatic hypoglycaemic episodes during 26 weeks of treatment

Rapporteur's comments

Endpoints are considered relevant.

Statistical Methods

At least 358 subjects were planned to be randomised in order to ensure 80% power to show non-inferiority of IDet to insulin NPH in the full analysis set and per protocol (PP) analysis set with respect to change in HbA_{1c} from baseline to week 26, using a non-inferiority limit of 0.4%. However, the trial was discontinued post randomisation of 42 subjects due to a very slow recruitment rate. As a result of the limited number of subjects enrolled in the trial, none of the planned statistical analyses described in the protocol for the secondary efficacy endpoints and for the safety endpoints, were performed.

Analysis sets

- Full analysis set – included all randomised subjects
- PP analysis set – included all randomised subjects, not violating any of the inclusion/exclusion criteria, and that had been treated for at least 12 weeks. Subjects in the PP analysis set contributed to the evaluation 'as treated'
- Safety analysis set – included all subjects receiving at least one dose of randomised treatment. Subjects in the safety analysis set contributed to the evaluation 'as treated'

All the 42 exposed subjects were included in the full and safety analysis sets, but 7 subjects were excluded from PP analysis set (5 subjects were incorrectly stratified at the time of randomisation, 1 subject was randomised in error and 1 subject was treated for less than 12 weeks).

The primary endpoint of change in HbA_{1c} from baseline to week 26 was analysed using a mixed model for repeated measurements with treatment, age group, prior antidiabetic therapy, and the interaction

between age group and prior antidiabetic therapy as factors, and baseline HbA_{1c} as a covariate, all variables nested within week as factor. The treatment difference at week 26 was estimated and the corresponding two-sided 95% confidence interval was calculated. The data from secondary endpoints were summarised using descriptive statistics.

Rapporteur's comments

Statistical methods are in line with guidelines.

Results

Recruitment / Number analysed

A total of 71 subjects were screened, of which 29 were screening failures. The majority of screening failures did not meet the inclusion criterion number 5 (HbA_{1c} between 7.0% and 10.5% inclusive).

Of the 42 subjects who were randomised, 39 subjects completed the trial. Of the 3 subjects who withdrew from the trial, 2 subjects in the insulin NPH group withdrew consent and 1 subject in the IDet group was withdrawn due to a withdrawal criterion (persistent hyperglycaemia despite initiation of rescue medication) (Table 1).

Table 1 Subject disposition - summary - all subjects

	IDet N (%)	NPH N (%)	Total N (%)
Screened			71
Screening failures			29
Randomised	20 (100.0)	22 (100.0)	42 (100.0)
Exposed	20 (100.0)	22 (100.0)	42 (100.0)
Withdrawal	1 (5.0)	2 (9.1)	3 (7.1)
Adverse event	0	0	0
Protocol violation*	1 (5.0)	0	1 (2.4)
Lost to follow-up	0	0	0
Pregnancy	0	0	0
Withdrawal by subject	0	1 (4.5)	1 (2.4)
Withdrawal by parent/guardian	0	1 (4.5)	1 (2.4)
Other	0	0	0
Completed trial	19 (95.0)	20 (90.9)	39 (92.9)
Full analysis set	20 (100.0)	22 (100.0)	42 (100.0)
Safety analysis set	20 (100.0)	22 (100.0)	42 (100.0)
Per protocol set	17 (85.0)	18 (81.8)	35 (83.3)

N: number of subjects, %: percentage of randomised subjects

*denotes a withdrawal criterion (persistent hyperglycaemia despite initiation of rescue medication)

Demographic and Baseline data

Overall, the demographics and baseline characteristics were similar between the two treatment groups. The mean age of subjects was 15 years (range: 10–17 years), and the majority of them were females (64.3%) (Table 2).

The mean duration of diabetes in subjects was 2.8 years (range: 0.3–7.8 years) with baseline HbA_{1c} of 8.84% (range: 7.1–10.5%) and FPG of 9.15 mmol/L (range: 4.5–18.2 mmol/L). One subject in the IDet group had diabetic nephropathy at screening.

Subjects treated with MTD of metformin were enrolled in this trial. The mean dose of metformin received by subjects at screening was 1802.4 mg per day.

The most common concomitant illnesses reported were from the system organ class of 'metabolism and nutrition disorders'. Obesity (14.3%) and hyperlipidaemia (11.9%) were the most commonly reported concomitant illnesses. The concomitant medications reported by the subjects generally reflected the concomitant illnesses reported.

Table 2 Summary of demographics by treatment – full analysis set

	IDet	NPH	Total
Number of subjects	20	22	42
Age group, N (%)			
N	20 (100.0)	22 (100.0)	42 (100.0)
10 - 14 Years	9 (45.0)	11 (50.0)	20 (47.6)
15 - 17 Years	11 (55.0)	11 (50.0)	22 (52.4)
Age (years)			
N	20	22	42
Mean (SD)	15.0 (2.1)	15.0 (2.2)	15.0 (2.1)
Median	15	15	15
Min ; Max	11 ; 17	10 ; 17	10 ; 17
Sex, N (%)			
N	20 (100.0)	22 (100.0)	42 (100.0)
Female	12 (60.0)	15 (68.2)	27 (64.3)
Male	8 (40.0)	7 (31.8)	15 (35.7)
Country, N (%)			
N	20 (100.0)	22 (100.0)	42 (100.0)
Brazil	1 (5.0)	0	1 (2.4)
Germany	1 (5.0)	0	1 (2.4)
India	4 (20.0)	0	4 (9.5)
Israel	0	1 (4.5)	1 (2.4)
Malaysia	2 (10.0)	2 (9.1)	4 (9.5)
Mexico	2 (10.0)	4 (18.2)	6 (14.3)
Russian Federation	1 (5.0)	0	1 (2.4)
South Korea	1 (5.0)	1 (4.5)	2 (4.8)
Taiwan	4 (20.0)	4 (18.2)	8 (19.0)
Turkey	1 (5.0)	2 (9.1)	3 (7.1)
United States	3 (15.0)	8 (36.4)	11 (26.2)

