Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for insulin detemir(rys)

Proprietary Product Name: Levemir Flexpen / Levemir Penfill / Levemir Innolet

Sponsor: Novo Nordisk Pharmaceuticals Pty Ltd

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TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
ADA	American Diabetes Association
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AUC_{0-24}	Area under the serum concentration–time curve from time 0 to 24 hours
$AUC_{GIR,0-24}$	Area under the glucose infusion rate curve from time 0 to 24 hours
B/T%	Percentage of bound antibodies versus total antibody level
CCDS	Core Company Data Sheet
CI	Confidence interval
C_{max}	Maximum concentration
CTR	Clinical trial report
DAE	Adverse event leading to discontinuation
DBP	Diastolic blood pressure
EMA	European Medicines Agency
FAS	Full analysis set
$FAS_{Pregnant}$	FAS for pregnant subjects
FFA	Free fatty acid
FPG	Fasting plasma glucose
GIR	Glucose infusion rate
GIR_{max}	Maximum glucose infusion rate
GW	Gestation week
h	Hour
HbA1c	Glycosylated haemoglobin

Abbreviation	Meaning
HDL-C	High density lipoprotein cholesterol
HOMA	Homeostasis model assessment
HOMA-B	HOMA index of beta-cell function
HOMA-IR	HOMA index of insulin resistance
IDF	International Diabetes Federation
IV/WRS	Interactive Voice/Web Response System
LDL-C	Low density lipoprotein cholesterol
LOCF	Last observation carried forwards
LS Mean	Least-square mean
MAA	Marketing Authorisation Application
MESI	Medical event of special interest
NPH	Neutral Protamine Hagedorn
OAD	Oral antidiabetic drug
PD	Pharmacodynamic(s)
PG	Plasma glucose
PK	Pharmacokinetic(s)
$PP_{Pregnant}$	Per-protocol data set for pregnant subjects
RPM	Repeated-measurement
SAE	Serious adverse event
SAS	Safety analysis set
SBP	Systolic blood pressure
SMPG	Self-measured plasma glucose
SOC	System organ class
t½	Terminal elimination half-life
TEAE	Treatment-emergent adverse event

Abbreviation	Meaning
TG	Triglycerides
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
t_{GIRmax}	Time to maximal glucose infusion
t_{max}	Time to maximal serum concentration
U	Unit(s)
UNL	Upper normal limit
VLDL-C	Very low density lipoprotein cholesterol

1. Clinical rationale

The rationales provided by the Sponsor for each change are:

Change 1:

In T2DM "basal insulin, co-administered with liraglutide, would provide additional glucose-lowering potency, while the presence of liraglutide may substantially reduce weight gain associated with insulin, reduce required insulin dose and maintain low risk of hypoglycaemia. Insulin detemir, a basal insulin analogue shown to provide lower risk of hypoglycaemia and less weight gain compared to NPH insulin (intermediate-acting insulin), is a promising candidate to be tested for efficacy and safety in combination with a once-daily human GLP-1 analogue, such as liraglutide."

Change 2:

"In connection with the approval of the paediatric indication of insulin detemir by EMA, a new long-term safety trial (NN304-1689) trial was discussed and agreed with EMA as part of a post-approval commitment". The purpose of the application is to update the PI with long-term safety data from this trial.

Change 3:

"The use of insulin analogues is increasing in Type 1 as well as in Type 2 diabetes. Their use expands into special populations, such as children, elderly patients and patients with kidney failure. Use of insulin analogues implies that an increasing number of women conceive during insulin analogue treatment. Switching their treatment may carry a risk of deteriorated glycaemic control with an inherent risk of adverse influence on the pregnancy outcome. Pregnant women with diabetes need optimal glycaemic control with as few hypoglycaemic episodes as possible to reduce their risk of diabetes complications and to reduce the risk of adverse pregnancy outcome as described above. Hence, there is a medical need for optimising diabetic control in this population."

Change 4:

The Sponsor proposes to align the PI more closely with the CCDS (v.12.0). The Sponsor also has made some editorial changes to align the PI with the format described in Appendix 8 of the Australian Regulatory Guidelines for Prescription Medicines.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission contained the following clinical information:

There was a separate Module 5 for each of Change 1, Change 2 and Change 3.

- Change 1 contained three studies: Study NN2211-3673 (PK/PD), Study NN2211-1842 (efficacy and safety), Study NN2211-1842-extension (long-term safety)
- Change 2 contained one study: Study NN304-1690 (long-term open label safety in children)
- Change 3 contained one study: Study NN304-1687 (efficacy and safety in pregnancy)

2.2. Paediatric data

The submission included paediatric safety data.

2.3. Good clinical practice

The studies submitted in the application were stated to have been conducted according to GCP.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

Study NN2211-3673 was an open label, three treatment phase, single sequence, PK and PD (euglycaemic clamp at 100 mg/dL) study of detemir, liraglutide and the combination of liraglutide and detemir (Table 1, Appendix 1). The study was conducted at a single centre in the US from April 2009 to September 2009. The study included male or female subjects ≥ 18 years of age; insulin naïve and diagnosed with T2DM; treated with stable doses of OAD(s) (one of which had to be metformin); BMI of ≤ 45 kg/m2, screening HbA1c of 7 to 10% on monotherapy and 7 to 9.5% on dual therapy; FPG ≤ 250 mg/dL at Visit 2; and FPG ≥ 140 and ≤ 240 mg/dL at Visit 5 (Study Day 1).

The study treatments were: insulin detemir 0.5 U/kg on Day 1, followed by 24 hour eugycaemic clamp; liraglutide titrated to 1.8 mg/day from Day 2 to Day 22, with 24 hour euglycaemic clamp on Day 22; liraglutide 1.8 mg daily from Day 22 to Day 36, and insulin detemir 0.5 U/kg on Day 36, with 24 hour euglycaemic clamp. All subjects were treated with metformin as a background medication.

There were 33 subjects: 23 (69.7%) male, 10 (30.3%) female, and the age range was 33 to 68 years (Table 2). Twenty subjects were treated with metformin alone and 13 with metformin and another OAD. There was no effect of liraglutide on exposure to detemir: the mean ratio (90% CI) detemir + liraglutide / detemir was 1.03 (0.97 to 1.09) for AUC_{0-24} and 1.05 (0.98 to 1.13) for C_{max} (Table 1, Appendix 1). There was no effect of detemir on exposure to liraglutide: the mean ratio (90% CI) detemir + liraglutide / liraglutide was 0.97 (0.87 to 1.09) for AUC_{0-24} and 1.03 (0.93 to 1.13) for C_{max}.

Table 2: Demography of Trial Population

	Mono* at Screening	Dual** at Screening	Total
Number of Subjects	20	13	33
Age (yrs)			
Mean (SD)	49.60 (9.16)	49.69 (7.65)	49.64 (8.47)
Min ; Max	33.0 ; 68.0	36.0 ; 61.0	33.0 ; 68.0
Sex (n (%))			
Male	12 (60.0)	11 (84.6)	23 (69.7)
Female	8 (40.0)	2 (15.4)	10 (30.3)
Race (n (%))			
White	16 (80.0)	10 (76.9)	26 (78.8)
Black Or African American	3 (15.0)	3 (23.1)	6 (18.2)
Asian	1 (5.0)	0	1 (3.0)
Ethnicity (n (%))			
Hispanic Or Latino	12 (60.0)	5 (38.5)	17 (51.5)
Not Hispanic Or Latino	8 (40.0)	8 (61.5)	16 (48.5)
Weight (kg)			
Mean (SD)	93.67 (22.12)	105.09 (20.57)	98.17 (21.94)
Min ; Max	59.4 ; 137.9	81.8 ; 143.6	59.4 ; 143.6
Height (cm)			
Mean (SD)	167.98 (9.07)	177.00 (7.97)	171.53 (9.63)
Min ; Max	147.0 ; 183.5	158.5 ; 189.0	147.0 ; 189.0
BMI (kg/m^2)			
Mean (SD)	33.05 (6.68)	33.55 (6.17)	33.25 (6.39)
Min ; Max	23.1 ; 44.0	26.8 ; 43.4	23.1 ; 44.0
HbA1c (%)			
Mean (SD)	8.32 (0.98)	8.25 (0.83)	8.29 (0.91)
Min ; Max	7.0 ; 10.0	7.0 ; 9.3	7.0 ; 10.0
FPG (mg/dL)			
Mean (SD)	175.3 (32.36)	172.1 (23.54)	174.0 (28.84)
Min ; Max	141 ; 230	142 ; 217	141 ; 230

No Subjects withdrew during washout.
* Subjects on Metformin monotherapy at screening.
** Subjects on dual therapy (Metformin + other OAD) at screening.

3.2. Evaluator's overall conclusions on pharmacokinetics

There was no evidence of a PK interaction between insulin detemir and liraglutide.

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic data

In Study NN2211-3673 summarised in Table 1 (Appendix 1), from the euglycaemic clamp studies, the AUC for glucose infusion rate (AUC_{GIR}) was greater for detemir and liraglutide in combination than for detemir alone, and for liraglutide alone compared with detemir alone, but there was no significant difference between detemir and liraglutide in combination and liraglutide alone (Table 3).

Table 3: Summary of Pharmacodynamic Endpoints - Full Analysis Sets

	Detemir	Liraglutide	Detemir + Liraglutide
Full Analysis Set	33	33	33
AUC(GIR(0-24h))(mg/kg)			
N	32	32	32
Mean (SD)	1057.6(803.18)	1981.6(1167.60)	2947.0(1460.57)
Median	849.93	1754.7	2577.0
Min ; Max	14.98 ; 3862.2	342.64 ; 4697.7	1.27 ; 6834.0
GIRmax(mg/(kg*min))			
N	32	32	32
Mean (SD)	5.10(2.50)	5.61(2.31)	6.30(2.29)
Median	4.67	4.53	5.78
Min ; Max	1.18 ; 12.12	2.16 ; 11.89	0.05 ; 10.58
tGIRmax(hours)			
N	32	32	32
Mean (SD)	13.38(5.85)	10.13(6.31)	11.76(4.38)
Median	13.26	9.85	11.87
Min ; Max	0.75 ; 22.58	0.22 ; 22.73	0.00 ; 18.02
SGIRmax(mg/(kg*min))			
N	32	32	32
Mean (SD)	2.16(1.03)	3.01(1.25)	3.87(1.68)
Median	1.95	2.79	3.52
Min ; Max	0.13 ; 5.33	1.45 ; 5.97	0.07 ; 8.99
tSGIRmax(hours)			
N	32	32	32
Mean (SD)	12.48(4.93)	11.85(5.77)	12.60(4.82)
Median	12.28	12.18	12.84
Min ; Max	4.32 ; 23.50	3.50 ; 24.00	0.00 ; 24.00

	Detemir+ Liraglutide/ Detemir*	Detemir+ Liraglutide/ Liraglutide**	Liraglutide/ Detemir***
AUC(GIR(0-24h))(mg/kg)			
Ratio Estimate	2.98	1.32	2.25
95% CI	[1.84 , 4.81]	[0.82 , 2.14]	[1.39 , 3.64]
P-value	.0000	.2516	.0013
SGIRmax(mg/(kg*min))			
Ratio Estimate	1.78	1.18	1.50
95% CI	[1.34 , 2.36]	[0.89 , 1.57]	[1.13 , 1.99]
P-value	.0001	.2360	.0055

*: The Least Square Means Estimate (Ratio) = (Detemir+Liraglutide)/Detemir
**: The Least Square Means Estimate (Ratio) = (Detemir+Liraglutide)/Liraglutide
***: The Least Square Means Estimate (Ratio) = (Liraglutide)/Detemir

The mean $AUC_{GIR(0-24)}$ (SD) was 1057.6 (803.18) mg/kg for detemir alone, 1981.6 (1167.60) mg/kg for liraglutide alone and 2947.0 (1460.57) mg/kg for detemir and liraglutide in combination. The mean (95% CI) ratio for $AUC_{GIR(0-24)}$ was 2.98 (1.84 to 4.81) for detemir+liraglutide/ detemir, 1.32 (0.82 to 2.14) for detemir+liraglutide/ liraglutide and 2.25 (1.39 to 3.64) for liraglutide/ detemir. Average C-peptide plasma concentrations over 24 hours were lower for detemir alone compared with detemir and liraglutide in combination, and higher for liraglutide alone (Table 4).

Table 4: Summary of AVG(0-24 hour), C_{max}, and C_{min} for C-peptide - Full Analysis Set

	Detemir	Liraglutide	Detemir+ Liraglutide
AVG(0-24hr)			
N	32	32	32
Mean (SD)	336.4 (180.73)	950.3 (405.27)	791.9 (438.46)
Median	296.3	921.9	604.2
Min ; Max	89.5 ; 657.1	378.0 ; 1914.9	146.8 ; 1779.8
Cmax			
N	32	32	32
Mean (SD)	544.0 (248.96)	1348.0 (528.73)	1162.5 (620.44)
Median	468.5	1342.5	927.0
Min ; Max	167.0 ; 1096.0	589.0 ; 2598.0	253.0 ; 2413.0
Cmin			
N	32	32	32
Mean (SD)	165.7 (95.73)	541.6 (303.14)	427.9 (291.31)
Median	83.0	478.5	318.0
Min ; Max	83.0 ; 351.0	83.0 ; 1417.0	83.0 ; 1109.0

	Detemir+Liraglutide vs Detemir*	Detemir+Liraglutide vs Liraglutide**
AVG(0-24hr)		
Ratio Estimate	2.35	0.78
95% CI	[1.99, 2.78]	[0.66, 0.92]
P-value	<0.0001	0.0038
Cmax		
Ratio Estimate	2.05	0.80
95% CI	[1.76, 2.38]	[0.69, 0.93]
P-value	<0.0001	0.0052
Cmin		
Ratio Estimate	2.40	0.73
95% CI	[1.93, 2.99]	[0.59, 0.91]
P-value	<0.0001	0.0052

Glucagon concentrations were lower with detemir and liraglutide in combination than with detemir alone, but there was no significant difference compared with liraglutide alone (Table 5).

Table 5: Summary of AVG(0-24 hour), C_{max}, and C_{min} for Glucagon - Full Analysis Set

	Detemir	Liraglutide	Detemir+ Liraglutide
AVG(0-24hr)			
N	32	32	32
Mean (SD)	65.1 (22.59)	48.7 (18.13)	43.7 (17.04)
Median	66.2	46.5	38.2
Min ; Max	28.7 ; 116.5	23.0 ; 86.0	23.0 ; 74.4
Cmax			
N	32	32	32
Mean (SD)	92.1 (21.84)	74.0 (17.98)	69.5 (21.47)
Median	89.5	74.0	70.0
Min ; Max	54.0 ; 136.0	23.0 ; 111.0	23.0 ; 110.0
Cmin			
N	32	32	32
Mean (SD)	42.8 (22.20)	32.5 (16.37)	28.5 (11.97)
Median	35.5	23.0	23.0
Min ; Max	23.0 ; 97.0	23.0 ; 73.0	23.0 ; 66.0

	Detemir+Liraglutide vs Detemir*	Detemir+Liraglutide vs Liraglutide**
AVG(0-24hr)		
Ratio Estimate	0.67	0.89
95% CI	[0.60, 0.74]	[0.81, 0.99]
P-value	<0.0001	0.0271
Cmax		
Ratio Estimate	0.73	0.91
95% CI	[0.66, 0.80]	[0.83, 1.01]
P-value	<0.0001	0.0701
Cmin		
Ratio Estimate	0.71	0.91
95% CI	[0.59, 0.86]	[0.75, 1.09]
P-value	0.0006	0.3032

4.2. Evaluator's overall conclusions on pharmacodynamics

Insulin detemir and liraglutide have a synergistic effect in decreasing plasma glucose. Insulin detemir when added to liraglutide decreases overall insulin secretion.

5. Dosage selection for the pivotal studies

Dosage selection was based on the approved dosing recommendations.

6. Clinical efficacy

6.1. Change 1

6.1.1. Pivotal efficacy study

6.1.1.1. Study NN2211-1842

6.1.1.1.1. Study design, objectives, locations and dates

Study NN2211-1842 was a multicentre, randomised, open label, two arm, parallel group trial with an additional open-label, non-randomised arm carrying subjects who achieved target glycaemic control after the run-in period (Table 6, Appendix 1). The study design is summarised in Table 7 (Appendix 1). The study was conducted at 202 centres in nine countries from March 2009 to April 2010.

6.1.1.1.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Subjects diagnosed with T2DM, insulin naïve and treated with metformin as monotherapy for ≥ three months prior to screening, at a stable dose of ≥ 1500 mg/day or metformin (≥ 1500 mg/day) and a sulphonylurea (≤ half of the maximum approved dose according to local label), both at a stable dose for ≥ 3 three months prior to screening.
- HbA1c 7.0 to 10.0% inclusive for subjects on metformin monotherapy, HbA1c 7.0 to 8.5% inclusive for subjects on metformin in combination with a sulphonylurea
- Age 18 to 80 years, inclusive

The exclusion criteria included:

- Previous treatment with insulin (except for short-term treatment in connection with inter-current illness at the discretion of the investigator)
- Treatment with glucose-lowering agent(s) other than those stated in the inclusion criteria for a period of three months prior to screening
- Impaired liver function, ALT ≥ 2.5 times ULN
- Impaired renal function defined as serum-creatinine ≥ 133 µmol/L for males and ≥ 124 µmol/L for females
- History of chronic pancreatitis or idiopathic acute pancreatitis
- Known history of unstable angina, acute coronary event, other significant cardiac event, or cerebral stroke within the past six months
- Heart failure NYHA Class IV
- Known proliferative retinopathy or maculopathy requiring acute treatment
- Uncontrolled treated or untreated hypertension (SBP ≥ 180 mmHg and/or DBP ≥ 110 mmHg)
- Cancer (except basal cell skin cancer or squamous cell skin cancer) or any clinically significant disorder, except for conditions associated with T2DM history, which in the investigator's opinion could interfere with the results of the trial
- Recurrent major hypoglycaemia or hypoglycaemic unawareness
- Use of any drug (except for those stated in the inclusion criteria), which in the investigator's opinion could interfere with the glucose level (such as systemic corticosteroids)

- Surgery scheduled during the trial period (excluding minor surgical procedures performed under local anaesthesia)
- Known or suspected abuse of alcohol or narcotics
- Females of child bearing potential who were pregnant, breast-feeding or intended to become pregnant or were not using adequate contraceptive methods

The randomisation criterion was HbA1c measured at the randomisation visit ≥ 7.0%.

6.1.1.1.3. Study treatments

1. Insulin detemir, starting at 10 U/day and adjusted by SMPG; liraglutide 1.8 mg/day; and metformin ≥ 1500 mg/day
2. Liraglutide 1.8 mg /day and metformin ≥ 1500 mg/day

6.1.1.1.4. Efficacy variables and outcomes

The primary efficacy outcome measure was the change in HbA1c from baseline to Week 26. The secondary outcome measures were:

- Proportion of subjects reaching HbA1c targets: < 7%, ≤ 6.5%
- FPG
- Seven-point SMPG profiles
- Body weight
- Waist and hip circumference (and derived waist to hip ratio)
- Beta-cell function: fasting insulin; fasting C-peptide; fasting pro-insulin (and derived pro-insulin to C-peptide ratio), HOMA-B, HOMA-IR
- Fasting lipid profile: total cholesterol; HDL-C; LDL-C; VLDL-C; TG; and FFA
- SBP and DBP

However, due to cross-reactivity between insulin detemir and the insulin assay used to determine individual insulin concentrations in this trial, data on fasting insulin and HOMA-B and HOMA-IR indexes could not be assessed.

The safety endpoints were: AEs, hypoglycaemic episodes, physical examination, pulse, laboratory safety parameters, calcitonin and formation of liraglutide and insulin detemir antibodies.

The schedule of study visits is summarised in Table 7 (Appendix 1).

6.1.1.1.5. Randomisation and blinding methods

Subjects were randomised 1:1 using IV/WRS. There was no blinding, and all treatments were open label. The Sponsor's argument in defence of this is that blinded treat-to-target administration of insulin detemir placebo was not feasible.

6.1.1.1.6. Analysis populations

The FAS included all randomised subjects with at least one efficacy value after the randomisation visit. The safety analysis set included all exposed subjects.

6.1.1.1.7. Sample size

The sample size calculation was based on a treatment difference (in HbA1c) of 0.5% (based on the liraglutide Phase III trials), SD of 1.2%, with a two-sided significance level of 0.05, a power of 90%, and a randomisation ratio of 1:1. This determined the sample size to be 123 subjects per group, and allowing for dropouts the final calculation was 150 subjects per treatment group.

6.1.1.1.8. Statistical methods

Hypothesis tests were performed using ANCOVA models with treatment, previous OAD and country as explanatory variables and baseline HbA1c as a covariate. Missing data were imputed using LOCF. A repeat measures analysis of HbA1c over the 26 weeks was also performed.

6.1.1.1.9. Participant flow

A total of 1658 subjects were screened; 162 were randomised to the detemir group; 161 to the control; and 498 were included in the non-randomised group. The most common reason for screening failure was HbA1c outside of the range required for inclusion. There were 144 (88.9%) subjects in the detemir group, 127 (78.9%) in the control and 470 (94.4%) in the non-randomised that completed the study (Table 8). There were 162 (100%) subjects in the detemir group and 157 (97.5%) in the control included in the FAS.

Table 8: Subject Disposition

	Lira 1.8 N (%)	Detemir + Lira 1.8 N (%)	Non-randomised Lira 1.8 N (%)	Early WD Lira 1.8 N (%)	All N (%)
Screened					1658
Screening failures					670
Run-in	161	162	498	167	988
Exposed to Liraglutide	161 (100)	162 (100)	498 (100)	166 (100)	987 (100)
Randomised	161 (100)	162 (100)	0 (0.0)	0 (0.0)	323 (32.7)
Main *	161 (100)	162 (100)	498 (100)	0 (0.0)	821 (83.2)
Exposed to Detemir	0 (0.0)	162 (100)	0 (0.0)	0 (0.0)	162 (16.4)
Withdrawals	34 (21.1)	18 (11.1)	28 (5.6)	167 (101)	247 (25.0)
Adverse Events	6 (3.7)	4 (2.5)	9 (1.8)	92 (55.4)	111 (11.2)
Non-compliance with protocol	3 (1.9)	2 (1.2)	7 (1.4)	14 (8.4)	26 (2.6)
Withdrawal criteria	11 (6.8)	0 (0.0)	3 (0.6)	10 (6.0)	24 (2.4)
Protocol deviations	1 (0.6)	3 (1.9)	0 (0.0)	10 (6.0)	14 (1.4)
Lost to follow up	1 (0.6)	1 (0.6)	2 (0.4)	11 (6.6)	15 (1.5)
Ineffective therapy	5 (3.1)	2 (1.2)	0 (0.0)	6 (3.6)	13 (1.3)
Other	7 (4.3)	6 (3.7)	7 (1.4)	24 (14.5)	44 (4.5)
Completers	127 (78.9)	144 (88.9)	470 (94.4)	0 (0.0)	741 (75.1)
Full analysis set	157 (97.5)	162 (100)	0 (0.0)	0 (0.0)	319 (32.3)
Safety analysis set	159 (98.8)	163 (101)	499 (100)	166 (100)	987 (100)

All subjects also received metmin
Early WD: Withdrawals before randomisation visit (visit 4b)
The Full analysis set is based on the treatment the subjects were randomised to.
The Safety analysis set is based on the actual treatment the subjects received.
* 39.3% of subjects entering main period were randomised and 60.7% were non-randomised

6.1.1.1.10. Major protocol violations/deviations

The most common protocol violation was non-compliance: 30% of protocol deviations.

6.1.1.1.11. Baseline data

In the randomised population there were 177 (54.8%) males, 146 (45.2%) females and the age range was 31 to 79 years. The treatment groups were similar in demographic characteristics (Table 9 (Appendix 1). Overall the BMI for the treatment groups was high: mean (SD) 34.4 (6.2) kg/m^2. The treatment groups were similar in baseline efficacy outcome measures (Table 10 (Appendix 1).

6.1.1.1.12. Results for the primary efficacy outcome

There was a significant decrease in HbA1c to Week 26 in the detemir group compared with control. The LS mean (SE) change was -0.51 (0.07) % for detemir and 0.02 (0.07) % for control, LS mean (95% CI) difference -0.52 (-0.68 to -0.36) %, p <0.0001 (Table 11). The repeated measures ANOVA estimated a mean (95% CI) treatment difference of -0.43 (-0.55 to -0.31) p

<0.0001 at Week 12 and -0.49 (-0.62 to -0.36) p <0.0001 at Week 26. A subgroup analysis was not performed for the primary efficacy outcome measure.

Table 11: Summary of Absolute Values and Change in HbA1c (%) - Full Analysis Set

	Lira 1.8	Detemir + Lira 1.8
Full Analysis Set	157	162
Week -12		
N	157	162
Mean (SD)	8.29 (0.82)	8.22 (0.74)
Median	8.10	8.10
Min ; Max	6.10 ; 11.20	6.70 ; 10.50
Change from Week -12 to Baseline		
N	157	162
Mean (SD)	-0.66 (0.91)	-0.60 (0.83)
Median	-0.60	-0.50
Min ; Max	-3.30 ; 1.80	-3.20 ; 1.80
Baseline (Week 0)		
N	157	162
Mean (SD)	7.64 (0.66)	7.63 (0.55)
Median	7.40	7.50
Min ; Max	6.20 ; 10.10	7.00 ; 10.30
Week 12		
N	139	154
Mean (SD)	7.50 (0.80)	7.13 (0.62)
Median	7.30	7.10
Min ; Max	6.00 ; 10.40	5.70 ; 9.50
Week 26 #		
N	125	141
Mean (SD)	7.53 (0.77)	7.12 (0.75)
Median	7.40	7.00
Min ; Max	5.70 ; 9.80	5.50 ; 9.70
Change from Baseline to Week 26 #		
N	125	141
Mean (SD)	-0.04 (0.68)	-0.51 (0.75)
Median	0.00	-0.50
Min ; Max	-2.60 ; 1.70	-2.30 ; 1.90
End of Treatment, LOCF		
N	149	160
Mean (SD)	7.64 (0.87)	7.15 (0.75)
Median	7.50	7.10
Min ; Max	5.70 ; 11.30	5.50 ; 9.70
Change from Baseline to End of Treatment,LOCF		
N	149	160
Mean (SD)	0.03 (0.72)	-0.48 (0.73)
Median	0.00	-0.50
Min ; Max	-2.60 ; 1.90	-2.30 ; 1.90
Change from Run-in to Week 26 #		
N	125	141
Mean (SD)	-0.76 (1.07)	-1.13 (0.96)
Median	-0.70	-1.20
Min ; Max	-3.20 ; 1.80	-3.50 ; 2.50

All subjects also received metformin
#: Completers - No imputation method applied

6.1.1.1.13. Results for other efficacy outcomes

- At Week 26 the proportion achieving HbA1c < 7% was 71 (44.4%) subjects in the detemir group and 30 (20.1%) in the control, OR (95% CI) 3.75 (2.19 to 6.45), p <0.0001.
- At Week 26 the proportion achieving HbA1c ≤ 6.5% was 31 (19.4%) subjects in the detemir group and 11 (7.4%) in the control, OR (95% CI) 3.32 (1.58 to 7.00), p = 0.0016.

- FPG decreased in the detemir group compared with control (Table 12). The mean (SD) change from baseline was -2.13 (2.17) mmol/L for detemir and -0.23 (2.13) mmol/L for control; LS mean difference (95% CI) -1.73 (-2.16 to -1.30) mmol/L, p <0.0001.

