



Clinical trial results:

A Randomized, Double-Blind, Placebo Controlled Trial to Assess Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Lixisenatide in Paediatric (10 - 17 Years Old) and Adult Patients With Type 2 Diabetes Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2011-004584-67 |
| Trial protocol | DE GB Outside EU/EEA |
| Global end of trial date | 04 March 2014 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 |
| This version publication date | 22 June 2016 |
| First version publication date | 20 March 2015 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | PKD11475 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01572649 |
| WHO universal trial number (UTN) | U1111-1124-3136 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Sanofi aventis recherche & développement |
| Sponsor organisation address | 1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380 |
| Public contact | Trial Transparency Team, Sanofi-Aventis Recherche & Développement, Contact-us@sanofi.com |
| Scientific contact | Trial Transparency Team, Sanofi-Aventis Recherche & Développement, Contact-us@sanofi.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000916-PIP01-10 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 14 April 2014 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 04 March 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to investigate the effects of a single subcutaneous lixisenatide dose of 5 microgram (mcg) and 10 mcg as compared to placebo in reducing postprandial plasma glucose (PPG) assessed as area under the plasma glucose concentration curve after a standardized liquid meal (breakfast) in type 2 diabetic paediatric population (10 to 17 years old) and adults as controls.

Protection of trial subjects:

Paediatric Subjects:

The study was conducted by investigators experienced in the treatment of paediatric subjects. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimized. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anaesthesia may have been used to minimize distress and discomfort.

Adult Subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency.

Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------|
| Actual start date of recruitment | 14 May 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United Kingdom: 4 |
| Country: Number of subjects enrolled | United States: 9 |
| Country: Number of subjects enrolled | Mexico: 7 |
| Country: Number of subjects enrolled | South Africa: 4 |
| Worldwide total number of subjects | 24 |
| EEA total number of subjects | 4 |

Notes:

| Subjects enrolled per age group | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 2 |
| Adolescents (12-17 years) | 10 |
| Adults (18-64 years) | 12 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 6 centres in 4 countries between 14 May 2012 and 04 March 2014.

Pre-assignment

Screening details:

A total of 78 subjects (25 paediatrics and 53 adults) were screened and 24 (12 in each paediatric and adult) subjects were randomized and treated.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Paediatric |

Arm description:

Paediatric subjects (10 years to less than [$<$] 18 years of age) received single dose of lixisenatide 5 microgram (mcg), 10 mcg and placebo (volume matched to lixisenatide 5 mcg or 10 mcg) as subcutaneous (SC) injection on Day 1 of either of the 3 treatment periods in a crossover design schedule with the administration of the 5 mcg dose preceding always the 10 mcg dose.

| | |
|--|---------------------------------|
| Arm type | Experimental-Placebo Cross-over |
| Investigational medicinal product name | Lixisenatide |
| Investigational medicinal product code | AVE0010 |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Lixisenatide 5 microgram (mcg) or 10 mcg using the pen-type injector (OptiClik[®]), 30 minutes prior to a standardized liquid breakfast meal.

| | |
|--|------------------------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Placebo matched to lixisenatide using the pen-type injector (OptiClik[®]), 30 minutes prior to a standardized liquid breakfast meal.

| | |
|------------------|-------|
| Arm title | Adult |
|------------------|-------|

Arm description:

Adult subjects (18 years to 65 years of age) received single dose of lixisenatide 5 mcg, 10 mcg and placebo (volume matched to lixisenatide 5 mcg or 10 mcg) as SC injection on Day 1 of either of the 3 treatment periods in a cross-over design schedule with the administration of the 5 mcg dose preceding always the 10 mcg dose.

| | |
|----------|---------------------------------|
| Arm type | Experimental-Placebo Cross-over |
|----------|---------------------------------|

| | |
|--|------------------------|
| Investigational medicinal product name | Lixisenatide |
| Investigational medicinal product code | AVE0010 |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Lixisenatide 5 mcg or 10 mcg using the pen-type injector (OptiClik ®), 30 minutes prior to a standardized liquid breakfast meal.

| | |
|--|------------------------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Placebo matched to lixisenatide using the pen-type injector (OptiClik ®), 30 minutes prior to a standardized liquid breakfast meal.

| Number of subjects in period 1 | Paediatric | Adult |
|---------------------------------------|------------|-------|
| Started | 12 | 12 |
| Completed | 12 | 12 |