	IDet	NPH	Total
Ethnicity, N (%)			
N	20 (100.0)	22 (100.0)	42 (100.0)
Hispanic or latino	5 (25.0)	10 (45.5)	15 (35.7)
Not hispanic or latino	15 (75.0)	12 (54.5)	27 (64.3)
Race, N (%)			
N	20 (100.0)	22 (100.0)	42 (100.0)
American indian or alaska native	0	1 (4.5)	1 (2.4)
Asian	11 (55.0)	7 (31.8)	18 (42.9)
Black or african american	0	1 (4.5)	1 (2.4)
White	8 (40.0)	11 (50.0)	19 (45.2)
Other	1 (5.0)	2 (9.1)	3 (7.1)
Strata, N (%)			
N	20 (100.0)	22 (100.0)	42 (100.0)
10<= Age <15 + Metformin In Combination With Basal Insulin And/Or Other OAD	8 (40.0)	10 (45.5)	18 (42.9)
10<= Age <15 + Metformin Only No Basal Insulin Nor Other OAD(s)	1 (5.0)	1 (4.5)	2 (4.8)
15<= Age <18 + Metformin In Combination With Basal Insulin And/Or Other OAD	8 (40.0)	7 (31.8)	15 (35.7)
15<= Age <18 + Metformin Only No Basal Insulin Nor Other OAD(s)	3 (15.0)	4 (18.2)	7 (16.7)

N: number of subjects, %: percentage of subjects, SD: standard deviation

Efficacy results

Primary endpoint – Change in HbA_{1c} from baseline to week 26 (end of trial)

The mean HbA_{1c} at baseline was 8.72% in the IDet group and 8.95% in the insulin NPH group. The observed mean HbA_{1c} decreased throughout the trial in both the treatment groups. At the end of trial, mean HbA_{1c} had decreased by 0.610 %-points to 8.11 % in the IDet group and by 0.836 %-points to 8.11% in the insulin NPH group (Table 3).

Table 3 Summary of HbA_{1c} (%) and change from baseline by treatment at visit 19 (end of trial) - full analysis set

	IDet	NPH	Total
Number of subjects	20	22	42
Visit 1 (Week -2)			
HbA1c (%)			
N	20	22	42
Mean (SD)	8.72 (0.86)	8.95 (1.05)	8.84 (0.96)
Median	8.6	9.0	8.9
Min ; Max	7.3; 10.3	7.1; 10.5	7.1; 10.5
Visit 19 (End of trial)			
HbA1c (%)			
N	20	22	42
Mean (SD)	8.11 (1.58)	8.11 (1.49)	8.11 (1.52)
Median	7.9	8.1	8.0
Min ; Max	5.3; 10.9	5.9; 11.0	5.3; 11.0
Ch HbA1c (%)			
N	20	22	42
Mean (SD)	-0.610 (1.719)	-0.836 (1.005)	-0.729 (1.378)
Median	-0.40	-0.75	-0.50
Min ; Max	-3.90; 2.60	-2.80; 1.20	-3.90; 2.60

N: number of subjects, SD: standard deviation, Ch: change from baseline
Baseline information is defined as the measurement at the latest assessment before dosing

The estimated mean treatment difference of change from baseline in HbA_{1c} between IDet and insulin NPH at the end of trial was 0.17% [95% CI: -0.74; 1.09]. However, efficacy conclusions could not be drawn from this primary analysis due to the low number of subjects included in the trial.

Mean HbA_{1c} and change from baseline in HbA_{1c} by visit for the PP analysis set was similar to the FAS.

Secondary endpoints

Confirmatory secondary endpoints

The following endpoints were planned to be confirmatory; however, due to the low number of subjects in the trial, these secondary endpoints were no longer considered to be confirmatory.

- Change in body weight SDS from baseline to week 26
- Proportion of subjects achieving HbA_{1c} <7.0% at week 26, who have not experienced any treatment-emergent severe hypoglycaemic episodes within the last 14 weeks of treatment

Change in body weight SDS from baseline to week 26 (end of trial)

The observed mean change from baseline in body weight SDS at the end of trial was 0.006 in the IDet group and 0.098 in the insulin NPH group (Table 4).

Table 4 Summary of SDS body weight and change from baseline by treatment at visit 19 (end of trial) - full analysis set

	IDet	NPH	Total
Number of subjects	20	22	42
Visit 19 (End of trial)			
Body weight SDS			
N	20	22	42
Mean (SD)	1.538 (0.690)	1.358 (0.840)	1.444 (0.768)
Median	1.50	1.37	1.46
Min ; Max	0.47 ; 3.40	0.01 ; 2.66	0.01 ; 3.40
Ch body weight SDS			
N	20	22	42
Mean (SD)	0.006 (0.192)	0.098 (0.139)	0.054 (0.171)
Median	0.02	0.11	0.07
Min ; Max	-0.36 ; 0.46	-0.17 ; 0.39	-0.36 ; 0.46

N: number of subjects, SD: standard deviation, Ch: change from baseline
SDS: standard deviation score
Baseline information is defined as the measurement at the latest assessment before dosing

Proportion of subjects achieving HbA_{1c} <7.0% at week 26 (end of trial) without treatment-emergent severe hypoglycaemic episodes

The proportion of subjects who achieved HbA_{1c} <7.0% without severe treatment-emergent hypoglycaemic episodes within the last 14 weeks of treatment at the end of trial was 25.0% in the IDet group and 33.3 % in the insulin NPH group (Table 5).

Table 5 Summary of subjects reaching HbA_{1c} target < 7.0% with no treatment-emergent severe hypoglycaemic episodes within last 14 weeks of exposure by treatment - full analysis set

	IDet N (%)	NPH N (%)	Total N (%)
Number of subjects	20	22	42
HbA1c (%)			
Visit 19 (End of trial)			
N	20 (100.0)	21 (95.5)	41 (97.6)
Yes	5 (25.0)	7 (33.3)	12 (29.3)
No	15 (75.0)	14 (66.7)	29 (70.7)

N: number of subjects, %: percentage of subjects
Only subjects who have been exposed for minimum 14 weeks are included for this display

Supportive secondary endpoints

Responders for HbA_{1c} at week 26 (end of trial)

Proportion of subjects who achieved HbA_{1c} <7.0% at the end of trial: 25.0% subjects in the IDet group and 31.8% subjects in the insulin NPH group.