Table 12: Summary of Absolute Values and Change in FPG (mmol/L) - Full Analysis Set

	Lira 1.8	Detemir + Lira 1.8
Full Analysis Set	157	162
Week -12		
N	154	162
Mean (SD)	10.27 (2.52)	10.15 (2.38)
Median	10.00	9.70
Min ; Max	5.00 ; 17.70	3.10 ; 17.60
Change from Week -12 to Baseline		
N	152	160
Mean (SD)	-1.47 (2.78)	-0.95 (2.56)
Median	-1.10	-1.05
Min ; Max	-9.80 ; 5.80	-8.40 ; 6.30
Baseline (Week 0)		
N	155	160
Mean (SD)	8.81 (2.10)	9.23 (1.86)
Median	8.60	9.00
Min ; Max	5.20 ; 18.40	6.00 ; 17.10
Week 4		
N	148	160
Mean (SD)	8.46 (2.09)	7.83 (1.84)
Median	8.25	7.55
Min ; Max	2.90 ; 19.00	4.50 ; 17.60
Week 12		
N	139	154
Mean (SD)	8.51 (2.19)	7.38 (1.68)
Median	8.60	7.20
Min ; Max	4.70 ; 22.20	4.30 ; 13.90
Week 26 #		
N	125	143
Mean (SD)	8.02 (1.80)	7.06 (1.80)
Median	7.90	6.70
Min ; Max	4.40 ; 13.90	4.00 ; 16.00
Change from Baseline to Week 26 #		
N	123	142
Mean (SD)	-0.50 (1.85)	-2.18 (2.21)
Median	-0.40	-2.10
Min ; Max	-6.20 ; 5.70	-12.1 ; 6.10
End of Treatment, LOCF		
N	156	162
Mean (SD)	8.52 (2.31)	7.09 (1.84)
Median	8.30	6.75
Min ; Max	4.40 ; 18.70	4.00 ; 16.00
Change from Baseline to End of Treatment,LOCF		
N	154	160
Mean (SD)	-0.23 (2.13)	-2.13 (2.17)
Median	-0.30	-2.00
Min ; Max	-6.20 ; 7.20	-12.1 ; 6.10

All subjects also received metformin
#: Completers - No imputation method applied

- The SMPG profiles were improved in the detemir group compared with control (Table 8). The LS mean difference (95% CI) in post-prandial PG at breakfast was -1.12 (-1.72 to -0.51) mmol/L, p = 0.0003; at lunch was -0.60 (-1.12 to -0.08) mmol/L, p = 0.0244; and at dinner was -0.70 (-1.25 to -0.14) mmol/L, p = 0.0141. There was no significant difference between the groups in prandial increase in PG at breakfast, lunch or dinner.

- The mean change in body weight to Week 26 was -0.31 (3.36) kg in the detemir group and -1.13 (3.17) in the control. The LS mean difference (95% CI) in the change in body weight was 0.79 (0.08 to 1.49) kg, p = 0.0283. This indicates greater weight loss in the control group. For waist circumference, there was no significant difference between treatments: LS mean difference (95% CI) detemir-control: -0.12 (-1.17 to 0.93) cm, p = 0.8229. There was no significant difference in waist circumference or in waist to hip ratio.
- Fasting insulin, HOMA-B and HOMA-IR could not be determined due to cross-reactivity between insulin detemir and the insulin assay.
- There was a decrease in proinsulin in the detemir group compared with control: LS mean difference (95% CI) detemir-control -8.66 (-16.1 to -1.21) pmol/L, p = 0.0230.
- There was a decrease in fasting C-peptide in the detemir group compared with control: LS mean difference (95% CI) detemir-control -0.24 (-0.33 to -0.15) nmol/L, p <0.0001. There was no difference between the groups in proinsulin to C-peptide ratio.
- There was no difference between the groups in the change in total cholesterol: LS mean difference (95% CI) detemir-control 0.01 (-0.15 to 0.17) mmol/L, p = 0.8600.
- There was no difference between the groups in the change in LDL-C: LS mean difference (95% CI) detemir-control 0.01 (-0.12 to 0.14) mmol/L, p = 0.8354.
- There was no difference between the groups in the change in VLDL-C: LS mean difference (95% CI) detemir-control -0.04 (-0.11 to 0.03) mmol/L, p = 0.3069.
- There was no significant difference between the groups in the change in VLDL-C: LS mean difference (95% CI) detemir-control 0.03 (-0.00 to 0.06) mmol/L, p = 0.0902.
- There was no significant difference between the groups in the change in TG: LS mean difference (95% CI) detemir-control -0.09 (-0.34 to 0.15) mmol/L, p = 0.4577.
- FFA decreased to a greater extend in the detemir group: LS mean difference (95% CI) detemir-control -0.08 (-0.13 to -0.03) mmol/L, p = 0.0017.
- There was no significant difference between the groups in the change in SBP: the LS mean difference (95% CI) detemir-control was -0.70 (-3.48 to 2.07) mmHg, p = 0.6192.
- There was no significant difference between the groups in the change in DBP: the LS mean difference (95% CI) detemir-control was 0.70 (-1.06 to 2.46) mmHg, p = 0.4325.

6.1.2. Other efficacy studies

Study NN2211-1842-extension included 140 subjects from the detemir group and 122 from the control. Of these, there were 130 subjects in the detemir group and 92 in the control that completed the 52 weeks of treatment. The mean (SD) change in HbA1c to Week 52 in the extension study was -1.12 (1.16) % in the detemir group and -0.76 (1.11) % in the control. The repeat measures ANOVA estimated the treatment difference at Week 56 to be -0.34 (-0.56 to -0.12) %, p = 0.0023. At Week 52, HbA1c <7% was achieved by 74 (59.2%) subjects in the detemir group and 27 (30.3%) in the control. HbA1c ≤6.5% was achieved by 37 (29.6%) subjects in the detemir group and ten (11.2%) in the control. The mean (SD) change from baseline in FPG was -2.18 (2.42) in the detemir group and -0.50 (1.90) in the control. The LS mean difference (95% CI) in post-prandial PG at breakfast was -1.74 (-2.32 to -1.16) mmol/L, p < 0.0001; at lunch was -0.63 (-1.21 to -0.04) mmol/L, p = 0.0357; and at dinner was -0.44 (-1.04 to 0.16) mmol/L, p = 0.1484. There was no significant difference between the groups in prandial increase in PG at breakfast, lunch or dinner. The mean (SD) change in body weight was -3.88 (5.49) kg in the detemir group and -5.09 (5.30) kg in the control.

6.1.3. Evaluator's conclusions on clinical efficacy for Change 1

Insulin detemir in combination with liraglutide and metformin resulted in an incremental decrease in mean HbA1c of 0.51% over 26 weeks. This is a clinically significant improvement in diabetes control. The improvement was maintained over a 52 week period. There was weight loss in the group treated with detemir, liraglutide and metformin in combination, but less than in those treated with liraglutide and metformin alone.

6.2. Change 2

6.2.1.1. Study NN304-1690

Study NN304-1690 was an open label, multicentre, single arm, 52-week extension of Study NN304-1689 investigating insulin detemir administered once or twice daily to children and adolescents diagnosed with T1DM (Table 13, Appendix 1). The Study was conducted at 29 sites in eleven countries from February 2008 to September 2009. The study included subjects who had completed 52 weeks of treatment in Study NN304-1689 (see Table 14) previously evaluated in application TGA PM-2010-01598-3-5. Insulin detemir was administered as a subcutaneous injection in the thigh once or twice daily, with the dose adjusted individually and aiming for FPG of 4 to 7 mmol/L. In addition, insulin aspart was administered as subcutaneous injections in the abdomen, pre-prandial, two to four times a day, in connection with main meals. The study was not primarily designed as an efficacy study, but some efficacy variables were included as secondary outcome measures. The outcome measures were: insulin detemir-insulin aspart cross reacting antibodies, insulin detemir specific antibodies, insulin aspart specific antibodies, HbA1c, FPG, hypoglycaemic episodes, BMI, weight, AEs, diabetic ketoacidosis, laboratory safety parameters, and vital signs.

The study included 146 subjects: 37 were aged 2 to 5 years, 59 were aged 6 to 12 years, and 50 were aged 13 to 16 years. A total of 141 (96.6%) subjects completed the study. All the subjects were included in the efficacy and safety analyses. There were 77 (52.7%) females, 69 (47.3%) males, and the age range was 3.1 to 17.9 years. The subject demographics are summarised in Table 14.

Table 14: Subject Characteristics at Baseline by Age Group, SAS, Extension Period

	2-5 Years	6-12 Years	13-16 Years	Total
Number of subjects	37	59	50	146
Age (years)				
N	37	59	50	146
Mean (SD)	5.3 (1.24)	10.8 (1.84)	15.6 (1.05)	11.1 (4.20)
Median	5.4	10.7	15.6	11.8
Min ; Max	3.1 ; 6.9	7.6 ; 13.9	14.1 ; 17.9	3.1 ; 17.9
Gender				
Female	21 (56.8%)	33 (55.9%)	23 (46.0%)	77 (52.7%)
Male	16 (43.2%)	26 (44.1%)	27 (54.0%)	69 (47.3%)
Race				
White	35 (94.6%)	59 (100%)	50 (100%)	144 (98.6%)
Unknown (*)	2 (5.4%)			2 (1.4%)
Pubertal status				
Tanner Grade 1	37 (100%)	30 (50.8%)	1 (2.0%)	68 (46.6%)
Tanner Grade 2+		29 (49.2%)	49 (98.0%)	78 (53.4%)
Height (m)				
N	37	59	50	146
Mean (SD)	1.10 (0.09)	1.45 (0.13)	1.68 (0.10)	1.44 (0.25)
Median	1.1	1.5	1.7	1.5
Min ; Max	0.92 ; 1.30	1.17 ; 1.68	1.47 ; 1.90	0.92 ; 1.90
Body weight (kg)				
N	37	59	50	146
Mean (SD)	19.1 (2.64)	40.1 (11.2)	57.9 (11.2)	40.9 (17.8)
Median	19.3	39.3	58.6	40.7
Min ; Max	14.3 ; 24.0	21.1 ; 66.0	34.5 ; 80.0	14.3 ; 80.0
BMI (kg/m2)				
N	37	59	50	146
Mean (SD)	15.68 (1.68)	18.55 (2.58)	20.36 (2.89)	18.44 (3.07)
Median	15.6	18.6	20.2	18.0
Min ; Max	12.31 ; 19.86	13.23 ; 25.81	14.93 ; 26.96	12.31 ; 26.96
Stratification[1]				
2-5 Years	37 (100%)			37 (25.3%)
6-16 Years		59 (100%)	50 (100%)	109 (74.7%)
HbA1c (%)				
N	37	59	50	146
Mean (SD)	8.15 (1.22)	8.52 (1.28)	8.93 (1.82)	8.57 (1.50)
Median	8.2	8.5	8.6	8.4
Min ; Max	5.70 ; 10.70	6.10 ; 11.60	6.40 ; 15.10	5.70 ; 15.10
FPG (mmol/L)				
N	37	57	50	144
Mean (SD)	7.66 (4.66)	7.52 (3.86)	7.31 (4.10)	7.48 (4.13)
Median	7.1	6.6	5.7	6.4
Min ; Max	1.55 ; 18.09	1.44 ; 20.04	2.33 ; 18.65	1.44 ; 20.04
Diabetes history (years)				
N	37	59	50	146
Mean (SD)	3.29 (1.02)	4.80 (2.43)	5.66 (3.31)	4.71 (2.68)
Median	3.2	4.1	4.6	3.9
Min ; Max	2.03 ; 6.05	2.00 ; 10.70	2.09 ; 15.27	2.00 ; 15.27

SD: Standard deviation, 2+: Tanner Grade 2 Or More*: Race not known for French subjects.
[1]: stratification was at Visit 1 in Trial NN304-1689.

Diabetic complications were not assessed when entering the extension period, but the most common other concomitant illnesses at the extension Visit 1 were lipohypertrophy (reported in 3.4 % of subjects), liver disorder and varicella (both reported in 2.7% of subjects), autoimmune thyroiditis, coeliac disease, dental caries, myopia, headache, asthma and adenoidectomy (reported in 2.1% of subjects). The daily dose of detemir ranged from 0.17 to 1.40 U/kg (Table 15).

Table 15: Daily Basal and Bolus Insulin Doses (U/kg) at Baseline by Age Group, Extension Period

	2-5 Years	6-12 Years	13-16 Years	Total
Number of Subjects	37	59	50	146
Basal Insulin Doses				
N	37	56	50	143
Mean (SD)	0.53 (0.23)	0.67 (0.24)	0.59 (0.24)	0.61 (0.24)
Median	0.52	0.63	0.55	0.57
Min ; Max	0.17 ; 0.97	0.22 ; 1.33	0.19 ; 1.40	0.17 ; 1.40
Bolus Insulin Doses				
N	36	57	50	143
Mean (SD)	0.46 (0.16)	0.46 (0.18)	0.50 (0.19)	0.47 (0.18)
Median	0.47	0.44	0.49	0.47
Min ; Max	0.12 ; 0.86	0.14 ; 1.00	0.13 ; 1.04	0.12 ; 1.04

N: Number of subjects; SD: Standard Deviation
For two subjects LOCF from previous telephone visits is applied as dose information from visit 1 extension is missing

There was a slight increase in HbA1c during the extension period for all the age groups: mean (SD) 0.10 (0.77) % for the 2 to 5 year age group, 0.27 (1.08) % for the 6 to 12 year, 0.11 (1.60) % for the 13 to 16 year and 0.17 (1.22) % for the total population (Table 16 and Figure 1). This translates to a mean (95% CI) change of 0.10 (-0.16 to 0.36) % for the 2 to 5 year age group, 0.27 (-0.01 to 0.55) % for the 6 to 12 year, 0.11 (-0.34 to 0.56) % for the 13 to 16 year and 0.17 (-0.03 to 0.37) % for the total population. Of the total population, 15 (10.3%) were within the target range for pre-prandial PG of ≥ 4 mmol/L and ≤ 7 mmol/L (Table 17). Mean FPG also increased slightly during the trial (Figure 2).

Table 16: Summary of Change from Visit 1 and Visit 1Ext in HbA1c (%) by Age Group, FAS

	2-5 Years	6-12 Years	13-16 Years	Total
Number of Subjects				
	37	59	50	146
Change from Visit 1				
Visit 5Ext				
N	37	59	50	146
Mean (SD)	0.08 (0.97)	0.31 (1.47)	0.64 (1.58)	0.36 (1.41)
Median	0.00	0.10	0.45	0.25
Min ; Max	-1.7 ; 2.30	-2.9 ; 5.00	-2.1 ; 6.50	-2.9 ; 6.50
Change from Visit 1Ext				
Visit 5Ext				
N	37	59	50	146
Mean (SD)	0.10 (0.77)	0.27 (1.08)	0.11 (1.60)	0.17 (1.22)
Median	-0.10	0.10	0.10	0.10
Min ; Max	-1.2 ; 2.80	-1.9 ; 4.20	-7.2 ; 5.00	-7.2 ; 5.00

Figure 1: Mean HbA1c (%) over Time by Age Group, FAS, Whole Treatment Period

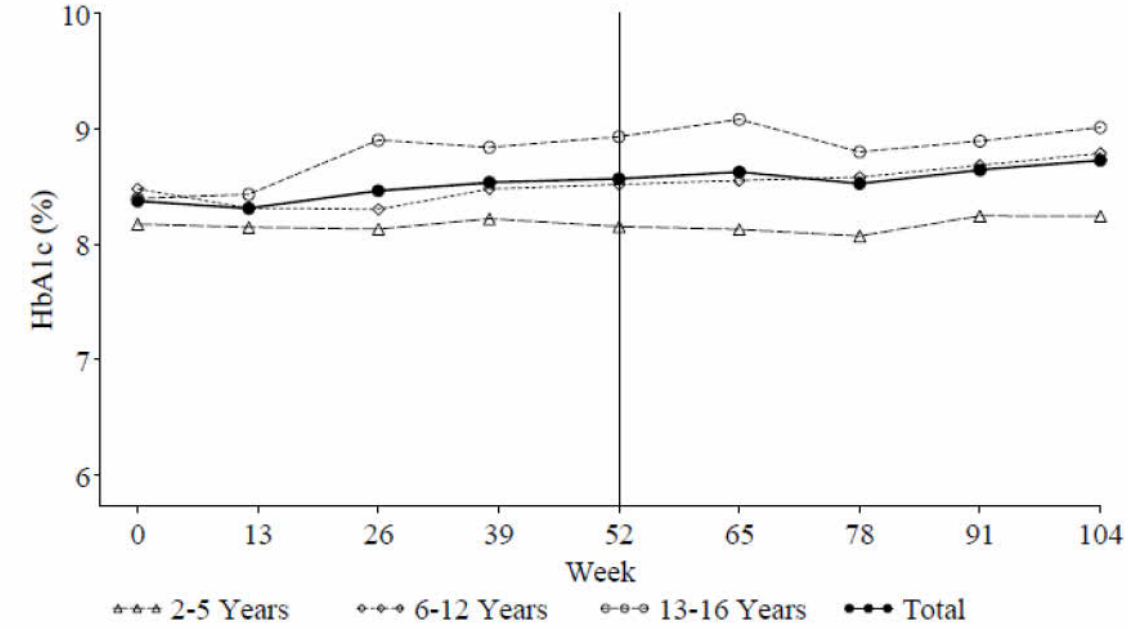


Figure 2: Mean FPG (mmol/L) over Time by Age Group, FAS, Whole Treatment Period

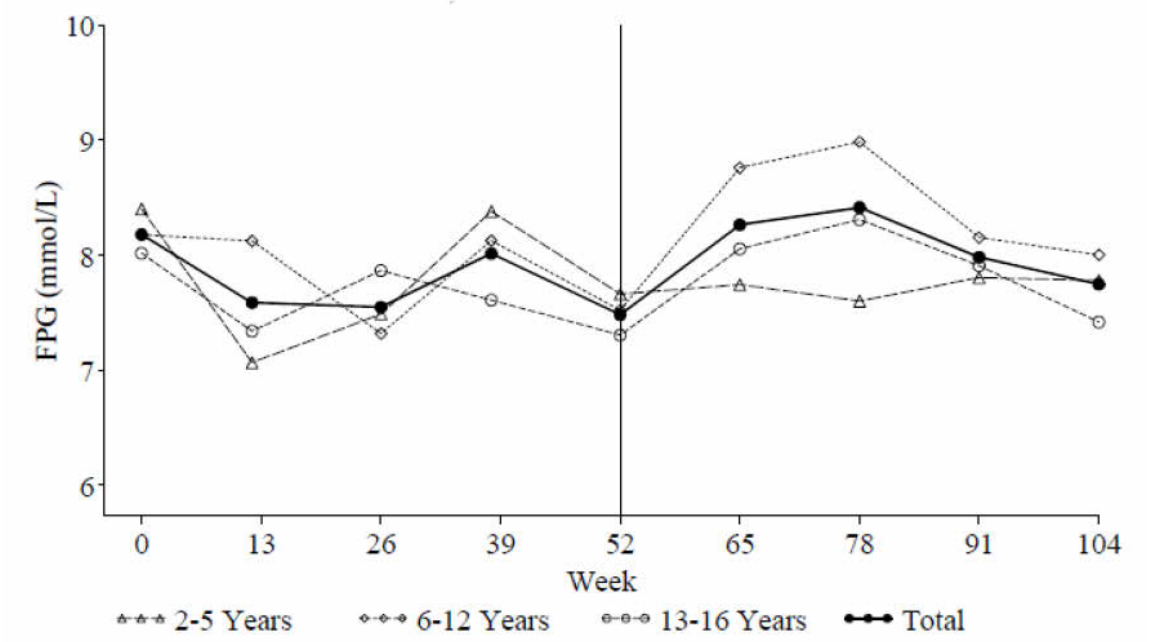


Table 17: Subjects Having Targeted Glucose Values at End of Trial by Age Group, FAS, Whole Treatment Period

	2-5 Years N (%)	6-12 Years N (%)	13-16 Years N (%)	Total N (%)
Full analysis set	37	59	50	146
4.0<= Pre-breakfast PG <=7	17 (45.9)	20 (33.9)	14 (28.0)	51 (34.9)
4.0<= Pre-dinner PG <=7.0	11 (29.7)	15 (25.4)	19 (38.0)	45 (30.8)
Both Targets	4 (10.8)	4 (6.8)	7 (14.0)	15 (10.3)

6.2.2. Evaluator's conclusions on clinical efficacy for Change 2

The data presented for Change 2 were primarily intended as safety data. The efficacy data are difficult to interpret in the absence of a control group. There appears to be a loss of efficacy over the second year of treatment but this most likely reflects the natural history of T1DM in a paediatric clinical trial population.

6.3. Change 3

6.3.1.1. Study NN304-1687

6.3.1.1.1. Study design, objectives, locations and dates

Study NN304-1687 was a multicentre, open label, randomised, parallel group efficacy and safety study to compare detemir with NPH insulin, in combination with insulin aspart as bolus insulin, in the treatment of pregnant women with T1DM (Table 18, Appendix 1). The study was conducted at 79 sites in 17 countries from May 2007 to August 2010.

6.3.1.1.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Female, aged ≥ 18 years
- T1DM treated with insulin for at least 12 months before randomisation
- The subject was either:

  - Planning to become pregnant in the immediate future and willing to undertake pregnancy counselling and a screening HbA1c ≤ 9.0% (National Glycohaemoglobin Standardisation Program) or
  - Pregnant with an intrauterine singleton living foetus, GW = 8-12 at randomisation, confirmed by an ultra sound scan and an HbA1c ≤ 8.0% at confirmation of pregnancy
- Willingness to take folic acid before pregnancy and during the first trimester according to local guidelines

For non-pregnant subjects only: willingness to discontinue any concomitant medication, for example, certain anti-hypertensives, like angiotensin converting enzyme inhibitors, contraindicated in pregnancy according to local labelling *prior* to conception

The exclusion criteria included:

- Untreated hyper or hypothyroidism
- Known or suspected abuse of alcohol or narcotics
- Cardiac problems as evaluated by either:
  - Cardiac failure or
  - Diagnosis of unstable angina pectoris or
  - Previous myocardial infarction
- Impaired renal function as evaluated by any of the following: diagnosis of diabetic nephropathy; serum creatinine ≥ 125 mmol/L; macro-albuminuria (urine albumin:creatinine ratio > 300 mg/g in random spot urine sample)
- History of severe hyperemesis gravidarum (requiring hospitalisation)
- Subject being treated or became pregnant with assistance of *in vitro* fertilisation or other medical infertility treatment
- Impaired hepatic function as evaluated by ALT, or ALP ≥ two times upper reference limit
- Uncontrolled hypertension (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg) in the supine position
- Proliferative retinopathy or maculopathy requiring acute treatment
- Any disease or condition which the investigator felt would interfere with the trial, for example, clinically significant gynaecological conditions
- Known to be human immunodeficiency virus positive
- Known to be Hepatitis B or C positive
- Any concomitant medication, for example, certain anti-hypertensives like angiotensin converting enzyme inhibitors, contraindicated in pregnancy

6.3.1.1.3. Study treatments

The study treatments were:

1. Insulin detemir 100 U/mL, 3 mL cartridge, administered using a NovoPen
2. NPH insulin 100 U/mL, 3 mL cartridge, administered using a NovoPen

All subjects also received insulin aspart as bolus insulin. The insulin dose was adjusted in order to achieve preprandial PG in the range 4.0 to 6.0 mmol/L, and 2 hour postprandial PG < 7.0 mmol/L.

6.3.1.1.4. Efficacy variables and outcomes

The primary efficacy outcome measure was HbA1c at GW36. Secondary efficacy outcome measures were:

- HbA1c through pregnancy
- Response categories: HbA1c ≤ 6.0% at GW24 and GW36
- 8-point SMPG
- FPG

The safety outcome measures were: hypoglycaemic episodes; mode of delivery; AEs and laboratory parameters during pregnancy; insulin antibodies; diabetic complications; birth weight; prematurity; perinatal mortality; neonatal mortality; insulin antibodies in cord blood; and presence of detemir in cord blood. The definition of neonatal hypoglycaemia as an AE was restrictive: AEs of neonatal hypoglycaemia were recorded only when they were SAEs according to the following: the infant had severe symptoms of hypoglycaemia (for example, convulsions) disappearing after treatment with glucose (irrespectively of whether it was per oral or as intravenous glucose).

The schedule of study visits is summarised in Table 19.

Table 19: Trial Flow Chart

Visit[a]	V1	V2	V3	V4	V5	P1	P2	P3	P4	End-of preg.	FU	Withdrawal /Early or termination[1] visit
	Scr	Ran. Non-preg.	Optimisation of glycaemic control / conception			Ran. Preg	Gestational week (GW)			Delivery visit	EoT	EoT
	Max -3 w	0	12 w (±1w)	24 w (±1w)	36 w (±1w)	GW 8-12	14w (±1w)	24 w (±1w)	36 w (±1w)	Delivery	6-w pp (±1w)	
Informed consent	X											
Incl. / Excl criteria	X	X				X						
Withdrawal criteria			X	X	X	X[1]	X	X	X			
Randomisation		X				X						
Demographics	X											
Mat. Medical history	X											
Concomitant illness	X											
Obstetric history	X											
Phys exam + ECG	X										X	X
Vital signs (BP + pulse)	X					X	X	X	X		X	X
Weight	X					X	X	X	X			
Height	X											
Fundoscopy[a]	X					X[2]			X		X	X
Insulin dose	X	X	X	X	X	X	X	X	X		X	X
Glucose meter dispense /instruction	X											
8-point profiles[4]		X	X	X	X	X	X	X	X			
Instruction of FPG	X											
FPG		X	X	X	X	X	X	X	X			
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
AE		X	X	X	X	X	X	X	X	X	X	X
Hypoglycaemia		X	X	X	X	X	X	X	X	X	X	X
Haematology/ Biochemistry	X					X	X	X	X		X	X
HbA_{1c}	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X					X	X	X	X		X	X
Dispensing of Diary	X	X	X	X	X	X	X	X	X	X		
Pregnancy test	X[3]											
Ultrasound scan[5]	X					X						
Current Pregnancy Information						X						
Pen/injection instr.		X				X[9]						
Trial drug supply		X	X	X	X	X	X	X	X	X		
Dispensing of pregnancy tests		X										
Drug accountability		X	X	X	X	X	X	X	X	X	X	X
IV/WRS call	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy outcome										X	X	X
Delivery information										X		
Insulin antibodies		X				X[9]			X	X[10]		
Foetal assessments												X[11]
Infant Health											X	
End of Trial form											X	X

6.3.1.1.5. Randomisation and blinding methods

Randomisation was performed using IV/WRS. The study was open label.

6.3.1.1.6. Analysis populations

The FAS for pregnant subjects ($FAS_{Pregnant}$) comprised all randomised subjects who were exposed to at least one dose of trial product and who were pregnant during the trial. The

$PP_{Pregnant}$ comprised all subjects from the $FAS_{Pregnant}$ analysis set except subjects who significantly violated the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the primary endpoint.

6.3.1.1.7. Sample size

The sample size calculation was performed for a non-inferiority analysis in the $PP_{Pregnant}$ population for the primary efficacy outcome measure. In previous trials, the range of SD for HbA1c was 0.8 to 1.5; and a SD of 1.1 was used for the calculation. The non-inferiority margin was 0.4%, the level of significance was 0.05, and the power was 80%. A total of 120 subjects in each treatment group would be required to complete to GW36. Given an expected dropout rate of 20%, and the expected pregnancy rate in randomised subjects, the final calculation was for 460 subjects.