Baseline characteristics

Reporting groups

| | |
|---|------------|
| Reporting group title | Paediatric |
| Reporting group description: | |
| Paediatric subjects (10 years to less than [$<$] 18 years of age) received single dose of lixisenatide 5 microgram (mcg), 10 mcg and placebo (volume matched to lixisenatide 5 mcg or 10 mcg) as subcutaneous (SC) injection on Day 1 of either of the 3 treatment periods in a crossover design schedule with the administration of the 5 mcg dose preceding always the 10 mcg dose. | |
| Reporting group title | Adult |
| Reporting group description: | |
| Adult subjects (18 years to 65 years of age) received single dose of lixisenatide 5 mcg, 10 mcg and placebo (volume matched to lixisenatide 5 mcg or 10 mcg) as SC injection on Day 1 of either of the 3 treatment periods in a cross-over design schedule with the administration of the 5 mcg dose preceding always the 10 mcg dose. | |

| Reporting group values | Paediatric | Adult | Total |
|---|-------------|------------|-------|
| Number of subjects | 12 | 12 | 24 |
| Age categorical | | | |
| Units: Subjects | | | |
| Children (2-11 years) | 2 | 0 | 2 |
| Adolescents (12-17 years) | 10 | 0 | 10 |
| Adults (18-64 years) | 0 | 12 | 12 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 13.9 | 51.3 | - |
| standard deviation | ± 2.2 | ± 5.9 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 6 | 3 | 9 |
| Male | 6 | 9 | 15 |
| Race | | | |
| Units: Subjects | | | |
| Caucasian/White | 1 | 6 | 7 |
| Asian/Oriental | 0 | 1 | 1 |
| Other | 11 | 5 | 16 |
| Weight | | | |
| Units: kilogram (kg) | | | |
| arithmetic mean | 84.69 | 92.58 | - |
| standard deviation | ± 23.31 | ± 17.8 | - |
| Body Mass Index (BMI) | | | |
| Units: kilogram per square meter (kg/m ²) | | | |
| arithmetic mean | 31.42 | 31.79 | - |
| standard deviation | ± 6.51 | ± 3.05 | - |
| Glycated hemoglobin (HbA1c) | | | |
| Units: percentage of haemoglobin | | | |
| arithmetic mean | 8.65 | 8.43 | - |
| standard deviation | ± 1.14 | ± 0.69 | - |

End points

End points reporting groups

| | |
|---|---------------------------------|
| Reporting group title | Paediatric |
| Reporting group description: Paediatric subjects (10 years to less than [$<$] 18 years of age) received single dose of lixisenatide 5 microgram (mcg), 10 mcg and placebo (volume matched to lixisenatide 5 mcg or 10 mcg) as subcutaneous (SC) injection on Day 1 of either of the 3 treatment periods in a crossover design schedule with the administration of the 5 mcg dose preceding always the 10 mcg dose. | |
| Reporting group title | Adult |
| Reporting group description: Adult subjects (18 years to 65 years of age) received single dose of lixisenatide 5 mcg, 10 mcg and placebo (volume matched to lixisenatide 5 mcg or 10 mcg) as SC injection on Day 1 of either of the 3 treatment periods in a cross-over design schedule with the administration of the 5 mcg dose preceding always the 10 mcg dose. | |
| Subject analysis set title | Placebo: Paediatric |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Paediatric subjects (10 years to <18 years of age) who received single dose of placebo volume matched to either lixisenatide 5 mcg (50 mL) or lixisenatide 10 mcg (100 mL) by SC route. | |
| Subject analysis set title | Lixisenatide 5 mcg: Paediatric |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Paediatric subjects (10 years to <18 years of age) who received single dose of lixisenatide 5 mcg (50 mL) by SC route (5 mcg preceding the 10 mcg lixisenatide dose level). | |
| Subject analysis set title | Lixisenatide 10 mcg: Paediatric |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Paediatric subjects (10 years to <18 years of age) who received single dose of lixisenatide 10 mcg (100 mL) by SC route. | |
| Subject analysis set title | Placebo: Adult |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Adult subjects (18 years to 65 years of age) who received single dose of placebo volume matched to either lixisenatide 5 mcg (50 mL) or lixisenatide 10 mcg (100 mL) by SC route. | |
| Subject analysis set title | Lixisenatide 5 mcg: Adult |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Adult subjects (18 years to 65 years of age) who received single dose of lixisenatide 5 mcg (50 mL) by SC route (5 mcg preceding the 10 mcg lixisenatide dose level). | |
| Subject analysis set title | Lixisenatide 10 mcg: Adult |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Adult subjects (18 years to 65 years of age) who received single dose of lixisenatide 10 mcg (100 mL) by SC route. | |

