Comparison of Insulin Detemir and Insulin Aspart in 2 Separate Injections Twice Daily to Extemporaneous Mixing Injection Regimen Twice Daily - The Paediatric Mixing Trial (MIXING)

This study has been completed.

Sponsor:
Novo Nordisk A/S

Information provided by (Responsible Party):
Novo Nordisk A/S

ClinicalTrials.gov Identifier:
NCT00542620

First received: October 10, 2007
Last updated: October 24, 2014
Last verified: October 2014
History of Changes

Results First Received: December 5, 2011

Study Type:	Interventional
Study Design:	Allocation: Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Parallel Assignment; Masking: Open Label; Primary Purpose: Treatment
Conditions:	Diabetes Diabetes Mellitus, Type 1
Interventions:	Drug: insulin detemir Drug: insulin aspart

Participant Flow

Hide Participant Flow

Recruitment Details

Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and locations
Four centres in France

Pre-Assignment Details

Significant events and approaches for the overall study following participant enrollment, but prior to group assignment
Children with type 1 diabetes currently treated with insulin detemir and insulin aspart and with a good glycaemic control. At trial entry, subjects must be 6-18 years old with a HbA1c (glycosylated haemoglobin) below or equal to 8.6%

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Participant Flow: Overall Study

	Mixed Injection	Separate Injection
STARTED	13	12
Exposed to Drug	12 [1]	13 [1]
COMPLETED	13	12
NOT COMPLETED	0	0

[1] One subject randomly assigned to receive mixed injections, but received a separate injection mode

Baseline Characteristics

Hide Baseline Characteristics

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
No text entered.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Total	Total of all reporting groups

Baseline Measures

	Mixed Injection	**Separate Injection**	**Total**
Number of Participants [units: participants]	**13**	**12**	**25**
Age [units: years] Mean (Standard Deviation)	**11.6 (2.6)**	**10.9 (2.5)**	**11.3 (2.5)**
Gender [units: participants]			
Female	**5**	**7**	**12**
Male	**8**	**5**	**13**
Region of Enrollment [units: participants]			
France	**13**	**12**	**25**
Diabetes history [1] **[units: years] Mean (Standard Deviation)**	**6.68 (3.51)**	**6.13 (2.38)**	**6.42 (2.97)**

[1] Number of years since diagnosis

Outcome Measures

Hide All Outcome Measures

1. Primary: Glycosylated Haemoglobin A1c (HbA1c) [Time Frame: Week 0 and Week 8]

Measure Type	Primary
Measure Title	Glycosylated Haemoglobin A1c (HbA1c)
Measure Description	Measured for the Per Protocol (PP) set
Time Frame	Week 0 and Week 8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Per Protocol (PP) analysis set consists of all the ITT (Intention-to-Treat) subjects who did not present any significant protocol deviations that could potentially affect the efficacy results. One subject was excluded from PP as subject received separate injections despite being randomised to receive mixed injections.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	Separate Injection
Number of Participants Analyzed [units: participants]	**12**	**12**
Glycosylated Haemoglobin A1c (HbA1c) [units: percentage of total haemoglobin] Mean (Standard Deviation)		
Week 0	**8.00 (0.54)**	**7.77 (0.55)**
Week 8	**7.63 (0.55)**	**8.15 (0.57)**

Statistical Analysis 1 for Glycosylated Haemoglobin A1c (HbA1c)

Groups [1]	All groups
Non-Inferiority/Equivalence Test [2]	Yes
Method [3]	ANCOVA
P Value [4]	0.001
Median Difference (Final Values) [5]	-0.691
95% Confidence Interval	-1.049 to -0.334

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Details of power calculation, definition of non-inferiority margin, and other key parameters:
	Non-inferiority was considered confirmed if the upper bound of the two-sided 95% confidence interval was below or equal to 0.25% or equivalently if the p-value for the one-sided test of H0: D>0.25% against HA: D=<0.25%, was less than or equal to 2.5%, where D is the mean treatment difference (mixing injections minus separate injections).
[3]	Other relevant method information, such as adjustments or degrees of freedom:
	Baseline HbA1c as covariate
[4]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	If non-inferiority was confirmed, the superiority of the mixed injection group over separate injection group was to be investigated
[5]	Other relevant estimation information:
	No text entered.

2. Primary: Glycosylated Haemoglobin A1c (HbA1c) [Time Frame: Week 0 and Week 8]

Measure Type	Primary
Measure Title	Glycosylated Haemoglobin A1c (HbA1c)
Measure Description	Measured for the ITT (Intention-to-Treat) set
Time Frame	Week 0 and Week 8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention-to-treat (ITT) analysis set consists of all randomised children with a signed informed consent and at least one HbA1c value determined after randomisation. Subjects are analysed based on initial randomisation.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	Separate Injection
Number of Participants Analyzed [units: participants]	**13**	**12**
Glycosylated Haemoglobin A1c (HbA1c) [units: percentage of total haemoglobin] Mean (Standard Deviation)		
Week 0	**7.93 (0.57)**	**7.77 (0.55)**
Week 8	**7.65 (0.53)**	**8.15 (0.57)**

Statistical Analysis 1 for Glycosylated Haemoglobin A1c (HbA1c)

Groups [1]	All groups
Non-Inferiority/Equivalence Test [2]	Yes
Method [3]	ANCOVA
P Value [4]	0.003
Mean Difference (Final Values) [5]	-0.594
95% Confidence Interval	-0.970 to -0.219

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Details of power calculation, definition of non-inferiority margin, and other key parameters:
	Non-inferiority was considered confirmed if the upper bound of the two-sided 95% confidence interval was below or equal to 0.25% or equivalently if the p-value for the one-sided test of H0: D>0.25% against HA: D=<0.25%, was less than or equal to 2.5%, where D is the mean treatment difference (mixing injections minus separate injections).
[3]	Other relevant method information, such as adjustments or degrees of freedom:
	Baseline HbA1c as covariate.
[4]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	If non-inferiority was confirmed, the superiority of the mixed injection group over separate injection group was to be investigated.
[5]	Other relevant estimation information:
	No text entered.