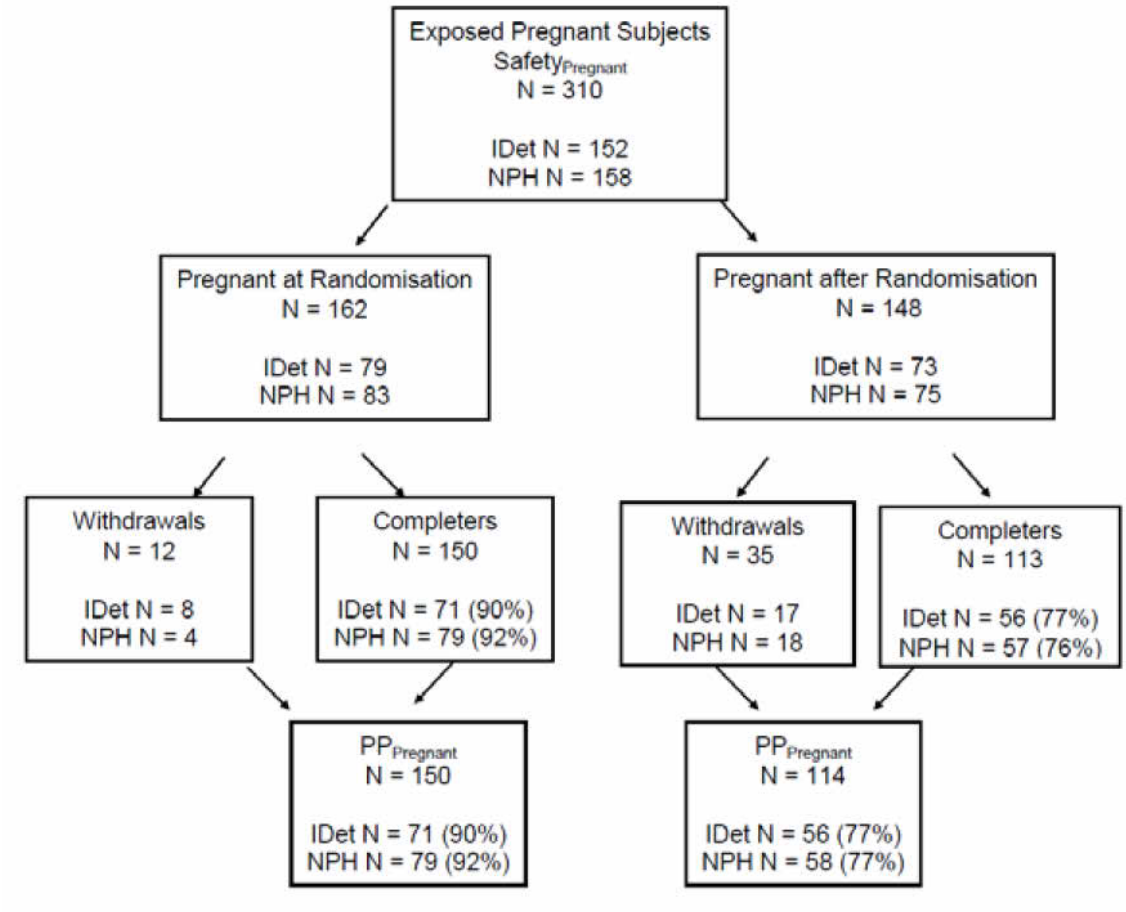
6.3.1.1.8. Statistical methods

The study was designed as a non-inferiority study with the margin for non-inferiority for the primary efficacy outcome measure (HbA1c at GW36) being 0.4%. Hypothesis tests were performed using the 95% CI. Missing values were imputed using LOCF.

6.3.1.1.9. Participant flow

There were 600 subjects screened, and 470 were randomised to treatment: 233 to detemir and 237 to NPH. Of these, 263 subjects completed: 127 (83.6%) in the detemir group and 136 (84.5%) in the NPH (Figure 3).

Figure 3: Subject Disposition by Pregnancy Status – $Safety_{Pregnant}$



There were 152 (65.2%) subjects in the $FAS_{Pregnant}$ population exposed to detemir and 158 (66.7%) exposed to NPH; and 127 (54.2%) in the $PP_{Pregnant}$ population exposed to detemir and 137 (57.8%) exposed to NPH (Table 20).

Table 20: Subject Disposition, All Subjects

	Detemir N (%)	NPH N (%)	Total N (%)
Screened			600
Screening Failures			130
Randomised	233 (100.0)	237 (100.0)	470 (100.0)
Exposed	233 (100.0)	232 (97.9)	465 (98.9)
Withdrawals	106 (45.5)	101 (42.6)	207 (44.0)
Withdrawn			
Adverse Event	18 (7.7)	8 (3.4)	26 (5.5)
Ineffective Therapy		9 (3.8)	9 (1.9)
Non-Compliance	8 (3.4)	8 (3.4)	16 (3.4)
Withdrawal Criteria	60 (25.8)	50 (21.1)	110 (23.4)
Lost to Follow-up	1 (0.4)	1 (0.4)	2 (0.4)
Protocol Deviation	2 (0.9)	4 (1.7)	6 (1.3)
Decision of Subject	16 (6.9)	18 (7.6)	34 (7.2)
Other	1 (0.4)	3 (1.3)	4 (0.9)
Completed Trial	127 (54.5)	136 (57.4)	263 (56.0)
Number of Pregnant Subjects	152 (65.2)	161 (67.9)	313 (66.6)
Number of Pregnancies	152 (65.2)	163 (68.8)	315 (67.0)
Safety All	233 (100.0)	232 (97.9)	465 (98.9)
Safety Pregnant	152 (65.2)	158 (66.7)	310 (66.0)
FAS Pregnant	152 (65.2)	158 (66.7)	310 (66.0)
PP Pregnant	127 (54.5)	137 (57.8)	264 (56.2)

FAS: Full Analysis Set, PP: Per Protocol
Two subjects in the NPH arm had a spontaneous abortion and became pregnant again.

6.3.1.1.10. Major protocol violations/deviations

For all the subjects that were included in the $FAS_{Pregnant}$, but excluded from the $PP_{Pregnant}$, the reason for exclusion was “delivery not after Gestational Week 32”.

6.3.1.1.11. Baseline data

All subjects were female and the age range was 20 to 43 years. The treatment groups were similar in demographic characteristics (Table 21).

Table 21: Subject Characteristics, Safety Pregnant

	Detemir	NPH	Total
Number of subjects	152	158	310
Age (years)			
N	152	158	310
Mean (SD)	29.7 (4.62)	30.4 (4.21)	30.1 (4.43)
Median	29.4	30.4	29.8
Min ; Max	21.1 ; 43.2	20.7 ; 41.7	20.7 ; 43.2
Race			
N	152 (100.0%)	158 (100.0%)	310 (100.0%)
American Indian or Alaska Native		1 (0.6%)	1 (0.3%)
Asian	1 (0.7%)	3 (1.9%)	4 (1.3%)
Black or African American	1 (0.7%)		1 (0.3%)
White	135 (88.8%)	142 (89.9%)	277 (89.4%)
Unknown	12 (7.9%)	10 (6.3%)	22 (7.1%)
Other	3 (2.0%)	2 (1.3%)	5 (1.6%)
Height (m)			
N	152	157	309
Mean (SD)	1.67 (0.07)	1.65 (0.06)	1.66 (0.07)
Median	1.65	1.65	1.65
Min ; Max	1.49 ; 1.85	1.52 ; 1.81	1.49 ; 1.85
Body weight (kg)			
N	152	157	309
Mean (SD)	67.6 (12.3)	68.7 (12.4)	68.2 (12.3)
Median	66.0	67.3	66.9
Min ; Max	45.0 ; 113.5	40.0 ; 115.0	40.0 ; 115.0
BMI (kg/m2)			
N	152	157	309
Mean (SD)	24.34 (3.95)	25.17 (4.22)	24.76 (4.10)
Median	23.91	24.26	24.08
Min ; Max	17.15 ; 40.77	16.44 ; 41.23	16.44 ; 41.23
Smoker			
N	152 (100.0%)	158 (100.0%)	310 (100.0%)
No	143 (94.1%)	147 (93.0%)	290 (93.5%)
Yes	9 (5.9%)	11 (7.0%)	20 (6.5%)
Daily use of alcohol			
N	152 (100.0%)	158 (100.0%)	310 (100.0%)
No	150 (98.7%)	158 (100.0%)	308 (99.4%)
Yes	2 (1.3%)		2 (0.6%)
Stratification			
N	152 (100.0%)	158 (100.0%)	310 (100.0%)
Pregnant after Randomisation	73 (48.0%)	75 (47.5%)	148 (47.7%)
Pregnant at Randomisation	79 (52.0%)	83 (52.5%)	162 (52.3%)

N: Number of subjects; SD: Standard deviation

The treatment groups were similar in baseline efficacy measures and duration of diabetes (Table 22).

Table 22: Diabetes History, Safety Pregnant

	Detemir	NPH	Total
Number of subjects	152	158	310
HbA_{1c} (%)			
N	152	158	310
Mean (SD)	6.95 (0.82)	7.08 (0.76)	7.01 (0.79)
Median	6.85	7.10	7.00
Min ; Max	5.1 ; 8.9	5.2 ; 8.8	5.1 ; 8.9
FPG (mmol/L)			
N	139	151	290
Mean (SD)	5.89 (3.29)	5.99 (3.23)	5.94 (3.25)
Median	5.27	5.49	5.33
Min ; Max	0.6 ; 19.2	0.7 ; 16.9	0.6 ; 19.2
Diabetes history (years)			
N	152	158	310
Mean (SD)	11.72 (8.08)	12.78 (7.94)	12.26 (8.02)
Median	11.4	12.5	11.9
Min ; Max	1.0 ; 29.8	1.1 ; 34.9	1.0 ; 34.9

N: Number of subjects; SD: Standard deviation; FPG: Fasting plasma glucose

More subjects in the detemir group had diabetic neuropathy at baseline: seven (4.6%) compared with three (1.9%) in the NPH (Table 23).

Table 23: Diabetic Complications at Baseline, Safety Pregnant

	Detemir N (%)	NPH N (%)	Total N (%)
Number of Subjects			
N	152	158	310
Diabetic Nephropathy			
N	152 (100.0)	158 (100.0)	310 (100.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)
No	152 (100.0)	158 (100.0)	310 (100.0)
Diabetic Neuropathy			
N	152 (100.0)	158 (100.0)	310 (100.0)
Yes	7 (4.6)	3 (1.9)	10 (3.2)
No	145 (95.4)	155 (98.1)	300 (96.8)
Diabetic Retinopathy			
N	152 (100.0)	158 (100.0)	310 (100.0)
Yes	43 (28.3)	40 (25.3)	83 (26.8)
No	109 (71.7)	118 (74.7)	227 (73.2)
Macro Angiopathy			
N	152 (100.0)	158 (100.0)	310 (100.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)
No	152 (100.0)	158 (100.0)	310 (100.0)

N: Number of subjects

Clinically significant fundoscopic abnormalities were present in 12 subjects in each group. Obstetric history was similar for the two treatment groups (Table 24).

Table 24: Obstetric History at Baseline, Safety Pregnant

		Detemir N (%)	NPH N (%)	Total N (%)
Number of Subjects		152	158	310
Previous number of Pregnancies		152 (100.0%)	158 (100.0%)	310 (100.0%)
	0	69 (45.39%)	74 (46.84%)	143 (46.13%)
	1	46 (30.26%)	47 (29.75%)	93 (30.00%)
	2	22 (14.47%)	22 (13.92%)	44 (14.19%)
	3	8 (5.26%)	4 (2.53%)	12 (3.87%)
	4	4 (2.63%)	3 (1.90%)	7 (2.26%)
	5	0 (0.00%)	3 (1.90%)	3 (0.97%)
	6	0 (0.00%)	1 (0.63%)	1 (0.32%)
	7	1 (0.66%)	0 (0.00%)	1 (0.32%)
	Unknown	2 (1.32%)	4 (2.53%)	6 (1.94%)
Previous number of Live Birth(s)		81 (100.0%)	80 (100.0%)	161 (100.0%)
	0	14 (17.28%)	13 (16.25%)	27 (16.77%)
	1	55 (67.90%)	51 (63.75%)	106 (65.84%)
	2	7 (8.64%)	14 (17.50%)	21 (13.04%)
	3	4 (4.94%)	1 (1.25%)	5 (3.11%)
	4	1 (1.23%)	1 (1.25%)	2 (1.24%)
Previous Maternal /Foetal Pregnancy Complications		81 (100.0%)	80 (100.0%)	161 (100.0%)
	Yes	58 (71.60%)	53 (66.25%)	111 (68.94%)
	No	23 (28.40%)	27 (33.75%)	50 (31.06%)
If Yes - the following complication(s)		58 (100.0%)	53 (100.0%)	111 (100.0%)
	Caesarean section(s)	31 (53.45%)	30 (56.60%)	61 (54.95%)
	Malformation	2 (3.45%)	4 (7.55%)	6 (5.41%)
	Miscarriage	31 (53.45%)	24 (45.28%)	55 (49.55%)
	Perinatal death(s)	2 (3.45%)	3 (5.66%)	5 (4.50%)
	Pre-eclampsia	6 (10.34%)	2 (3.77%)	8 (7.21%)
	Preterm delivery(ies)	12 (20.69%)	13 (24.53%)	25 (22.52%)

N: Number of subjects
%: Proportion of subjects

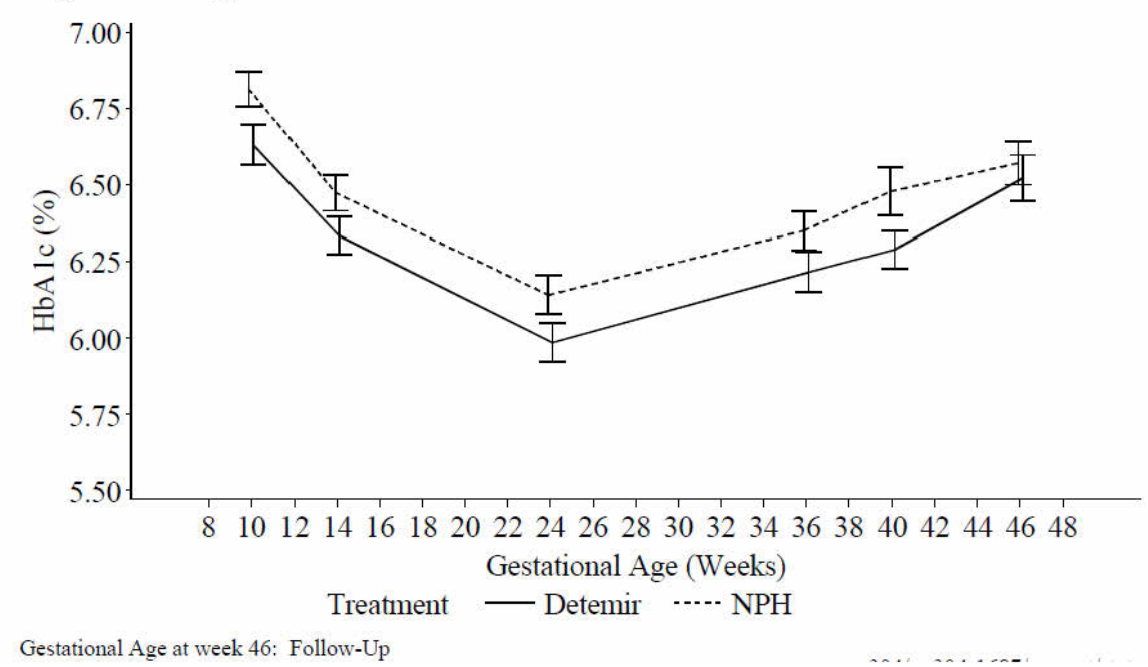
6.3.1.1.12. Results for the primary efficacy outcome

Insulin detemir was not inferior to insulin NPH. The mean (SE) HbA1c at GW36 for the PP population was 6.22 (0.069) % for detemir and 6.37 (0.067) % for NPH, mean (95% CI) difference -0.15 (-0.34 to 0.04) %. For the FAS the mean (SE) HbA1c at GW36 was 6.27 (0.053) % for detemir and 6.33 (0.052) % for NPH, mean (95% CI) difference -0.06 (-0.21 to 0.08) %. For subjects pregnant at randomisation, mean (SE) HbA1c was 6.39 (0.072) % in the detemir group and 6.44 (0.070) % in the NPH. For subjects pregnant after randomisation mean (SE) HbA1c was 6.11 (0.080) % in the detemir group and 6.19 (0.082) % in the NPH.

6.3.1.1.13. Results for other efficacy outcomes

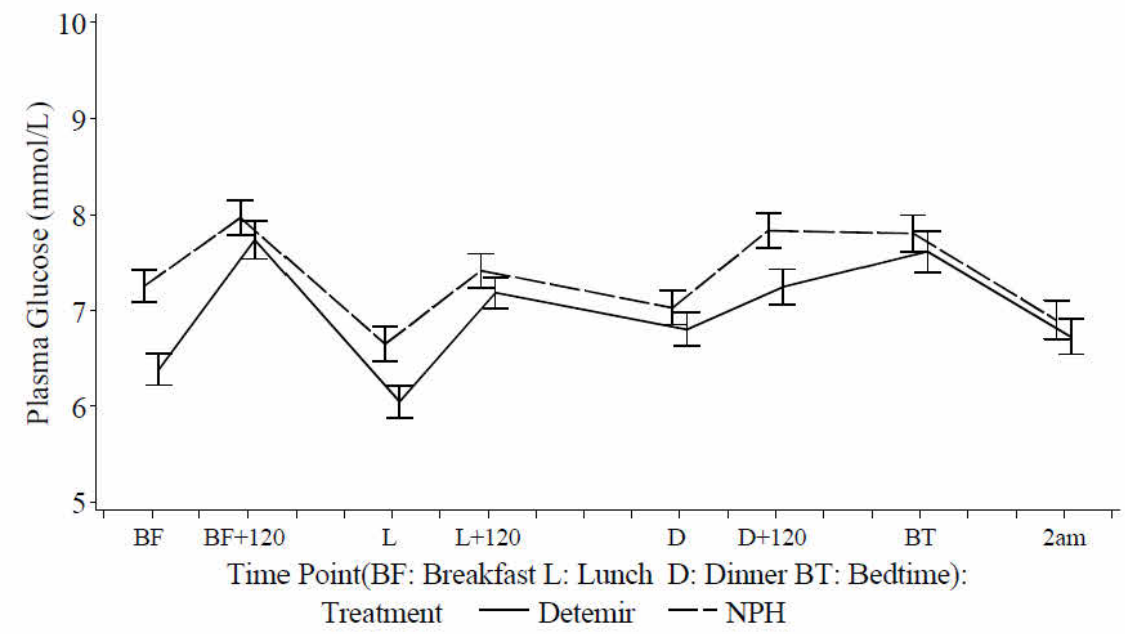
- At each time point there was no significant difference between detemir and NPH in HbA1c (Figure 4). At GW24 mean SE HbA1c was 6.04 (0.050) % in the detemir group and 6.14 (0.049) % in the NPH.

Figure 4: Mean (±SEM) HbA1c (%) during Pregnancy and at Follow-up, LOCF, Full Analysis Set Pregnant

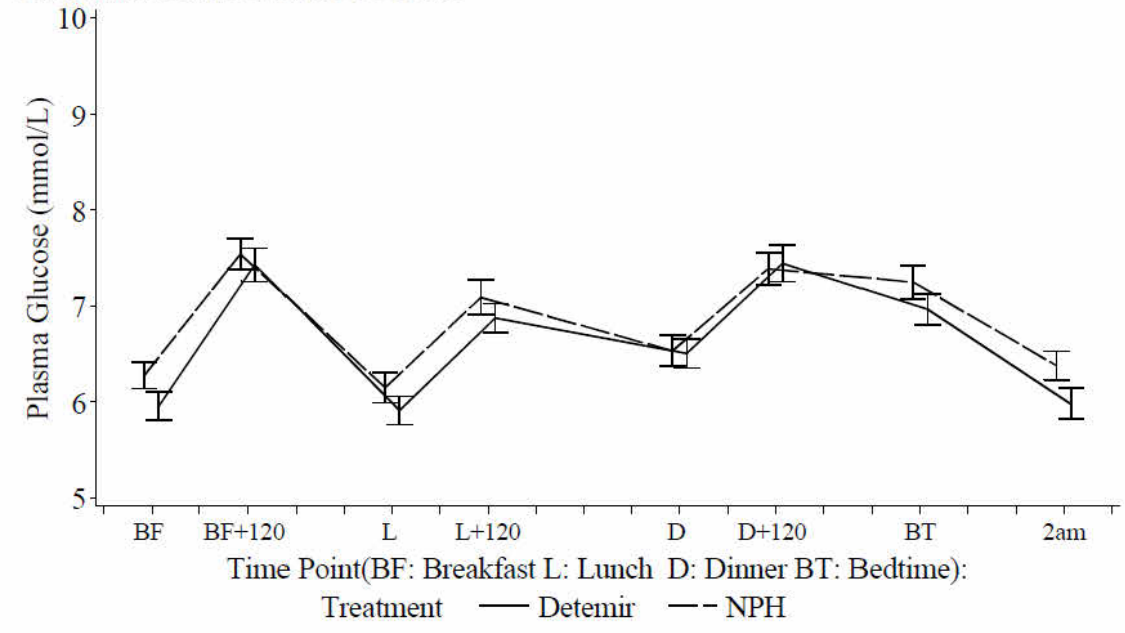


- HbA1c ≤ 6% at GW24 and GW36 was achieved by 57 (41.3%) subjects in the detemir group and 46 (31.5%) in the NPH.
- At the GW24 visit mean (SE) FPG was 5.38 (0.271) mmol/L in the detemir group and 6.32 (0.255) mmol/L in the NPH, mean (95% CI) difference -0.94 (-1.67 to -0.21) mmol, p = 0.012.
- At the GW36 visit mean (SE) FPG was 4.76 (0.200) mmol/L in the detemir group and 5.41 (0.187) mmol/L in the NPH, mean (95% CI) difference -0.94 (-1.19 to -0.12) mmol, p = 0.017.
- The 8 point SMPG profiles were similar for the two treatment groups at the GW24 and GW36 visits (Figure 5). A mixed model estimation of mean (SE) plasma glucose at GW24 was 6.95 (0.105) mmol/L for detemir and 7.38 (0.101) mmol/L for NPH, mean (95% CI) difference -0.43 (-0.72 to -0.14) mmol/L, p = 0.003; and at GW36 was 6.61 (0.098) mmol/L for detemir and 6.85 (0.094) mmol/L for NPH, mean (95% CI) difference -0.24 (-0.51 to 0.03) mmol/L, p = 0.082.

Figure 5: Mean (±SEM) 8-point PG Profile (mmol/L) at GW24 (Top) and GW36 (Bottom), LOCF, FAS Pregnant



BF: Breakfast L: Lunch D: Dinner BT: Bedtime



BF: Breakfast L: Lunch D: Dinner BT: Bedtime

6.3.2. Evaluator's conclusions on clinical efficacy for Change 3

Insulin detemir has similar efficacy to NPH in the management of diabetes during pregnancy.

7. Clinical safety

7.1. Studies providing evaluable safety data

Evaluable safety data were available from all the clinical studies. These were:

- Change 1: Study NN2211-3673 (PK/PD), Study NN2211-1842 (efficacy and safety), and Study NN2211-1842-extension (long-term safety).
- Change 2: Study NN304-1690 (long-term open label safety in children)
- Change 3: Study NN304-1687 (efficacy and safety in pregnancy)

7.2. Pivotal studies that assessed safety as a primary outcome

There were no additional pivotal safety studies.

7.3. Patient exposure

Change 1:

In Study NN2211-3673, summarised in Table 1(Appendix 1), there were 32 subjects exposed to a single dose of detemir 0.5 U/kg in combination with liraglutide 1.8 mg during a PK/PD study.

In Study NN2211-1842, summarised in Table 6 (Appendix 1), there were 162 subjects exposed to detemir in combination with liraglutide and metformin for up to 26 weeks. The median duration of exposure was 182.5 days. In the extension study, Study NN2211-1842-extension, 140 subjects from the detemir group and that had completed 26 weeks treatment were included. Of these, 130 subjects completed the 52 weeks of treatment. The total patient years exposure to detemir in this study was 144.5 years.

Change 2:

In Study NN304-1690 summarised in Table 13 (Appendix 1), there were 146 subjects exposed to detemir for up to one year. There were 37 subjects aged 2 to 5 years, 59 aged 6 to 12 years and 50 aged 13 to 16 years. There were 105 subjects exposed to detemir for a total duration of 104 weeks in the original and extension studies. At the end of the study the median (range) daily dose of detemir was 0.61 (0.09 to 1.63) U/kg.

Change 3:

In Study NN304-1687, summarised in Table 18 (Appendix 1), there were 152 subjects exposed to detemir during pregnancy, corresponding to 119.4 subject years exposure. The mean duration of exposure during pregnancy was 6.5 months.

7.4. Adverse events

7.4.1. All adverse events (irrespective of relationship to study treatment)

Change 1:

In Study NN2211-3673, summarised in Table 1 (Appendix 1), there were 16 TEAEs reported in 14 (42%) subjects with insulin detemir alone (Day 1), 20 in 17 (52%) treated with liraglutide at steady state; and 13 in 13 (39%) when both trial drugs were co-administered. Detemir in combination with liraglutide did not appear to result in an increased rate of TEAEs (Table 25, Appendix 1).

In Study NN2211-1842 and its extension, there were 845 TEAEs reported in 132 (81.0%) subjects in the detemir group and 716 in 124 (78.0%) in the control. The non-randomised group, which was not exposed to detemir, had 2389 TEAEs reported in 433 (86.8%) subjects. Increased serum lipase was reported as a TEAE in 26 (16.0%) subjects in the detemir group compared with 16 (10.1%) in the control (Table 26, Appendix 1). The most commonly reported TEAEs were diarrhoea, nausea and vomiting.

Change 2:

In Study NN304-1690, there were 714 TEAEs reported in 116 (79.5%) subjects in the combined population including 178 in 29 (78.4%) subjects in the 2 to 5 year age group, 383 in 50 (84.7%) in the 6 to 12 year and 153 in 37 (74.0%) in the 13 to 16 year. The overall rate of TEAEs was 246.9/100 exposure years, in the 2 to 5 year group 243.1/100 exposure years, in the 6 to 12 year group 325.9/100 patient years exposure and in the 13 to 16 year group 155.4/100 patient years exposure. The most common TEAEs fitted the pattern of common childhood illnesses (Table 27).

Table 27: Common Treatment Emergent AEs (> 5%) by System Organ Class, SAS, Whole Treatment Period

	N	(%)	E	R
Infections and infestations				
Nasopharyngitis	71	(48.6)	164	56.7
Upper respiratory tract infection	21	(14.4)	44	15.2
Pharyngitis	20	(13.7)	41	14.2
Influenza	18	(12.3)	39	13.5
Gastroenteritis	17	(11.6)	23	8.0
Bronchitis	9	(6.2)	16	5.5
Viral infection	11	(7.5)	13	4.5
Rhinitis	9	(6.2)	11	3.8
Acute tonsillitis	8	(5.5)	8	2.8
Nervous system disorders				
Headache	25	(17.1)	84	29.0
Gastrointestinal disorders				
Abdominal pain upper	8	(5.5)	13	4.5
Abdominal pain	9	(6.2)	10	3.5
Vomiting	10	(6.8)	10	3.5

N: Number of subjects; %: Percentage of subjects; E: Number of events;
R: Rate - Number of events per 100 exposure years

Change 3:

In Study NN304-1687, there were 650 TEAEs reported in 138 (90.8%) subjects in the detemir group (corresponding to an event rate of 788.9/100 exposure years) and 678 in 141 (89.2%) in the NPH (corresponding to an event rate of 785.9/100 exposure years). The pattern of TEAEs was similar for the two groups (Table 28, Appendix 1).

In the neonatal population, there were 121 TEAEs reported in 56 (36.8%) subjects in the detemir group and 152 in 55 (34.8%) in the NPH. The pattern of TEAEs was similar for the two groups (Table 29, Appendix 1).

7.4.2. Treatment-related adverse events (adverse drug reactions)

Change 1:

In Study NN2211-1842 there were 95 treatment related TEAEs in 46 (28.2%) subjects in the detemir group and 57 in 29 (18.2%) in the control. There were more subjects with diarrhoea and vomiting attributed to treatment in the detemir group than in the control group (Table 30).