Primary: Plasma Glucose Corrected Area Under The Plasma Concentration-Time Curve From Time 0.5 Hours to 4.5 Hours

| | |
|-----------------|--|
| End point title | Plasma Glucose Corrected Area Under The Plasma Concentration-Time Curve From Time 0.5 Hours to 4.5 Hours |
|-----------------|--|

End point description:

Plasma glucose was assessed using the Gluco-quant Glucose/hexokinase assay. The range of the method was 3-1000 milligram per deciliter (mg/dL), with 1 mg/dL as limit of detection (LOD). Measurement was done using the linear trapezoidal rule from time of breakfast start (30 minutes after IMP injection [time: 0.5 hours]) to 4 hours after breakfast start (time: 4.5 hours) and corrected by subtracting premeal plasma glucose concentration (time: 0.5 hours). Evaluable pharmacodynamic (PD)

population included all randomized and treated subjects without any critical/major deviation related to IMP administration, for whom at least 1 PD parameter was considered sufficient and interpretable.

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|--|---------|
| End point type | Primary |
| End point timeframe: | |
| 0.5 (prior to standardized breakfast), 1, 1.5, 2, 2.5, 3.5, 4.5 hours post-dose on Day 1 of Treatment Period 1, 2, and 3 | |

| End point values | Placebo: Paediatric | Lixisenatide 5 mcg: Paediatric | Lixisenatide 10 mcg: Paediatric | Placebo: Adult |
|--|----------------------|--------------------------------|---------------------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 9 | 9 | 9 | 12 |
| Units: millimole*hour per litre (mmol*h/L) | | | | |
| least squares mean (standard error) | 9.63 (± 3.95) | 5.72 (± 3.99) | 8.11 (± 4.08) | 16.6 (± 2.46) |

| End point values | Lixisenatide 5 mcg: Adult | Lixisenatide 10 mcg: Adult | | |
|--|---------------------------|----------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 12 | 12 | | |
| Units: millimole*hour per litre (mmol*h/L) | | | | |
| least squares mean (standard error) | 8.03 (± 2.95) | 1.11 (± 2.85) | | |

Statistical analyses

| Statistical analysis title | Lixisenatide 5 mcg vs Placebo: Paediatric |
|--|--|
| Statistical analysis description: | |
| The linear fixed effects model used includes treatment, sequence and period as fixed effects, and subject-within-sequence as random effect, and the corresponding pre-meal value (T0.5h) as covariate. The comparison analysis was done and provided Lixisenatide 5 mcg vs Placebo. As per the cross-over design of the study the actual number of subjects included in analysis were 9 instead of 18. | |
| Comparison groups | Placebo: Paediatric v Lixisenatide 5 mcg: Paediatric |
| Number of subjects included in analysis | 18 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0681 |
| Method | Linear fixed effects model |
| Parameter estimate | Least squares mean difference |
| Point estimate | -3.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.17 |
| upper limit | 0.34 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.97 |

| | |
|---|---|
| Statistical analysis title | Lixisenatide 10 mcg vs Placebo: Paediatric |
| Statistical analysis description: | |
| The linear fixed effects model used includes treatment, sequence and period as fixed effects, and patient-within-sequence as random effect, and the corresponding pre-meal value (T0.5h) as covariate. The comparison analysis was done and provided Lixisenatide 10 mcg vs Placebo. As per the cross-over design of the study the actual number of subjects included in analysis were 9 instead of 18. | |
| Comparison groups | Placebo: Paediatric v Lixisenatide 10 mcg: Paediatric |
| Number of subjects included in analysis | 18 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.4359 |
| Method | Linear fixed effects model |
| Parameter estimate | Least squares mean difference |
| Point estimate | -1.52 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.59 |
| upper limit | 2.56 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.89 |