Proportion of subjects who achieved HbA_{1c} <7.5% at the end of trial: 30.0% subjects in the IDet group and 36.4% subjects in the insulin NPH group.

Proportion of subjects who achieved HbA_{1c} <7.5% without treatment-emergent severe hypoglycaemic episodes within the last 14 weeks of treatment at the end of trial: 30.0% in the IDet group and 38.1 % in the insulin NPH group.

7-point SMPG profiles at week 26 (end of trial)

All the 7-point SMPG values decreased from baseline in both the treatment groups at the end of trial. In both the treatment groups, the mean 7-point SMPG profiles decreased from baseline to the end of trial (Table 6). The observed mean at baseline was 9.76 mmol/L in the IDet group and 10.99 mmol/L in the insulin NPH group. The observed mean decreased to 8.28 mmol/L in the IDet group and 8.45 mmol/L in the insulin NPH group by the end of trial.

Table 6 Summary of mean 7-point SMPG profiles (mmol/L) by treatment at baseline and visit 19 (end of trial) - full analysis set

	IDet	NPH	Total
Number of subjects	20	22	42
Mean SMPG (mmol/L)			
Visit 2 (Week 0)			
N	20	19	39
Mean (SD)	9.76 (2.57)	10.99 (2.84)	10.36 (2.74)
Median	9.7	10.4	10.4
Min ; Max	5.9; 14.6	5.9; 17.6	5.9; 17.6
Visit 19 (End of trial)			
N	20	20	40
Mean (SD)	8.28 (2.72)	8.45 (3.06)	8.37 (2.86)
Median	7.5	7.5	7.5
Min ; Max	4.7; 15.2	5.5; 15.7	4.7; 15.7

N: number of subjects, SD: standard deviation

Mean SMPG is calculated as the arithmetic mean of 7-point SMPG (mmol/L) profiles

Baseline information is defined as the measurement at the latest assessment before dosing

Change in fasting plasma glucose from baseline to week 26 (end of trial)

The observed mean FPG at baseline was 7.99 mmol/L in the IDet group and 10.20 mmol/L in the insulin NPH group. The higher mean baseline values observed in the insulin NPH group were mainly due to 4 subjects having high baseline FPG values. This led to a mean change in FPG from baseline to the end of trial of -0.335 mmol/L in the IDet group and -2.332 mmol/L in the insulin NPH group (Table 7).

Table 7 Change in FPG (mmol/L) from baseline by treatment at visit 19 (end of trial) - full analysis set

	IDet	NPH	Total
Number of subjects	20	22	42
Visit 2 (Week 0)			
FPG (mmol/L)			
N	20	22	42
Mean (SD)	7.99 (2.51)	10.20 (3.51)	9.15 (3.24)
Median	7.8	9.7	8.7
Min ; Max	4.5; 12.8	4.6; 18.2	4.5; 18.2
Visit 19 (End of trial)			
FPG (mmol/L)			
N	20	22	42
Mean (SD)	7.66 (2.63)	7.86 (2.88)	7.76 (2.73)
Median	6.5	7.0	6.7
Min ; Max	5.0; 14.9	3.7; 15.2	3.7; 15.2
Ch FPG (mmol/L)			
N	20	22	42
Mean (SD)	-0.335 (2.961)	-2.332 (4.147)	-1.381 (3.727)
Median	-0.45	-2.60	-1.15
Min ; Max	-5.50; 5.20	-10.70; 10.60	-10.70; 10.60

N: number of subjects, SD: standard deviation, Ch: change from baseline

Baseline information is defined as the measurement at the latest assessment before dosing

Body measurements

Change in body weight from baseline to week 26 (end of trial)

At baseline, the observed mean body weight was 75.9 kg in the IDet group and 73.2 kg in the insulin NPH group. The mean body weight slightly increased from baseline to the end of trial in both the treatment groups. The observed mean weight change from baseline to the end of trial was 1.89 kg in the IDet group and 4.00 kg in the insulin NPH group (Table 8).

Table 8 Change in body weight (kg) from baseline by treatment at visit 19 (end of trial) - full analysis set

	IDet	NPH	Total
Number of subjects	20	22	42
Visit 2 (Week 0)			
Body Weight (kg)			
N	20	22	42
Mean (SD)	75.90 (16.56)	73.20 (23.38)	74.49 (20.22)
Median	70.7	72.8	71.9
Min ; Max	55.4; 109.3	35.4; 126.6	35.4; 126.6
Visit 19 (End of trial)			
Body Weight (kg)			
N	20	22	42
Mean (SD)	77.79 (16.16)	77.20 (24.60)	77.48 (20.76)
Median	72.4	74.4	73.6
Min ; Max	57.0; 111.4	39.9; 130.5	39.9; 130.5
Ch body weight (kg)			
N	20	22	42
Mean (SD)	1.89 (3.40)	4.00 (3.75)	2.99 (3.70)
Median	2.1	3.7	3.4
Min ; Max	-5.0; 8.3	-1.4; 15.2	-5.0; 15.2

N: number of subjects, SD: standard deviation, Ch: change from baseline

Baseline information is defined as the measurement at the latest assessment before dosing.

Change in height SDS from baseline to week 26 (end of trial)

At baseline, the mean height SDS was -0.087 in the IDet group and -0.166 in the insulin NPH group. The change in height SDS from baseline to the end of trial was -0.042 in the IDet group and -0.019 in the insulin NPH group.

Change in BMI and BMI SDS from baseline to week 26 (end of trial)

At baseline, the mean BMI was 28.74 kg/m^2 in the IDet group and 27.70 kg/m^2 in the insulin NPH group. The change in BMI from baseline to the end of trial was 0.35 kg/m^2 in the IDet group and 1.20 kg/m^2 in the insulin NPH group.