Table 30: Possibly or Probably Related to Treatment Emergent Adverse Events (TEAE) During Main Period by System Organ Class and Preferred Term - Safety Analysis Set

	Lira 1.8			Detemir + Lira 1.8			Non-randomised Lira 1.8		
	N	(%)	E	N	(%)	E	N	(%)	E
Safety Analysis Set	159			163			499		
Adverse Events	29	(18.2)	57	46	(28.2)	95	83	(16.6)	144
Gastrointestinal disorders	19	(11.9)	25	23	(14.1)	39	29	(5.8)	46
Diarrhoea	6	(3.8)	6	14	(8.6)	16	10	(2.0)	10
Vomiting	1	(0.6)	1	5	(3.1)	8	9	(1.8)	30
Abdominal Pain Upper				2	(1.2)	3	2	(0.4)	2
Constipation	1	(0.6)	1	2	(1.2)	3	4	(0.8)	4
Abdominal Pain	2	(1.3)	2	2	(1.2)	2	1	(0.2)	1
Dyspepsia	2	(1.3)	2	2	(1.2)	2	3	(0.6)	3
Nausea	6	(3.8)	6	2	(1.2)	2	6	(1.2)	8
Abdominal Distension				1	(0.6)	1	2	(0.4)	2
Eructation				1	(0.6)	1	1	(0.2)	1
Haematemesis				1	(0.6)	1			
Abdominal Discomfort	1	(0.6)	2						
Flatulence	1	(0.6)	1				1	(0.2)	1
Gastrooesophageal Reflux Disease	2	(1.3)	2				2	(0.4)	3
Irritable Bowel Syndrome							1	(0.2)	1
Pancreatitis Chronic	1	(0.6)	1						
Retching	1	(0.6)	1						
Investigations	6	(3.8)	14	17	(10.4)	20	26	(5.2)	31
Lipase Increased	3	(1.9)	4	14	(8.6)	14	15	(3.0)	15
Blood Amylase Increased	2	(1.3)	2	2	(1.2)	2	6	(1.2)	6
Blood Insulin Increased				1	(0.6)	1			
Blood Proinsulin Increased				1	(0.6)	1			
Pancreatic Enzymes Increased	1	(0.6)	1	1	(0.6)	1			
Weight Increased				1	(0.6)	1			
Alanine Aminotransferase Increased							1	(0.2)	1
Blood Alkaline Phosphatase Increased	1	(0.6)	1						
Blood Calcitonin Increased							4	(0.8)	4
Blood Creatine Phosphokinase Abnormal							1	(0.2)	1
Blood Creatine Phosphokinase Increased	2	(1.3)	2				1	(0.2)	1
Blood Creatinine Increased	1	(0.6)	1						
Blood Potassium Increased	1	(0.6)	1						
Blood Pressure Increased							1	(0.2)	1
Blood Urea Increased	1	(0.6)	1						
Glomerular Filtration Rate Decreased							1	(0.2)	1
Weight Decreased	1	(0.6)	1				1	(0.2)	1
General disorders and administration site conditions	4	(2.5)	5	10	(6.1)	16	4	(0.8)	4
Injection Site Reaction				3	(1.8)	5			
Injection Site Haematoma	1	(0.6)	1	2	(1.2)	4	3	(0.6)	3
Injection Site Haemorrhage				1	(0.6)	2			
Application Site Haematoma				1	(0.6)	1			
Asthenia				1	(0.6)	1			
Fatigue	1	(0.6)	1	1	(0.6)	1			
Injection Site Atrophy				1	(0.6)	1			
Injection Site Pain				1	(0.6)	1	1	(0.2)	1
Feeling Cold	1	(0.6)	1						
Injection Site Pruritus	1	(0.6)	1						
Injection Site Rash	1	(0.6)	1						
Nervous system disorders	3	(1.9)	4	5	(3.1)	9	6	(1.2)	12
Headache	1	(0.6)	1	4	(2.5)	4	2	(0.4)	2
Lethargy				2	(1.2)	3			
Dizziness				1	(0.6)	1	2	(0.4)	6
Tremor	1	(0.6)	2	1	(0.6)	1			
Benign Intracranial Hypertension	1	(0.6)	1						
Burning Sensation							1	(0.2)	1
Dysgeusia							1	(0.2)	1
Somnolence							1	(0.2)	2
Skin and subcutaneous tissue disorders	1	(0.6)	1	3	(1.8)	7	9	(1.8)	10
Pruritus	1	(0.6)	1	2	(1.2)	3	1	(0.2)	1

Table 30: Possibly or Probably Related to Treatment Emergent Adverse Events (TEAE) During Main Period by System Organ Class and Preferred Term - Safety Analysis Set continued

	Lira 1.8			Detemir + Lira 1.8			Non-randomised Lira 1.8		
	N	(%)	E	N	(%)	E	N	(%)	E
Rash Papular				1	(0.6)	1			
Hyperhidrosis				1	(0.6)	1	1	(0.2)	1
Urticaria				1	(0.6)	1	1	(0.2)	1
Ecchymosis							1	(0.2)	1
Eczema							2	(0.4)	2
Lipodystrophy Acquired							1	(0.2)	1
Prurigo							1	(0.2)	1
Skin Nodule							1	(0.2)	2
Metabolism and nutrition disorders	1	(0.6)	1	2	(1.2)	2	1	(0.2)	1
Decreased Appetite	1	(0.6)	1	2	(1.2)	2	1	(0.2)	1
Injury, poisoning and procedural complications				1	(0.6)	1	2	(0.4)	2
Incorrect Dose Administered				1	(0.6)	1	1	(0.2)	1
Underdose							1	(0.2)	1
Respiratory, thoracic and mediastinal disorders	2	(1.3)	2	1	(0.6)	1			
Allergic Sinusitis				1	(0.6)	1			
Epistaxis	1	(0.6)	1						
Hiccups	1	(0.6)	1						
Blood and lymphatic system disorders							1	(0.2)	1
Lymphocytosis							1	(0.2)	1
Endocrine disorders							1	(0.2)	1
Thyroid C-Cell Hyperplasia							1	(0.2)	1
Hepatobiliary disorders	1	(0.6)	1				1	(0.2)	1
Cholelithiasis	1	(0.6)	1						
Hepatic Steatosis							1	(0.2)	1
Infections and infestations	2	(1.3)	2				5	(1.0)	6
Gastroenteritis							1	(0.2)	1
Influenza	1	(0.6)	1						
Injection Site Abscess							1	(0.2)	1
Localised Infection							1	(0.2)	1
Onychomycosis							1	(0.2)	1
Pharyngotonsillitis	1	(0.6)	1						
Sinusitis							1	(0.2)	1
Urinary Tract Infection							1	(0.2)	1
Musculoskeletal and connective tissue disorders							4	(0.8)	4
Back Pain							1	(0.2)	1
Muscle Spasms							1	(0.2)	1
Neck Pain							1	(0.2)	1
Polymyalgia Rheumatica							1	(0.2)	1
Psychiatric disorders	1	(0.6)	2				1	(0.2)	1
Anxiety	1	(0.6)	1						
Insomnia							1	(0.2)	1
Nervousness	1	(0.6)	1						
Vascular disorders							4	(0.8)	4
Hot Flush							1	(0.2)	1
Hypertension							1	(0.2)	1
Hypotension							1	(0.2)	1
Orthostatic Hypotension							1	(0.2)	1

In the extension there were 14 treatment related TEAEs in 12 (7.4%) subjects in the detemir group and 17 in 12 (7.5%) in the control. The patterns of treatment related TEAEs were similar for the detemir and control groups (Table 31).

Table 31: Possibly or Probably Related to Treatment Emergent Adverse Events (TEAE) During Extension Period by System Organ Class and Preferred Term - Safety Analysis Set

	Lira 1.8			Detemir + Lira 1.8			Non-randomised Lira 1.8			Intensified		
	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E
Safety Analysis Set	159			163			499			24		
Intensified	17						7			24		
All Adverse Events	12	(7.5)	17	12	(7.4)	14	60	(12.0)	102	7	(29.2)	8
Gastrointestinal disorders	7	(4.4)	10	4	(2.5)	5	28	(5.6)	51	2	(8.3)	2
Nausea	1	(0.6)	1	2	(1.2)	2	8	(1.6)	10	1	(4.2)	1
Abdominal Discomfort				1	(0.6)	1	1	(0.2)	1			
Diarrhoea	1	(0.6)	1	1	(0.6)	1	10	(2.0)	10	1	(4.2)	1
Vomiting	3	(1.9)	3	1	(0.6)	1	9	(1.8)	15			
Abdominal Distension	1	(0.6)	1									
Abdominal Pain	1	(0.6)	1				1	(0.2)	1			
Abdominal Pain Upper							5	(1.0)	5			
Aphthous Stomatitis							1	(0.2)	1			
Constipation							1	(0.2)	1			
Dyspepsia	2	(1.3)	2				1	(0.2)	1			
Faecaloma							1	(0.2)	1			
Flatulence							2	(0.4)	2			
Gastritis							2	(0.4)	2			
Pancreatitis							1	(0.2)	1			
Pancreatitis Acute	1	(0.6)	1									
Investigations	2	(1.3)	2	3	(1.8)	3	22	(4.4)	29	4	(16.7)	4
Blood Creatinine Increased				1	(0.6)	1						
Blood Proinsulin Increased				1	(0.6)	1						
Lipase Increased	1	(0.6)	1	1	(0.6)	1	19	(3.8)	19	4	(16.7)	4
Alanine Aminotransferase Increased							1	(0.2)	1			
Blood Amylase Increased							4	(0.8)	4			
Blood Calcitonin Increased	1	(0.6)	1				1	(0.2)	1			
Blood Calcium Increased							1	(0.2)	1			
Blood Triglycerides Increased							2	(0.4)	2			
Pancreatic Enzymes Increased							1	(0.2)	1			
Very Low Density Lipoprotein Increased							1	(0.2)	1			
General disorders and administration site conditions				2	(1.2)	2	6	(1.2)	7	1	(4.2)	1
Injection Site Haematoma				2	(1.2)	2	1	(0.2)	1			
Asthenia							1	(0.2)	1			
Injection Site Haemorrhage							1	(0.2)	1			
Injection Site Nodule							1	(0.2)	1			
Injection Site Pruritus							1	(0.2)	1	1	(4.2)	1
Oedema Peripheral							2	(0.4)	2			
Injury, poisoning and procedural complications				1	(0.6)	1	1	(0.2)	1			
Accidental Overdose				1	(0.6)	1						
Road Traffic Accident							1	(0.2)	1			
Renal and urinary disorders	1	(0.6)	1	1	(0.6)	1	1	(0.2)	1			
Renal Failure				1	(0.6)	1	1	(0.2)	1			
Renal Failure Acute	1	(0.6)	1									
Respiratory, thoracic and mediastinal disorders				1	(0.6)	1						
Epistaxis				1	(0.6)	1						
Skin and subcutaneous tissue disorders				1	(0.6)	1	3	(0.6)	3			
Lipohypertrophy				1	(0.6)	1						
Hyperhidrosis							1	(0.2)	1			
Pruritus							1	(0.2)	1			
Rash							1	(0.2)	1			
Cardiac disorders							1	(0.2)	1			
Atrioventricular Block First Degree							1	(0.2)	1			
Eye disorders	1	(0.6)	1									
Eye Oedema	1	(0.6)	1									
Infections and infestations	1	(0.6)	1				2	(0.4)	2			
Cystitis	1	(0.6)	1									
Diverticulitis							1	(0.2)	1			
Gastroenteritis							1	(0.2)	1			
Metabolism and nutrition disorders							2	(0.4)	2			
Decreased Appetite							1	(0.2)	1			
Hyponatraemia							1	(0.2)	1			
Musculoskeletal and connective tissue disorders	1	(0.6)	1							1	(4.2)	1
Intervertebral Disc Protrusion	1	(0.6)	1									
Pain In Extremity										1	(4.2)	1
Nervous system disorders							2	(0.4)	3			
Dizziness Postural							1	(0.2)	1			
Somnolence							1	(0.2)	1			
Tremor							1	(0.2)	1			
Psychiatric disorders	1	(0.6)	1				1	(0.2)	1			
Depression	1	(0.6)	1									
Insomnia							1	(0.2)	1			
Vascular disorders							1	(0.2)	1			
Hypotension							1	(0.2)	1			

Change 2:

In Study NN304-1690, there were ten probable treatment (with detemir) related TEAEs reported in nine (6.2%) subjects in the combined population including one in one (2.7%) subjects in the 2 to 5 year age group, four in three (5.1%) in the 6 to 12 year and five in five (10.0%) in the 13 to 16 year. The overall rate of TEAEs was 3.5/100 exposure years, in the 2 to 5 year group 1.4/100 exposure years, in the 6 to 12 year group 3.4/100 patient years exposure

and in the 13 to 16 year group 5.1/100 patient years exposure. Most of the detemir treatment related TEAEs were those commonly associated with insulin administration but there were three subjects with pruritus and one with urticaria (Table 32).

Table 32: Treatment Emergent AEs Probably/Possibly Related to Basal Insulin by System Organ Class, SAS, Whole Treatment Period

	N	(%)	E	R
All subjects	146			
Total exposure (yr)	289.2			
All Events	17	(11.6)	23	8.0
Skin and subcutaneous tissue disorders	8	(5.5)	10	3.5
Pruritus	3	(2.1)	4	1.4
Lipodystrophy acquired	2	(1.4)	3	1.0
Lipoatrophy	1	(0.7)	1	0.3
Lipohypertrophy	1	(0.7)	1	0.3
Urticaria	1	(0.7)	1	0.3
General disorders and administration site conditions	5	(3.4)	5	1.7
Injection site erythema	3	(2.1)	3	1.0
Application site nodule	1	(0.7)	1	0.3
Injection site atrophy	1	(0.7)	1	0.3
Metabolism and nutrition disorders	4	(2.7)	5	1.7
Hypoglycaemia	2	(1.4)	3	1.0
Hypoglycaemic unconsciousness	1	(0.7)	1	0.3
Ketosis	1	(0.7)	1	0.3
Infections and infestations	1	(0.7)	1	0.3
Tonsillitis	1	(0.7)	1	0.3
Investigations	1	(0.7)	1	0.3
Weight decreased	1	(0.7)	1	0.3
Nervous system disorders	1	(0.7)	1	0.3
Headache	1	(0.7)	1	0.3

N: Number of subjects; %: Percentage of subjects; E: Number of events;
R: Rate - Number of events per 100 exposure years

Change 3:

In Study NN304-1687, there were 21 treatment related TEAEs reported in 18 (11.8%) subjects in the detemir group (corresponding to an event rate of 25.5/100 exposure years) and 27 in 16 (10.1%) in the NPH (corresponding to an event rate of 31.3/100 exposure years). Four subjects in each group were reported with hypoglycaemia. Hypoglycaemic unconsciousness was reported in one subject in the detemir group and seven in the NPH (Table 33).

Table 33: Treatment Emergent AEs Possibly/Probably Related to Basal Insulin by System Organ Class and Preferred Term, During Pregnancy, Mother, Safety Pregnant

System Organ Class - Preferred Term	Detemir				NPH			
	N	(%)	E	R	N	(%)	E	R
All subjects	152				158			
Exposure (yr)	82.4				86.3			
Events	18	(11.8)	21	25.5	16	(10.1)	27	31.3
Metabolism and nutrition disorders	8	(5.3)	9	10.9	12	(7.6)	20	23.2
Hypoglycaemia	4	(2.6)	4	4.9	6	(3.8)	10	11.6
Hypoglycaemic unconsciousness	1	(0.7)	1	1.2	7	(4.4)	9	10.4
Diabetes mellitus inadequate control	2	(1.3)	2	2.4	1	(0.6)	1	1.2
Diabetic ketoacidosis	1	(0.7)	1	1.2				
Hyperglycaemia	1	(0.7)	1	1.2				
General disorders and administration site conditio	6	(3.9)	6	7.3				
Injection site rash	2	(1.3)	2	2.4				
Injection site extravasation	1	(0.7)	1	1.2				
Injection site haematoma	1	(0.7)	1	1.2				
Injection site pruritus	1	(0.7)	1	1.2				
Injection site urticaria	1	(0.7)	1	1.2				
Nervous system disorders					2	(1.3)	3	3.5
Headache					2	(1.3)	2	2.3
Migraine					1	(0.6)	1	1.2
Injury, poisoning and procedural complications					2	(1.3)	2	2.3
Incorrect dose administered					2	(1.3)	2	2.3
Pregnancy, puerperium and perinatal conditions	2	(1.3)	2	2.4				
Intra-uterine death	1	(0.7)	1	1.2				
Premature labour	1	(0.7)	1	1.2				
Eye disorders	1	(0.7)	1	1.2				
Retinopathy proliferative	1	(0.7)	1	1.2				
Hepatobiliary disorders	1	(0.7)	1	1.2				
Cytolytic hepatitis	1	(0.7)	1	1.2				
Immune system disorders	1	(0.7)	1	1.2				
Hypersensitivity	1	(0.7)	1	1.2				
Investigations					1	(0.6)	1	1.2
Amniocentesis abnormal					1	(0.6)	1	1.2
Musculoskeletal and connective tissue disorders	1	(0.7)	1	1.2				
Muscle spasms	1	(0.7)	1	1.2				
Skin and subcutaneous tissue disorders					1	(0.6)	1	1.2
Lipohypertrophy					1	(0.6)	1	1.2

In In the neonatal population, treatment related TEAEs were reported in one (0.7%) subject in the detemir group (foetal distress syndrome) and none in the NPH.

7.4.1. Deaths and other serious adverse events

Change 1:

In Study NN2211-3673 there were no deaths or SAEs.

In Study NN2211-1842, there were no deaths reported during the main period of the trial (to Week 26) but there were two deaths in the control groups (treated with liraglutide and metformin): bronchogenic cancer, gall bladder cancer. There were 21 SAEs reported in 17 (10.4%) subjects in the detemir group and 16 in eleven (6.9%) in the control. There was no clear pattern to the SAEs to Week 26 (Table 34).

Table 34: SAEs during Main Period by System Organ Class and Preferred Term - Safety Analysis Set

	Lira 1.8			Detemir + Lira 1.8			Non-randomised		
	N	(%)	E	N	(%)	E	N	(%)	E
Safety Analysis Set	159			163			499		
Adverse Events	6	(3.8)	8	9	(5.5)	13	27	(5.4)	35
Injury, poisoning and procedural complications				2	(1.2)	3	5	(1.0)	6
Ankle Fracture				1	(0.6)	1			
Head Injury				1	(0.6)	1			
Joint Injury				1	(0.6)	1			
Fall							2	(0.4)	2
Femur Fracture							1	(0.2)	1
Ligament Rupture							1	(0.2)	1
Traumatic Fracture							1	(0.2)	1
Traumatic Intracranial Haemorrhage							1	(0.2)	1
Gastrointestinal disorders	1	(0.6)	1	1	(0.6)	1	2	(0.4)	2
Abdominal Pain				1	(0.6)	1			
Abdominal Hernia Obstructive							1	(0.2)	1
Intestinal Infarction							1	(0.2)	1
Pancreatitis Chronic	1	(0.6)	1						
Immune system disorders				1	(0.6)	1			
Sarcoidosis				1	(0.6)	1			
Infections and infestations	3	(1.9)	3	1	(0.6)	1	2	(0.4)	2
Clostridium Difficile Colitis				1	(0.6)	1			
Abdominal Wall Abscess							1	(0.2)	1
Abscess Soft Tissue	1	(0.6)	1						
Helicobacter Gastritis	1	(0.6)	1						
Post Procedural Infection	1	(0.6)	1						
Viral Infection							1	(0.2)	1
Musculoskeletal and connective tissue disorders				1	(0.6)	1	5	(1.0)	6
Osteoarthritis				1	(0.6)	1			
Arthritis							1	(0.2)	1
Bursitis							1	(0.2)	1
Intervertebral Disc Degeneration							1	(0.2)	2
Intervertebral Disc Protrusion							1	(0.2)	1
Polymyalgia Rheumatica							1	(0.2)	1
Nervous system disorders	1	(0.6)	1	1	(0.6)	1	2	(0.4)	3
Convulsion				1	(0.6)	1			
Benign Intracranial Hypertension	1	(0.6)	1						
Cerebrovascular Accident							1	(0.2)	1
Syncope							1	(0.2)	1
Transient Ischaemic Attack							1	(0.2)	1
Psychiatric disorders				1	(0.6)	1			
Depression				1	(0.6)	1			
Renal and urinary disorders				1	(0.6)	1	2	(0.4)	2
Nephrolithiasis				1	(0.6)	1	1	(0.2)	1
Urinary Retention							1	(0.2)	1
Respiratory, thoracic and mediastinal disorders				1	(0.6)	1	1	(0.2)	1
Bronchopulmonary Disease				1	(0.6)	1			
Nasal Septum Deviation							1	(0.2)	1
Vascular disorders	1	(0.6)	1	1	(0.6)	2			
Peripheral Ischaemia				1	(0.6)	1			
Thrombosis				1	(0.6)	1			
Peripheral Arterial Occlusive Disease	1	(0.6)	1						
Cardiac disorders	1	(0.6)	1				3	(0.6)	5
Angina Pectoris	1	(0.6)	1						
Coronary Artery Disease							2	(0.4)	3
Supraventricular Tachycardia							1	(0.2)	1
Eye disorders							1	(0.2)	2
Macular Ischaemia							1	(0.2)	1
Macular Oedema							1	(0.2)	1
General disorders and administration site conditions							1	(0.2)	1
Chest Pain							1	(0.2)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(0.6)	1				4	(0.8)	4
Breast Cancer							1	(0.2)	1
Metastases To Central Nervous System	1	(0.6)	1						
Renal Cancer							1	(0.2)	1
Thyroid Cancer							1	(0.2)	1
Uterine Leiomyoma							1	(0.2)	1
Skin and subcutaneous tissue disorders							1	(0.2)	1
Eczema							1	(0.2)	1

Chronic pancreatitis was reported in one subject in the control group. In the extension study there were four subjects in the detemir group with neoplasia, but none in the control (Table 35).

Table 35: Serious Treatment Emergent Adverse Event (TEAE) during Extension Period by System Organ Class and Preferred Term – Safety Analysis Set

	Lira 1.8			Detemir + Lira 1.8			Non-randomised Lira 1.8			Intensified		
	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E
Safety Analysis Set	159			163			499			24		
Intensified	17						7			24		
All Adverse Events	4	(2.5)	5	8	(4.9)	8	25	(5.0)	29	1	(4.2)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				4	(2.5)	4	3	(0.6)	4			
B-Cell Lymphoma				1	(0.6)	1						
Breast Cancer				1	(0.6)	1						
Fibroadenoma Of Breast				1	(0.6)	1						
Lung Squamous Cell Carcinoma Stage				1	(0.6)	1						
Unspecified												
Gallbladder Cancer							1	(0.2)	1			
Gastric Cancer							1	(0.2)	1			
Metastases To Liver							1	(0.2)	1			
Prostate Cancer							1	(0.2)	1			
Cardiac disorders	1	(0.6)	1	2	(1.2)	2	2	(0.4)	3			
Angina Pectoris				1	(0.6)	1						
Coronary Artery Disease				1	(0.6)	1	1	(0.2)	1			
Cardiac Failure	1	(0.6)	1									
Supraventricular Tachycardia							1	(0.2)	1			
Tachycardia							1	(0.2)	1			
Gastrointestinal disorders	1	(0.6)	1	1	(0.6)	1	2	(0.4)	2			
Food Poisoning				1	(0.6)	1						
Abdominal Pain							1	(0.2)	1			
Abdominal Pain Upper							1	(0.2)	1			
Pancreatitis Acute	1	(0.6)	1									
Injury, poisoning and procedural complications				1	(0.6)	1	1	(0.2)	1	1	(4.2)	1
Tendon Rupture				1	(0.6)	1						
Rib Fracture							1	(0.2)	1			
Thermal Burn										1	(4.2)	1
Blood and lymphatic system disorders							1	(0.2)	1			
Febrile Neutropenia							1	(0.2)	1			
Ear and labyrinth disorders							1	(0.2)	1			
Vertigo Positional							1	(0.2)	1			
Endocrine disorders							1	(0.2)	1			
Goitre							1	(0.2)	1			
General disorders and administration site conditions							1	(0.2)	1			
Chest Pain							1	(0.2)	1			
Infections and infestations	1	(0.6)	1				1	(0.2)	1			
Cellulitis	1	(0.6)	1									
Diverticulitis							1	(0.2)	1			
Investigations							2	(0.4)	2			
Electrocardiogram Abnormal							1	(0.2)	1			
Electrocardiogram Change							1	(0.2)	1			
Musculoskeletal and connective tissue disorders							1	(0.2)	1			
Periarthritis							1	(0.2)	1			
Nervous system disorders	1	(0.6)	1				4	(0.8)	4			
Carotid Artery Stenosis							1	(0.2)	1			
Cerebrovascular Accident							1	(0.2)	1			
Partial Seizures	1	(0.6)	1									
Syncope							1	(0.2)	1			
Transient Ischaemic Attack							1	(0.2)	1			
Renal and urinary disorders	1	(0.6)	1				2	(0.4)	2			
Renal Colic							1	(0.2)	1			
Renal Failure							1	(0.2)	1			
Renal Failure Acute	1	(0.6)	1									
Reproductive system and breast disorders							3	(0.6)	3			
Erectile Dysfunction							1	(0.2)	1			
Fibrocystic Breast Disease							1	(0.2)	1			
Vaginal Haemorrhage							1	(0.2)	1			
Vascular disorders							1	(0.2)	2			
Poor Peripheral Circulation							1	(0.2)	2			

Change 2:

In Study NN304-1690, there were no deaths reported during the study. There were 17 SAEs reported in 116 (79.5%) subjects in the combined population including four in three (8.1%) subjects in the 2 to 5 year age group, nine in six (10.2%) in the 6 to 12 year and four in three (6.0%) in the 13 to 16 year. The overall rate of SAEs was 5.9/100 exposure years, in the 2 to 5 year group 5.5/100 exposure years, in the 6 to 12 year group 7.7/100 patient years exposure and in the 13 to 16 year group 4.1/100 patient years exposure. There were three subjects with ketoacidosis and two with hypoglycaemia (Table 36).

Table 36: Treatment Emergent SAEs by System Organ Class, SAS, Whole Treatment Period

	N	(%)	E	R
All subjects	146			
Total exposure (yr)	289.2			
All Events	12	(8.2)	17	5.9
Infections and infestations	8	(5.5)	8	2.8
Gastroenteritis	2	(1.4)	2	0.7
Abscess limb	1	(0.7)	1	0.3
Gastroenteritis shigella	1	(0.7)	1	0.3
Influenza	1	(0.7)	1	0.3
Otitis media acute	1	(0.7)	1	0.3
Soft tissue infection	1	(0.7)	1	0.3
Viral infection	1	(0.7)	1	0.3
Metabolism and nutrition disorders	7	(4.8)	8	2.8
Diabetic ketoacidosis	3	(2.1)	3	1.0
Hypoglycaemia	2	(1.4)	3	1.0
Diabetes mellitus inadequate control	1	(0.7)	1	0.3
Hypoglycaemic unconsciousness	1	(0.7)	1	0.3
Injury, poisoning and procedural complications	1	(0.7)	1	0.3
Burns second degree	1	(0.7)	1	0.3

N: Number of subjects; %: Percentage of subjects; E: Number of events;
R: Rate - Number of events per 100 exposure years

Change 3:

In Study NN304-1687 there were no maternal deaths. There were three perinatal deaths: two in the detemir group (stillbirth, intrauterine death) and one in the NPH (Dandy-Walker malformation/pulmonary hypoplasia). In addition there were two early pregnancy losses: one in the detemir group (intrauterine death) and one in the NPH (spontaneous abortion). There were 94 SAEs reported in 61 (40.1%) maternal subjects in the detemir group (corresponding to an event rate of 114.1/100 exposure years) and 76 in 49 (31.0%) in the NPH (corresponding to an event rate of 88.1/100 exposure years). There was a higher rate of spontaneous abortion in the detemir group: eight (5.3%) subjects compared with four (2.5%) in the NPH; and also of pre-eclampsia: eight (5.3%) subjects compared with one (0.6%) in the NPH (Table 37).