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|---|--|
| Statistical analysis title | Lixisenatide 5 mcg vs Placebo: Adult |
| Statistical analysis description: | |
| The linear fixed effects model used includes treatment, sequence and period as fixed effects, and patient-within-sequence as random effect, and the corresponding pre-meal value (T0.5h) as covariate. The comparison analysis was done and provided Lixisenatide 5 mcg vs Placebo. As per the cross-over design of the study the actual number of subjects included in analysis were 12 instead of 24. | |
| Comparison groups | Placebo: Adult v Lixisenatide 5 mcg: Adult |
| Number of subjects included in analysis | 24 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.0104 |
| Method | Linear fixed effects model |
| Parameter estimate | Least squares mean difference |
| Point estimate | -8.57 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14.91 |
| upper limit | -2.23 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.05 |

| | |
|---|---|
| Statistical analysis title | Lixisenatide 10 mcg vs Placebo: Adult |
| Statistical analysis description: | |
| The linear fixed effects model used includes treatment, sequence and period as fixed effects, and patient-within-sequence as random effect, and the corresponding pre-meal value (T0.5h) as covariate. The comparison analysis was done and provided Lixisenatide 5 mcg vs Placebo. As per the cross-over design of the study the actual number of subjects included in analysis were 12 instead of 24. | |
| Comparison groups | Placebo: Adult v Lixisenatide 10 mcg: Adult |
| Number of subjects included in analysis | 24 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 |
| Method | Linear fixed effects model |
| Parameter estimate | Least squares mean difference |
| Point estimate | -15.48 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -21.59 |
| upper limit | -9.38 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.93 |

Secondary: Plasma Glucose Area Under The Plasma Concentration-Time Curve From Time 0.5 Hours to 4.5 Hours

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|--|--|
| End point title | Plasma Glucose Area Under The Plasma Concentration-Time Curve From Time 0.5 Hours to 4.5 Hours |
| End point description: | |
| Plasma glucose was assessed using the Gluco-quant Glucose/hexokinase assay. The range of the method was 3-1000 mg/dL, with 1 mg/dL LOD. The area under the plasma glucose concentration time curve (AUC0:30-4:30h) was calculated using the linear trapezoidal rule from time of breakfast start (30 minutes after IMP injection [time: 0.5 hours]) to 4 hours after breakfast start (time: 4.5 hours). Analysis was performed in evaluable PD population. | |
| End point type | Secondary |
| End point timeframe: | |
| 0.5 (prior to standardized breakfast), 1, 1.5, 2, 2.5, 3.5, 4.5 hours post-dose on Day 1 of Treatment Period 1, 2, and 3 | |

| End point values | Placebo: Paediatric | Lixisenatide 5 mcg: Paediatric | Lixisenatide 10 mcg: Paediatric | Placebo: Adult |
|-------------------------------------|----------------------|--------------------------------|---------------------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 9 | 9 | 9 | 12 |
| Units: mmol*h/L | | | | |
| least squares mean (standard error) | 44.5 (± 3.91) | 40.53 (± 3.94) | 42.94 (± 4.03) | 54.32 (± 2.46) |

| End point values | Lixisenatide 5 mcg: Adult | Lixisenatide 10 mcg: Adult | | |
|------------------|---------------------------|----------------------------|--|--|
|------------------|---------------------------|----------------------------|--|--|

| | | | | |
|-------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 12 | 12 | | |
| Units: mmol*h/L | | | | |
| least squares mean (standard error) | 45.75 (± 2.95) | 38.83 (± 2.85) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Postprandial Plasma Glucose (PPG) Excursion

| | |
|-----------------|---|
| End point title | Postprandial Plasma Glucose (PPG) Excursion |
|-----------------|---|

End point description:

Plasma glucose was assessed using the Gluco-quant Glucose/hexokinase assay. The range of the method was 3-1000 mg/dL, with 1 mg/dL LOD. The PPG excursion was calculated as the maximum PPG level determined from time of standardized breakfast (time: 0.5 hours) until 4 hours after breakfast start (time: 4.5 hours) minus the premeal plasma glucose level (time: 0.5 hours). Analysis was performed in evaluable PD population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