3. Secondary: Fructosamine [Time Frame: Week 0 and Week 8]

Measure Type	Secondary
Measure Title	Fructosamine
Measure Description	No text entered.

Time Frame	Week 0 and Week 8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention-to-treat (ITT) analysis set consists of all randomised children with a signed informed consent and at least one HbA1c value determined after randomisation. Subjects are analysed based on initial randomisation.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	**Separate Injection**
Number of Participants Analyzed [units: participants]	**13**	**12**
Fructosamine [units: mmol/L] Mean (Standard Deviation)		
Week 0, n=13, 12	**334.8 (35.9)**	**319.8 (22.6)**
Week 8, n=12, 12	**316.4 (30.1)**	**334.8 (41.9)**

Statistical Analysis 1 for Fructosamine

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.573
Mean Difference (Final Values) [4]	-8.35
Standard Error of the mean	(14.59)
95% Confidence Interval	-38.77 to 22.08

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	With adjustment on baseline fructosamine and the change in insulin administration mode
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.
[4]	Other relevant estimation information:
	No text entered.

4. Secondary: Self-measured Plasma Glucose Profile (Before Breakfast) [Time Frame: Week 0 and Week 8]

Measure Type	Secondary
Measure Title	Self-measured Plasma Glucose Profile (Before Breakfast)
Measure Description	No text entered.

Time Frame	Week 0 and Week 8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention-to-treat (ITT) analysis set consists of all randomised children with a signed informed consent and at least one HbA1c value determined after randomisation. Subjects are analysed based on initial randomisation.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	**Separate Injection**
Number of Participants Analyzed [units: participants]	**13**	**12**
Self-measured Plasma Glucose Profile (Before Breakfast) [units: mg/dL] Mean (Standard Deviation)		
Week 0	**190.31 (56.80)**	**165.39 (70.28)**
Week 8	**162.96 (57.46)**	**204.75 (59.25)**

Statistical Analysis 1 for Self-measured Plasma Glucose Profile (Before Breakfast)

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.063

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	With adjustment on baseline value
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.

5. Secondary: Self-measured Plasma Glucose Profile (After Breakfast) [Time Frame: Week 0 and Week 8]

Measure Type	Secondary
Measure Title	Self-measured Plasma Glucose Profile (After Breakfast)
Measure Description	No text entered.
Time Frame	Week 0 and Week 8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.

Intention-to-treat (ITT) analysis set consists of all randomised children with a signed informed consent and at least one HbA1c value determined after randomisation. Subjects are analysed based on initial randomisation.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	Separate Injection
Number of Participants Analyzed [units: participants]	**5**	**7**
Self-measured Plasma Glucose Profile (After Breakfast) [units: mg/dL] Mean (Standard Deviation)		
Week 0, n=5, 6	**123.00 (61.9)**	**164.89 (73.33)**
Week 8, n=4, 7	**208.08 (48.19)**	**167.98 (70.64)**

Statistical Analysis 1 for Self-measured Plasma Glucose Profile (After Breakfast)

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.389

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	With adjustment on baseline value
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.

6. Secondary: Self-measured Plasma Glucose Profile (Before Dinner) [Time Frame: Week 0 and Week 8]

Measure Type	Secondary
Measure Title	Self-measured Plasma Glucose Profile (Before Dinner)
Measure Description	No text entered.
Time Frame	Week 0 and Week 8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention-to-treat (ITT) analysis set consists of all randomised children with a signed informed consent and at least one HbA1c value determined after randomisation. Subjects are analysed based on initial randomisation.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice

	daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	Separate Injection
Number of Participants Analyzed [units: participants]	**13**	**12**
Self-measured Plasma Glucose Profile (Before Dinner) [units: mg/dL] Mean (Standard Deviation)		
Week 0	**199.14 (42.05)**	**201.44 (57.50)**
Week 8	**185.23 (66.30)**	**181.03 (68.41)**

Statistical Analysis 1 for Self-measured Plasma Glucose Profile (Before Dinner)

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.856

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	With adjustment on baseline value
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.

7. Secondary: Self-measured Plasma Glucose Profile (After Dinner) [Time Frame: Week 0 and Week 8]

Measure Type	Secondary
Measure Title	Self-measured Plasma Glucose Profile (After Dinner)
Measure Description	No text entered.
Time Frame	Week 0 and Week 8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention-to-treat (ITT) analysis set consists of all randomised children with a signed informed consent and at least one HbA1c value determined after randomisation. Subjects are analysed based on initial randomisation. CGMS® data not available/sufficient for pre-study evaluation in five subjects or at post-study evaluation in four subjects.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	Separate Injection
Number of Participants Analyzed [units: participants]	**8**	**6**
Self-measured Plasma Glucose Profile (After Dinner) [units: mg/dL] Mean (Standard Deviation)		
Week 0, n=8, 5	**175.38 (58.47)**	**201.80 (59.12)**
Week 8, n=7, 6	**198.00 (53.85)**	**187.67 (85.63)**

Statistical Analysis 1 for Self-measured Plasma Glucose Profile (After Dinner)

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.917

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	With adjustment on baseline value
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.