Table 37: Treatment Emergent Serious AEs by System Organ Class and Preferred Term, During Pregnancy, Mother, Safety Pregnant

System Organ Class - Preferred Term	Detemir				NPH			
	n	(%)	E	R	n	(%)	E	R
All subjects	152				159			
Exposure (yr)	82.4				86.3			
Events	61	(40.1)	94	114.1	49	(31.0)	76	88.1
Pregnancy, puerperium and perinatal conditions	39	(25.7)	39	47.3	26	(16.5)	31	35.9
Abortion spontaneous	8	(5.3)	8	9.7	4	(2.5)	4	4.6
Pre-eclampsia	8	(5.3)	8	9.7	1	(0.6)	1	1.2
Threatened labour	3	(2.0)	3	3.6	4	(2.5)	4	4.6
Failed induction of labour	3	(2.0)	3	3.6	3	(1.9)	3	3.5
Abortion missed	1	(0.7)	1	1.2	2	(1.3)	2	2.3
Abortion threatened	3	(2.0)	3	3.6				
Hyperemesis gravidarum	1	(0.7)	1	1.2	2	(1.3)	2	2.3
Ectopic pregnancy	1	(0.7)	1	1.2	1	(0.6)	1	1.2
Gestational hypertension	1	(0.7)	1	1.2	1	(0.6)	1	1.2
Intra-uterine death	1	(0.7)	1	1.2	1	(0.6)	1	1.2
Placenta praevia					1	(1.3)	2	2.3
Placenta praevia haemorrhage					1	(0.6)	1	1.2
Premature labour	2	(1.3)	2	2.4				
Premature separation of placenta					2	(1.3)	2	2.3
Abortion incomplete	1	(0.7)	1	1.2				
Antepartum haemorrhage					1	(0.6)	1	1.2
Blighted ovum					1	(0.6)	1	1.2
Breech presentation	1	(0.7)	1	1.2				
Cephalo-pelvic disproportion	1	(0.7)	1	1.2				
Cervical incompetence					1	(0.6)	1	1.2
Imminent abortion	1	(0.7)	1	1.2				
Labour complication	1	(0.7)	1	1.2				
Placental insufficiency					1	(0.6)	1	1.2
Polyhydramnios					1	(0.6)	1	1.2
Premature rupture of membranes					1	(0.6)	1	1.2
Stillbirth	1	(0.7)	1	1.2				
Uterine contractions abnormal	1	(0.7)	1	1.2				
Metabolism and nutrition disorders	17	(11.2)	19	23.1	13	(8.2)	22	25.5
Hypoglycaemia	5	(3.3)	5	6.1	5	(3.1)	12	13.9
Hypoglycaemic unconsciousness	2	(1.3)	4	4.9	7	(4.4)	9	10.4
Diabetes mellitus inadequate control	5	(3.3)	5	6.1	1	(0.6)	1	1.2
Diabetic ketoacidosis	3	(2.0)	3	3.6				
Hyperglycaemia	2	(1.3)	2	2.4				
Gastrointestinal disorders	5	(3.3)	10	12.1	4	(2.5)	8	9.3
Vomiting	5	(3.3)	5	6.1	2	(1.3)	2	2.3
Nausea	2	(1.3)	3	3.6	2	(1.3)	2	2.3
Abdominal pain upper					1	(0.6)	2	2.3
Diarrhoea	1	(0.7)	1	1.2	1	(0.6)	1	1.2
Abdominal pain					1	(0.6)	1	1.2
Impaired gastric emptying	1	(0.7)	1	1.2				
Infections and infestations	7	(4.6)	7	8.5	2	(1.3)	2	2.3
Gastroenteritis	4	(2.6)	4	4.9	1	(0.6)	1	1.2
Beta haemolytic streptococcal infection					1	(0.6)	1	1.2
Pyelonephritis	1	(0.7)	1	1.2				
Urinary tract infection	1	(0.7)	1	1.2				
Urogenital infection bacterial	1	(0.7)	1	1.2				
Reproductive system and breast disorders	3	(2.0)	3	3.6	5	(3.2)	5	5.8
Uterine haemorrhage	1	(0.7)	1	1.2	2	(1.3)	2	2.3
Metrorrhagia	1	(0.7)	1	1.2	1	(0.6)	1	1.2
Genital haemorrhage	1	(0.7)	1	1.2				
Pelvic pain					1	(0.6)	1	1.2
Vaginal haematoma					1	(0.6)	1	1.2
Nervous system disorders	4	(2.6)	4	4.9	2	(1.3)	2	2.3
Headache	3	(2.0)	3	3.6	2	(1.3)	2	2.3
Migraine	1	(0.7)	1	1.2				
Vascular disorders	2	(1.3)	3	3.6	1	(0.6)	1	1.2
Hypertension	2	(1.3)	3	3.6	1	(0.6)	1	1.2
Injury, poisoning and procedural complications					3	(1.9)	3	3.5
Incorrect dose administered					2	(1.3)	2	2.3
Wrong drug administered					1	(0.6)	1	1.2
Eye disorders	2	(1.3)	2	2.4				
Retinopathy	1	(0.7)	1	1.2				
Visual impairment	1	(0.7)	1	1.2				
General disorders and administration site conditio	2	(1.3)	2	2.4				
Device failure	1	(0.7)	1	1.2				
Malaise	1	(0.7)	1	1.2				
Hepatobiliary disorders	2	(1.3)	2	2.4				
Cholestasis of pregnancy	1	(0.7)	1	1.2				
Cytolytic hepatitis	1	(0.7)	1	1.2				
Social circumstances	1	(0.7)	1	1.2	1	(0.6)	1	1.2
Inadequate diet	1	(0.7)	1	1.2				
Social stay hospitalisation					1	(0.6)	1	1.2
Investigations	1	(0.7)	1	1.2				
Amniotic fluid volume decreased	1	(0.7)	1	1.2				
Renal and urinary disorders	1	(0.7)	1	1.2				
Albuminuria	1	(0.7)	1	1.2				
Skin and subcutaneous tissue disorders					1	(0.6)	1	1.2
Polymorphic eruption of pregnancy					1	(0.6)	1	1.2

In the neonatal population, there were 51 SAEs reported in 36 (23.7%) subjects in the detemir group and 53 in 32 (20.3%) in the NPH. The pattern of SAEs in neonates was similar for the two treatment groups (Table 38).

Table 38: Treatment Emergent Serious AEs by System Organ Class and Preferred Term, Child, Safety Pregnant

System Organ Class - Preferred Term	Detemir n	Detemir (%)	Detemir E	Detemir E	UTH n	UTH (%)	UTH E	UTH E
All subjects	152				150			
Events	34	(22.7)	51	NA	32	(20.3)	53	NA
Pregnancy, puerperium and perinatal conditions	15	(9.9)	17	NA	16	(10.1)	17	NA
Foetal distress syndrome	7	(4.6)	7	NA	4	(2.5)	4	NA
Premature baby	5	(3.3)	5	NA	4	(2.5)	4	NA
Jaundice neonatal	4	(2.6)	4	NA	3	(1.9)	3	NA
Breech presentation	1	(0.7)	1	NA				
Foetal growth restriction					1	(0.6)	1	NA
Foetal hypokinesia					1	(0.6)	1	NA
Foetal macrosomia					1	(0.6)	1	NA
Shoulder dystocia					1	(0.6)	1	NA
Congenital, familial and genetic disorders	7	(4.6)	8	NA	10	(6.3)	12	NA
Atrial septal defect	1	(0.7)	1	NA	2	(1.3)	2	NA
Congenital pneumonia	1	(0.7)	1	NA	2	(1.3)	2	NA
Heart disease congenital	1	(0.7)	1	NA	1	(0.6)	1	NA
Cleft lip	1	(0.7)	1	NA				
Congenital laryngeal stridor					1	(0.6)	1	NA
Congenital syphilis	1	(0.7)	1	NA				
Dandy-Walker syndrome					1	(0.6)	1	NA
Glucose-6-phosphate dehydrogenase deficiency					1	(0.6)	1	NA
Haemangioma congenital	1	(0.7)	1	NA				
Hip dysplasia	1	(0.7)	1	NA				
Meningomyelocele	1	(0.7)	1	NA				
Patent ductus arteriosus					1	(0.6)	1	NA
Polydactyly					1	(0.6)	1	NA
Pulmonary hypoplasia					1	(0.6)	1	NA
Ventricular septal defect					1	(0.6)	1	NA
Respiratory, thoracic and mediastinal disorders	9	(5.9)	9	NA	9	(5.7)	7	NA
Neonatal respiratory distress syndrome	3	(2.0)	3	NA				
Apnoea					1	(0.6)	2	NA
Transient tachypnoea of the newborn	2	(1.3)	2	NA				
Acute respiratory failure	1	(0.7)	1	NA				
Immature respiratory system	1	(0.7)	1	NA				
Neonatal asphyxia					1	(0.6)	1	NA
Neonatal aspiration					1	(0.6)	1	NA
Pneumonia aspiration					1	(0.6)	1	NA
Respiratory distress	1	(0.7)	1	NA				
Respiratory failure					1	(0.6)	1	NA
Tachypnoea					1	(0.6)	1	NA
Infections and infestations	3	(1.9)	3	NA	6	(3.8)	6	NA
Sepsis neonatal					3	(1.9)	3	NA
Neonatal infection	1	(0.7)	1	NA	1	(0.6)	1	NA
Bronchiolitis					1	(0.6)	1	NA
Bronchitis					1	(0.6)	1	NA
Pneumonia	1	(0.7)	1	NA				
Cardiac disorders	3	(2.0)	3	NA	6	(3.8)	6	NA
Foetal heart rate deceleration					3	(1.9)	3	NA
Bradycardia foetal	2	(1.3)	2	NA				
Cardiac hypertrophy					1	(0.6)	1	NA
Foetal arrhythmia	1	(0.7)	1	NA				
Gastrointestinal disorders	3	(2.0)	3	NA				
Haematemesis	1	(0.7)	1	NA				
Regurgitation	1	(0.7)	1	NA				
Umbilical hernia	1	(0.7)	1	NA				
General disorders and administration site conditio					3	(1.9)	3	NA
Fever neonatal					1	(0.6)	1	NA
Hypothermia					1	(0.6)	1	NA
No adverse event					1	(0.6)	1	NA
Investigations	1	(0.7)	1	NA	2	(1.3)	2	NA
Blood bilirubin increased	1	(0.7)	1	NA				
Cardiac murmur					1	(0.6)	1	NA
Foetal heart rate abnormal					1	(0.6)	1	NA
Hepatobiliary disorders	2	(1.3)	2	NA				
Hyperbilirubinaemia	1	(0.7)	1	NA				
Hyperbilirubinaemia neonatal	1	(0.7)	1	NA				
Metabolism and nutrition disorders	1	(0.7)	1	NA	1	(0.6)	1	NA
Hypoglycaemia neonatal	1	(0.7)	1	NA	1	(0.6)	1	NA
Renal and urinary disorders	2	(1.3)	2	NA				
Hydronephrosis	1	(0.7)	1	NA				
Pelvi-ureteric obstruction	1	(0.7)	1	NA				
Blood and lymphatic system disorders					1	(0.6)	1	NA
Polycythaemia					1	(0.6)	1	NA
Immune system disorders	1	(0.7)	1	NA				
ABO incompatibility	1	(0.7)	1	NA				
Injury, poisoning and procedural complications	1	(0.7)	1	NA				
Humerus fracture	1	(0.7)	1	NA				
Reproductive system and breast disorders	1	(0.7)	1	NA				
Testicular infarction	1	(0.7)	1	NA				
Skin and subcutaneous tissue disorders	1	(0.7)	1	NA				
Erythema toxicum neonatorum	1	(0.7)	1	NA				

The rates and patterns of congenital malformations for both populations were consistent with the known patterns of malformations in infants of diabetic mothers (Table 39).

Table 39: Congenital Malformations

Subject ID	MedDRA Preferred Term	Treatment During Organogenesis [a)]	Major / Minor
IDet Group, Pregnant AT Randomisation, N = 79			
232002	Hip dysplasia	IDet	Major
235004	Cleft lip	NPH	Major
333001	Meningomyelocele	NPH	Major
276003	Atrial septal defect Haemangioma congenital	NPH and Humalog	Minor Minor
601001	Haemangioma cong. – Diagnosed after the end of the trial.	NPH	Minor
IDet Group, Pregnant AFTER Randomisation, N = 73			
233001	Congenital hydronephrosis Pelvi-ureteric obstruction Pyelocaliectasis	IDet	Major Major Major
508015	Hydronephrosis	IDet	Major
334024	Heart disease congenital	IDet	Minor
NPH Group, Pregnant AT Randomisation, N = 83			
602008	Dandy-Walker syndrome Pulmonary hypoplasia	NPH	Major Major
101017	Polydactyly	Lantus	Minor
226012	Cardiac hypertrophy Patent ductus arteriosus	NPH	Minor Minor
339002	Atrial septal defect	NPH and Actrapid	Minor
NPH Group, Pregnant AFTER Randomisation, N = 75			
701008	Pelvic kidney – Diagnosed after mother was withdrawn due to HbA_{1c} > 8.0% at confirmation of pregnancy. The event is not in the trial database but is included in Narratives.	NPH	Major
334013	Heart disease congenital	NPH	Minor
605004	Congenital laryngeal stridor	NPH	Minor
680002	Atrial septal defect	NPH	Minor
680003	Ventricular septal defect	NPH	Minor

a) Data on treatment during organogenesis is from NovoNordisk Global Safety; please see Narratives of SAEs.

Abbreviations: IDet = insulin detemir; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; NPH = Neutral Protamine Hagedorn; SAE = serious adverse event.

7.4.1. Discontinuation due to adverse events

Change 1:

In Study NN2211-3673 there were no DAEs.

In Study NN2211-1842 and its extension, there were eight DAEs in seven (4.3%) subjects in the detemir group and 13 in nine (5.7%) in the control discontinued due to AEs (Table 40, Appendix 1). The events in the detemir group were: lipase increased, pancreatic enzymes increased, convulsion, bronchopulmonary disease, abdominal pain/diarrhoea, breast cancer and renal failure.

Change 2:

In Study NN304-1690 there were no DAEs.

Change 3:

In Study NN304-1687, DAE occurred in 13 (8.6%) subjects in the detemir group and six (3.8%) in the NPH. The AEs leading to discontinuation primarily related to pregnancy loss (Table 41). One AE in a neonate in the NPH group resulted in withdrawal: neonatal death.

Table 41: Possibly or Probably Related to Treatment Emergent Adverse Events (TEAE) During Extension Period by System Organ Class and Preferred Term - Safety Analysis Set

	Lira 1.8			Detemir + Lira 1.8			Non-randomised Lira 1.8			Intensified		
	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E
Safety Analysis Set	159			163			499			24		
Intensified	17						7			24		
All Adverse Events	12	(7.5)	17	12	(7.4)	14	60	(12.0)	102	7	(29.2)	8
Gastrointestinal disorders	7	(4.4)	10	4	(2.5)	5	28	(5.6)	51	2	(8.3)	2
Nausea	1	(0.6)	1	2	(1.2)	2	8	(1.6)	10	1	(4.2)	1
Abdominal Discomfort				1	(0.6)	1	1	(0.2)	1			
Diarrhoea	1	(0.6)	1	1	(0.6)	1	10	(2.0)	10	1	(4.2)	1
Vomiting	2	(1.3)	3	1	(0.6)	1	9	(1.8)	15			
Abdominal Distension	1	(0.6)	1									
Abdominal Pain	1	(0.6)	1				1	(0.2)	1			
Abdominal Pain Upper							5	(1.0)	5			
Aphthous Stomatitis							1	(0.2)	1			
Constipation							1	(0.2)	1			
Dyspepsia	2	(1.3)	2				1	(0.2)	1			
Faecaloma							1	(0.2)	1			
Flatulence							2	(0.4)	2			
Gastritis							2	(0.4)	2			
Pancreatitis							1	(0.2)	1			
Pancreatitis Acute	1	(0.6)	1									
Investigations	2	(1.3)	2	3	(1.8)	3	22	(4.4)	29	4	(16.7)	4
Blood Creatinine Increased				1	(0.6)	1						
Blood Proinsulin Increased				1	(0.6)	1						
Lipase Increased	1	(0.6)	1	1	(0.6)	1	10	(3.6)	10	4	(16.7)	4
Alanine Aminotransferase Increased							1	(0.2)	1			
Blood Amylase Increased							4	(0.8)	4			
Blood Calcitonin Increased	1	(0.6)	1				1	(0.2)	1			
Blood Calcium Increased							1	(0.2)	1			
Blood Triglycerides Increased							2	(0.4)	2			
Pancreatic Enzymes Increased							1	(0.2)	1			
Very Low Density Lipoprotein Increased							1	(0.2)	1			
General disorders and administration site conditions				2	(1.2)	2	6	(1.2)	7	1	(4.2)	1
Injection Site Haematoma				2	(1.2)	2	1	(0.2)	1			
Asthenia							1	(0.2)	1			
Injection Site Haemorrhage							1	(0.2)	1			
Injection Site Nodule							1	(0.2)	1			
Injection Site Pruritus							1	(0.2)	1	1	(4.2)	1
Oedema Peripheral							2	(0.4)	2			
Injury, poisoning and procedural complications				1	(0.6)	1	1	(0.2)	1			
Accidental Overdose				1	(0.6)	1						
Road Traffic Accident							1	(0.2)	1			
Renal and urinary disorders	1	(0.6)	1	1	(0.6)	1	1	(0.2)	1			
Renal Failure				1	(0.6)	1	1	(0.2)	1			
Renal Failure Acute	1	(0.6)	1									
Respiratory, thoracic and mediastinal disorders				1	(0.6)	1						
Epistaxis				1	(0.6)	1						
Skin and subcutaneous tissue disorders				1	(0.6)	1	3	(0.6)	3			
Lipohypertrophy				1	(0.6)	1						
Hyperhidrosis							1	(0.2)	1			
Pruritus							1	(0.2)	1			
Rash							1	(0.2)	1			
Cardiac disorders							1	(0.2)	1			
Atrioventricular Block First Degree							1	(0.2)	1			
Eye disorders	1	(0.6)	1									
Eye Oedema	1	(0.6)	1									
Infections and infestations	1	(0.6)	1				2	(0.4)	2			
Cystitis	1	(0.6)	1									
Diverticulitis							1	(0.2)	1			
Gastroenteritis							1	(0.2)	1			
Metabolism and nutrition disorders							2	(0.4)	2			
Decreased Appetite							1	(0.2)	1			
Hyponatraemia							1	(0.2)	1			
Musculoskeletal and connective tissue disorders	1	(0.6)	1							1	(4.2)	1
Intervertebral Disc Protrusion	1	(0.6)	1									
Pain In Extremity										1	(4.2)	1
Nervous system disorders							2	(0.4)	3			
Dizziness Postural							1	(0.2)	1			
Somnolence							1	(0.2)	1			
Tremor							1	(0.2)	1			
Psychiatric disorders	1	(0.6)	1				1	(0.2)	1			
Depression	1	(0.6)	1									
Insomnia							1	(0.2)	1			
Vascular disorders							1	(0.2)	1			
Hypotension							1	(0.2)	1			

7.5. Laboratory tests

7.5.1. Liver function

There were no indications of drug induced liver injury.

7.5.2. Kidney function

There were no indications of drug induced renal injury.

7.5.3. Other clinical chemistry

Change 1:

In Study NN2211-3673 there were no clinically significant treatment emergent abnormalities of laboratory tests. There were no hypoglycaemic episodes on study days.

In Study NN2211-1842 and its extension, to Week 52 the most commonly reported clinically significant abnormality in laboratory tests was elevated lipase: 26 (16.0%) subjects in the detemir group compared with 16 (10.1%) in the control (Table 42, Appendix 1). Two subjects in the detemir group and one in the control were reported with elevated ALT.

Change 2:

In Study NN304-1690, there were no clinically significant abnormalities in biochemistry or haematology reported during the study.

Change 3:

The abnormalities in laboratory values were consistent with those seen in normal pregnancy. These were primarily anaemia (28 events in the detemir group and 27 in the NPH). No subjects were withdrawn due to laboratory AEs.

7.5.4. Haematology

Change 3:

Anaemia was reported at a similar rate in the detemir group and the NPH.

7.5.5. Immunology

7.5.5.1.1. Pivotal studies

Change 1:

In Study NN2211-3673 no subjects were positive for antibodies to insulin detemir.

In Study NN2211-1842 and its extension two subjects in the detemir group developed antibodies to liraglutide. The level of antibodies to detemir was mean 1.59 % B/T at Week 0; 2.20 % B/T at Week 26; and 4.30 % B/T at Week 53.

Change 2:

Levels of cross-reacting, detemir-specific and aspart-specific antibodies increased during the first year of treatment, and then decreased during the second year - Table 43, Table 44 and Table 45. At end of study the levels were slightly higher than at baseline.

Table 43: Estimated Cross-reacting Antibodies (% B/T), Time Intervals 3 h, 2.5 h, Sensitivity, Corrected Data, SAS, Whole Treatment Period

		3 Hours		2.5 Hours		Sensitivity	
Visit	Week	Est. AB	Std. Err	Est. AB	Std. Err	Est. AB	Std. Err
Visit 2	0	31.11	1.25	31.22	1.23	30.71	1.14
Visit 8	26	40.16	1.03	40.29	1.02	40.45	0.97
Visit 9	38	42.58	1.02	42.70	1.01	43.04	0.96
Visit 1Ext	52	43.99	1.02	44.09	1.01	44.52	0.96
Visit 2Ext	65	43.94	1.01	44.02	1.00	44.41	0.96
Visit 3Ext	78	42.59	1.01	42.64	0.99	42.89	0.95
Visit 4Ext	91	39.93	1.03	39.93	1.02	39.94	0.98
Visit 5Ext	104	35.96	1.14	35.92	1.13	35.57	1.10

Table 44 Estimated Insulin Detemir Specific Antibodies (% B/T), Time Intervals 3 h, 2.5 H, Sensitivity, Corrected Data, SAS, Whole Treatment Period

		3 Hours		2.5 Hours		Sensitivity	
Visit	Week	Est. AB	Std. Err	Est. AB	Std. Err	Est. AB	Std. Err
Visit 2	0	2.81	1.28	2.84	1.28	2.56	1.27
Visit 8	26	3.97	1.27	3.99	1.26	3.88	1.26
Visit 9	38	4.26	1.27	4.28	1.26	4.21	1.26
Visit 1Ext	52	4.40	1.27	4.41	1.26	4.37	1.26
Visit 2Ext	65	4.34	1.27	4.34	1.26	4.32	1.26
Visit 3Ext	78	4.09	1.26	4.09	1.26	4.06	1.26
Visit 4Ext	91	3.66	1.27	3.65	1.26	3.59	1.26
Visit 5Ext	104	3.05	1.27	3.03	1.27	2.92	1.27

Table 45: Estimated Insulin Aspart-specific Antibodies (% B/T), Time Intervals 3 h, 2.5 H, Sensitivity, Corrected Data, SAS, Whole Treatment Period

		3 Hours		2.5 Hours		Sensitivity	
Visit	Week	Est. AB	Std. Err	Est. AB	Std. Err	Est. AB	Std. Err
Visit 2	0	1.32	0.67	1.35	0.66	1.57	0.64
Visit 8	26	2.34	0.64	2.34	0.63	2.60	0.62
Visit 9	38	2.62	0.64	2.61	0.63	2.87	0.62
Visit 1Ext	52	2.79	0.64	2.78	0.63	3.04	0.62
Visit 2Ext	65	2.80	0.64	2.80	0.63	3.03	0.62
Visit 3Ext	78	2.67	0.64	2.68	0.63	2.88	0.62
Visit 4Ext	91	2.40	0.64	2.42	0.63	2.59	0.62
Visit 5Ext	104	1.99	0.65	2.03	0.64	2.14	0.64

Change 3:

The mean (SD) level of detemir specific antibodies was 1.29 (0.98) % B/T at baseline and 1.80 (1.72) % B/T at GW36.

7.5.6. Electrocardiograph

Change 1:

In Study NN2211-1842 and its extension in the detemir group, there was one shift in ECG finding from abnormal not clinically significant to abnormal clinically significant at Week 26. There were no changes to Week 52.

7.5.7. Vital signs

Change 1:

In Study NN2211-1842 and its extension, to Week 52 there were eleven (6.75%) subjects with a change in physical examination in the detemir group and five (3.52%) in the control.

Change 2:

There were no clinically significant changes in vital signs. Weight SD did not change significantly during the study (Figure 6). Mean BMI did not change significantly during the study (Figure 7).

Figure 6: Mean Weight SD-score over Time by Age Group, SAS, Whole Treatment Period

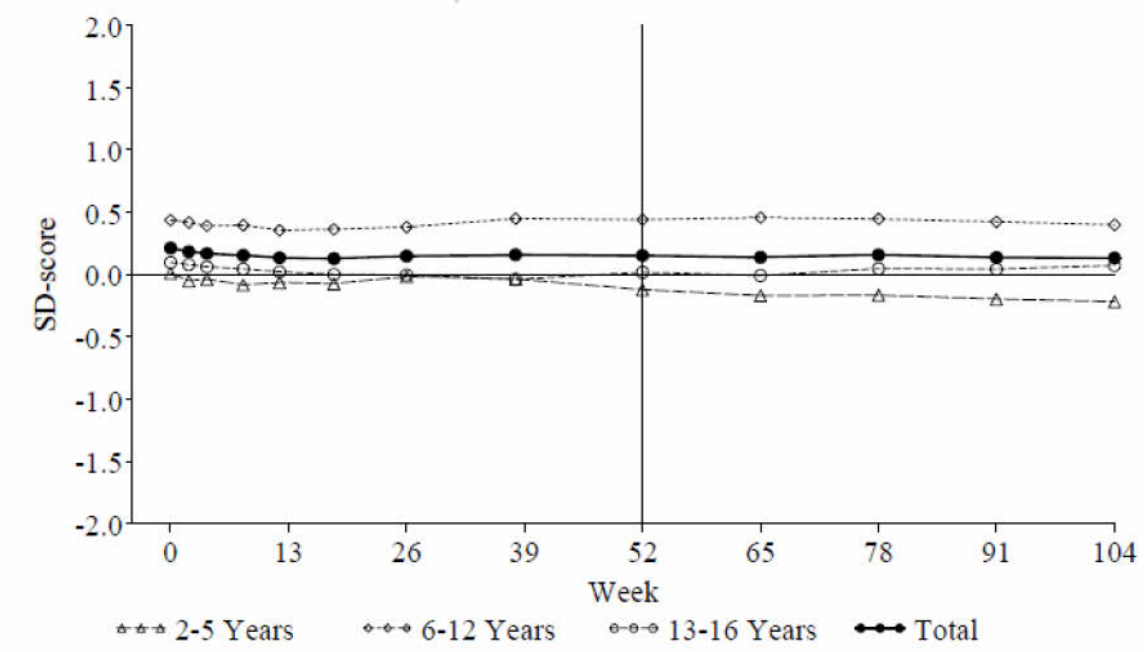
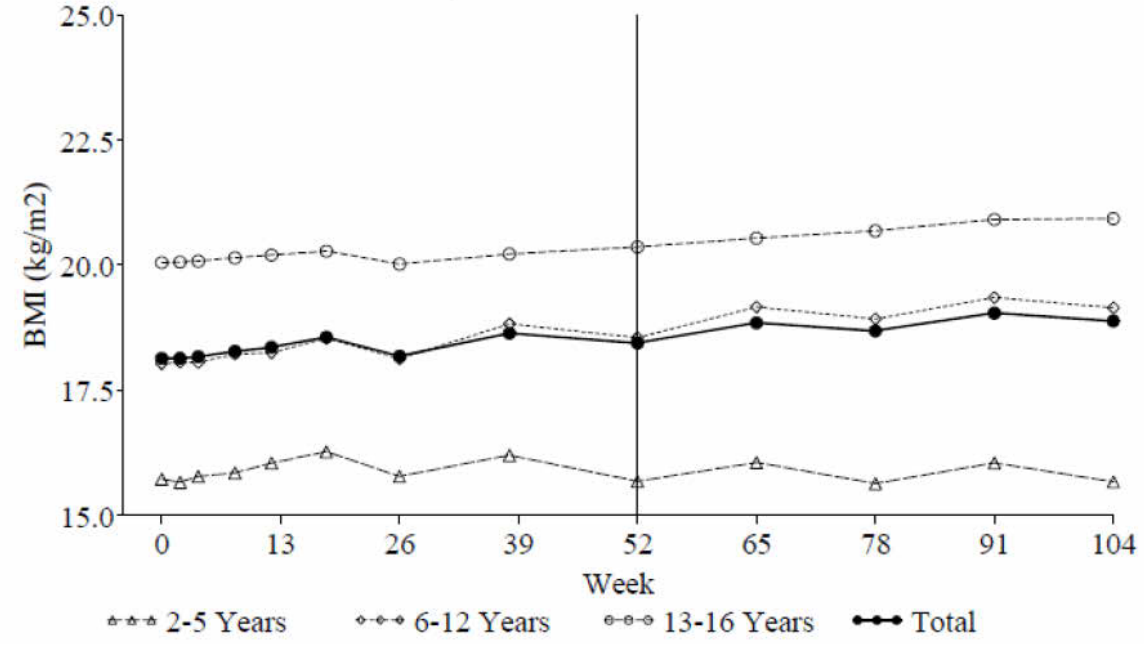


Figure 7: Mean BMI (kg/m^2) over Time by Age Group, SAS, Whole Treatment Period



7.5.8. Pancreatitis

Change 1:

In Study NN2211-1842, there were two subjects with pancreatitis, both during the run-in period (liraglutide and metformin treated). Pancreas related AEs were reported in 18 (11%)

subjects in the detemir group and 14 (8.8%) in the control (Table 46, Appendix 1). There was one report of chronic pancreatitis and one of acute pancreatitis in the control group.

7.5.9. Medullary C-cell carcinoma

Change 1:

In Study NN2211-1842, one subject was diagnosed with medullary C-call thyroid cancer but this appears to have been pre-existing. One subject discontinued due to suspected medullary C-cell carcinoma but this was not proven.

7.5.10. Hypoglycaemia

Change 1:

In Study NN2211-1842 and its extension one major hypoglycaemic event was reported in a subject during the run-in period (liraglutide and metformin). To Week 52, minor hypoglycaemic events were reported in 21 (12.9%) subjects in the detemir group and four (2.5%) in the control. The rate ratio (95% CI) for hypoglycaemic episodes (detemir compared with control) was 4.13 (1.75 to 9.73) p = 0.0012.

Change 2:

In Study NN304-1690, there were 16074 hypoglycaemic episodes reported in 145 (99.3%) subjects in the combined population including 4028 in 37 (100%) subjects in the 2 to 5 year age group, 7438 in 59 (100%) in the 6 to 12 year and 4608 in 49 (98.0%) in the 13 to 16 year. Severe hypoglycaemic episodes were reported in two (5.4%) subjects in the 2 to 5 year age group, two (3.4%) in the 6 to 12 year and two (4.0%) in the 13 to 16 year. Severe nocturnal hypoglycaemic episodes were reported in one subject in each age group.

Change 3:

The rates of hypoglycaemic events were similar for the two treatment groups (Table 47).

Table 47: All Hypoglycaemic Episodes during Pregnancy, Safety Pregnant

	Detemir				NPH				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	152				158				310			
Exposure (yrs)	82.4				86.3				168.7			
All episodes	144	(95)	9496	115.3	146	(92)	9453	109.6	290	(94)	18949	112.4
Major	25	(16)	90	1.1	33	(21)	105	1.2	58	(19)	195	1.2
Minor	144	(95)	8601	104.4	146	(92)	8711	101.0	290	(94)	17312	102.6
Symptoms Only	78	(51)	805	9.8	72	(46)	637	7.4	150	(48)	1442	8.5
Diurnal	144	(95)	8045	97.6	146	(92)	7810	90.5	290	(94)	15855	94.0
Major	17	(11)	66	0.8	30	(19)	84	1.0	47	(15)	150	0.9
Minor	144	(95)	7317	88.8	146	(92)	7211	83.6	290	(94)	14528	86.1
Symptoms Only	75	(49)	662	8.0	64	(41)	515	6.0	139	(45)	1177	7.0
Nocturnal	119	(78)	1451	17.6	130	(82)	1643	19.0	249	(80)	3094	18.3
Major	13	(9)	24	0.3	10	(6)	21	0.2	23	(7)	45	0.3
Minor	116	(76)	1284	15.6	126	(80)	1500	17.4	242	(78)	2784	16.5
Symptoms Only	34	(22)	143	1.7	39	(25)	122	1.4	73	(24)	265	1.6

N: Number of subjects; %: Percentage of subjects
E: Number of episodes; R: Episodes/year

There were 9496 hypoglycaemic events reported in 144 (95.0%) subjects in the detemir group (corresponding to an event rate of 115.3/100 exposure years) and 9453 in 146 (92.0%) in the NPH (corresponding to an event rate of 109.6/100 exposure years). There were 90 major hypoglycaemic events reported in 25 (16.0%) subjects in the detemir group (corresponding to an event rate of 1.1/100 exposure years) and 105 in 33 (21.0%) in the NPH (corresponding to an event rate of 1.2/100 exposure years). There were 24 major nocturnal hypoglycaemic events reported in 13 (9.0%) subjects in the detemir group (corresponding to an event rate of 0.3/100

exposure years) and 21 in ten (6.0%) in the NPH (corresponding to an event rate of 0.2/100 exposure years).

7.5.11. Pregnancy

Change 3:

Pregnancy outcome was slightly better in the NPH group. There were 128 (90.14%) live children at follow up in the detemir group and 135 (93.10%) in the NPH (Table 48).

Table 48: Pregnancy Outcome at Follow-up, Safety Pregnant

	Detemir N (%)	NPH N (%)
Number of subjects	152	158
Number of pregnancies	152	160
Pregnancy Outcome at Follow Up		
N	142 (100.0%)	145 (100.0%)
Live Children	128 (90.14%)	135 (93.10%)
Early Foetal Death	11 (7.75%)	9 (6.21%)
Spontaneous Abortion	10 (7.04%)	8 (5.52%)
Ectopic Pregnancy	1 (0.70%)	1 (0.69%)
Induced Abortion	1 (0.70%)	0 (0.00%)
Perinatal Death (22 Weeks =< Death < 1 Week After Delivery)	2 (1.41%)	1 (0.69%)
Neonatal Death (7 days =< death < 28 days after delivery)	0 (0.00%)	0 (0.00%)
Death During Follow Up (28 days after delivery =< death =< Follow Up)	0 (0.00%)	0 (0.00%)

N: Number of subjects/pregnancies; %: Proportion of pregnancies
Two subjects in the NPH arm had a spontaneous abortion and became pregnant again.

Three subjects in the detemir group and six in the NPH developed clinically significant abnormalities in fundoscopy. Two subjects in the detemir group and one in the NPH developed a high urine albumin creatinine ratio.

A total of 26 (26.5%) of 98 neonates had quantifiable detimir concentrations in cord blood. The highest concentration was 209.6 pmol/L.

7.6. Post-marketing experience

No post-marketing data were included in the submission for Change 1 or Change 2.

The amendments to the PI for the section on pregnancy refer to post-marketing data presented in the Summary of Clinical Safety for Change 3. These data relate to a total of 528 pregnancies and are limited in detail (Table 49).

Table 49: Pregnancy Outcomes Based on Post-marketing Surveillance

	Report Source		
Pregnancy Outcome[1]	**Spontaneous**	**Solicited**	**Total**
Live birth without congenital anomalies	199	56	**255**
Live birth with congenital anomalies	14	-	**14**
Termination (no information reported on foetal defects)	3	7	**10**
Termination with foetal defects	4	1	**5**
Termination without foetal defects	-	0	**0**
Spontaneous abortion	16	9	**25**
Ectopic pregnancy	1	-	**1**
Stillbirth without foetal defects	2	2	**4**
Stillbirth (no information reported on foetal defects)	1	1	**2**
Unknown or still pregnant	187	25	**212**
Total	**427[2]**	**101**	**528**

1) Terminology for pregnancy outcomes as coded in the Global Safety database.
2) Two were twin pregnancies (Case No. 300556 and 283388) with 2 outcomes each; one 'Live birth without congenital anomalies' and three 'Live birth with congenital anomalies'.

In the absence of a comparator group it is difficult to make conclusions from these data but the outcomes, and spectrum of congenital malformations, appear to be typical for T1DM in pregnancy (Table 50).

Table 50: Post-marketing Cases with Congenital Anomalies or Foetal Defects

Case No.	**Congenital anomaly/ foetal defect**	**Comment**
Cases with congenital anomalies, spontaneous sources		
268006 (child)	Ventricular septal defect	
269893 (mother) 269889 (child)	Fallot's tetralogy Atresia of biliary ducts Spleen malformation Patent ductus arteriosus Caudal regression syndrome Hyperspadias Congential genital malformation Vertical talus Spina bifida	Baby died after 6 months.
275206 (child)	Atrial septal defect Ventricular septal defect Macrosomia	Both defects were closed at follow-up after 2 months.
275592 (mother) 269390 (child)	Tricuspid valve incompetence Pulmonary arterial pressure increased Diabetic foetopathy Hypoglycaemia	Baby was discharged after glucose treatment. No need for further controls.

Table 50: Post-marketing Cases with Congenital Anomalies or Foetal Defects continued

Case No.	Congenital anomaly/ foetal defect	Comment
275791(mother) 284409(child)	Low birth weight Respiratory distress syndrome Severe pulmonary hypoplasia Bilateral pneumothorax Intraventricular haemorrhage grade II	Baby treated with surfactant but died the day after birth.
278202 (mother) 286990 (child)	Preterm baby, diagnosed with cleft lip both sides and cleft palate/lip one side	
279450 (mother) 286573 (child)	Double thumb on left hand	Polydactyly exists in the family of the baby's father.
286606 (child)	Aplasia Cutis Congenita	The baby had congenital absence of hair follicles on top of scalp.
280167 (mother) 286766 (child)	Hypoglycaemia neonatal Neonatal aspiration infection Encephalopathy neonatal Hyperbilirubinaemia neonatal Pulmonary arterial hypertension Hypertonia neonatal	
280779 (mother) 280750 (child)	Hypoglycaemia Open arterial duct Ventricular septal defect	
289546 (child)	Foetal malformation	Unknown what kind of malformation
289592 (child)	Pyelectasis on right kidney	Diagnosed at GW 20 with ultrasound scan. At 8 weeks of age, the baby was healthy.
300285 (child)	Heterotaxia Multiple cardiac defects Pulmonary artery atresia Ventricular hypoplasia	The mother was exposed to insulin detemir in the third trimester.
303211 (child)	Caudal regression syndrome	
Case 309388 (mother) Case 323778 (Child)	Cardiac hypertrophy Cardiac murmur Hydrocele Hypoglycaemia Jaundice Premature baby Tachypnoea	Born in GW 32. At the age of 14 weeks the infant was healthy.
Case 334952 (child) Case 334843 (mother)	Craniocencephalic malformation Hypertelorism of orbit Microcephaly Ear malformation	In GW 23 an ultrasound scan revealed several malformations. Outcome unknown.
Termination with foetal defects, spontaneous sources		
269064 (mother)	Cranial malformation	Pregnancy termination at 3 months
285039 (mother)	Anencephaly	Pregnancy termination at GW 13 + 0
259408 (mother)	Anencephaly	GW 12
322772 (child) 322703 (mother)	Caudal regression syndrome	Pregnancy termination at GW 21
Termination with foetal defects, solicited sources		
220242 (mother)	Bilateral renal agenesis Uterine agenesis Absence of the second phalanx of the fifth fingers	Intra-uterine death of the foetus at GW 15 due to tight umbilical cord loop.

7.7. Evaluator's overall conclusions on clinical safety

Change 1:

The rate of TEAEs with detemir in combination with liraglutide and metformin was similar to that for liraglutide and metformin. There were no deaths in the detemir treated patients. More subjects were reported with neoplasia in the detemir group in the extension study but there was no apparent pattern to this. The rates of DAE were similar for detemir and control. To Week 52, elevated lipase was reported at a greater rate in the detemir group than in the control: 26 (16.0%) subjects in the detemir group compared with 16 (10.1%) in the control. Levels of antibodies to detemir increased through the study to 4.30 % B/T at Week 53. Minor hypoglycaemic events were more common with detemir than control: 21 (12.9%) subjects in the detemir group and four (2.5%) in the control.

Change 2:

The rate of TEAEs with detemir was not influenced by age and the profile was predominantly that expected for the paediatric age group alone. Treatment related TEAEs were as expected for insulins. The rate of SAEs was not affected by age group. The rate of hypoglycaemic events was similar for the three age groups.

Change 3:

The rates and patterns of TEAEs were similar for detemir and NPH for both mothers and infants. Treatment related TEAEs were similar for detemir and NPH. There were no maternal deaths. There were three perinatal deaths: two in the detemir group (stillbirth, intrauterine death) and one in the NPH (Dandy-Walker malformation/pulmonary hypoplasia). In addition there were two early pregnancy losses: one in the detemir group (intrauterine death) and one in the NPH (spontaneous abortion). There was a higher rate of spontaneous abortion in the detemir group: eight (5.3%) subjects compared with four (2.5%) in the NPH; and also of pre-eclampsia: eight (5.3%) subjects compared with one (0.6%) in the NPH. The rates of SAEs for infants were similar for detemir and NPH. The rates and patterns of congenital malformations for both populations were consistent with the known patterns of malformations in infants of diabetic mothers. DAE occurred at a higher rate in the detemir group: 13 (8.6%) subjects compared with six (3.8%) in the NPH. The rates of hypoglycaemia were similar for detemir and NPH.

Pregnancy outcome was slightly better in the NPH group. There were 128 (90.14%) live ldren at follow up in the detemir group and 135 (93.10%) in the NPH. This was not statistically significant (Chi2 Fisher's exact test performed by the Evaluator, p = 0.40).

8. First round benefit-risk assessment

8.1. First round assessment of benefits

Change 1:

Insulin detemir in combination with liraglutide and metformin resulted in an incremental decrease in mean HbA1c of 0.51% over 26 weeks. This is a clinically significant improvement in diabetes control. The improvement was maintained over a 52 week period. There was weight loss in the group treated with detemir, liraglutide and metformin in combination, but less than in those treated with liraglutide and metformin alone. The evaluator considers that the usual sequence of treatment would be liraglutide and metformin, with detemir added if patients were not adequately controlled on that combination.

Change 2:

The data presented for Change 2 were primarily intended as safety data. The efficacy data are difficult to interpret in the absence of a control group. There appears to be a loss of efficacy over

the second year of treatment but this most likely reflects the natural history of T1DM in a paediatric clinical trial population.

Change 3:

Insulin detemir has similar efficacy to NPH in the management of diabetes during pregnancy.

8.2. First round assessment of risks

Change 1:

The rate of TEAEs with detemir in combination with liraglutide and metformin was similar to that for liraglutide and metformin. There were no deaths in the detemir treated patients. More subjects were reported with neoplasia in the detemir group in the extension study but there was no apparent pattern to this. The rates of DAE were similar for detemir and control. To Week 52, elevated lipase was reported at a greater rate in the detemir group than in the control: 26 (16.0%) subjects in the detemir group compared with 16 (10.1%) in the control. Levels of antibodies to detemir increased through the study to 4.30 % B/T at Week 53. Minor hypoglycaemic events were more common with detemir than control: 21 (12.9%) subjects in the detemir group and four (2.5%) in the control.

Change 2:

The rate of TEAEs with detemir was not influenced by age and the profile was predominantly that expected for the paediatric age group alone. Treatment related TEAEs were as expected for insulins. The rate of SAEs was not affected by age group. The rate of hypoglycaemic events was similar for the three age groups.

Change 3:

The rates and patterns of TEAEs were similar for detemir and NPH for both mothers and infants. Treatment related TEAEs were similar for detemir and NPH. There were no maternal deaths. There were three perinatal deaths: two in the detemir group (stillbirth, intrauterine death) and one in the NPH (Dandy-Walker malformation/pulmonary hypoplasia). In addition there were two early pregnancy losses: one in the detemir group (intrauterine death) and one in the NPH (spontaneous abortion). There was a higher rate of spontaneous abortion in the detemir group: eight (5.3%) subjects compared with four (2.5%) in the NPH; and also of pre-eclampsia: eight (5.3%) subjects compared with one (0.6%) in the NPH. The rates of SAEs for infants were similar for detemir and NPH. The rates and patterns of congenital malformations for both populations were consistent with the known patterns of malformations in infants of diabetic mothers. DAE occurred at a higher rate in the detemir group: 13 (8.6%) subjects compared with six (3.8%) in the NPH. The rates of hypoglycaemia overall and nocturnal hypoglycaemia were similar for detemir and NPH.

Pregnancy outcome was slightly better in the NPH group. There were 128 (90.14%) live children at follow up in the detemir group and 135 (93.10%) in the NPH. This was not statistically significant (Chi2 Fisher's exact test performed by the Evaluator, p = 0.40).

8.3. First round assessment of risks

Change 1:

The rate of TEAEs with detemir in combination with liraglutide and metformin was similar to that for liraglutide and metformin. There were no deaths in the detemir treated patients. More subjects were reported with neoplasia in the detemir group in the extension study but there was no apparent pattern to this. The rates of DAE were similar for detemir and control. To Week 52, elevated lipase was reported at a greater rate in the detemir group than in the control: 26 (16.0%) subjects in the detemir group compared with 16 (10.1%) in the control. Levels of

antibodies to detemir increased through the study to 4.30 % B/T at Week 53. Minor hypoglycaemic events were more common with detemir than control: 21 (12.9%) subjects in the detemir group and four (2.5%) in the control.

Change 2:

The rate of TEAEs with detemir was not influenced by age and the profile was predominantly that expected for the paediatric age group alone. Treatment related TEAEs were as expected for insulins. The rate of SAEs was not affected by age group. The rate of hypoglycaemic events was similar for the three age groups.

Change 3:

The rates and patterns of TEAEs were similar for detemir and NPH for both mothers and infants. Treatment related TEAEs were similar for detemir and NPH. There were no maternal deaths. There were three perinatal deaths: two in the detemir group (stillbirth, intrauterine death) and one in the NPH (Dandy-Walker malformation/pulmonary hypoplasia). In addition there were two early pregnancy losses: one in the detemir group (intrauterine death) and one in the NPH (spontaneous abortion). There was a higher rate of spontaneous abortion in the detemir group: eight (5.3%) subjects compared with four (2.5%) in the NPH; and also of pre-eclampsia: eight (5.3%) subjects compared with one (0.6%) in the NPH. The rates of SAEs for infants were similar for detemir and NPH. The rates and patterns of congenital malformations for both populations were consistent with the known patterns of malformations in infants of diabetic mothers. DAE occurred at a higher rate in the detemir group: 13 (8.6%) subjects compared with six (3.8%) in the NPH. The rates of hypoglycaemia overall and nocturnal hypoglycaemia were similar for detemir and NPH.

Pregnancy outcome was slightly better in the NPH group. There were 128 (90.14%) live children at follow up in the detemir group and 135 (93.10%) in the NPH. This was not statistically significant (Chi2 Fisher's exact test performed by the Evaluator, p = 0.40).

8.4. First round assessment of benefit-risk balance

Change 1:

The benefit-risk balance of insulin detemir, given the proposed usage, is favourable.

Change 2:

The benefit-risk balance of insulin detemir, given the proposed usage, is favourable.

Change 3:

The benefit-risk balance of insulin detemir, given the proposed usage, is favourable.

Change 4:

No data were presented for this proposed change as it relates to alignment of the PI with the CCDS.

9. First round recommendation regarding authorisation

The Evaluator recommends that the proposed changes to the conditions of registration for Levemir Flexpen/Levermir Penfill / Levemir Innolet should be approved. The proposed changes are:

Change 1: Update of the Product Information (PI) to include information on the use of Levemir® (insulin detemir [rys]) as add-on therapy to Victoza®(liraglutide [rys]).

Change 2: Update of the Product Information (PI) to include safety data from long-term trials in use of Levemir® in adolescents and children (from 2 years old) with T1DM.

Change 3: Update of the Product Information (PI) to allow use of Levemir® in pregnancy.

Change 4: Update of the Product Information (PI) to more closely align with the Core Company Data Sheet (CCDS) (v. 12.0).

10. Clinical questions

The Evaluator does have any clinical questions.

11. Second round evaluation of clinical data submitted in response to questions

[Insert all information]

12. Second round benefit-risk assessment

[Insert all information]

13. Second round recommendation regarding authorisation

[Insert all information]

14. Appendix 1: Additional tables

Table 1: Studies providing pharmacokinetic data

Study Year Author Reference	Study Design	Medication	No. of Volunteers Entered (M/F) Age range	Pharmacokinetics
Study NN2211-3673 Module 5, Section 5.3.4.2 Single centre in the US from April 2009 to September 2009	Open label, three treatment phase, single sequence, PK and PD (euglycaemic clamp at 100 mg/dL) study of detemir, liraglutide and the combination of liraglutide and detemir	Insulin detemir 0.5 U/kg on Day 1, followed by 24 hour euglycaemic clamp Liraglutide titrated to 1.8 mg /day from Day 2 to Day 22, with 24 hour euglycaemic clamp on Day 22 Liraglutide 1.8 mg daily from Day 22 to Day 36, insulin detemir 0.5 U/kg on Day 36, with 24 hour euglycaemic clamp All subjects treated with metformin as a background medication	33 subjects: 23 (69.7%) male, 10 (30.3%) female, age range 33 to 68 years **Adverse Reactions** There were 16 TEAEs reported in 14 (42%) subjects with insulin detemir alone (Day 1), 20 in 17 (52%) treated with liraglutide at steady state; and 13 in 13 (39%) when both trial drugs were coadministered. There were no deaths or SAEs. There were no DAEs.	

	Detemir	Detemir + Liraglutide	90% CI for the Ratio*
AUC(0-24hr) (pmol·hr/L)			
N	32	32	
Mean (SD)	51878.0 (11807.2)	53774.2 (13940.2)	
Median	52252	53865	
Min ; Max	32346 ; 79680	30522 ; 79213	
Ratio Estimate			1.03
90% CI			[0.97, 1.09]
Cmax (pmol/L)			
N	32	32	
Mean (SD)	3729.4 (912.3)	3962.5 (1119.2)	
Median	3620	3965	
Min ; Max	2320 ; 5250	2170 ; 6180	
Ratio Estimate			1.05
90% CI			[0.98, 1.13]
Tmax (hr)			
N	32	32	
Mean (SD)	9.94 (2.963)	10.16 (2.931)	
Median	9.50	9.50	
Min ; Max	6.0 ; 18.0	4.0 ; 18.0	

	Liraglutide	Detemir + Liraglutide	90% CI for the Ratio*
AUC(0-24hr) (pmol*hr/L)			
N	32	32	
Mean (SD)	328167 (93262.5)	319835 (107679.2)	
Median	333894	309354	
Min ; Max	130015 ; 486358	146817 ; 614400	
Ratio Estimate			0.97
90% CI			[0.87, 1.08]
Cmax (pmol/L)			
N	32	32	
Mean (SD)	17639 (5155.1)	18189 (6162.0)	
Median	17550	18100	
Min ; Max	7210 ; 27300	9470 ; 35300	
Ratio Estimate			1.03
90% CI			[0.93, 1.13]
Tmax (hr)			
N	32	32	
Mean (SD)	11.17 (5.068)	10.77 (3.538)	
Median	11.00	10.00	
Min ; Max	4.0 ; 18.1	4.0 ; 18.0	

Table 6: Tabular summary of Study NN2211-1842

Study -investigator -coordinating centre centre(s) -report n°	Design	Nr. Of subjects with age and sex	Diagnosis + criteria for incl/exclusion	Duration of Treatment	Test Product Dosage Regimen Route of administration, Formulation	Reference therapy Dose regimen Route of administration	Criteria for evaluation	Results (efficacy)	Adverse Reactions
Study NN2211-1842 Module 5, Section 5.3.5.1 202 centres in 9 countries: Belgium (2), Canada (7), France (19), Germany (37), Italy (18), the Netherlands (16), Spain (14), the UK (32) and the US (57) March 2009 to April 2010	Multicentre, randomised, open label, two arm, parallel group trial with an additional open-label, non-randomised arm carrying subjects who achieved target glycaemic control after the run-in period.	1658 subjects were screened; 162 randomised to detemir; 161 to control; and 498 were included in the non-randomised group. 144 (88.9%) subjects in the detemir group, 127 (78.9%) in the control and 470 (94.4%) in the non-randomised completed In the randomised population there were 177 (54.8%) males, 146 (45.2%) females, age range 31 to 79 years.	Subjects diagnosed with T2DM, insulin naïve and treated with metformin as monotherapy for ≥3 months prior to screening, at a stable dose of ≥1500 mg/day or metformin (≥1500 mg/day) and a sulphonylurea (less than or equal to ½ of the maximum approved dose according to local label), both at a stable dose for ≥3 months prior to screening. HbA1c 7.0-10.0% inclusive for subjects on metformin monotherapy, HbA1c 7.0-8.5% inclusive for subjects on metformin in combination with a sulphonylurea Age 18 to 80 years, inclusive	12 week run-in period, 26 week treatment period (26 week extension reported separately)	Insulin detemir, starting at 10 U/day and adjusted by SMPG All subjects received liraglutide 1.8 mg per day and metformin ≥1500 mg per day Subjects were randomised 1:1 using IV/WRS	All subjects received liraglutide 1.8 mg per day and metformin ≥1500 mg per day No blinding, all treatments were open label as blinded treat-to-target administration of insulin detemir placebo was not feasible	HbA1c Fasting plasma glucose (FPG) 7-point SMPG profiles Body weight Waist and hip circumference (and derived waist to hip ratio) Beta-cell function: fasting insulin; fasting C-peptide; fasting pro-insulin (and derived pro-insulin to C-peptide ratio) Fasting lipid profile: total cholesterol; HDL-C; LDL-C; VLDL-C; TG; and FFA SBP and DBP	There was a significant decrease in HbA1c to Week 26 in the detemir group compared with control. The LS mean (SE) change was -0.51 (0.07) % for detemir and 0.02 (0.07) % for control, LS mean (95% CI) difference -0.52 (-0.68 to -0.36) %, p <0.0001 (Table 7.1.1.1.5). The repeated measures ANOVA estimated a mean (95% CI) treatment difference of -0.43 (-0.55 to -0.31) p <0.0001 at Week 12 and -0.49 (-0.62 to -0.36) p <0.0001 at Week 26. At Week 26 the proportion achieving HbA1c <7% was 71 (44.4%) in the detemir group and 30 (20.1%) in the control, OR (95% CI) 3.75 (2.19 to 6.45), p <0.0001; and the proportion achieving HbA1c ≤6.5% was 31 (19.4%) in the detemir group and 11 (7.4%) in the control, OR (95% CI) 3.32 (1.58 to 7.00), p = 0.0016.	631 TEAEs reported in 125 (76.7%) subjects in the detemir group and 559 in 121 (76.1%) in the control. Increased serum lipase was reported as a TEAE in 18 (11%) subjects in the detemir group compared with six (3.8%) in the control. There were no deaths reported during the main period of the trial. There were 14 SAEs reported in nine (5.5%) subjects in the detemir group and eleven in eight (5.0%) in the control. Four (2.5%) subjects in the detemir group and six (3.8%) in the control discontinued due to AEs. Pancreas related AEs were reported in 18 (11%) subjects in the detemir group and twelve (7.5%) in the control. There was one report of chronic pancreatitis in the control group. Minor hypoglycaemic events were reported in 15 (9.2%) subjects in the detemir group and two (1.3%) in the control. The level of antibodies to detemir was mean 1.59 %B/T at Week 0 and 2.20 %B/T at Week 26.