0.5 (prior to standardized breakfast), 1, 1.5, 2, 2.5, 3.5, 4.5 hours post-dose on Day 1 of Treatment Period 1, 2, and 3

| End point values | Placebo: Paediatric | Lixisenatide 5 mcg: Paediatric | Lixisenatide 10 mcg: Paediatric | Placebo: Adult |
|-------------------------------------|----------------------|--------------------------------|---------------------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 9 | 9 | 9 | 12 |
| Units: mmol/L | | | | |
| least squares mean (standard error) | 4.58 (± 1.22) | 3.08 (± 1.23) | 3.46 (± 1.27) | 6.58 (± 0.64) |

| End point values | Lixisenatide 5 mcg: Adult | Lixisenatide 10 mcg: Adult | | |
|-------------------------------------|---------------------------|----------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 12 | 12 | | |
| Units: mmol/L | | | | |
| least squares mean (standard error) | 3.81 (± 0.75) | 2.26 (± 0.72) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Glucagon AUC(0:30-4:30h)

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|-----------------|---------------------------------|
| End point title | Plasma Glucagon AUC(0:30-4:30h) |
|-----------------|---------------------------------|

End point description:

Plasma glucagon was assessed using the radioimmunoassay. The range of the method was 4.7-150 picomol per liter (pmol/L). Plasma Glucagon AUC(0:30-4:30h) was calculated using the linear trapezoidal rule from time of breakfast start (30 minutes after IMP injection [time: 0.5 hours]) to 4 hours after breakfast start (time: 4.5 hours) and corrected by subtracting premeal plasma glucagon concentration (time: 0.5 hours). Analysis was performed in evaluable PD population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

0.5 (prior to standardized breakfast), 1, 1.5, 2.5, 3.5, 4.5 hours post-dose on Day 1 of Treatment Period 1, 2, and 3

| End point values | Placebo: Paediatric | Lixisenatide 5 mcg: Paediatric | Lixisenatide 10 mcg: Paediatric | Placebo: Adult |
|---|----------------------|--------------------------------|---------------------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 9 | 8 | 9 | 12 |
| Units: nanogram*hour per litre (ng*h/L) | | | | |
| least squares mean (standard error) | 664.83 (± 19.92) | 652.63 (± 22.22) | 621.48 (± 20.77) | 628.98 (± 26.47) |

| End point values | Lixisenatide 5 mcg: Adult | Lixisenatide 10 mcg: Adult | | |
|---|---------------------------|----------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 12 | 12 | | |
| Units: nanogram*hour per litre (ng*h/L) | | | | |
| least squares mean (standard error) | 612.44 (± 27.9) | 575.3 (± 27.95) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Insulin AUC(0:30-4:30h)

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|-----------------|-------------------------------|
| End point title | Serum Insulin AUC(0:30-4:30h) |
|-----------------|-------------------------------|

End point description:

Serum insulin was assessed using Electro Chemiluminescence Immuno Assay (ECLIA). The range of the method was 1-875 milli-international units per litre (mIU/L), with 0.3 mIU/L as LOD. Serum Insulin AUC(0:30-4:30h) was calculated using the linear trapezoidal rule from time of breakfast start (30 minutes after IMP injection [time: 0.5 hours]) to 4 hours after breakfast start (time: 4.5 hours) and corrected by subtracting premeal serum insulin concentration (time: 0.5 hours). Analysis was performed in evaluable PD population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

0.5 (prior to standardized breakfast), 1, 1.5, 2.5, 3.5, 4.5 hours post-dose on Day 1 of Treatment Period 1, 2, and 3

| End point values | Placebo: Paediatric | Lixisenatide 5 mcg: Paediatric | Lixisenatide 10 mcg: Paediatric | Placebo: Adult |
|---|-------------------------|--------------------------------|---------------------------------|------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 8 | 8 | 12 |
| Units: picomole*hour per litre (pmol*h/L) | | | | |
| least squares mean (standard error) | 1843.81 (\pm 297.88) | 1973.88 (\pm 243.52) | 1602.8 (\pm 239.93) | 1276.36 (\pm 85.63) |

| End point values | Lixisenatide 5 mcg: Adult | Lixisenatide 10 mcg: Adult | | |
|---|---------------------------|----------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 11 | 12 | | |
| Units: picomole*hour per litre (pmol*h/L) | | | | |
| least squares mean (standard error) | 1181.62 (\pm 103.75) | 802.65 (\pm 104.2) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Serum C-Peptide AUC(0:30-4:30h)

| | |
|-----------------|---------------------------------|
| End point title | Serum C-Peptide AUC(0:30-4:30h) |
|-----------------|---------------------------------|