At baseline, the mean BMI SDS was 1.681 in the IDet group and 1.452 in the insulin NPH group.

The change in BMI SDS from baseline to the end of trial was 0.013 in the IDet group and 0.086 in the insulin NPH group.

Efficacy conclusions

The trial was terminated early due to a slow recruitment rate. No efficacy conclusions could be drawn due to the low number of subjects included in the trial. The efficacy results are presented

below:

- The estimated mean treatment difference of change from baseline in HbA_{1c} between IDet and insulin NPH at the end of trial was 0.17% [95% CI: -0.74; 1.09]. The observed mean change in HbA_{1c} from baseline to the end of trial was -0.610% in the IDet group and -0.836% in the insulin NPH group
- The observed mean weight change from baseline to the end of trial was 1.89 kg in the IDet group and 4.00 kg in the insulin NPH group
- The proportion of responders with HbA_{1c} <7.0% without severe treatment-emergent hypoglycaemic episodes in the last 14 weeks of treatment at the end of trial was 25.0% in the IDet group and 33.3% in the insulin NPH group
- The proportion of responders with HbA_{1c} <7.5% without severe treatment-emergent hypoglycaemic episodes in the last 14 weeks of treatment at the end of trial was 30.0% in the IDet group and 38.1 % in the insulin NPH group
- The observed mean of the mean 7-point SMPG profiles at the end of trial was 8.28 mmol/L in the IDet group and 8.45 mmol/L in the insulin NPH group
- The observed mean change in FPG from baseline to the end of trial was -0.335 mmol/L in the IDet group and -2.332 mmol/L in the insulin NPH group
- The observed mean change in body weight from baseline to the end of trial was 1.89 kg in the IDet group and 4.00 kg in the insulin NPH group

Rapporteur's comments

Since the trial was terminated early due to a slow recruitment rate and therefore a low number of subjects were included in the trial, no firm efficacy conclusions could be drawn. However, overall the results are in line with the known effects of insulin in adults with regards to glucose lowering and weight gain.

Both treatments resulted in a reduction of HbA_{1c} compared to baseline. With an observed mean HbA_{1c} baseline values decreased from 8.72% to 8.11% in the IDet group and from 8.95% to 8.11% in the insulin NPH group at the end of trial.

Body weight gain was seen for both the treatments, but was lower for the IDet group.

Safety results

Extent of exposure

A total of 42 subjects were exposed to trial products; 20 subjects to IDet and 22 subjects to insulin NPH. The total exposure (in subject years) was 9.83 years in the IDet group and 10.49 years in the insulin NPH group (Table 9). Approximately 95% of the total subjects in both the treatment groups were exposed to the trial products for 20−26 weeks.

Table 9 Summary of exposure by treatment - full analysis set

	IDet	NPH	Total
Number of subjects	20	22	42
Total exposure (years)	9.83	10.49	20.33
Exposure (weeks)			
N	20	22	42
Mean (SD)	25.65 (1.22)	24.89 (4.20)	25.25 (3.14)
Median	25.9	25.9	25.9
Min ; Max	20.9 ; 26.6	8.0 ; 28.6	8.0 ; 28.6

N: number of subjects, SD: standard deviation

Brief summary of adverse events

A total of 30 AEs were reported in 8 subjects in the IDet group (rate: 305.1 events per 100 patient years of exposure (PYE)) and 41 AEs were reported in 13 subjects in the insulin NPH group (rate: 390.7 events per 100 PYE). The majority of AEs were non-serious, mild in severity and unlikely related to trial product. Subjects recovered or were recovering from all the AEs except 2 AEs which were not resolved at the end of the trial (Table 10).

The most frequently reported AEs (in ≥10% of subjects in any of the two treatment groups) were gastroenteritis, headache, oropharyngeal pain, pyrexia and vomiting.

No deaths were reported in this trial. One SAE was reported in the insulin NPH group that was moderate in severity and was considered unlikely related to the trial product.

No AEs led to withdrawal from the trial.

Table 10 Treatment-emergent adverse events – summary – safety analysis set

	IDet				NPH				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	20				22				42			
Exposure (years)	9.83				10.49				20.33			
Events	8	(40.0)	30	305.1	13	(59.1)	41	390.7	21	(50.0)	71	349.3
Serious												
Yes	0				1	(4.5)	1	9.5	1	(2.4)	1	4.9
No	8	(40.0)	30	305.1	13	(59.1)	40	381.2	21	(50.0)	70	344.4
Severity												
Severe	0				0				0			
Moderate	2	(10.0)	2	20.3	6	(27.3)	18	171.5	8	(19.0)	20	98.4
Mild	7	(35.0)	28	284.8	11	(50.0)	23	219.2	18	(42.9)	51	250.9
Relationship to investigational product												
Probable	0				0				0			
Possible	1	(5.0)	1	10.2	1	(4.5)	1	9.5	2	(4.8)	2	9.8
Unlikely	8	(40.0)	29	295.0	13	(59.1)	40	381.2	21	(50.0)	69	339.5
MESI												
Yes	0				0				0			
No	8	(40.0)	30	305.1	13	(59.1)	41	390.7	21	(50.0)	71	349.3
Technical Complaints												
Yes	0				0				0			
No	8	(40.0)	30	305.1	13	(59.1)	41	390.7	21	(50.0)	71	349.3
Outcome												
Recovered/Resolved	8	(40.0)	29	295.0	13	(59.1)	38	362.1	21	(50.0)	67	329.6
Recovering/Resolving	1	(5.0)	1	10.2	0				1	(2.4)	1	4.9
Recovered/Resolved With Sequelae	0				1	(4.5)	1	9.5	1	(2.4)	1	4.9
Not Recovered/Not Resolved	0				2	(9.1)	2	19.1	2	(4.8)	2	9.8
Fatal	0				0				0			
Unknown	0				0				0			
Action												
Drug Interrupted	0				1	(4.5)	4	38.1	1	(2.4)	4	19.7
Drug Withdrawn	0				0				0			
Dose Reduced	0				0				0			
Dose Increased	0				0				0			
Dose Not Changed	8	(40.0)	30	305.1	13	(59.1)	37	352.6	21	(50.0)	67	329.6
Unknown	0				0				0			
Not Applicable	0				0				0			

N: number of subjects, %: percentage of subjects, E: number of events, R: event rate per 100 exposure years, MESI: medical events of special interest

Relationship to trial product is based on investigator(s)'s assessment

Analysis of adverse events

Adverse events by system organ class/preferred term

The majority of AEs reported were in the infections and infestations SOC (rate: 88.6 events per 100 PYE) followed by nervous system disorders SOC (rate: 54.1 events per 100 PYE). The most frequently reported AEs by preferred terms were headache and oropharyngeal pain. A summary of AEs by SOC and preferred term is provided in Table 11.