8. Secondary: Pharmacokinetics: Cmax of Free Insulin [Time Frame: Week 0 and Week 8]

Measure Type	Secondary
Measure Title	Pharmacokinetics: Cmax of Free Insulin
Measure Description	The observed peak drug concentration at time (T): T0, T0.5hour (hr), T1hr, T1.5hr, T2 hours (hrs), T2.5hrs, T3hrs, T3.5hrs, T4hrs
Time Frame	Week 0 and Week 8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention-to-treat (ITT) analysis set consists of all randomised children with a signed informed consent and at least one HbA1c value determined after randomisation. Subjects are analysed based on initial randomisation.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	Separate Injection
Number of Participants Analyzed [units: participants]	**13**	**12**
Pharmacokinetics: Cmax of Free Insulin [units: pmol/L] Median (Standard Deviation)		

Week 0	**216 (542.4)**	**167 (130.4)**
Week 8	**274 (109.2)**	**186 (105.5)**

Statistical Analysis 1 for Pharmacokinetics: Cmax of Free Insulin

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.209

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	With adjustment on baseline value
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.

9. Secondary: Pharmacokinetics: Tmax of Free Insulin [Time Frame: Week 0 and Week 8]

Measure Type	Secondary
Measure Title	Pharmacokinetics: Tmax of Free Insulin
Measure Description	The observed peak drug concentration at time (T): T0, T0.5hour (hr), T1hr, T1.5hr, T2hrs, T2.5hrs, T3hrs, T3.5hrs, T4hrs
Time Frame	Week 0 and Week 8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention-to-treat (ITT) analysis set consists of all randomised children with a signed informed consent and at least one HbA1c value determined after randomisation. Subjects are analysed based on initial randomisation.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	**Separate Injection**
Number of Participants Analyzed [units: participants]	**13**	**12**
Pharmacokinetics: Tmax of Free Insulin [units: hours] Median (Standard Deviation)		
Week 0	**2.5 (0.74)**	**3.0 (0.98)**
Week 8	**2.5 (0.8)**	**1.8 (0.72)**

Statistical Analysis 1 for Pharmacokinetics: Tmax of Free Insulin

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.220

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	With adjustment on baseline value
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.

10. Secondary: Pharmacokinetics: Area Under the Concentration vs. Time Curve From Time Zero to the Time of the Last Measured Level of Free Insulin [Time Frame: Week 0 and Week 8]

Measure Type	Secondary
Measure Title	Pharmacokinetics: Area Under the Concentration vs. Time Curve From Time Zero to the Time of the Last Measured Level of Free Insulin
Measure Description	The observed peak drug concentration at time (T): T0, T0.5hour (hr), T1hr, T1.5hr, T2hrs, T2.5hrs, T3hrs, T3.5hrs, T4hrs
Time Frame	Week 0 and Week 8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention-to-treat (ITT) analysis set consists of all randomised children with a signed informed consent and at least one HbA1c value determined after randomisation. Subjects are analysed based on initial randomisation.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	**Separate Injection**
Number of Participants Analyzed [units: participants]	**13**	**12**
Pharmacokinetics: Area Under the Concentration vs. Time Curve From Time Zero to the Time of the Last Measured Level of Free Insulin [units: pmol.h/L] Median (Standard Deviation)		
Week 0	**638.4 (1022.95)**	**398.9 (395.19)**
Week 8	**819.6 (310.41)**	**466.2 (266.93)**

Statistical Analysis 1 for Pharmacokinetics: Area Under the Concentration vs. Time Curve From Time Zero to the Time of the Last Measured Level of Free Insulin

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.234

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	With adjustment for baseline value
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.

11. Secondary: Pharmacokinetics: Area Under the Concentration vs. Time Curve From Time Zero to Infinity of Free Insulin [Time Frame: Week 0 and Week 8]

Measure Type	Secondary
Measure Title	Pharmacokinetics: Area Under the Concentration vs. Time Curve From Time Zero to Infinity of Free Insulin
Measure Description	The observed peak drug concentration at time (T): T0, T0.5hour (hr), T1hr, T1.5hr, T2hrs, T2.5hrs, T3hrs, T3.5hrs, T4hrs
Time Frame	Week 0 and Week 8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention-to-treat (ITT) analysis set consists of all randomised children with a signed informed consent and at least one HbA1c value determined after randomisation. Subjects are analysed based on initial randomisation. CGMS® data not available/sufficient for pre-study evaluation in five subjects or at post-study evaluation in four subjects.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	**Separate Injection**
Number of Participants Analyzed [units: participants]	**11**	**11**
Pharmacokinetics: Area Under the Concentration vs. Time Curve From Time Zero to Infinity of Free Insulin [units: pmol.h/L] Median (Standard Deviation)		
Week 0, n=8, 9	**1441.3 (7516.22)**	**752.1 (4128.04)**
Week 8, n=11, 11	**1981.1 (1442.49)**	**672.8 (7156.05)**

Statistical Analysis 1 for Pharmacokinetics: Area Under the Concentration vs. Time Curve From Time Zero to Infinity of Free Insulin

Groups [1]	All groups

Method [2]	ANCOVA
P Value [3]	0.534

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	With adjustment on baseline value
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.