End point description:

Serum C-peptide was assessed using ECLIA. The range of the method was 0.2-25 nanogram per millilitre (ng/mL) with 0.07 ng/mL as LOD. Serum C-Peptide AUC(0:30-4:30h) was calculated using the linear trapezoidal rule from time of breakfast start (30 minutes after IMP injection [time: 0.5 hours]) to 4 hours after breakfast start (time: 4.5 hours) and corrected by subtracting premeal serum C-peptide concentration (time: 0.5 hours). Analysis was performed in evaluable PD population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

0.5 (prior to standardized breakfast), 1, 1.5, 2.5, 3.5, 4.5 hours post-dose on Day 1 of Treatment Period 1, 2, and 3

| End point values | Placebo: Paediatric | Lixisenatide 5 mcg: Paediatric | Lixisenatide 10 mcg: Paediatric | Placebo: Adult |
|---|----------------------|--------------------------------|---------------------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 8 | 8 | 8 | 12 |
| Units: nanomole*hour per litre (nmol*h/L) | | | | |
| least squares mean (standard error) | 9.92 (\pm 0.56) | 9.87 (\pm 0.59) | 9.21 (\pm 0.58) | 8.9 (\pm 0.48) |

| End point values | Lixisenatide 5 mcg: Adult | Lixisenatide 10 mcg: Adult | | |
|------------------|---------------------------|----------------------------|--|--|
|------------------|---------------------------|----------------------------|--|--|

| | | | | |
|---|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 11 | 12 | | |
| Units: nanomole*hour per litre (nmol*h/L) | | | | |
| least squares mean (standard error) | 8.42 (\pm 0.56) | 6.81 (\pm 0.56) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) of Lixisenatide

| | |
|-----------------|---|
| End point title | Maximum Plasma Concentration (Cmax) of Lixisenatide |
|-----------------|---|

End point description:

Lixisenatide plasma concentrations were determined using a validated double-antibody sandwich enzyme-linked immunosorbent assay method with an LLOQ of 5.5 pg/mL. Analysis was performed in evaluable PK population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Hour 0 (predose), Hour 0.5, 1, 1.5, 2.5, 3.5, 4.5 and 6.5 Post-Dose on Day 1 of Treatment Period 1, 2, and 3

| End point values | Lixisenatide 5 mcg: Paediatric | Lixisenatide 10 mcg: Paediatric | Lixisenatide 5 mcg: Adult | Lixisenatide 10 mcg: Adult |
|--|--------------------------------|---------------------------------|---------------------------|----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 8 | 8 | 10 | 10 |
| Units: picogram per millilitre (pg/mL) | | | | |
| arithmetic mean (standard deviation) | 29.7 (\pm 14.2) | 34.3 (\pm 25.4) | 26 (\pm 15.4) | 56.9 (\pm 21.3) |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Cmax (tmax) of Lixisenatide

| | |
|-----------------|---|
| End point title | Time to Reach Cmax (tmax) of Lixisenatide |
|-----------------|---|

End point description:

Analysis was performed in evaluable PK population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Hour 0 (predose), Hour 0.5, 1, 1.5, 2.5, 3.5, 4.5 and 6.5 Post-Dose on Day 1 of Treatment Period 1, 2, and 3

| End point values | Lixisenatide 5 mcg: Paediatric | Lixisenatide 10 mcg: Paediatric | Lixisenatide 5 mcg: Adult | Lixisenatide 10 mcg: Adult |
|-------------------------------|--------------------------------|---------------------------------|---------------------------|----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 8 | 8 | 10 | 10 |
| Units: hour (h) | | | | |
| median (full range (min-max)) | 1.25 (0.48 to 3.5) | 0.49 (0.48 to 3.55) | 1.5 (0.42 to 3.5) | 2.5 (0.42 to 3.5) |