Table 7: Trial Flow Chart – Randomised Subjects

Flow Chart for Randomised subjects Visit number/Telephone contact	1	2[1]	3	4 4a[2]	4 4b[3]	5, 6, 7 ☎[4]	8[4]	9, 10, 11 ☎[4]	12[4]	13, 14, 15 ☎[4]	16	17, 18 ☎[4]	19[4]	20, 21, 22, 23, 24 ☎[4]	25[3]	26, 27 ☎[4]	28[3]	29, 30, 31, 32 ☎[4]	33	34
Time of visit (weeks in relation to visit 4)	Between -14 and -12	-12	-8	0		1, 2, 3	4	5, 6, 7	8	9, 10, 11	12	14, 16	18	20, 22, 23, 24, 25	26	30, 34	38	42, 46, 48, 50	52	53
Visit window (days)		±4	±3			±3	±3	±3	±3	±3	±3	±3	±3	±3	±5	±3	±5	±3	±5	±3
Visit type or trial period	Screen	Run-in		Rand		Maintenance										Extension			End of treat-ment	Follow -up
SUBJECT RELATED INFO/ASSESSMENTS																				
Informed consent[17]	X														X		X			
In/exclusion criteria	X	X																		
Randomisation criteria					X															
Withdrawal criteria			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Demography	X																			
Diabetes history	X																			
Concomitant illness/Medical history	X																			
Concomitant medication	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																			
Attend visit fasting[7]		X	X	X			X				X				X		X		X	X
Sulphonylurea discontinuation		X																		
Current diabetes treatment																				X
End of trial[8]																			(X)	X
EFFICACY																				
HbA_{1c}	X	X		X							X				X		X		X	
Fasting Plasma Glucose[5]		X	X	X			X				X				X		X		X	
Fasting insulin, C-peptide and proinsulin[9]		X		X											X				X	
7-point profile[7]		X			X						X				X		X		X	
Fasting SMPG measurements[8]						X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Lipids[5]		X		X											X				X	
Body weight	X	X	X		X		X		X		X		X		X		X		X	
Waist and hip circumference		X			X						X				X		X		X	

Flow Chart for Randomised subjects				4																
Visit number/Telephone contact	1	2[1]	3	4a[2]	4b[3]	5, 6, 7 ☎[4]	8[4]	9, 10, 11 ☎[4]	12[4]	13, 14, 15 ☎[4]	16	17, 18 ☎[4]	19[4]	20, 21, 22, 23, 24 ☎[4]	25[3]	26, 27 ☎[4]	28[3]	29, 30, 31, 32 ☎[4]	33	34
Time of visit (weeks in relation to visit 4)	Between -14 and -12	-12	-8	0		1, 2, 3	4	5, 6, 7	8	9, 10, 11	12	14, 16	18	20, 22, 23, 24, 25	26	30, 34	38	42, 46, 48, 50	52	53
Visit window (days)		±4	±3			±3	±3	±3	±3	±3	±3	±3	±3	±3	±5	±3	±5	±3	±5	±3
Systolic and diastolic blood pressure	X	X	X		X		X		X		X		X		X		X		X	
SAFETY																				
Adverse events		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Liraglutide antibodies		X		X											X				X	X
Insulin detemir antibodies[9]				X											X				X	X
Biochemistry	X	X		X							X				X		X		X	
Haematology	X	X		X							X				X		X		X	
Urinalysis	X				X										X				X	
Pregnancy test[10]	X	(X)	(X)		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X	(X)	(X)	(X)	X	
ECG[11]	X				X										X				X	
Physical examination	X				X										X				X	
Hypoglycaemic episodes		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulse	X	X	X		X		X		X		X		X		X		X		X	
Intensification of treatment with insulin detemir[12]															X		X			

Table 9: Summary of Subject Demographics and Characteristics - All Exposed Subjects

	Lira 1.8	Detemir + Lira 1.8	All Randomised	Non-randomised Lira 1.8	Early WD Lira 1.8	All
All exposed subjects	161	162	323	498	166	987
Age (years)						
N	161	162	323	498	166	987
Mean (SD)	57.3 (9.8)	56.8 (9.4)	57.0 (9.6)	56.5 (9.7)	59.7 (10.8)	57.1 (9.9)
Median	58.0	57.0	57.0	57.0	60.0	58.0
Min : Max	33.0 : 79.0	31.0 : 77.0	31.0 : 79.0	18.0 : 80.0	20.0 : 80.0	18.0 : 80.0
Sex, N (%)						
N	161 (100)	162 (100)	323 (100)	498 (100)	166 (100)	987 (100)
Male	89 (55.3)	88 (54.3)	177 (54.8)	282 (56.6)	91 (54.8)	550 (55.7)
Female	72 (44.7)	74 (45.7)	146 (45.2)	216 (43.4)	75 (45.2)	437 (44.3)
Race, N (%)						
N	161 (100)	162 (100)	323 (100)	498 (100)	166 (100)	987 (100)
White	141 (87.6)	144 (88.9)	285 (88.2)	470 (94.4)	146 (88.0)	901 (91.3)
Black or African American	17 (10.6)	8 (4.9)	25 (7.7)	19 (3.8)	11 (6.6)	55 (5.6)
Asian	1 (0.6)	4 (2.5)	5 (1.5)	5 (1.0)	4 (2.4)	14 (1.4)
American Indian or Alaska Native	0 (0.0)	1 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Other	2 (1.2)	4 (2.5)	6 (1.9)	4 (0.8)	5 (3.0)	15 (1.5)
Ethnicity, N (%)						
N	161 (100)	162 (100)	323 (100)	498 (100)	166 (100)	987 (100)
Hispanic or Latino	25 (15.5)	22 (13.6)	47 (14.6)	48 (9.6)	28 (16.9)	123 (12.5)
Not Hispanic or Latino	136 (84.5)	140 (86.4)	276 (85.4)	450 (90.4)	138 (83.1)	864 (87.5)
Height (m)						
N	161	162	323	498	166	987
Mean (SD)	1.70 (0.10)	1.69 (0.11)	1.69 (0.10)	1.70 (0.10)	1.68 (0.10)	1.69 (0.10)
Median	1.70	1.68	1.70	1.70	1.70	1.70
Min : Max	1.47 : 1.91	1.38 : 1.96	1.38 : 1.96	1.45 : 2.06	1.47 : 1.92	1.38 : 2.06

All subjects also received metformin
Early WD: Withdrawals before randomisation visit (visit 4b)
N: Number of subjects, %: Percentage of exposed subjects, BMI: body mass index, SD: standard deviation

Table 9: Summary of Subject Demographics and Characteristics - All Exposed Subjects continued

	Lira 1.8	Detemir + Lira 1.8	All Randomised	Non-randomised Lira 1.8	Early WD Lira 1.8	All
Weight (kg)						
N	161	162	323	498	166	987
Mean (SD)	98.6 (21.3)	99.5 (21.2)	99.1 (21.2)	99.0 (20.8)	90.2 (18.5)	97.5 (20.8)
Median	96.6	97.0	96.7	96.2	87.6	94.6
Min ; Max	51.8 ; 177.2	50.8 ; 201.0	50.8 ; 201.0	50.0 ; 206.8	53.2 ; 153.8	50.0 ; 206.8
BMI (kg/m^2)						
N	161	162	323	498	166	987
Mean (SD)	33.9 (6.0)	34.9 (6.3)	34.4 (6.2)	34.4 (6.7)	31.8 (6.0)	34.0 (6.5)
Median	33.0	33.5	33.2	33.4	30.6	33.0
Min ; Max	22.4 ; 60.6	22.6 ; 56.2	22.4 ; 60.6	20.6 ; 75.9	19.7 ; 54.2	19.7 ; 75.9
Duration of diabetes (years)						
N	161	162	323	498	166	987
Mean (SD)	8.5 (6.0)	8.6 (5.8)	8.5 (5.9)	6.6 (5.7)	8.4 (6.4)	7.6 (5.9)
Median	7.5	7.7	7.7	5.4	6.9	6.4
Min ; Max	0.4 ; 30.5	0.4 ; 30.5	0.4 ; 30.5	0.3 ; 47.3	0.3 ; 33.2	0.3 ; 47.3
Previous anti-diabetic treatment, N (%)						
N	161 (100)	162 (100)	323 (100)	498 (100)	166 (100)	987 (100)
Metformin	81 (50.3)	81 (50.0)	162 (50.2)	371 (74.5)	97 (58.4)	630 (63.8)
Metformin/Sulphonylurea Combination	80 (49.7)	81 (50.0)	161 (49.8)	127 (25.5)	69 (41.6)	357 (36.2)

All subjects also received metformin
Early WD: Withdrawals before randomisation visit (visit 4b)
N: Number of subjects, %: Percentage of exposed subjects, BMI: body mass index, SD: standard deviation

Table 10: Summary of Run-in Efficacy Parameters - All Exposed Subjects

	Lira 1.8	Detemir + Lira 1.8	All Randomised	Non-randomised Lira 1.8	Early WD Lira 1.8	All
All exposed subjects	161	162	323	498	166	987
HbA1c (%)						
N	161	162	323	498	165	986
Mean (SD)	8.3 (0.8)	8.2 (0.7)	8.3 (0.8)	7.7 (0.7)	8.0 (0.8)	7.9 (0.8)
Median	8.1	8.1	8.1	7.6	7.9	7.8
Min ; Max	6.1 ; 11.2	6.7 ; 10.5	6.1 ; 11.2	6.6 ; 10.2	6.6 ; 10.1	6.1 ; 11.2
FPG (mmol/L)						
N	158	162	320	492	165	977
Mean (SD)	10.3 (2.5)	10.2 (2.4)	10.2 (2.5)	9.2 (1.8)	9.5 (3.0)	9.6 (2.3)
Median	10.0	9.7	9.8	8.9	9.0	9.2
Min ; Max	5.0 ; 17.7	3.1 ; 17.6	3.1 ; 17.7	5.3 ; 16.6	4.4 ; 36.5	3.1 ; 36.5
Weight (kg)						
N	161	162	323	498	166	987
Mean (SD)	98.6 (21.3)	99.5 (21.2)	99.1 (21.2)	99.0 (20.8)	90.2 (18.5)	97.5 (20.8)
Median	96.6	97.0	96.7	96.2	87.6	94.6
Min ; Max	51.8 ; 177.2	50.8 ; 201.0	50.8 ; 201.0	50.0 ; 206.8	53.2 ; 153.8	50.0 ; 206.8
Waist (cm)						
N	160	162	322	496	166	984
Mean (SD)	111.3 (14.6)	113.3 (14.5)	112.3 (14.5)	112.0 (13.8)	106.5 (13.1)	111.1 (14.1)
Median	109.9	111.1	110.5	110.2	106.0	109.7
Min ; Max	75.8 ; 148.8	74.0 ; 167.0	74.0 ; 167.0	80.9 ; 177.9	74.7 ; 151.5	74.0 ; 177.9
Hip (cm)						
N	160	162	322	493	165	980
Mean (SD)	114.0 (14.3)	115.2 (15.3)	114.6 (14.8)	115.1 (14.8)	110.9 (13.0)	114.2 (14.6)
Median	112.7	113.1	112.8	112.3	108.6	112.0
Min ; Max	86.8 ; 174.5	88.9 ; 200.0	86.8 ; 200.0	84.3 ; 191.6	87.3 ; 163.0	84.3 ; 200.0
Waist-to-hip ratio						
N	160	162	322	493	165	980
Mean (SD)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)
Median	1.0	1.0	1.0	1.0	1.0	1.0
Min ; Max	0.8 ; 1.3	0.8 ; 1.3	0.8 ; 1.3	0.6 ; 1.2	0.7 ; 1.2	0.6 ; 1.3
Fasting Insulin (pmol/L)						
N	157	156	313	481	162	956
Mean (SD)	113.0 (70.1)	127.0 (88.5)	120.0 (80.0)	122.7 (82.8)	110.1 (85.3)	119.7 (82.4)
Median	97.0	105.5	102.0	108.0	92.0	102.0
Min ; Max	7.0 ; 338	7.0 ; 403	7.0 ; 403	7.0 ; 644	7.0 ; 614	7.0 ; 644

All subjects also received metformin
Early WD: Withdrawals before randomisation visit (visit 4b)

Table 10: Summary of Run-in Efficacy Parameters - All Exposed Subjects continued

	Lira 1.8	Detemir + Lira 1.8	All Randomised	Non-randomised Lira 1.8	Early WD Lira 1.8	All
Fasting Pro-insulin (pmol/L)						
N	159	160	319	486	164	969
Mean (SD)	43.1 (35.5)	50.6 (46.6)	46.9 (41.6)	39.6 (34.8)	37.2 (35.0)	41.6 (37.4)
Median	34.0	34.0	34.0	30.0	25.0	30.0
Min ; Max	4.0 ; 227	2.0 ; 273	2.0 ; 273	1.0 ; 289	1.0 ; 198	1.0 ; 289
Fasting C-peptide (nmol/L)						
N	157	155	312	482	164	958
Mean (SD)	1.2 (0.5)	1.2 (0.6)	1.2 (0.6)	1.2 (0.6)	1.1 (0.6)	1.2 (0.6)
Median	1.1	1.1	1.1	1.1	1.0	1.1
Min ; Max	0.1 ; 2.8	0.0 ; 3.6	0.0 ; 3.6	0.3 ; 4.0	0.0 ; 3.9	0.0 ; 4.0
Pro-insulin to C-peptide ratio						
N	156	155	311	475	163	949
Mean (SD)	0.04 (0.02)	0.04 (0.04)	0.04 (0.03)	0.03 (0.02)	0.03 (0.02)	0.03 (0.02)
Median	0.03	0.03	0.03	0.03	0.03	0.03
Min ; Max	0.01 ; 0.14	0.01 ; 0.31	0.01 ; 0.31	0.00 ; 0.14	0.01 ; 0.16	0.00 ; 0.31
HOMA-B (%)						
N	152	155	307	473	160	940
Mean (SD)	51.2 (34.9)	59.0 (50.8)	55.1 (43.7)	63.7 (46.1)	59.4 (51.5)	60.2 (46.4)
Median	40.0	43.6	42.5	54.7	48.1	49.5
Min ; Max	4.3 ; 177	1.8 ; 327	1.8 ; 327	2.3 ; 384	0.6 ; 364	0.6 ; 384
HOMA-IR						
N	152	155	307	473	160	940
Mean (SD)	7.3 (5.3)	8.1 (6.2)	7.7 (5.8)	7.1 (5.5)	6.4 (5.6)	7.2 (5.6)
Median	6.2	6.0	6.0	5.9	5.1	5.8
Min ; Max	0.3 ; 27.2	0.3 ; 31.2	0.3 ; 31.2	0.3 ; 50.9	0.2 ; 44.6	0.2 ; 50.9
TC (mmol/L)						
N	160	160	320	493	164	977
Mean (SD)	4.7 (1.2)	4.8 (1.1)	4.8 (1.2)	4.5 (1.0)	4.7 (1.2)	4.6 (1.1)
Median	4.6	4.7	4.6	4.4	4.6	4.5
Min ; Max	2.5 ; 8.9	2.3 ; 8.4	2.3 ; 8.9	2.3 ; 9.2	2.4 ; 12.1	2.3 ; 12.1
LDL-C (mmol/L)						
N	160	160	320	493	164	977
Mean (SD)	2.7 (0.9)	2.7 (0.9)	2.7 (0.9)	2.5 (0.9)	2.7 (1.0)	2.6 (0.9)
Median	2.7	2.6	2.7	2.4	2.7	2.5
Min ; Max	1.2 ; 5.1	0.6 ; 5.4	0.6 ; 5.4	0.2 ; 6.7	0.7 ; 8.0	0.2 ; 8.0

All subjects also received metformin
Early WD: Withdrawals before randomisation visit (visit 4b)

Table 10: Summary of Run-in Efficacy Parameters - All Exposed Subjects continued

	Lira 1.8	Detemir + Lira 1.8	All Randomised	Non-randomised Lira 1.8	Early WD Lira 1.8	All
VLDL-C (mmol/L)						
N	160	160	320	493	164	977
Mean (SD)	0.9 (0.8)	1.0 (0.7)	0.9 (0.7)	0.8 (0.5)	0.8 (0.6)	0.8 (0.6)
Median	0.7	0.8	0.8	0.7	0.7	0.7
Min ; Max	0.1 ; 6.5	0.1 ; 5.4	0.1 ; 6.5	0.1 ; 7.2	0.2 ; 4.9	0.1 ; 7.2
HDL-C (mmol/L)						
N	160	160	320	493	164	977
Mean (SD)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	1.2 (0.3)	1.1 (0.3)
Median	1.1	1.1	1.1	1.1	1.1	1.1
Min ; Max	0.4 ; 2.2	0.5 ; 2.1	0.4 ; 2.2	0.5 ; 2.6	0.5 ; 2.2	0.4 ; 2.6
Triglycerides (mmol/L)						
N	158	157	315	479	161	955
Mean (SD)	2.3 (2.1)	2.5 (2.0)	2.4 (2.0)	2.1 (1.9)	2.0 (1.8)	2.2 (2.0)
Median	1.7	2.0	1.9	1.8	1.7	1.8
Min ; Max	0.4 ; 19.7	0.6 ; 16.1	0.4 ; 19.7	0.4 ; 33.0	0.6 ; 20.7	0.4 ; 33.0
Free fatty acids (mmol/L)						
N	154	149	303	459	148	910
Mean (SD)	0.6 (0.2)	0.6 (0.3)	0.6 (0.3)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)
Median	0.6	0.6	0.6	0.6	0.6	0.6
Min ; Max	0.2 ; 1.8	0.2 ; 1.7	0.2 ; 1.8	0.1 ; 1.7	0.2 ; 1.8	0.1 ; 1.8
Diastolic BP (mmHg)						
N	161	162	323	498	166	987
Mean (SD)	80.8 (9.8)	80.1 (9.7)	80.4 (9.8)	81.5 (9.2)	80.2 (9.4)	80.9 (9.5)
Median	80.0	80.3	80.0	80.5	80.0	80.0
Min ; Max	54.0 ; 108	51.0 ; 100	51.0 ; 108	57.0 ; 110	52.5 ; 108	51.0 ; 110
Systolic BP (mmHg)						
N	161	162	323	498	166	987
Mean (SD)	135.7 (16.8)	134.0 (16.9)	134.8 (16.8)	134.4 (15.3)	134.3 (14.9)	134.5 (15.7)
Median	135.0	135.0	135.0	133.8	132.5	133.5
Min ; Max	97.5 ; 194	74.5 ; 182	74.5 ; 194	97.5 ; 179	98.0 ; 177	74.5 ; 194

All subjects also received metformin
Early WD: Withdrawals before randomisation visit (visit 4b)

Table 13: Tabular summary of Study NN304-1690

Study -investigator -coordinating centre centre(s) -report n°	Design	Nr. Of subjects with age and sex	Diagnosis + criteria for incl/exclusion	Duration of Treatment	Test Product Dosage Regimen Route of administration, Formulation	Reference therapy Dose regimen Route of administration	Criteria for evaluation	Results (efficacy)	Adverse Reactions
Study NN304-1690 Module 5, Section 5.3.5.1 29 sites in 11 countries: Bulgaria 2, Czech Republic 3, Denmark 2, Finland 4, France 1, Hungary 2, Macedonia 1, Poland 4, Russian Federation 4, Turkey 4, UK 1 February 2008 to September 2009	Open label, multicentre, single arm, 52-week extension trial of NN304-1689 of insulin detemir administered once or twice daily to children and adolescents diagnosed with T1DM	146 subjects: 37 aged 2 to 5 years, 59 aged 6 to 12 years, 50 aged 13 to 16 years 141 (96.6%) completed the study All subjects included in the analysis 77 (52.7%) females, 69 (47.3%) males, age range 3.1 to 17.9 years	Subjects who had completed 52 weeks of treatment in Study NN304-1689 (see Table 1.3.2)	52 weeks	Insulin detemir administered as a subcutaneous injection in the thigh once or twice daily, dose adjusted individually aiming for FPG of 4 to 7 mmol/L Insulin aspart, administered as subcutaneous injections in the abdomen, pre-prandial, two to four times a day, in connection with main meals	Not applicable	Insulin detemir-insulin aspart cross reacting antibodies, insulin detemir specific antibodies, insulin aspart specific antibodies, HbA1c, FPG, hypoglycaemic episodes, BMI, weight, AEs, diabetic ketoacidosis, laboratory safety parameters, vital signs	There was a slight increase in HbA1c during the extension period for all the age groups: mean (SD) 0.10 (0.77) % for the 2 to 5 year age group, 0.27 (1.08) % for the 6 to 12 year, 0.11 (1.60) % for the 13 to 16 year and 0.17 (1.22) % for the total population. This translates to a mean (95% CI) change of 0.10 (-0.16 to 0.36) % for the 2 to 5 year age group, 0.27 (-0.01 to 0.55) % for the 6 to 12 year, 0.11 (-0.34 to 0.56) % for the 13 to 16 year and 0.17 (-0.03 to 0.37) % for the total population. Of the total population, 15 (10.3%) were within the target range for pre-prandial PG of ≥4 mmol/L and ≤7 mmol/L. Mean FPG also increased slightly during the trial.	There were 714 TEAEs reported in 116 (79.5%) subjects in the combined population including 178 in 29 (78.4%) subjects in the 2 to 5 year age group, 383 in 50 (84.7%) in the 6 to 12 year and 153 in 37 (74.0%) in the 13 to 16 year. There were no deaths reported during the study. There were 17 SAEs reported in 116 (79.5%) subjects in the combined population including four in three (8.1%) subjects in the 2 to 5 year age group, nine in six (10.2%) in the 6 to 12 year and four in three (6.0%) in the 13 to 16 year. There were no DAEs. There were 16074 hypoglycaemic episodes reported in 145 (99.3%) subjects in the combined population including 4028 in 37 (100%) subjects in the 2 to 5 year age group, 7438 in 59 (100%) in the 6 to 12 year and 4608 in 49 (98.0%) in the 13 to 16 year. Severe hypoglycaemic episodes were reported in two (5.4%) subjects in the 2 to 5 year age group, two (3.4%) in the 6 to 12 year and two (4.0%) in the 13 to 16 year. Severe nocturnal hypoglycaemic episodes were reported in one subject in each age group.

Table 14: Tabular summary of Study NN304-1689

Study -investigator -coordinating centre centre(s) -report n°	Design	Nr. Of subjects with age and sex	Diagnosis + criteria for incl/exclusion	Duration of Treatment	Test Product Dosage Regimen Route of administration, Formulation	Reference therapy Dose regimen Route of administration	Criteria for evaluation	Results (efficacy)	Adverse Reactions
Study NN304-1689 Module 5, Part2, Section 5.3.5.1 V Peterkova and N K S Thalange Sponsored and coordinated by Novo Nordisk 35 centres in 11 countries: Bulgaria (3), Czech Republic (3) , Denmark (3), Finland (5), France (2), Hungary (2), Macedonia (1), Poland (4), Russian Federation (4), Turkey (4) and the UK (4)	Multi-national, multi-centre, open-label, randomised 1:1, two-armed parallel group trial comparing insulin detemir and NPH insulin administered once or twice daily (according to their pretrial regimen) to children and adolescents (2-16 years) diagnosed with type 1 diabetes.	347 children and adolescents 2-16 years (IDet: 177; NPH: 170); Young children 2-5 years (IDet: 42; NPH: 40); Children 6-12 years (IDet: 79; NPH: 88); Adolescents 13- 16 years (IDet: 56; NPH: 42) 180 (51.9%) males, 167 (48.1%) females	Boy or girl diagnosed with type 1 diabetes Age: 2-16 years at randomisation Diagnosed with type 1 diabetes ≥12 months prior to inclusion Insulin detemir naïve (all other insulins and insulin regimens are allowed) Total daily dose of insulin ≤2 U/kg Maximum BMI according to below table HbA1c ≤11% Fertile girls (girls who have had their first menstrual period) must use adequate contraception if there is any risk of pregnancy in the opinion of the investigator. Ability and willingness to perform PG profiles using a blood glucose meter at home as evidenced by a complete 9-point SMPG profile obtained over a single 24-hour period during the screening period	52 weeks	Insulin detemir (Levemir®), 100 U/mL, 3 mL Penfill® cartridge, Novo Nordisk A/S The basal insulin was administered with a NovoPen® Junior Green. Bolus insulin: Insulin aspart, 100 U/mL, 3 mL Penfill® cartridge, Novo Nordisk A/S The bolus insulin was administered with a NovoPen® Junior Yellow. Randomised 1:1 to treatment group using IV/WRS Stratifed by age group: age 2-5 years and 6-16 years	Human isophane insulin (NPH) (Insulatard®), 100 IU/mL, 3 mL Penfill® cartridge, Novo Nordisk A/S	Efficacy: HbA1c, end of trial FPG, end of trial SMPG, end of trial 9-point SMPG profile, end of trial NPG, end of trial Safety: AEs Physical examination Body weight, BMI and SD score (z-score) for weight Vital signs Fundoscopy/funduspho tography Injection pain assessment Diabetic ketoacidosis requiring hospitalisation Hypoglycaemic episodes Laboratory tests (including insulin antibodies and pregnancy test) Height Pubertal status Insulin doses	Non-inferiority was demonstrated for the PP population (treatment difference 0.12% (-0.12% to 0.36%) and the ITT population (treatment difference 0.13 (-0.12; 0.37) for the total study population. In the 2 to 5 year age group there were similar values of mean HbA1c in the two treatment groups throughout the study. There was no difference between the treatment groups in FPG at end of study. The model estimates of within subject variability in SMPG were greater for the NPH insulin group than the insulin detemir group. There was no difference between the treatment groups in 9-point SMPG profile at 26 weeks or 52 weeks. There was no significant difference in NPG	537 TEAEs were reported in 132 (74.6%) subjects in the detemir group and 554 in 135 (79.4%) subjects in the NPH. In the 2 to 5 year age group 121 TEAEs were reported in 29 (69.0%) subjects in the detemir group and 160 in 31 (77.5%) subjects in the NPH. Hypoglycaemic events were less frequent in the detemir group. The rate of nocturnal hypoglycaemic events in the detemir group was half that of the NPH 16 SAEs were reported in 14 (7.9%) subjects in the detemir group and 24 in 20 (11.8%) subjects in the NPH. There were no deaths reported. The expression of insulin aspart specific, cross-reacting and detemir specific antibodies was higher in the insulin detemir group

Table 18: Tabular summary of Study NN304-1687

Study -investigator -coordinating centre centre(s) -report n°	Design	Nr. Of subjects with age and sex	Diagnosis + criteria for incl/exclusion	Duration of Treatment	Test Product Dosage Regimen Route of administration, Formulation	Reference therapy Dose regimen Route of administration	Criteria for evaluation	Results (efficacy)	Adverse Reactions
Study NN304-1687 Module 5, Section 5.3.5.1 79 sites in 17 countries May 2007 to August 2010	Multicentre, open label, randomised, parallel group efficacy and safety study to compare detemir with NPH insulin, in conmbination with insulin aspart as bolus insulin, in the treatment of pregnant women with T1DM	600 subjects screened, 470 randomised: 233 to detemir and 237 to NPH 263 subjects completed: 127 (83.6%) in the detemir group and 136 (84.5%) in the NPH There were 152 (65.2%) subjects in the FAS prenant group exposed to detemir and 158 (66.7%) exposed to NPH; and 127 (54.2%) in the PP population exposed to detemir and 137 (57.8%) exposed to NPH All subjects were female and the age range was 20 to 43 years	Female, aged ≥18 years T1DM treated with insulin for at least 12 months before randomisation The subject was either: Planning to become pregnant in the immediate future and willing to undertake pregnancy counselling and a screening HbA1c ≤9.0% *or* Pregnant with an intrauterine singleton living foetus, GW = 8-12 at randomisation, confirmed by an ultra sound scan and an HbA1c ≤8.0% at confirmation of pregnancy Willingness to take folic acid before pregnancy and during the first trimester	Before and during pregnancy for up to 23 months	Insulin detemir 100 U/mL, 3 mL cartridge, administered using a NovoPen All subjects also received insulin aspart as bolus insulin Insulin dose was adjusted in order to achieve preprandial PG in the range 4.0 to 6.0 mmol/L, and 2 hour postprandial glucose <7.0 mmol/L	NPH insulin 100 U/mL, 3 mL cartridge, administered using a NovoPen	Efficacy: HbA1c Response categories: HbA1c ≤6.0% at GW24 and GW36 8-point SMPG FPG Safety: Hypoglycaemic episodes Mode of delivery AEs and laboratory parameters during pregnancy Insulin antibodies Diabetic complications Birth weight Prematurity Perinatal mortality Neonatal mortality Insulin antibodies in cord blood Presence of detemir in cord blood	Insulin detemir was not inferior to insulin NPH. The mean (SE) HbA1c at GW36 for the PP population was 6.22 (0.069) % for detemir and 6.37 (0.067) % for NPH, mean (95% CI) difference -0.15 (-0.34 to 0.04) %. For the FAS the mean (SE) HbA1c at GW36 was 6.27 (0.053) % for detemir and 6.33 (0.052) % for NPH, mean (95% CI) difference -0.06 (-0.21 to 0.08) %. HbA1c ≤6% at GW24 and GW36 was achieved by 57 (41.3%) subjects in the detemir group and 46 (31.5%) in the NPH. At the GW36 visit mean (SE) FPG was 4.76 (0.200) mmol/L in the detemir group and 5.41 (0.187) mmol/L in the NPH, mean (95% CI) difference -0.94 (-1.19 to -0.12) mmol, p = 0.017.	There were 650 TEAEs reported in 138 (90.8%) subjects in the detemir group (and 678 in 141 (89.2%) in the NPH. In the neonatal population, there were 121 TEAEs reported in 56 (36.8%) subjects in the detemir group and 152 in 55 (34.8%) in the NPH. There were no maternal deaths. There were three perinatal deaths: two in the detemir group and one in the NPH; and two early pregnancy losses: one in each group. There were 94 SAEs reported in 61 (40.1%) maternal subjects in the detemir group and 76 in 49 (31.0%) in the NPH. In the neonatal population, there were 51 SAEs reported in 36 (23.7%) subjects in the detemir group and 53 in 32 (20.3%) in the NPH. DAE occurred in 13 (8.6%) subjects in the detemir group and six (3.8%) in the NPH.

Table 26: Treatment Emergent Adverse Events Occurring in >10% of Subjects (SOC and Preferred Terms) - Full Analysis Set

	Detemir Alone (Day 1)		Liraglutide Titration (Day 2-21)		Liraglutide Alone (Day 22)		Liraglutide Maintenance (Day 23-35)		Detemir + Liraglutide (Day 36)		Day 37 and after		Total	
	N (%)	E	N (%)	E	N (%)	E	N (%)	E	N (%)	E	N (%)	E	N (%)	E
Adverse Events	14 (42.4)	16	21 (63.6)	37	17 (51.5)	20	6 (18.2)	10	13 (39.4)	13	11 (33.3)	11	32 (97.0)	107
Blood and lymphatic system disorders	0	0	0	0	0	0	0	0	0	0	4 (12.1)	4	4 (12.1)	4
Anaemia	0	0	0	0	0	0	0	0	0	0	2 (6.1)	2	2 (6.1)	2
Iron deficiency anaemia	0	0	0	0	0	0	0	0	0	0	2 (6.1)	2	2 (6.1)	2
Gastrointestinal disorders	0	0	11 (33.3)	16	3 (9.1)	3	4 (12.1)	8	1 (3.0)	1	1 (3.0)	1	16 (48.5)	29
Abdominal discomfort	0	0	1 (3.0)	1	2 (6.1)	2	1 (3.0)	1	0	0	0	0	4 (12.1)	4
Diarrhoea	0	0	4 (12.1)	4	0	0	3 (9.1)	3	0	0	1 (3.0)	1	8 (24.2)	8
Nausea	0	0	6 (18.2)	6	0	0	3 (9.1)	3	0	0	0	0	8 (24.2)	9
General disorders and administration site conditions	0	0	5 (15.2)	7	1 (3.0)	1	0	0	2 (6.1)	2	0	0	8 (24.2)	10
Investigations	0	0	4 (12.1)	4	0	0	0	0	0	0	0	0	4 (12.1)	4
Weight decreased	0	0	4 (12.1)	4	0	0	0	0	0	0	0	0	4 (12.1)	4
Infections and infestations	0	0	3 (9.1)	3	0	0	0	0	0	0	2 (6.1)	2	4 (12.1)	5
Musculoskeletal and connective tissue disorders	3 (9.1)	3	0	0	3 (9.1)	3	0	0	2 (6.1)	2	2 (6.1)	2	7 (21.2)	10
Nervous system disorders	11 (33.3)	11	3 (9.1)	3	10 (30.3)	10	0	0	7 (21.2)	7	0	0	17 (51.5)	31
Headache	10 (30.3)	10	2 (6.1)	2	9 (27.3)	9	0	0	7 (21.2)	7	0	0	14 (42.4)	28

The Classification of an AE into Day 1, Day 2-21, Day 22, Day 23-35, Day 36 or Day 37 and after is based on the onset date of the AE.
N: Number of subjects with adverse events.
%: Proportion of subjects in analysis set having adverse event.
E: Number of adverse events.

Table 25: Treatment Emergent Adverse Events (TEAE) with an Incidence ≥ 5% of Subjects in Any Treatment group by System Organ Class and Preferred Term - Safety Analysis Set

	Lira 1.8			Detemir + Lira 1.8			Non-randomised Lira 1.8			Intensified			Early Withdrawals		
	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E
Safety Analysis Set	159			163			499			24			166		
Intensified	17						7			24					
All Adverse Events	124	(78.0)	716	132	(81.0)	845	433	(86.8)	2389	14	(58.3)	30	122	(73.5)	383
Gastrointestinal disorders	74	(46.5)	182	77	(47.2)	202	241	(48.3)	696	3	(12.5)	4	98	(59.0)	212
Diarrhoea	26	(16.4)	29	29	(17.8)	42	74	(14.8)	108	1	(4.2)	1	21	(12.7)	25
Nausea	37	(23.3)	51	30	(18.4)	40	136	(27.3)	204	1	(4.2)	1	66	(39.8)	72
Vomiting	19	(11.9)	21	17	(10.4)	26	50	(10.0)	115				21	(12.7)	25
Dyspepsia	8	(5.0)	11	10	(6.1)	11	42	(8.4)	54				33	(19.9)	42
Constipation	11	(6.9)	11	8	(4.9)	10	25	(5.0)	30				11	(6.6)	11
Abdominal Pain	8	(5.0)	11	6	(3.7)	7	14	(2.8)	17				5	(3.0)	6
Infections and infestations	74	(46.5)	140	72	(44.2)	153	196	(39.3)	352	4	(16.7)	5	8	(4.8)	10
Nasopharyngitis	40	(25.2)	57	33	(20.2)	45	72	(14.4)	97	3	(12.5)	3	2	(1.2)	2
Upper Respiratory Tract Infection	9	(5.7)	14	13	(8.0)	13	21	(4.2)	24						
Nervous system disorders	38	(23.9)	74	35	(21.5)	84	123	(24.6)	241	2	(8.3)	2	21	(12.7)	34
Headache	23	(14.5)	41	21	(12.9)	54	73	(14.6)	144	2	(8.3)	2	13	(7.8)	22
Investigations	34	(21.4)	58	42	(25.8)	66	109	(21.8)	163	4	(16.7)	4	14	(8.4)	18
Lipase Increased	16	(10.1)	17	26	(16.0)	27	55	(11.0)	60	4	(16.7)	4	6	(3.6)	7
General disorders and administration site conditions	22	(13.8)	35	31	(19.0)	62	81	(16.2)	114	1	(4.2)	1	25	(15.1)	31
Fatigue	9	(5.7)	10	12	(7.4)	13	15	(3.0)	16				6	(3.6)	8
Musculoskeletal and connective tissue disorders	33	(20.8)	47	27	(16.6)	53	115	(23.0)	182	3	(12.5)	3	9	(5.4)	11
Back Pain	10	(6.3)	10	4	(2.5)	6	26	(5.2)	30	1	(4.2)	1	4	(2.4)	5
Respiratory, thoracic and mediastinal disorders	24	(15.1)	34	26	(16.0)	34	69	(13.8)	92				4	(2.4)	4
Oropharyngeal Pain	10	(6.3)	11	5	(3.1)	5	17	(3.4)	19				2	(1.2)	2
Metabolism and nutrition disorders	17	(10.7)	19	19	(11.7)	20	66	(13.2)	72	1	(4.2)	1	19	(11.4)	19
Decreased Appetite	9	(5.7)	9	13	(8.0)	13	50	(10.0)	53				17	(10.2)	17

All subjects also received metformin
AEs of intensified subjects are tabulated in initial treatment group if the AE occur before intensification. If the AE increase in severity after intensification it will be tabulated in both treatment groups
N: Number of subjects with adverse event
%: Proportion of subjects in analysis set having adverse event
E: Number of adverse events

Table 28: Common Treatment-emergent AEs (≥5%) by SOC and Preferred Term, during Pregnancy, Mother, Safety Pregnant

System Organ Class - Preferred Term	Detemir N	Detemir (%)	Detemir E	Detemir R	NPH N	NPH (%)	NPH E	NPH R
All subjects	152				158			
Exposure (yr)	82.4				86.3			
Events	138	(90.8)	650	788.9	141	(89.2)	678	785.9
Infections and infestations	88	(57.9)	166	201.5	86	(54.4)	156	180.8
Nasopharyngitis	40	(26.3)	64	77.7	40	(25.3)	51	59.1
Urinary tract infection	15	(9.9)	16	19.4	9	(5.7)	10	11.6
Gastroenteritis	13	(8.6)	13	15.8	8	(5.1)	10	11.6
Upper respiratory tract infection	6	(3.9)	7	8.5	11	(7.0)	14	16.2
Influenza	3	(2.0)	3	3.6	13	(8.2)	13	15.1
Pregnancy, puerperium and perinatal conditions	63	(41.4)	87	105.6	73	(46.2)	106	122.9
Pre-eclampsia	16	(10.5)	16	19.4	11	(7.0)	11	12.8
Threatened labour	5	(3.3)	5	6.1	10	(6.3)	13	15.1
Polyhydramnios	5	(3.3)	5	6.1	8	(5.1)	8	9.3
Abortion spontaneous	8	(5.3)	8	9.7	4	(2.5)	4	4.6
Cervical incompetence	2	(1.3)	2	2.4	2	(1.3)	2	2.3
Abortion missed	1	(0.7)	1	1.2	2	(1.3)	2	2.3
Abortion incomplete	1	(0.7)	1	1.2				
Blighted ovum					1	(0.6)	1	1.2
Nervous system disorders	47	(30.9)	91	110.5	38	(24.1)	94	109.0
Headache	37	(24.3)	77	93.5	32	(20.3)	79	91.6
Gastrointestinal disorders	51	(33.6)	92	111.7	46	(29.1)	80	92.7
Diarrhoea	18	(11.8)	23	27.9	8	(5.1)	10	11.6
Abdominal pain	8	(5.3)	8	9.7	10	(6.3)	12	13.9
Abdominal pain upper	9	(5.9)	10	12.1	6	(3.8)	8	9.3
Vomiting	8	(5.3)	9	10.9	7	(4.4)	8	9.3
Toothache	5	(3.3)	7	8.5	8	(5.1)	9	10.4
Blood and lymphatic system disorders	23	(15.1)	24	29.1	21	(13.3)	22	25.5
Anaemia	20	(13.2)	21	25.5	17	(10.8)	17	19.7
Eye disorders	19	(12.5)	22	26.7	17	(10.8)	23	26.7
Diabetic retinopathy	5	(3.3)	5	6.1	8	(5.1)	10	11.6
Respiratory, thoracic and mediastinal disorders	13	(8.6)	18	21.8	18	(11.4)	21	24.3
Oropharyngeal pain	8	(5.3)	10	12.1	10	(6.3)	11	12.8

N: Number of subjects; %: Percentage of subjects; E: Number of events; R: Rate - Number of events per 100 exposure years

Table 28: Common Adverse Events (Occurring in ≥4 Children in Any Treatment Group) by System Organ Class and Preferred Term, Child, Safety Pregnant

System Organ Class - Preferred Term	Detemir N	Detemir (%)	Detemir E	NPH N	NPH (%)	NPH E
All subjects	152			158		
Events	56	(36.8)	121	55	(34.8)	152
Pregnancy, puerperium and perinatal conditions	26	(17.1)	34	27	(17.1)	34
Foetal distress syndrome	10	(6.6)	10	9	(5.7)	9
Jaundice neonatal	8	(5.3)	8	6	(3.8)	6
Premature baby	6	(3.9)	6	7	(4.4)	7
Foetal macrosomia				4	(2.5)	4
Respiratory, thoracic and mediastinal disorders	13	(8.6)	14	11	(7.0)	15
Neonatal respiratory distress syndrome	4	(2.6)	4	2	(1.3)	2
Transient tachypnoea of the newborn	4	(2.6)	4	2	(1.3)	2
Nervous system disorders	5	(3.3)	5	9	(5.7)	16
Depressed level of consciousness	1	(0.7)	1	4	(2.5)	4
Investigations	3	(2.0)	3	7	(4.4)	7
Cardiac murmur				4	(2.5)	4
Hepatobiliary disorders	5	(3.3)	5	3	(1.9)	3
Jaundice	3	(2.0)	3	2	(1.3)	2

N: Number of subjects; %: Percentage of subjects; E: Number of events;
R: Rate - Number of events per 100 exposure years

Table 40: Treatment Emergent Adverse Event Leading to Discontinuation by System Organ Class - Safety Analysis Set

	Lira 1.8			Detemir + Lira 1.8			Non-randomised Lira 1.8			Intensified			Early Withdrawals		
	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E
Safety Analysis Set	159			163			499			24			166		
Intensified	17						7			24					
All Adverse Events	9	(5.7)	13	7	(4.3)	8	19	(3.8)	25				91	(54.8)	193
Investigations	3	(1.9)	5	2	(1.2)	2	9	(1.8)	11				3	(1.8)	3
Lipase Increased	3	(1.9)	3	1	(0.6)	1	8	(1.6)	8						
Pancreatic Enzymes Increased				1	(0.6)	1									
Blood Alkaline Phosphatase Increased	1	(0.6)	1												
Blood Amylase Increased	1	(0.6)	1				2	(0.4)	2						
Blood Calcitonin Increased							1	(0.2)	1						
Renal Function Test Abnormal													1	(0.6)	1
Weight Decreased													2	(1.2)	2
Gastrointestinal disorders	3	(1.9)	4	1	(0.6)	2	5	(1.0)	6				76	(45.8)	125
Abdominal Pain	1	(0.6)	1	1	(0.6)	1							4	(2.4)	4
Diarrhoea				1	(0.6)	1	2	(0.4)	2				11	(6.6)	11
Abdominal Discomfort													5	(3.0)	5
Abdominal Distension	1	(0.6)	1										4	(2.4)	4
Abdominal Pain Upper							1	(0.2)	1				5	(3.0)	5
Change Of Bowel Habit													1	(0.6)	1
Constipation													4	(2.4)	4
Dyspepsia													4	(2.4)	4
Eructation													2	(1.2)	2
Flatulence							1	(0.2)	1				2	(1.2)	2
Gastritis													1	(0.6)	1
Gastrointestinal Disorder													1	(0.6)	1
Gastrooesophageal Reflux Disease													3	(1.8)	3
Nausea							1	(0.2)	1				49	(29.5)	49
Pancreatitis							1	(0.2)	1						
Pancreatitis Acute	1	(0.6)	1										1	(0.6)	1
Pancreatitis Chronic	1	(0.6)	1												
Vomiting													28	(16.9)	28
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(0.6)	1	1	(0.6)	1	2	(0.4)	2				1	(0.6)	1
Breast Cancer				1	(0.6)	1									
Gastric Cancer							1	(0.2)	1						
Metastases To Central Nervous System	1	(0.6)	1												
Renal Cancer							1	(0.2)	1						
Thyroid Cancer													1	(0.6)	1

Table 40: Treatment Emergent Adverse Event Leading to Discontinuation by System Organ Class - Safety Analysis Set continued

	Lira 1.8			Detemir + Lira 1.8			Non-randomised Lira 1.8			Intensified			Early Withdrawals		
	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E
Safety Analysis Set	159			163			499			24			166		
Intensified	17						7			24					
All Adverse Events	9	(5.7)	13	7	(4.3)	8	19	(3.8)	25				91	(54.8)	193
Investigations	3	(1.9)	5	2	(1.2)	2	9	(1.8)	11				3	(1.8)	3
Lipase Increased	3	(1.9)	3	1	(0.6)	1	8	(1.6)	8						
Pancreatic Enzymes Increased				1	(0.6)	1									
Blood Alkaline Phosphatase Increased	1	(0.6)	1												
Blood Amylase Increased	1	(0.6)	1				2	(0.4)	2						
Blood Calcitonin Increased							1	(0.2)	1						
Renal Function Test Abnormal													1	(0.6)	1
Weight Decreased													2	(1.2)	2
Gastrointestinal disorders	3	(1.9)	4	1	(0.6)	2	5	(1.0)	6				76	(45.8)	125
Abdominal Pain	1	(0.6)	1	1	(0.6)	1							4	(2.4)	4
Diarrhoea				1	(0.6)	1	2	(0.4)	2				11	(6.6)	11
Abdominal Discomfort													5	(3.0)	5
Abdominal Distension	1	(0.6)	1										4	(2.4)	4
Abdominal Pain Upper							1	(0.2)	1				5	(3.0)	5
Change Of Bowel Habit													1	(0.6)	1
Constipation													4	(2.4)	4
Dyspepsia													4	(2.4)	4
Eructation													2	(1.2)	2
Flatulence							1	(0.2)	1				2	(1.2)	2
Gastritis													1	(0.6)	1
Gastrointestinal Disorder													1	(0.6)	1
Gastrooesophageal Reflux Disease													3	(1.8)	3
Nausea							1	(0.2)	1				49	(29.5)	49
Pancreatitis							1	(0.2)	1						
Pancreatitis Acute	1	(0.6)	1										1	(0.6)	1
Pancreatitis Chronic	1	(0.6)	1												
Vomiting													28	(16.9)	28
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(0.6)	1	1	(0.6)	1	2	(0.4)	2				1	(0.6)	1
Breast Cancer				1	(0.6)	1									
Gastric Cancer							1	(0.2)	1						
Metastases To Central Nervous System	1	(0.6)	1												
Renal Cancer							1	(0.2)	1						
Thyroid Cancer													1	(0.6)	1

Table 40: Treatment Emergent Adverse Event Leading to Discontinuation by System Organ Class - Safety Analysis Set continued

	Lira 1.8			Detemir + Lira 1.8			Non-randomised Lira 1.8			Intensified			Early Withdrawals		
	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E
Nervous system disorders				1	(0.6)	1	1	(0.2)	1				10	(6.0)	10
Convulsion				1	(0.6)	1									
Dizziness													2	(1.2)	2
Headache							1	(0.2)	1				7	(4.2)	7
Tremor													1	(0.6)	1
Renal and urinary disorders	1	(0.6)	1	1	(0.6)	1	1	(0.2)	1						
Renal Failure				1	(0.6)	1	1	(0.2)	1						
Renal Failure Acute	1	(0.6)	1												
Respiratory, thoracic and mediastinal disorders				1	(0.6)	1									
Bronchopulmonary Disease				1	(0.6)	1									
Cardiac disorders													4	(2.4)	4
Angina Pectoris													1	(0.6)	1
Palpitations													1	(0.6)	1
Tachyarrhythmia													1	(0.6)	1
Tachycardia													1	(0.6)	1
Endocrine disorders							1	(0.2)	1						
Thyroid C-Cell Hyperplasia							1	(0.2)	1						
Eye disorders													1	(0.6)	1
Vision Blurred													1	(0.6)	1
General disorders and administration site conditions													18	(10.8)	19
Asthenia													9	(5.4)	9
Drug Therapeutic Incompatibility													1	(0.6)	1
Fatigue													4	(2.4)	4
Irritability													1	(0.6)	1
Malaise													3	(1.8)	3
Sensation Of Foreign Body													1	(0.6)	1
Hepatobiliary disorders	1	(0.6)	1												
Cholelithiasis	1	(0.6)	1												
Infections and infestations	1	(0.6)	1										1	(0.6)	1
Cystitis													1	(0.6)	1
Helicobacter Gastritis	1	(0.6)	1												

Table 42: Laboratory abnormalities reported as TEAEs – safety set

	Lira 1.8			Detemir + Lira 1.8			Non-randomised Lira 1.8			Intensified			Early WD		
	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E
Investigations	34	(21.4)	58	42	(25.8)	66	109	(21.8)	163	4	(16.7)	4	14	(8.4)	18
Lipase Increased	16	(10.1)	17	26	(16.0)	27	55	(11.0)	60	4	(16.7)	4	6	(3.6)	7
Blood Amylase Increased	3	(1.9)	3	4	(2.5)	4	17	(3.4)	20				1	(0.6)	1
Blood Creatine Phosphokinase Increased	3	(1.9)	3	3	(1.8)	4	8	(1.6)	8						
White Blood Cell Count Increased	1	(0.6)	1	3	(1.8)	4	3	(0.6)	3						
Alanine Aminotransferase Increased	1	(0.6)	1	2	(1.2)	2	4	(0.8)	5						
Blood Proinsulin Increased				2	(1.2)	2									
Blood Calcitonin Increased	4	(2.5)	4	1	(0.6)	1	10	(2.0)	10						
Blood Cholesterol Increased				1	(0.6)	1									
Blood Creatinine Decreased				1	(0.6)	1									
Blood Creatinine Increased	3	(1.9)	3	1	(0.6)	1	3	(0.6)	3						
Blood Glucose Abnormal				1	(0.6)	1									
Blood Glucose Increased	2	(1.3)	2	1	(0.6)	1	1	(0.2)	1						
Blood Insulin Increased				1	(0.6)	1	1	(0.2)	1						
Blood Parathyroid Hormone Increased				1	(0.6)	1									
Blood Potassium Increased	2	(1.3)	2	1	(0.6)	1	3	(0.6)	4						
Cardiac Murmur	1	(0.6)	1	1	(0.6)	1									
Haematocrit Decreased	2	(1.3)	2	1	(0.6)	1	1	(0.2)	1				1	(0.6)	1
Haemoglobin Decreased	3	(1.9)	3	1	(0.6)	1	4	(0.8)	4						
Insulin C-Peptide Increased				1	(0.6)	1									
Lipase Abnormal				1	(0.6)	1									
Lipids Increased				1	(0.6)	1									
Neutrophil Count Abnormal				1	(0.6)	1									
Neutrophil Count Increased				1	(0.6)	1									
Pancreatic Enzymes Increased	1	(0.6)	1	1	(0.6)	1	1	(0.2)	1						
Platelet Count Increased				1	(0.6)	2									
Red Blood Cell Count Decreased	2	(1.3)	2	1	(0.6)	1							1	(0.6)	1
Weight Decreased	1	(0.6)	1	1	(0.6)	1	2	(0.4)	2				2	(1.2)	2
Weight Increased				1	(0.6)	1	1	(0.2)	1						
Aortic Bruit	1	(0.6)	1												
Aspartate Aminotransferase Increased							3	(0.6)	3						
Biopsy Prostate							1	(0.2)	1						
Blood Alkaline Phosphatase Increased	1	(0.6)	1				1	(0.2)	1						
Blood Bilirubin Increased							1	(0.2)	1						
Blood Calcium Decreased	1	(0.6)	1				1	(0.2)	1						
Blood Calcium Increased							1	(0.2)	1						
Blood Creatine Phosphokinase Abnormal							1	(0.2)	1						
Blood Pressure Increased							4	(0.8)	4						
Blood Thyroid Stimulating Hormone Increased							1	(0.2)	1						
Blood Triglycerides Increased	3	(1.9)	3				4	(0.8)	4				1	(0.6)	1
Blood Urea Increased	2	(1.3)	2				2	(0.4)	2						
Blood Urine Present							1	(0.2)	1						
Borrelia Test Positive							1	(0.2)	1						
Colonoscopy							1	(0.2)	1						
Electrocardiogram Abnormal							1	(0.2)	1						
Electrocardiogram Change							1	(0.2)	1						
Eosinophil Count Increased							1	(0.2)	1						
Glomerular Filtration Rate Decreased							1	(0.2)	1						
Glucose Urine Present	1	(0.6)	1												
Glycosylated Haemoglobin Increased	1	(0.6)	1										1	(0.6)	1

Table 42: Laboratory abnormalities reported as TEAEs – safety set continued

	Lira 1.8			Detemir + Lira 1.8			Non-randomised Lira 1.8			Intensified			Early WD		
	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E
Haemoglobin Urine Present							1	(0.2)	1						
Hepatic Enzyme Increased							1	(0.2)	1						
Intraocular Pressure Increased							1	(0.2)	1						
Liver Function Test Abnormal	1	(0.6)	1				1	(0.2)	1						
Neutrophil Count Decreased							1	(0.2)	1						
Prostatic Specific Antigen Increased							1	(0.2)	1						
Protein Urine													1	(0.6)	1
Protein Urine Present	1	(0.6)	1				2	(0.4)	2				1	(0.6)	1
Renal Function Test Abnormal													1	(0.6)	1
Thyroid Function Test Abnormal							1	(0.2)	1						
Very Low Density Lipoprotein Increased							1	(0.2)	1						
Vitamin D Decreased							1	(0.2)	1						
White Blood Cell Count Decreased							1	(0.2)	1				1	(0.6)	1

Table 46: Pancreas Related Treatment Emergent Adverse Events (TEAEs) Classified as MESIs by System Organ Class and Preferred Term - Safety Analysis Set

	Lira 1.8			Detemir + Lira 1.8			Non-randomised Lira 1.8			Intensified			Early Withdrawals		
	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E
Safety Analysis Set	159			163			499			24			166		
Intensified	17						7			24					
All Adverse Events	14	(8.8)	15	18	(11.0)	18	39	(7.8)	42	2	(8.3)	2	5	(3.0)	6
Investigations	12	(7.5)	13	16	(9.8)	16	38	(7.6)	41	2	(8.3)	2	4	(2.4)	5
Lipase Increased	12	(7.5)	13	16	(9.8)	16	37	(7.4)	38	2	(8.3)	2	4	(2.4)	5
Blood Amylase Increased							3	(0.6)	3						
Gastrointestinal disorders	2	(1.3)	2	1	(0.6)	1	1	(0.2)	1				1	(0.6)	1
Pancreatic Disorder				1	(0.6)	1									
Pancreatitis							1	(0.2)	1						
Pancreatitis Acute	1	(0.6)	1										1	(0.6)	1
Pancreatitis Chronic	1	(0.6)	1												
Metabolism and nutrition disorders				1	(0.6)	1									
Hyperlipasaemia				1	(0.6)	1									

All subjects also received metformin
AEs of intensified subjects are tabulated in initial treatment group if the AE occurs before intensification. If the AE increases in severity after intensification it will be tabulated in both treatment groups
N: Number of subjects with adverse event
%: Proportion of subjects in analysis set having adverse event
E: Number of adverse events

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