12. Secondary: Pharmacokinetics: Terminal Phase Elimination Half-life (T½) - Parameter of Free Insulin [Time Frame: Week 0 and Week 8]

Measure Type	Secondary
Measure Title	Pharmacokinetics: Terminal Phase Elimination Half-life (T½) - Parameter of Free Insulin
Measure Description	The observed peak drug concentration at time (T): T0, T0.5hour (hr), T1hr, T1.5hr, T2hrs, T2.5hrs, T3hrs, T3.5hrs, T4hrs
Time Frame	Week 0 and Week 8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention-to-treat (ITT) analysis set consists of all randomised children with a signed informed consent and at least one HbA1c value determined after randomisation. Subjects are analysed based on initial randomisation. CGMS® data not available/sufficient for pre-study evaluation in five subjects or at post-study evaluation in four subjects

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	**Separate Injection**
Number of Participants Analyzed [units: participants]	**11**	**11**
Pharmacokinetics: Terminal Phase Elimination Half-life (T½) - Parameter of Free Insulin [units: hours] Median (Standard Deviation)		
Week 0, n=8, 9	**3.6 (17.84)**	**2.3 (10.93)**
Week 8, n=11, 11	**2.9 (3.34)**	**2.0 (11.62)**

Statistical Analysis 1 for Pharmacokinetics: Terminal Phase Elimination Half-life (T½) - Parameter of Free Insulin

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.722

[1]	Additional details about the analysis, such as null hypothesis and power calculation:

	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	With adjustment on baseline value
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.

13. Secondary: Pharmacokinetics: Cmax of Insulin Detemir [Time Frame: Week 0 and Week 8]

Measure Type	Secondary
Measure Title	Pharmacokinetics: Cmax of Insulin Detemir
Measure Description	The observed peak drug concentration at time (T): T0, T0.5hour (hr), T1hr, T1.5hr, T2hrs, T2.5hrs, T3hrs, T3.5hrs, T4hrs
Time Frame	Week 0 and Week 8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention-to-treat (ITT) analysis set consists of all randomised children with a signed informed consent and at least one HbA1c value determined after randomisation. Subjects are analysed based on initial randomisation.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	Separate Injection
Number of Participants Analyzed [units: participants]	**13**	**12**
Pharmacokinetics: Cmax of Insulin Detemir [units: pmol/L] Median (Standard Deviation)		
Week 0	**10700 (25149.9)**	**10500 (6840.2)**
Week 8	**12000 (23807.2)**	**12600 (8426.6)**

Statistical Analysis 1 for Pharmacokinetics: Cmax of Insulin Detemir

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.727

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	With adjustment on baseline value
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

	No text entered.

14. Secondary: Pharmacokinetics: Tmax of Insulin Detemir [Time Frame: Week 0 and Week 8]

Measure Type	Secondary
Measure Title	Pharmacokinetics: Tmax of Insulin Detemir
Measure Description	The observed peak drug concentration at time (T): T0, T0.5hour (hr), T1hr, T1.5hr, T2hrs, T2.5hrs, T3hrs, T3.5hrs, T4hrs
Time Frame	Week 0 and Week 8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention-to-treat (ITT) analysis set consists of all randomised children with a signed informed consent and at least one HbA1c value determined after randomisation. Subjects are analysed based on initial randomisation.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	Separate Injection
Number of Participants Analyzed [units: participants]	**13**	**12**
Pharmacokinetics: Tmax of Insulin Detemir [units: hours] Median (Standard Deviation)		
Week 0	**3.5 (0.93)**	**3.5 (0.48)**
Week 8	**3.5 (0.38)**	**3.3 (0.78)**

Statistical Analysis 1 for Pharmacokinetics: Tmax of Insulin Detemir

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.411

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	With adjustment on baseline value
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.

15. Secondary: Pharmacokinetics: Area Under the Concentration vs. Time Curve From Time Zero to the Time of the Last Measured Level of Insulin Detemir [Time Frame: Week 0 and Week 8]

Measure Type	Secondary
Measure Title	Pharmacokinetics: Area Under the Concentration vs. Time Curve From Time Zero to the Time of the Last Measured Level of Insulin Detemir
Measure Description	The observed peak drug concentration at time (T): T0, T0.5hour (hr), T1hr, T1.5hr, T2hrs, T2.5hrs, T3hrs, T3.5hrs, T4hrs
Time Frame	Week 0 and Week 8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention-to-treat (ITT) analysis set consists of all randomised children with a signed informed consent and at least one HbA1c value determined after randomisation. Subjects are analysed based on initial randomisation.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	**Separate Injection**
Number of Participants Analyzed [units: participants]	**13**	**12**
Pharmacokinetics: Area Under the Concentration vs. Time Curve From Time Zero to the Time of the Last Measured Level of Insulin Detemir [units: pmol.h/L] Median (Standard Deviation)		
Week 0	**36591.2 (70709.5)**	**34653.4 (21243.3)**
Week 8	**36055.0 (73609.6)**	**39757.0 (23076.5)**

Statistical Analysis 1 for Pharmacokinetics: Area Under the Concentration vs. Time Curve From Time Zero to the Time of the Last Measured Level of Insulin Detemir

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.471

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	With adjustment on baseline value
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.