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration Time Curve from Time Zero to the Real Time Corresponding to the Last Quantifiable Concentration (AUClast) of Lixisenatide

| | |
|--|--|
| End point title | Area Under the Concentration Time Curve from Time Zero to the Real Time Corresponding to the Last Quantifiable Concentration (AUClast) of Lixisenatide |
| End point description: Area under the serum concentration versus time curve calculated using the trapezoidal method from time zero to the real time corresponding to the last concentration above the limit of quantification. LLOQ = 5.5 pg/mL. Analysis was performed in evaluable PK population. | |
| End point type | Secondary |
| End point timeframe: Hour 0 (predose), Hour 0.5, 1, 1.5, 2.5, 3.5, 4.5 and 6.5 Post-Dose on Day 1 of Treatment Period 1, 2, and 3 | |

| End point values | Lixisenatide 5 mcg: Paediatric | Lixisenatide 10 mcg: Paediatric | Lixisenatide 5 mcg: Adult | Lixisenatide 10 mcg: Adult |
|---|--------------------------------|---------------------------------|---------------------------|----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 8 | 8 | 10 | 10 |
| Units: picogram*hour per millilitre (pg*h/mL) | | | | |
| arithmetic mean (standard deviation) | 99.4 (± 77.7) | 108 (± 109) | 101 (± 58) | 242 (± 90) |

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under The Concentration Time Curve Extrapolated to Infinity (AUC) of Lixisenatide

| | |
|---|--|
| End point title | Area Under The Concentration Time Curve Extrapolated to Infinity (AUC) of Lixisenatide |
| End point description: AUC is the area under the serum concentration-time curve from time zero extrapolated to infinite time. Analysis was performed in evaluable PK population. | |
| End point type | Secondary |
| End point timeframe: Hour 0 (predose), Hour 0.5, 1, 1.5, 2.5, 3.5, 4.5 and 6.5 Post-Dose on Day 1 of Treatment Period 1, 2, | |

| End point values | Lixisenatide 5 mcg: Paediatric | Lixisenatide 10 mcg: Paediatric | Lixisenatide 5 mcg: Adult | Lixisenatide 10 mcg: Adult |
|--------------------------------------|--------------------------------|---------------------------------|---------------------------|----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 0 ^[1] | 0 ^[2] | 0 ^[3] | 0 ^[4] |
| Units: pg*hour/mL | | | | |
| arithmetic mean (standard deviation) | () | () | () | () |

Notes:

[1] - Analysis was not performed due to insufficient data.

[2] - Analysis was not performed due to insufficient data.

[3] - Analysis was not performed due to insufficient data.

[4] - Analysis was not performed due to insufficient data.

Statistical analyses

No statistical analyses for this end point

Secondary: Lixisenatide AUC(0:30-4:30h)

| | |
|-----------------|------------------------------|
| End point title | Lixisenatide AUC(0:30-4:30h) |
|-----------------|------------------------------|

End point description:

Lixisenatide plasma concentrations were determined using a validated double-antibody sandwich enzyme-linked immunosorbent assay method with an LLOQ of 5.5 pg/mL. The area under the concentration time curve (AUC_{0:30-4:30h}) was calculated using the linear trapezoidal rule from time of breakfast start (30 minutes after IMP injection [time: 0.5 hours]) to 4 hours after breakfast start (time: 4.5 hours). Analysis was performed in evaluable PK population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

0.5 (prior to standardized breakfast), 1, 1.5, 2.5, 3.5, 4.5 hours post-dose on Day 1 of Treatment Period 1, 2, and 3

| End point values | Lixisenatide 5 mcg: Paediatric | Lixisenatide 10 mcg: Paediatric | Lixisenatide 5 mcg: Adult | Lixisenatide 10 mcg: Adult |
|--------------------------------------|--------------------------------|---------------------------------|---------------------------|----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 7 | 10 | 10 |
| Units: pg*h/mL | | | | |
| arithmetic mean (standard deviation) | 82.5 (± 54.6) | 88 (± 76) | 77.2 (± 42.4) | 181 (± 71.9) |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Day 2-7 after treatment period 3) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported adverse events are treatment-emergent adverse events that is AEs that developed/worsened during the 'on treatment period' (the time from study drug injection up to 1 day after study drug injection [included] in each treatment period).