Table 11 Treatment emergent adverse events by system organ class and preferred term – summary - safety analysis set

	IDet			NPH			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	20			22			42		
Exposure (years)	9.83			10.49			20.33		
Events	8 (40.0)	30	305.1	13 (59.1)	41	390.7	21 (50.0)	71	349.3
Infections and infestations	5 (25.0)	6	61.0	8 (36.4)	12	114.3	13 (31.0)	18	88.6
Influenza	0			2 (9.1)	3	28.6	2 (4.8)	3	14.8
Upper respiratory tract infection	1 (5.0)	1	10.2	1 (4.5)	2	19.1	2 (4.8)	3	14.8
Gastroenteritis	2 (10.0)	2	20.3	0			2 (4.8)	2	9.8
Gastrointestinal viral infection	0			1 (4.5)	2	19.1	1 (2.4)	2	9.8
Nasopharyngitis	0			2 (9.1)	2	19.1	2 (4.8)	2	9.8
Atypical pneumonia	0			1 (4.5)	1	9.5	1 (2.4)	1	4.9
Ear infection	0			1 (4.5)	1	9.5	1 (2.4)	1	4.9
Gastroenteritis viral	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9
Hand-foot-and-mouth disease	0			1 (4.5)	1	9.5	1 (2.4)	1	4.9
Impetigo	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9
Viral infection	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9
Nervous system disorders	3 (15.0)	4	40.7	2 (9.1)	7	66.7	5 (11.9)	11	54.1
Headache	3 (15.0)	4	40.7	1 (4.5)	4	38.1	4 (9.5)	8	39.4
Migraine	0			2 (9.1)	2	19.1	2 (4.8)	2	9.8
Presyncope	0			1 (4.5)	1	9.5	1 (2.4)	1	4.9
Gastrointestinal disorders	4 (20.0)	6	61.0	3 (13.6)	4	38.1	7 (16.7)	10	49.2
Vomiting	2 (10.0)	4	40.7	0			2 (4.8)	4	19.7
Abdominal pain	1 (5.0)	1	10.2	1 (4.5)	1	9.5	2 (4.8)	2	9.8
Toothache	0			2 (9.1)	2	19.1	2 (4.8)	2	9.8
Lip dry	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9
Nausea	0			1 (4.5)	1	9.5	1 (2.4)	1	4.9

Treatment emergent adverse events by system organ class and preferred term - summary - safety analysis set - continued

	IDet			NPH			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Respiratory, thoracic and mediastinal disorders	1 (5.0)	3	30.5	3 (13.6)	6	57.2	4 (9.5)	9	44.3
Oropharyngeal pain	1 (5.0)	1	10.2	3 (13.6)	3	28.6	4 (9.5)	4	19.7
Cough	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9
Epistaxis	0			1 (4.5)	1	9.5	1 (2.4)	1	4.9
Productive cough	0			1 (4.5)	1	9.5	1 (2.4)	1	4.9
Rhinitis allergic	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9
Rhinorrhoea	0			1 (4.5)	1	9.5	1 (2.4)	1	4.9
Musculoskeletal and connective tissue disorders	1 (5.0)	4	40.7	2 (9.1)	4	38.1	3 (7.1)	8	39.4
Pain in extremity	1 (5.0)	4	40.7	0			1 (2.4)	4	19.7
Neck pain	0			1 (4.5)	3	28.6	1 (2.4)	3	14.8
Musculoskeletal pain	0			1 (4.5)	1	9.5	1 (2.4)	1	4.9
General disorders and administration site conditions	3 (15.0)	3	30.5	1 (4.5)	1	9.5	4 (9.5)	4	19.7
Pyrexia	2 (10.0)	2	20.3	0			2 (4.8)	2	9.8
Injection site erythema	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9
Injection site mass	0			1 (4.5)	1	9.5	1 (2.4)	1	4.9
Reproductive system and breast disorders	0			2 (9.1)	3	28.6	2 (4.8)	3	14.8
Dysmenorrhoea	0			1 (4.5)	2	19.1	1 (2.4)	2	9.8
Ovarian cyst	0			1 (4.5)	1	9.5	1 (2.4)	1	4.9
Injury, poisoning and procedural complications	1 (5.0)	2	20.3	1 (4.5)	1	9.5	2 (4.8)	3	14.8
Arthropod bite	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9
Soft tissue injury	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9
Sunburn	0			1 (4.5)	1	9.5	1 (2.4)	1	4.9
Ear and labyrinth disorders	1 (5.0)	2	20.3	0			1 (2.4)	2	9.8
Vertigo	1 (5.0)	2	20.3	0			1 (2.4)	2	9.8
Vascular disorders	0			1 (4.5)	1	9.5	1 (2.4)	1	4.9
Hypertension	0			1 (4.5)	1	9.5	1 (2.4)	1	4.9
Immune system disorders	0			1 (4.5)	1	9.5	1 (2.4)	1	4.9
Multiple allergies	0			1 (4.5)	1	9.5	1 (2.4)	1	4.9
Surgical and medical procedures	0			1 (4.5)	1	9.5	1 (2.4)	1	4.9
Tooth extraction	0			1 (4.5)	1	9.5	1 (2.4)	1	4.9

N: number of subjects, %: percentage of subjects, E: number of events

R: event rate per 100 patient years of exposure, MedDRA Version 19.0

Adverse events by relation to trial product(s)

Two AEs were considered possibly related to trial product; 1 event of localised injection site erythema in the IDet group and 1 event of injection site mass in the insulin NPH group. The remaining 69 AEs were considered unlikely related to trial product.

Adverse events by severity

No severe AEs were reported in this trial. All AEs reported were of mild or moderate severity.

A total of 2 moderate AEs were reported in 2 subjects in the IDet group (rate: 20.3 events per 100 PYE) and 18 moderate AEs were reported in 6 subjects in the insulin NPH group (rate: 171.5 events per 100 PYE).

A total of 28 mild AEs were reported in 7 subjects in the IDet group (rate: 284.8 events per 100 PYE) and 23 mild AEs were reported in 11 subjects in the insulin NPH group (rate: 219.2 events per 100 PYE).

Adverse events by relation to technical complaints

No AEs related to technical complaints were reported in this trial (Table 12–2).

Deaths and other serious adverse events

Deaths

No deaths were reported during this trial.

Serious adverse events

Overall, only 1 SAE (migraine) was reported in this trial by a subject from the insulin NPH group (Table 12). The event was moderate in severity, unlikely related to the trial product and the subject recovered from the event. The trial product was temporarily interrupted due to this SAE.

Table 12 Treatment-emergent serious adverse events by system organ class and preferred term – summary - safety analysis set

	IDet			NPH			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	20			22			42		
Exposure (years)	9.83			10.49			20.33		
Events	0			1 (4.5)	1	9.5	1 (2.4)	1	4.9
Nervous system disorders	0			1 (4.5)	1	9.5	1 (2.4)	1	4.9
Migraine	0			1 (4.5)	1	9.5	1 (2.4)	1	4.9

N: number of subjects, %: percentage of subjects, E: number of events
R: event rate per 100 patient years of exposure, MedDRA Version 19.0

No SAEs occurred in ≥5% or ≥10% of the subjects. No SAEs were possibly or probably related to trial product.

Other significant adverse events

No subjects withdrew from the trial due to AEs. A total of 3 AEs and 1 SAE experienced by 1 subject in the insulin NPH group led to temporary trial product interruption. No AEs led to dose reduction. No MESIs were reported (Table 10).

No AEs related to clinical laboratory abnormalities were reported.

No AEs related to abnormal vital signs, physical examinations or other safety assessment evaluations were reported.

Suspected hypersensitive events were derived using the standard MedDRA queries.

Two suspected hypersensitivity events (rhinitis allergic in the IDet group and multiple allergies in the insulin NPH group) were reported by two subjects (Table 13). Both events were mild in severity and unlikely related to trial products. Subjects had recovered from both events at the end of the trial.

Table 13 Treatment-emergent suspected hypersensitive events by system organ class and preferred term – summary - safety analysis set

	IDet			NPH			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	20			22			42		
Exposure (years)	9.83			10.49			20.33		
Events	1 (5.0)	1	10.2	1 (4.5)	1	9.5	2 (4.8)	2	9.8
Immune system disorders	0			1 (4.5)	1	9.5	1 (2.4)	1	4.9
Multiple allergies	0			1 (4.5)	1	9.5	1 (2.4)	1	4.9
Respiratory, thoracic and mediastinal disorders	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9
Rhinitis allergic	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9

N: number of subjects, %: percentage of subjects, E: number of events

R: event rate per 100 patient years of exposure, MedDRA Version 19.0

Suspected hypersensitive events were derived using the standard MedDRA queries

One subject in the IDet group had an AE of localised injection site erythema. This AE was mild in severity, possibly related to the trial product and the subject recovered from the event.

Hypoglycaemia

Hypoglycaemic episodes

Hypoglycaemic episodes are summarised by classification in Table 14. There were no severe hypoglycaemic episodes in any of the treatment groups. The overall event rate of hypoglycaemia per 100 PYE was 172.9 in the IDet group and 533.6 in the insulin NPH group.

The proportion of subjects who experienced symptomatic BG confirmed hypoglycaemic episodes was 5.0% (rate: 40.7 episodes per 100 PYE) in the IDet group and 22.7% (rate: 114.3 episodes per 100 PYE) in the insulin NPH group.

Nocturnal hypoglycaemic episodes

Nocturnal hypoglycaemic episodes are summarised by classification in Table 15. There were no severe nocturnal hypoglycaemic episodes in any of the treatment groups. The overall event rate of nocturnal hypoglycaemia per 100 PYE was 40.7 in the IDet group and 76.2 in the insulin NPH group.

No subjects experienced symptomatic BG confirmed nocturnal hypoglycaemic episodes in the IDet group whereas 1 subject experienced a symptomatic BG confirmed nocturnal hypoglycaemic episode in the insulin NPH group.

Table 14 Hypoglycaemic episodes by classification – treatment-emergent – summary - safety analysis set

	IDet			NPH			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	20			22			42		
Exposure (years)	9.83			10.49			20.33		
Episodes	8 (40.0)	17	172.9	10 (45.5)	56	533.6	18 (42.9)	73	359.1
NN	1 (5.0)	4	40.7	7 (31.8)	15	142.9	8 (19.0)	19	93.5
Severe	0			0			0		
Symptomatic BG confirmed	1 (5.0)	4	40.7	5 (22.7)	12	114.3	6 (14.3)	16	78.7
Asymptomatic BG confirmed	0			3 (13.6)	3	28.6	3 (7.1)	3	14.8
NN unclassifiable	8 (40.0)	13	132.2	10 (45.5)	41	390.7	18 (42.9)	54	265.7
ADA	8 (40.0)	17	172.9	10 (45.5)	56	533.6	18 (42.9)	73	359.1
Severe	0			0			0		
Documented symptomatic	5 (25.0)	10	101.7	7 (31.8)	32	304.9	12 (28.6)	42	206.6
Asymptomatic	4 (20.0)	6	61.0	9 (40.9)	24	228.7	13 (31.0)	30	147.6
Probable symptomatic	1 (5.0)	1	10.2	0			1 (2.4)	1	4.9
Pseudo-hypoglycaemia	0			0			0		
ADA unclassifiable	0			0			0		

E: number of events, N: number of subjects, %: percentage of randomised subjects, R: event rate per 100 exposure years

Table 15 Nocturnal hypoglycaemic episodes by classification – treatment-emergent – summary - safety analysis set

	IDet			NPH			Total		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	20			22			42		
Exposure (years)	9.83			10.49			20.33		
Episodes	2 (10.0)	4	40.7	4 (18.2)	8	76.2	6 (14.3)	12	59.0
NN	0			1 (4.5)	1	9.5	1 (2.4)	1	4.9
Severe	0			0			0		
Symptomatic BG confirmed	0			1 (4.5)	1	9.5	1 (2.4)	1	4.9
Asymptomatic BG confirmed	0			0			0		
NN unclassifiable	2 (10.0)	4	40.7	4 (18.2)	7	66.7	6 (14.3)	11	54.1
ADA	2 (10.0)	4	40.7	4 (18.2)	8	76.2	6 (14.3)	12	59.0
Severe	0			0			0		
Documented symptomatic	0			2 (9.1)	4	38.1	2 (4.8)	4	19.7
Asymptomatic	2 (10.0)	4	40.7	3 (13.6)	4	38.1	5 (11.9)	8	39.4
Probable symptomatic	0			0			0		
Pseudo-hypoglycaemia	0			0			0		
ADA unclassifiable	0			0			0		

E: number of events, N: number of subjects, %: percentage of randomised subjects, R: event rate per 100 exposure years
Nocturnal episodes are the episodes reported with the time of onset between (23:00 – 06:59)

Clinical laboratory evaluation

Laboratory values over time

Haematology

No clinically relevant changes in haematology parameters were observed from baseline to the end of trial in any of the treatment groups.

Biochemistry

No clinically relevant changes in biochemistry parameters were observed from baseline to the end of trial in any of the treatment groups.

Lipids

No clinically relevant changes in lipid parameters were observed from baseline to the end of trial in any of the treatment groups.

Individual subject changes

Most subjects had normal haematology, biochemistry, and lipid laboratory value levels throughout the trial. A few subjects had changes from normal to high or low levels during the trial, and there were no apparent differences between the treatment groups for any of the parameters.

Individual clinically significant abnormalities

No individual clinically significant abnormalities were reported during the clinical laboratory evaluation.

Antibodies

Overall, an increase in the mean levels of anti-insulin antibodies was observed in both the treatment groups from baseline to the end of trial. The change in anti-insulin antibodies was 8.258 %B/T in the IDet group and 4.099 %B/T in the insulin NPH group at the end of trial (Table 12–8).

Table 16 Change in antibodies from baseline by treatment at visit 19 (end of trial) – safety analysis set

	IDet	NPH	Total
Number of subjects	20	22	42
Ch anti-insulin antibody (%B/T)			
N	18	21	39
Mean (SD)	8.258 (15.901)	4.099 (7.088)	6.018 (11.999)
Median	6.53	0.79	2.44
Min ; Max	-18.81 ; 42.27	-6.68 ; 26.97	-18.81 ; 42.27
Ch anti-detemir antibody (%B/T)			
N	18		
Mean (SD)	2.137 (4.568)		
Median	0.72		
Min ; Max	-4.28 ; 16.63		
Ch total anti-insulin antibody (%B/T)			
N	18	21	39
Mean (SD)	10.395 (16.325)	4.099 (7.088)	7.005 (12.481)
Median	5.78	0.79	2.44
Min ; Max	-18.47 ; 43.00	-6.68 ; 26.97	-18.47 ; 43.00

Ch: change from baseline, N: number of subjects, SD: standard deviation
Baseline information is defined as the measurement at the latest assessment before dosing

There were no clinically relevant changes in the development of antibodies in any of the treatment groups.

Vital signs, physical findings and other observations related to safety

Vital signs

There were no clinically relevant changes in vital signs from baseline to the end of the trial in any of the treatment groups.

Physical examination

No abnormal physical examination findings were observed in any of the two treatment groups at the end of trial.

Pubertal assessments

Pubertal assessments done at baseline and at the end of trial are summarised in Table 17. The majority of subjects had Tanner Grade 5 (71.4%) at baseline. The pubertal changes observed in this trial were normal as expected with this trial population.

The pubertal status for 14 subjects (33.3%) was categorised as 'unknown' at the end of trial. Of these, 13 subjects already had Tanner Grade 5 at baseline (they were no longer required to undergo tanner assessment at the end of trial) and 1 subject was withdrawn.

Table 17 Summary of pubertal assessments by visit and treatment - safety analysis set

Pubertal stage	IDet N (%)	NPH N (%)	Total N (%)
Number of subjects	20	22	42
Visit 2 (Week 0)			
N	20 (100.0)	22 (100.0)	42 (100.0)
Tanner Grade 1	0	0	0
Tanner Grade 2	0	1 (4.5)	1 (2.4)
Tanner Grade 3	6 (30.0)	0	6 (14.3)
Tanner Grade 4	2 (10.0)	3 (13.6)	5 (11.9)
Tanner Grade 5	12 (60.0)	18 (81.8)	30 (71.4)
Unknown	0	0	0
Visit 19 (End of trial)			
N	20 (100.0)	22 (100.0)	42 (100.0)
Tanner Grade 1	0	0	0
Tanner Grade 2	0	0	0
Tanner Grade 3	3 (15.0)	1 (4.5)	4 (9.5)
Tanner Grade 4	4 (20.0)	3 (13.6)	7 (16.7)
Tanner Grade 5	10 (50.0)	7 (31.8)	17 (40.5)
Unknown	3 (15.0)	11 (50.0)	14 (33.3)

N: number of subjects, %: percentage of subjects

For each subject the maximum score among the pubertal assessments (pubertal hair and pubertal breasts/penis) were considered as tanner grade for that visit

Pregnancy

No pregnancies were reported during this trial.

Safety conclusions

- 30 AEs were reported in the IDet group and 41 AEs were reported in the insulin NPH group
- No deaths were reported in this trial. One SAE (migraine) was reported in the insulin NPH group. The event was unlikely related to trial product and the subject recovered. No AEs led to withdrawal of any subjects
- There were no severe hypoglycaemic episodes in any of the treatment groups
- The proportion of subjects who experienced symptomatic BG confirmed hypoglycaemic episodes was 5.0% in the IDet group and 22.7% in the insulin NPH group
- No symptomatic BG confirmed nocturnal hypoglycaemic episodes were reported in the IDet group whereas 1 episode was reported in the insulin NPH group
- No safety issues were observed in vital signs, physical examinations, laboratory assessments and pubertal assessments in any of the treatment groups

- No clinically relevant changes were observed in the antibody development in any of the treatment groups

Rapporteur's comments

The rate of AEs related to trial drug was higher in the NPH group compared to IDet (390.7 vs. 305.1 events per 100 PYE, respectively). In this regard, the most frequently reported AE was gastroenteritis, headache, oropharyngeal pain, pain, pyrexia and vomiting. The majority of AEs were non-serious, mild in severity and unlikely related to trial product. No severe AEs were reported in this trial and no deaths occurred during the trial.

There were no severe hypoglycaemic episodes in any of the treatment groups. The overall event rate of hypoglycaemia per 100 PYE was 172.9 in the IDet group and 533.6 in the insulin NPH group. There were no severe nocturnal hypoglycaemic episodes in any of the treatment groups. The overall event rate of nocturnal hypoglycaemia per 100 PYE was 40.7 in the IDet group and 76.2 in the insulin NPH group.

No clinically relevant differences from baseline to end of treatment or between the two treatment groups were observed for vital signs, physical examination, laboratory values and antibody development.

2.3.3. Discussion on clinical aspects

With this submission a final abbreviated clinical trial report for study NN304-4093, a 26-week open label, randomised, 2-armed, parallel group, multi-centre trial investigating efficacy and safety of insulin detemir versus insulin neutral protamine Hagedorn in combination with the maximum tolerated dose of metformin and diet/exercise on glycaemic control in children and adolescents with type 2 diabetes insufficiently controlled on the maximum tolerated dose of metformin ± other oral antidiabetic drug(s) ± basal insulin was submitted in accordance with Article 46 of Regulation (EC) No1901/2006. The study was not part of the paediatric development program for Insulatard.

The primary objective of the trial was to compare the efficacy of IDet and NPH in controlling glycaemia in children and adolescents (aged 10−17 years) with T2DM, who were previously insufficiently treated with the MTD of metformin ± other OAD(s) ± basal insulin.

The secondary objective was to compare the efficacy of the two treatments in managing body weight and in achieving glycaemic control without experiencing severe hypoglycaemia and to assess and compare the safety and tolerability between the two treatments and safety between the two treatment groups.

The general study design was adequate. A randomised, open-label trial was chosen since it was not possible to blind the 2 formulations (insulin NPH is a suspension while IDet is a solution). This is acceptable.

The inclusion and exclusion criteria were adequate. Due to the rise in the incidence of T2DM noted in many countries, as a consequence of the global obesity epidemic. The treatment options for these patients are not fully explored, and an insulin analogue offering less weight gain and a reduced number of hypoglycaemic episodes could be a choice.

The choice of comparator NPH is acceptable, since both treatments are approved in the paediatric population.

The statistical methods were adequate. At least 358 subjects were planned to be randomised in order to ensure 80% power to show non-inferiority of IDet to insulin NPH in the full analysis set and per protocol (PP) analysis set with respect to change in HbA_{1c} from baseline to week 26, using a non-inferiority limit of 0.4%. However, the trial was discontinued post randomisation of 42 subjects due to a very slow recruitment rate. As a result of the limited number of subjects enrolled in the trial, none of the planned statistical analyses described in the protocol for the efficacy endpoints and for the safety endpoints, were performed.

The study included 42 subjects randomised 1:1 to the two treatment groups where 39 subjects completed the trial. The baseline characteristics were generally well balanced between groups. The mean age of subjects was 15 years (range: 10–17 years), and the majority of them were females (64.3%)

No efficacy conclusions could be drawn since the trial was terminated early due to a slow recruitment rate and therefore a low number of subjects were included in the trial. But both treatments resulted in a reduction of HbA_{1c} compared to baseline. With an observed mean HbA_{1c} baseline values decreased from 8.72% to 8.11% in the IDet group and from 8.95% to 8.11% in the insulin NPH group at the end of trial. Body weight gain was seen for both the treatments, but was lower for the IDet group (1.89 kg in the IDet group compared to 4.00 kg in the insulin NPH group.

The rate of AEs related to trial drug was higher in the NPH group compared to IDet (390.7 vs. 305.1 events per 100 PYE, respectively). In this regard, the most frequently reported AE was gastroenteritis, headache, oropharyngeal pain, pain, pyrexia and vomiting. The majority of AEs were non-serious, mild in severity and unlikely related to trial product. No severe AEs were reported in this trial and no deaths occurred during the trial.

There were no severe hypoglycaemic episodes in any of the treatment groups and the overall event rate of hypoglycaemia per 100 PYE was 172.9 in the IDet group and 533.6 in the insulin NPH group. No severe nocturnal hypoglycaemic episodes were seen in any of the treatment groups. The overall event rate of nocturnal hypoglycaemia per 100 PYE was 40.7 in the IDet group and 76.2 in the insulin NPH group.

No clinically relevant differences from baseline to end of treatment or between the two treatment groups were observed for vital signs, physical examination, laboratory values and antibody development.

Thus the reporting of adverse events does not evoke any new safety concerns.

In conclusion no efficacy conclusion could be made, since the number of subjects included in the trial was too low for assessment. No obvious differences between the two treatment groups with respect to AEs and standard safety parameters were seen and the early termination of the trial did not have any consequences on the overall benefit-risk assessment of Insulatard

3. CHMP's overall conclusion and recommendation

Based on the results of the paediatric trial assessed in this report, it is concluded that no regulatory consequences for the Marketing Authorisation for Insulatard was identified and no further action is required.

☒ Fulfilled:

No regulatory action required.