16. Secondary: Pharmacokinetics: Area Under the Concentration vs. Time Curve From Time Zero to Infinity of Insulin Detemir [Time Frame: Week 0 and Week 8]

Measure Type	Secondary
Measure Title	Pharmacokinetics: Area Under the Concentration vs. Time Curve From Time Zero to Infinity of Insulin Detemir
Measure Description	The observed peak drug concentration at time (T): T0, T0.5hour (hr), T1hr, T1.5hr, T2hrs, T2.5hrs, T3hrs, T3.5hrs, T4hrs
Time Frame	Week 0 and Week 8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention-to-treat (ITT) analysis set consists of all randomised children with a signed informed consent and at least one HbA1c value determined after randomisation. Subjects are analysed based on initial randomisation. CGMS® data not available/sufficient for pre-study evaluation in five subjects or at post-study evaluation in four subjects

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	**Separate Injection**
Number of Participants Analyzed [units: participants]	**4**	**6**
Pharmacokinetics: Area Under the Concentration vs. Time Curve From Time Zero to Infinity of Insulin Detemir [units: pmol.h/L] Median (Standard Deviation)		
Week 0, n=4, 3	**230728.2 (304790.62)**	**68509.6 (116350.34)**
Week 8, n=3, 6	**123555.7 (141207.72)**	**362313.5 (4287360.41)**

No statistical analysis provided for Pharmacokinetics: Area Under the Concentration vs. Time Curve From Time Zero to Infinity of Insulin Detemir

17. Secondary: Pharmacokinetics: Terminal Phase Elimination Half-life (T½) - Parameter of Insulin Detemir [Time Frame: Week 0 and Week 8]

Measure Type	Secondary
Measure Title	Pharmacokinetics: Terminal Phase Elimination Half-life (T½) - Parameter of Insulin Detemir
Measure Description	The observed peak drug concentration at time (T): T0, T0.5hour (hr), T1hr, T1.5hr, T2hrs, T2.5hrs, T3hrs, T3.5hrs, T4hrs
Time Frame	Week 0 and Week 8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention-to-treat (ITT) analysis set consists of all randomised children with a signed informed consent and at least one HbA1c value determined after randomisation. CGMS® data not available/sufficient for pre-study evaluation in five subjects or at post-study evaluation in four subjects

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	Separate Injection
Number of Participants Analyzed [units: participants]	**4**	**6**
Pharmacokinetics: Terminal Phase Elimination Half-life (T½) - Parameter of Insulin Detemir [units: hours] Median (Standard Deviation)		
Week 0, n=4, 3	**16.2 (4.12)**	**8.2 (6.53)**
Week 8, n=3, 6	**5.6 (4.2)**	**20.8 (249.57)**

No statistical analysis provided for Pharmacokinetics: Terminal Phase Elimination Half-life (T½) - Parameter of Insulin Detemir

18. Secondary: Pharmacokinetics: Cmax of Insulin Aspart [Time Frame: Week 0 and Week 8]

Measure Type	Secondary
Measure Title	Pharmacokinetics: Cmax of Insulin Aspart
Measure Description	The observed peak drug concentration at time (T): T0, T0.5hour (hr), T1hr, T1.5hr, T2hrs, T2.5hrs, T3hrs, T3.5hrs, T4hrs
Time Frame	Week 0 and Week 8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention-to-treat (ITT) analysis set consists of all randomised children with a signed informed consent and at least one HbA1c value determined after randomisation. Subjects are analysed based on initial randomisation.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	Separate Injection
Number of Participants Analyzed [units: participants]	**13**	**12**
Pharmacokinetics: Cmax of Insulin Aspart [units: pmol/L] Median (Standard Deviation)		
Week 0	**557 (2784.2)**	**762 (378.3)**
Week 8	**662 (576.3)**	**601 (355.3)**

Statistical Analysis 1 for Pharmacokinetics: Cmax of Insulin Aspart

Groups [1]	All groups

Method [2]	ANCOVA
P Value [3]	0.127

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	With adjustment on baseline value
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.

19. Secondary: Pharmacokinetics: Tmax of Insulin Aspart [Time Frame: Week 0 and Week 8]

Measure Type	Secondary
Measure Title	Pharmacokinetics: Tmax of Insulin Aspart
Measure Description	The observed peak drug concentration at time (T): T0, T0.5hour (hr), T1hr, T1.5hr, T2hrs, T2.5hrs, T3hrs, T3.5hrs, T4hrs
Time Frame	Week 0 and Week 8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention-to-treat (ITT) analysis set consists of all randomised children with a signed informed consent and at least one HbA1c value determined after randomisation. Subjects are analysed based on initial randomisation.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	**Separate Injection**
Number of Participants Analyzed [units: participants]	**13**	**12**
Pharmacokinetics: Tmax of Insulin Aspart [units: hours] Median (Standard Deviation)		
Week 0	**2 (0.99)**	**2 (0.97)**
Week 8	**2 (0.53)**	**1.5 (0.51)**

Statistical Analysis 1 for Pharmacokinetics: Tmax of Insulin Aspart

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.1

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.

[2]	Other relevant method information, such as adjustments or degrees of freedom:
	With adjustment on baseline value
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.

20. Secondary: Pharmacokinetics: Area Under the Concentration vs. Time Curve From Time Zero to the Time of the Last Measured Level of Insulin Aspart [Time Frame: Week 0 and Week 8]

Measure Type	Secondary
Measure Title	Pharmacokinetics: Area Under the Concentration vs. Time Curve From Time Zero to the Time of the Last Measured Level of Insulin Aspart
Measure Description	The observed peak drug concentration at time (T): T0, T0.5hour (hr), T1hr, T1.5hr, T2hrs, T2.5hrs, T3hrs, T3.5hrs, T4hrs
Time Frame	Week 0 and Week 8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention-to-treat (ITT) analysis set consists of all randomised children with a signed informed consent and at least one HbA1c value determined after randomisation. Subjects are analysed based on initial randomisation.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	**Separate Injection**
Number of Participants Analyzed [units: participants]	**13**	**12**
Pharmacokinetics: Area Under the Concentration vs. Time Curve From Time Zero to the Time of the Last Measured Level of Insulin Aspart [units: pmol.h/L] Median (Standard Deviation)		
Week 0	**1546.3 (3163.27)**	**1510.9 (963.37)**
Week 8	**2102.4 (1378.73)**	**1540 (894.4)**

Statistical Analysis 1 for Pharmacokinetics: Area Under the Concentration vs. Time Curve From Time Zero to the Time of the Last Measured Level of Insulin Aspart

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.166

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.

[2]	Other relevant method information, such as adjustments or degrees of freedom:
	With adjustment on baseline value
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.

21. Secondary: Pharmacokinetics: Area Under the Concentration vs. Time Curve From Time Zero to Infinity of Insulin Aspart [Time Frame: Week 0 and Week 8]

Measure Type	Secondary
Measure Title	Pharmacokinetics: Area Under the Concentration vs. Time Curve From Time Zero to Infinity of Insulin Aspart
Measure Description	The observed peak drug concentration at time (T): T0, T0.5hour (hr), T1hr, T1.5hr, T2hrs, T2.5hrs, T3hrs, T3.5hrs, T4hrs
Time Frame	Week 0 and Week 8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention-to-treat (ITT) analysis set consists of all randomised children with a signed informed consent and at least one HbA1c value determined after randomisation. Subjects are analysed based on initial randomisation.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	**Separate Injection**
Number of Participants Analyzed [units: participants]	**13**	**12**
Pharmacokinetics: Area Under the Concentration vs. Time Curve From Time Zero to Infinity of Insulin Aspart [units: pmol.h/L] Median (Standard Deviation)		
Week 0, n=10, 11	**3008.1 (7689.04)**	**3006.3 (4458.12)**
Week 8, n=13, 12	**5674.3 (10668.8)**	**3019.9 (1013.19)**

Statistical Analysis 1 for Pharmacokinetics: Area Under the Concentration vs. Time Curve From Time Zero to Infinity of Insulin Aspart

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.023

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:

	With adjustment on baseline value
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.

22. Secondary: Pharmacokinetics: Terminal Phase Elimination Half-life (T½) - Parameter of Insulin Aspart [Time Frame: Week 0 and Week 8]

Measure Type	Secondary
Measure Title	Pharmacokinetics: Terminal Phase Elimination Half-life (T½) - Parameter of Insulin Aspart
Measure Description	The observed peak drug concentration at time (T): T0, T0.5hour (hr), T1hr, T1.5hr, T2hrs, T2.5hrs, T3hrs, T3.5hrs, T4hrs
Time Frame	Week 0 and Week 8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention-to-treat (ITT) analysis set consists of all randomised children with a signed informed consent and at least one HbA1c value determined after randomisation. Subjects are analysed based on initial randomisation.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	Separate Injection
Number of Participants Analyzed [units: participants]	**13**	**12**
Pharmacokinetics: Terminal Phase Elimination Half-life (T½) - Parameter of Insulin Aspart [units: hours] Median (Standard Deviation)		
Week 0, n=10, 11	**2.2 (6.75)**	**2 (3.09)**
Week 8, n=13, 12	**3.5 (41.88)**	**1.7 (1.62)**

Statistical Analysis 1 for Pharmacokinetics: Terminal Phase Elimination Half-life (T½) - Parameter of Insulin Aspart

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.439

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	With adjustment on baseline value
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.

23. Secondary: Weight Z Score [Time Frame: Week 0 and Week 8]

Measure Type	Secondary
Measure Title	Weight Z Score
Measure Description	Z score of weight. To estimate the growth of children, standardised mean weight values were calculated for each month of age and for each sex
Time Frame	Week 0 and Week 8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention-to-treat (ITT) analysis set consists of all randomised children with a signed informed consent and at least one HbA1c value determined after randomisation. Subjects are analysed based on initial randomisation.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	**Separate Injection**
Number of Participants Analyzed [units: participants]	**13**	**12**
Weight Z Score [units: Z-score] Mean (Standard Deviation)		
Week 0, n=13, 12	**-0.42 (0.71)**	**0.19 (0.69)**
Week 8, n=11, 12	**-0.29 (0.65)**	**0.26 (0.67)**

Statistical Analysis 1 for Weight Z Score

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.202

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	With adjustment on baseline value
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.

24. Secondary: Body Mass Index (BMI) Z Score [Time Frame: Week 0 and Week 8]

Measure Type	Secondary
Measure Title	Body Mass Index (BMI) Z Score

Measure Description	Z score of BMI index. To estimate the growth of children, standardised mean BMI values were calculated for each month of age and for each sex
Time Frame	Week 0 and Week 8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention-to-treat (ITT) analysis set consists of all randomised children with a signed informed consent and at least one HbA1c value determined after randomisation. Subjects are analysed based on initial randomisation.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	**Separate Injection**
Number of Participants Analyzed [units: participants]	**13**	**12**
Body Mass Index (BMI) Z Score [units: Z-score] Mean (Standard Deviation)		
Week 0, n=13, 12	**-0.32 (0.63)**	**0.04 (0.86)**
Week 8, n=11, 12	**-0.07 (0.52)**	**0.26 (0.73)**

Statistical Analysis 1 for Body Mass Index (BMI) Z Score

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.665

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	With adjustment on baseline value
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No text entered.

25. Secondary: Incidence of Hypoglycaemic Episodes - All Episodes [Time Frame: Weeks 0-8]

Measure Type	Secondary
Measure Title	Incidence of Hypoglycaemic Episodes - All Episodes
Measure Description	Number of hypoglycaemic episodes from Week 0 to Week 8, defined as self-measurement plasma glucose less than 56 mg/dL (3.1 mmol/L). Classified as major, minor or symptoms only. Major if unable to treat her/himself (given the age of the study population, the definition of major hypoglycemia was to be adapted through the investigator's judgment). Minor if able to treat her/himself and plasma glucose below 3.1 mmol/L (56 mg/dL). Symptoms only if able to treat her/himself and no plasma glucose measurement or plasma glucose higher than or equal to 3.1 mmol/L.
Time Frame	Weeks 0-8

Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
All randomised subjects who received at least one treatment dose are taken into account in the safety analysis set. Subjects are analysed based on treatments actually received.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	**Separate Injection**
Number of Participants Analyzed [units: participants]	**12**	**13**
Incidence of Hypoglycaemic Episodes - All Episodes [units: episodes]	**351**	**293**

No statistical analysis provided for Incidence of Hypoglycaemic Episodes - All Episodes

26. Secondary: Incidence of Hypoglycaemic Episodes - Glycaemia Below 0.56 g/L [Time Frame: Weeks 0-8]

Measure Type	Secondary
Measure Title	Incidence of Hypoglycaemic Episodes - Glycaemia Below 0.56 g/L
Measure Description	Number of minor hypoglycaemic episodes from Week 0 to Week 8, defined as self-measurement plasma glucose below 3.1 mmol/L (56 mg/dL) and the child is able to treat her/himself.
Time Frame	Weeks 0-8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
All randomised subjects who received at least one treatment dose are taken into account in the safety analysis set. Subjects are analysed based on treatments actually received.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	**Separate Injection**
Number of Participants Analyzed [units: participants]	**12**	**13**
Incidence of Hypoglycaemic Episodes - Glycaemia Below 0.56 g/L [units: episodes]		
With symptoms	**68**	**159**

Without (w/o) symptoms	**75**	**48**
W/o info on presence of symptoms	**23**	**6**

No statistical analysis provided for Incidence of Hypoglycaemic Episodes - Glycaemia Below 0.56 g/L

27. Secondary: Incidence of Hypoglycaemic Episodes - Glycaemia Above or Equal to 0.56 g/L [Time Frame: Weeks 0-8]

Measure Type	Secondary
Measure Title	Incidence of Hypoglycaemic Episodes - Glycaemia Above or Equal to 0.56 g/L
Measure Description	Number of “symptoms only” hypoglycaemic episodes from Week 0 to Week 8, defined as self-measurement plasma glucose higher than or equal to 3.1 mmol/L (56 mg/dL) or no plasma glucose measurement and the child is able to treat her/himself.
Time Frame	Weeks 0-8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
All randomised subjects who received at least one treatment dose are taken into account in the safety analysis set. Subjects are analysed based on treatments actually received.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	**Separate Injection**
Number of Participants Analyzed [units: participants]	**12**	**13**
Incidence of Hypoglycaemic Episodes - Glycaemia Above or Equal to 0.56 g/L [units: episodes]		
With symptoms	**49**	**46**
Without (w/o) symptoms	**131**	**33**
W/o information on presence of symptoms	**5**	**1**

No statistical analysis provided for Incidence of Hypoglycaemic Episodes - Glycaemia Above or Equal to 0.56 g/L

28. Secondary: Percentage of Children Assessing Insulin Therapy Injection Pain as "Sad Face" [Time Frame: Week 0 and Week 8]

Measure Type	Secondary
Measure Title	Percentage of Children Assessing Insulin Therapy Injection Pain as "Sad Face"
Measure Description	Via a paper diary, the children perceived insulin therapy injection pain by using a four-grade facial visual analogue scale (VAS): very sad face, sad face, happy face or very happy face.
Time Frame	Week 0 and Week 8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.

All randomised subjects who received at least one treatment dose are taken into account in the safety analysis set. Subjects are analysed based on treatments actually received.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	Separate Injection
Number of Participants Analyzed [units: participants]	**12**	**13**
Percentage of Children Assessing Insulin Therapy Injection Pain as "Sad Face" [units: percentage of subjects]		
Week 0	**45**	**33**
Week 8	**0**	**23**

No statistical analysis provided for Percentage of Children Assessing Insulin Therapy Injection Pain as "Sad Face"

29. Secondary: Percentage of Children Assessing Insulin Therapy Injection Pain as "Happy Face" [Time Frame: Week 0 and week 8]

Measure Type	Secondary
Measure Title	Percentage of Children Assessing Insulin Therapy Injection Pain as "Happy Face"
Measure Description	Via a paper diary, the children perceived insulin therapy injection pain by using a four-grade facial visual analogue scale (VAS): very sad face, sad face, happy face or very happy face.
Time Frame	Week 0 and week 8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
All randomised subjects who received at least one treatment dose are taken into account in the safety analysis set. Subjects are analysed based on treatments actually received.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	Separate Injection
Number of Participants Analyzed [units: participants]	**12**	**13**
Percentage of Children Assessing Insulin Therapy Injection Pain as "Happy Face" [units: percentage of subjects]		
Week 0	**27**	**50**
Week 8	**81**	**69**

No statistical analysis provided for Percentage of Children Assessing Insulin Therapy Injection Pain as "Happy Face"

30. Secondary: Percentage of Children Assessing Insulin Therapy Injection Pain as "Very Happy Face" [Time Frame: Week 0 and Week 8]

Measure Type	Secondary
Measure Title	Percentage of Children Assessing Insulin Therapy Injection Pain as "Very Happy Face"
Measure Description	Via a paper diary, the children perceived insulin therapy injection pain by using a four-grade facial visual analogue scale (VAS): very sad face, sad face, happy face or very happy face.
Time Frame	Week 0 and Week 8
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
All randomised subjects who received at least one treatment dose are taken into account in the safety analysis set. Subjects are analysed based on treatments actually received.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Measured Values

	Mixed Injection	**Separate Injection**
Number of Participants Analyzed [units: participants]	**12**	**13**
Percentage of Children Assessing Insulin Therapy Injection Pain as "Very Happy Face" [units: percentage of subjects]		
Week 0	**27.3**	**16.7**
Week 8	**18.2**	**7.7**

No statistical analysis provided for Percentage of Children Assessing Insulin Therapy Injection Pain as "Very Happy Face"

Serious Adverse Events

Hide Serious Adverse Events

Time Frame	Adverse events are collected during treatment period (8 weeks)
Additional Description	All randomised subjects who received at least one treatment dose are taken into account in the safety analysis set. Subnjects are analysed based on treatments actually received.

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Serious Adverse Events

	Mixed Injection	**Separate Injection**
Total, serious adverse events		

# participants affected / at risk	0/12 (0.00%)	0/13 (0.00%)

Other Adverse Events

Hide Other Adverse Events

Time Frame	Adverse events are collected during treatment period (8 weeks)
Additional Description	All randomised subjects who received at least one treatment dose are taken into account in the safety analysis set. Subnjects are analysed based on treatments actually received.

Frequency Threshold

Threshold above which other adverse events are reported	5%

Reporting Groups

	Description
Mixed Injection	Individually adjusted insulin detemir extemporaneous mixed with individually adjusted insulin aspart injected s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed
Separate Injection	Individually adjusted insulin detemir and individually adjusted insulin aspart injected separately s.c. twice daily (in the morning and in the evening) + extra insulin aspart at lunch and breaks, if needed

Other Adverse Events

	Mixed Injection	Separate Injection
Total, other (not including serious) adverse events		
# participants affected / at risk	5/12 (41.67%)	9/13 (69.23%)
Eye disorders		
Conjunctivitis allergic † 1		
# participants affected / at risk	1/12 (8.33%)	0/13 (0.00%)
# events	1	0
Gastrointestinal disorders		
Abdominal pain † 1		
# participants affected / at risk	0/12 (0.00%)	3/13 (23.08%)
# events	0	3
General disorders		
Injection site reaction † 1		
# participants affected / at risk	0/12 (0.00%)	1/13 (7.69%)
# events	0	1
Pyrexia † 1		
# participants affected / at risk	0/12 (0.00%)	1/13 (7.69%)
# events	0	1
Infections and infestations		
Rhinitis † 1		
# participants affected / at risk	1/12 (8.33%)	2/13 (15.38%)
# events	1	2
Gastroenteritis † 1		
# participants affected / at risk	1/12 (8.33%)	1/13 (7.69%)
# events	1	1
Bronchitis † 1		
# participants affected / at risk	1/12 (8.33%)	0/13 (0.00%)
# events	1	0
Enterobiasis † 1		
# participants affected / at risk	0/12 (0.00%)	1/13 (7.69%)
# events	0	1

Nasopharyngitis † 1		
# participants affected / at risk	0/12 (0.00%)	1/13 (7.69%)
# events	0	1
Viral infection † 1		
# participants affected / at risk	1/12 (8.33%)	0/13 (0.00%)
# events	1	0
Injury, poisoning and procedural complications		
Fall † 1		
# participants affected / at risk	0/12 (0.00%)	1/13 (7.69%)
# events	0	1
Reproductive system and breast disorders		
Gynaecomastia † 1		
# participants affected / at risk	0/12 (0.00%)	1/13 (7.69%)
# events	0	1
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain † 1		
# participants affected / at risk	0/12 (0.00%)	1/13 (7.69%)
# events	0	1
Skin and subcutaneous tissue disorders		
Eczema † 1		
# participants affected / at risk	1/12 (8.33%)	0/13 (0.00%)
# events	1	0
Surgical and medical procedures		
Orthodontic procedure † 1		
# participants affected / at risk	0/12 (0.00%)	1/13 (7.69%)
# events	0	1
Tooth extraction † 1		
# participants affected / at risk	1/12 (8.33%)	0/13 (0.00%)
# events	1	0

† Events were collected by systematic assessment
1 Term from vocabulary, MedDRA 13.0

Limitations and Caveats

Hide Limitations and Caveats

Limitations of the study, such as early termination leading to small numbers of participants analyzed and technical problems with measurement leading to unreliable or uninterpretable data
No text entered.

More Information

Hide More Information

Certain Agreements:

Principal Investigators are **NOT** employed by the organization sponsoring the study.
There **IS** an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.
The agreement is: ☐ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **less than or equal to 60 days**. The sponsor cannot require changes to the communication and cannot extend the embargo. ☐ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **more than 60 days but less than or equal to 180 days.** The sponsor cannot require changes to the communication and cannot extend the embargo.

Other disclosure agreement that restricts the right of the PI to discuss or publish trial results after the trial is completed.

Restriction Description: The Steering Committee has the right to publish the entire results of the trial. Any such scientific paper, presentation, communication, or other information concerning the investigation must be approved by the Steering Committee, and copies submitted in writing to Novo Nordisk prior to submission for publication/presentation for comments. Comments will be given within four weeks from receipt of the manuscript.

Results Point of Contact:

Name/Title: Public Access to Clinical Trials
Organization: Novo Nordisk A/S
e-mail: clinicaltrials@novonordisk.com

No publications provided

Responsible Party:	Novo Nordisk A/S
ClinicalTrials.gov Identifier:	NCT00542620 History of Changes
Other Study ID Numbers:	NN304-1813
	2006-006715-77 (EudraCT Number)
Study First Received:	October 10, 2007
Results First Received:	December 5, 2011
Last Updated:	October 24, 2014
Health Authority:	France: Afssaps - Agence française de sécurité sanitaire des produits de santé (Saint-Denis)