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Placebo: Paediatric |
|-----------------------|---------------------|

Reporting group description:

Paediatric subjects (10 years to <18 years of age) who received single dose of placebo volume matched to either lixisenatide 5 mcg (50 mL) or lixisenatide 10 mcg (100 mL) by SC route.

| | |
|-----------------------|----------------------------|
| Reporting group title | Lixisenatide 10 mcg: Adult |
|-----------------------|----------------------------|

Reporting group description:

Adult subjects (18 years to 65 years of age) who received single dose of lixisenatide 10 mcg (100 mL) by SC route.

| | |
|-----------------------|----------------|
| Reporting group title | Placebo: Adult |
|-----------------------|----------------|

Reporting group description:

Adult subjects (18 years to 65 years of age) who received single dose of placebo volume matched to either lixisenatide 5 mcg (50 mL) or lixisenatide 10 mcg (100 mL) by SC route.

| | |
|-----------------------|---------------------------|
| Reporting group title | Lixisenatide 5 mcg: Adult |
|-----------------------|---------------------------|

Reporting group description:

Adult subjects (18 years to 65 years of age) who received single dose of lixisenatide 5 mcg (50 mL) by SC route (5 mcg preceding the 10 mcg lixisenatide dose level).

| | |
|-----------------------|--------------------------------|
| Reporting group title | Lixisenatide 5 mcg: Paediatric |
|-----------------------|--------------------------------|

Reporting group description:

Paediatric subjects (10 years to <18 years of age) who received single dose of lixisenatide 5 mcg (50 mL) by SC route (5 mcg preceding the 10 mcg lixisenatide dose level).

| | |
|-----------------------|---------------------------------|
| Reporting group title | Lixisenatide 10 mcg: Paediatric |
|-----------------------|---------------------------------|

Reporting group description:

Paediatric subjects (10 years to <18 years of age) who received single dose of lixisenatide 10 mcg (100 mL) by SC route.

| Serious adverse events | Placebo: Paediatric | Lixisenatide 10 mcg: Adult | Placebo: Adult |
|---|---------------------|----------------------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |

| Serious adverse events | Lixisenatide 5 mcg: | Lixisenatide 5 mcg: | Lixisenatide 10 mcg: |
|------------------------|---------------------|---------------------|----------------------|
|------------------------|---------------------|---------------------|----------------------|

| | Adult | Paediatric | Paediatric |
|---|----------------|----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Placebo: Paediatric | Lixisenatide 10 mcg: Adult | Placebo: Adult |
|---|---------------------|----------------------------|----------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Nausea | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| Non-serious adverse events | Lixisenatide 5 mcg: Adult | Lixisenatide 5 mcg: Paediatric | Lixisenatide 10 mcg: Paediatric |
|---|---------------------------|--------------------------------|---------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | 2 / 12 (16.67%) |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Nausea | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Vomiting | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 12 (0.00%) 0 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 12 (8.33%) 1 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 04 June 2012 | <p>In the context of this single dose study in paediatric and adult patients with Type 2 diabetes mellitus (T2DM) , information given in the clinical protocol about the measurement of plasma glucose in case of eventual hypoglycaemia was clarified. A new secondary endpoint, defined as the area under the plasma glucose concentration-time profile from time of the standardized breakfast start until 4 hours later (T4H30) without subtracting the premeal value, was included in addition to the similar primary endpoint defined as the area under the plasma glucose concentration-time profile from time of the standardized breakfast start until 4 hours later (T4H30) subtracting the premeal value.</p> <p>Moreover, detailed information for timing of metformin administration, if any, and Electrocardiogram were added and discrepancies between sections of the protocol were clarified.</p> |
| 25 January 2013 | <p>Change to the inclusion/exclusion criteria for the paediatric population.</p> <p>An upper limit of body mass index for paediatric subjects, that is, 50 kg/m^2 , was added to avoid inclusion of paediatric subjects with extreme obesity in this study.</p> <p>For the paediatric population: male or female subjects were eligible if their T2DM had been diagnosed at least 3 months earlier instead of 1 year at the time of screening. This was to facilitate the recruitment since in the management of T2DM in adolescents and children, therapy should be intensified whenever glucose control was not achieved after 3 to 6 months.</p> <p>For the paediatric population: systolic blood pressure (SBP)/diastolic blood pressure (DBP) levels were too restrictive for obese subjects taking into account the figures presented per age and height percentile. The exclusion would concern children/adolescents with abnormal blood pressure requiring pharmacological treatment as judged by the Investigator.</p> <p>Appendix B "Blood pressure levels by gender, age and height percentile" was consequently removed and the order of appendices following this initial Appendix B was revised and listed in the description of changes.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported