



## Clinical trial results:

### Randomized, Double-blind, Placebo-controlled, Dose escalation, Study on Safety, Pharmacokinetics and Pharmacodynamics of Lixisenatide in Pediatric Patients with Type 2 Diabetes Mellitus not Adequately Controlled With Metformin and/or Basal Insulin

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2015-005789-42    |
| Trial protocol           | ES Outside EU/EEA |
| Global end of trial date | 27 January 2020   |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 01 August 2020 |
| First version publication date | 01 August 2020 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | TDR14311 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |                 |
|------------------------------------|-----------------|
| ISRCTN number                      | -               |
| ClinicalTrials.gov id (NCT number) | NCT02803918     |
| WHO universal trial number (UTN)   | U1111-1176-6142 |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Sanofi-aventis Recherche & Développement   |
| Sponsor organisation address | 1, Avenue Pierre Brossolette, Chilly Mazarin, France, 91385                              |
| 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? | Yes                 |

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 26 February 2020 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 27 January 2020  |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate safety of 14-day repeated lixisenatide doses of 5 microgram [mcg], 10 mcg and 20 mcg as compared to placebo in paediatric subjects with Type 2 diabetes mellitus (T2DM).

Protection of trial 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 minimised. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia may have been used to minimise distress and discomfort.

Background therapy:

Metformin and/or basal insulin was used as non-investigational medicinal product and were administered according to local label.

Evidence for comparator: -

|   |             |
|---|-------------|
| Actual start date of recruitment                          | 17 May 2017 |
| 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 | Spain: 1         |
| Country: Number of subjects enrolled | United States: 5 |
| Country: Number of subjects enrolled | Mexico: 8        |
| Country: Number of subjects enrolled | Mauritius: 5     |
| Country: Number of subjects enrolled | Turkey: 3        |
| Country: Number of subjects enrolled | South Africa: 1  |
| Worldwide total number of subjects   | 23               |
| EEA total number of subjects         | 1                |

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)                    | 0  |
| Adolescents (12-17 years)                | 23 |
| Adults (18-64 years)                     | 0  |
| From 65 to 84 years                      | 0  |
| 85 years and over                        | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 11 sites in 6 countries. A total of 23 subjects were screened between 17 May 2017 and 23 November 2019.

### Pre-assignment

Screening details:

A total of 23 subjects were randomised and treated in the study.

### 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, Carer   |

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Placebo |

Arm description:

Subjects received a dose of placebo (matched to lixisenatide) as subcutaneous (SC) injection from Day 1 to Day 42.

|  |                        |
|--|------------------------|
| Arm type                               | Placebo                |
| 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) was administered in abdominal area. Subjects were fasted for at least 1 hour prior to dosing.

|                  |              |
|------------------|--------------|
| <b>Arm title</b> | Lixisenatide |
|------------------|--------------|

Arm description:

Subjects received 3 doses of lixisenatide (5 mcg, 10 mcg and 20 mcg) as SC injection in incremental sequential dose escalation steps of 2 weeks from Day 1 to Day 42.

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

Dosage and administration details:

Lixisenatide was administered in abdominal area. Each subject underwent a dose escalation according to the following paradigm: 5 mcg (Day 1 to 14), then 10 mcg (Day 15 to 28) and 20 mcg (Day 29 to 42). Subjects were fasted for at least 1 hour prior to dosing.

| <b>Number of subjects in period 1</b> | Placebo | Lixisenatide |
|---------------------------------------|---------|--------------|
| Started                               | 5       | 18           |
| Completed                             | 5       | 17           |
| Not completed                         | 0       | 1            |
| Poor compliance to protocol           | -       | 1            |

## Baseline characteristics

### Reporting groups

|   |              |
|---|--------------|
| Reporting group title   | Placebo      |
| Reporting group description:  |              |
| Subjects received a dose of placebo (matched to lixisenatide) as subcutaneous (SC) injection from Day 1 to Day 42.  |              |
| Reporting group title   | Lixisenatide |
| Reporting group description:  |              |
| Subjects received 3 doses of lixisenatide (5 mcg, 10 mcg and 20 mcg) as SC injection in incremental sequential dose escalation steps of 2 weeks from Day 1 to Day 42. |              |

| Reporting group values  | Placebo       | Lixisenatide  | Total |
|---|---------------|---------------|-------|
| Number of subjects  | 5             | 18            | 23    |
| Age categorical<br>Units: Subjects  |               |               |       |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation   | 15.4<br>± 1.5 | 15.6<br>± 1.0 | -     |
| Gender categorical<br>Units: Subjects   |               |               |       |
| Female  | 3             | 13            | 16    |
| Male  | 2             | 5             | 7     |
| Body mass index (BMI)<br>Units: Kilogram per square meter (kg/m <sup>2</sup> )<br>arithmetic mean<br>standard deviation | 37.4<br>± 3.6 | 33.2<br>± 4.8 | -     |
| Duration of diabetes<br>Units: years<br>arithmetic mean<br>standard deviation   | 3.5<br>± 2.2  | 1.6<br>± 1.2  | -     |

## End points

### End points reporting groups

|   |                     |
|---|---------------------|
| Reporting group title   | Placebo             |
| Reporting group description:<br>Subjects received a dose of placebo (matched to lixisenatide) as subcutaneous (SC) injection from Day 1 to Day 42.  |                     |
| Reporting group title   | Lixisenatide        |
| Reporting group description:<br>Subjects received 3 doses of lixisenatide (5 mcg, 10 mcg and 20 mcg) as SC injection in incremental sequential dose escalation steps of 2 weeks from Day 1 to Day 42. |                     |
| Subject analysis set title  | Lixisenatide 5 mcg  |
| Subject analysis set type   | Safety analysis     |
| Subject analysis set description:<br>Subjects received a dose of lixisenatide 5 mcg as SC injection from Day 1 to Day 14.   |                     |
| Subject analysis set title  | Lixisenatide 10 mcg |
| Subject analysis set type   | Safety analysis     |
| Subject analysis set description:<br>Subjects received a dose of lixisenatide 10 mcg as SC injection from Day 15 to Day 28.   |                     |
| Subject analysis set title  | Lixisenatide 20 mcg |
| Subject analysis set type   | Safety analysis     |
| Subject analysis set description:<br>Subjects received a dose of lixisenatide 20 mcg as SC injection from Day 29 to Day 42.   |                     |

### Primary: Safety profile: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs)

|   |   |
|---|---|
| End point title   | Safety profile: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) <sup>[1][2]</sup> |
| End point description:<br>Adverse event (AE): any untoward medical occurrence in a subject who received study drug and did not necessarily had a causal relationship with study treatment. Serious AEs (SAEs): Any untoward medical occurrence that resulted in any of the following outcomes: death, life-threatening, required initial or prolonged in-patient hospitalisation, persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered as medically important event. AE of special interest (AESI): AE (serious/nonserious) of scientific and medical concern, specific to study drug or program, which were monitored and immediately notified to Sponsor. TEAEs: AEs that occurred or worsened or became serious during on-treatment phase (time from first study drug administration up to 3 days after last study drug administration [i.e., up to 45 days]). Analysis was performed on safety population which included subjects who were exposed to study drug regardless of amount of treatment administered. |   |
| End point type  | Primary   |
| End point timeframe:<br>From Baseline up to end-of-study (EOS; up to Day 45)  |   |

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As the endpoint was descriptive in nature, no statistical analysis was provided.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data were planned to be collected and analysed for specified arms only.

| End point values                              | Placebo         | Lixisenatide 5 mcg   | Lixisenatide 10 mcg  | Lixisenatide 20 mcg  |
|---|-----------------|----------------------|----------------------|----------------------|
| Subject group type                            | Reporting group | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed                   | 5               | 18                   | 18                   | 18                   |
| Units: subjects                               |                 |                      |                      |                      |
| number (not applicable)                       |                 |                      |                      |                      |
| Any TEAE                                      | 3               | 6                    | 3                    | 4                    |
| Severe TEAE                                   | 0               | 0                    | 0                    | 1                    |
| Ant TESAE                                     | 0               | 0                    | 0                    | 1                    |
| Any TEAE leading to death                     | 0               | 0                    | 0                    | 0                    |
| Any TEAE leading to permanent discontinuation | 0               | 0                    | 0                    | 0                    |
| Any TEAE of special interest (AESI)           | 1               | 0                    | 0                    | 0                    |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Subjects by Anti-lixisenatide Antibodies (ADAs) Status (Positive/Negative)

|                 |  |
|-----------------|--|
| End point title | Number of Subjects by Anti-lixisenatide Antibodies (ADAs) Status (Positive/Negative) <sup>[3]</sup> <sup>[4]</sup> |
|-----------------|--|

End point description:

Number of subjects with ADAs status categorised as negative and positive were reported. Baseline was defined as the last values done on Baseline (Day -1) before first study drug administration. Analysis was performed on safety population.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline (Day -1), Day 14, Day 28 and Day 42

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As the endpoint was descriptive in nature, no statistical analysis was provided.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data was planned to be collected and analysed for specified arms only.

| End point values            | Placebo         | Lixisenatide 5 mcg   | Lixisenatide 10 mcg  | Lixisenatide 20 mcg  |
|-----------------------------|-----------------|----------------------|----------------------|----------------------|
| Subject group type          | Reporting group | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 5               | 18                   | 18                   | 18                   |
| Units: subjects             |                 |                      |                      |                      |
| number (not applicable)     |                 |                      |                      |                      |
| Baseline: Negative          | 5               | 17                   | 17                   | 17                   |
| Baseline: Positive          | 0               | 1                    | 1                    | 1                    |
| Day 14: Negative            | 5               | 16                   | 0                    | 0                    |
| Day 14: Positive            | 0               | 2                    | 0                    | 0                    |
| Day 28: Negative            | 5               | 0                    | 8                    | 0                    |
| Day 28: Positive            | 0               | 0                    | 9                    | 0                    |
| Day 42: Negative            | 4               | 0                    | 0                    | 4                    |
| Day 42: Positive            | 1               | 0                    | 0                    | 14                   |



## Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetic (PK) Parameter: Maximum Plasma Concentration Observed (C<sub>max</sub>) of Lixisenatide Following Repeated Dosing of 20 mcg Dose by Anti-lixisenatide Antibodies Status

|                 |   |
|-----------------|---|
| End point title | Pharmacokinetic (PK) Parameter: Maximum Plasma Concentration Observed (C <sub>max</sub> ) of Lixisenatide Following Repeated Dosing of 20 mcg Dose by Anti-lixisenatide Antibodies Status |
|-----------------|---|

#### End point description:

C<sub>max</sub> was defined as maximum plasma concentration observed during the respective treatment period, evaluated as per subject ADA status. Analysis was performed on PK population which included all subjects without any major deviations related to study drug administration and provided at least one blood sample for drug concentration measurement. Here, 'n' = subjects with available data for each specified category.

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

#### End point timeframe:

Pre-dose (0 hour), 0.5 hour, 1, 1.5, 2, 2.5, 3.5 and 4.5 hours post-dose on Day 42

|                                      |                      |  |  |  |
|--------------------------------------|----------------------|--|--|--|
| <b>End point values</b>              | Lixisenatide 20 mcg  |  |  |  |
| Subject group type                   | Subject analysis set |  |  |  |
| Number of subjects analysed          | 18                   |  |  |  |
| Units: picogram/millilitre (pg/mL)   |                      |  |  |  |
| arithmetic mean (standard deviation) |                      |  |  |  |
| ADA Negative (n = 4)                 | 83.9 (± 25.2)        |  |  |  |
| ADA Positive (n = 11)                | 508 (± 453)          |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetic Parameter : Time to Reach Maximum Plasma Concentration (t<sub>max</sub>) of Lixisenatide Following Repeated Dosing of 20 mcg Dose by Anti-lixisenatide Antibodies Status

|                 |  |
|-----------------|--|
| End point title | Pharmacokinetic Parameter : Time to Reach Maximum Plasma Concentration (t <sub>max</sub> ) of Lixisenatide Following Repeated Dosing of 20 mcg Dose by Anti-lixisenatide Antibodies Status |
|-----------------|--|

#### End point description:

t<sub>max</sub> was defined as the time to reach C<sub>max</sub>, evaluated as per subject ADA status. Analysis was performed on the PK population. Here, 'n' = subjects with available data for each specified category.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Pre-dose (0 hour), 0.5 hour, 1, 1.5, 2, 2.5, 3.5 and 4.5 hours post-dose on Day 42 |           |

|                               |                      |  |  |  |
|-------------------------------|----------------------|--|--|--|
| <b>End point values</b>       | Lixisenatide 20 mcg  |  |  |  |
| Subject group type            | Subject analysis set |  |  |  |
| Number of subjects analysed   | 18                   |  |  |  |
| Units: hours                  |                      |  |  |  |
| median (full range (min-max)) |                      |  |  |  |
| ADA Negative (n = 4)          | 1.24 (0.98 to 2.50)  |  |  |  |
| ADA Positive (n = 11)         | 2.00 (0.50 to 4.50)  |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Plasma Concentration (AUC) From Time 0 Hour to 4.5 Hours (AUC0-4.5) of Lixisenatide Following Repeated Dosing of 20 mcg Dose by Anti-lixisenatide Antibodies Status

|                 |  |
|-----------------|--|
| End point title | Area Under the Plasma Concentration (AUC) From Time 0 Hour to 4.5 Hours (AUC0-4.5) of Lixisenatide Following Repeated Dosing of 20 mcg Dose by Anti-lixisenatide Antibodies Status |
|-----------------|--|

End point description:

AUC0-4.5 was defined as area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero (lixisenatide scale) to time 4.5 hours post-dose, evaluated as per subject ADA status. Analysis was performed on PK population. Here, 'n' = subjects with available data for each specified category.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Pre-dose (0 hour), 0.5 hour, 1, 1.5, 2, 2.5, 3.5 and 4.5 hours post-dose on Day 42 |           |

|   |                      |  |  |  |
|---|----------------------|--|--|--|
| <b>End point values</b>                       | Lixisenatide 20 mcg  |  |  |  |
| Subject group type                            | Subject analysis set |  |  |  |
| Number of subjects analysed                   | 18                   |  |  |  |
| Units: picogram*hour per millilitre (pg*h/mL) |                      |  |  |  |
| arithmetic mean (standard deviation)          |                      |  |  |  |
| ADA Negative (n = 4)                          | 267 (± 96.1)         |  |  |  |
| ADA Positive (n = 9)                          | 2300 (± 1940)        |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Area Under the Plasma Glucose Concentration From Time 0 Hour to 4.5 Hours (AUC0-4.5) at Day 42

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Area Under the Plasma Glucose Concentration From Time 0 Hour to 4.5 Hours (AUC0-4.5) at Day 42 <sup>[5]</sup> |
|-----------------|---|

End point description:

AUC0-4.5 was defined as area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero (lixisenatide scale) to time 4.5 hours post-dose. Analysis was performed on pharmacodynamic (PD) population which included all randomised subjects without any important deviation related to study drug administration for whom the PD data was considered sufficient and interpretable. Here, 'number of subjects analysed' = subjects evaluable and had available data for this endpoint

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

End point timeframe:

0.5 hour (prior to standardised breakfast), 1, 1.5, 2, 2.5, 3.5, 4.5 hours on Day -1 (baseline), pre-dose (0 hour), 1, 1.5, 2, 2.5, 3.5, 4.5 hours post-dose on Day 42

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data were planned to be collected and analysed for specified arms only.

| End point values                            | Placebo         | Lixisenatide 20 mcg  |  |  |
|---|-----------------|----------------------|--|--|
| Subject group type                          | Reporting group | Subject analysis set |  |  |
| Number of subjects analysed                 | 5               | 17                   |  |  |
| Units: millimoles*hour per litre (mmol*h/L) |                 |                      |  |  |
| arithmetic mean (standard deviation)        | 13.84 (± 18.93) | -17.33 (± 12.19)     |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Fasting Plasma Glucose (FPG) at Day 14, Day 28 and Day 42

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Fasting Plasma Glucose (FPG) at Day 14, Day 28 and Day 42 <sup>[6]</sup> |
|-----------------|--|

End point description:

Change in FPG was calculated by subtracting baseline value from Day 14, Day 28 and Day 42 values. Baseline was defined as the last values done on Day -1 before first study drug administration. Analysis was performed on PD population. Here, 'n' = subjects with available data for each specified category and '99999' was used as a space filler and indicated that no subjects were involved in the PD analysis at the specified time points.

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

End point timeframe:

Baseline, Days 14, 28 and 42

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data were planned to be collected and analysed for specified arms only.

| End point values                     | Placebo         | Lixisenatide 5 mcg   | Lixisenatide 10 mcg  | Lixisenatide 20 mcg  |
|--------------------------------------|-----------------|----------------------|----------------------|----------------------|
| Subject group type                   | Reporting group | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed          | 5               | 18                   | 18                   | 18                   |
| Units: millimoles per litre (mmol/L) |                 |                      |                      |                      |
| arithmetic mean (standard deviation) |                 |                      |                      |                      |
| Day 14 (n = 5, 17, 0, 0)             | 1.73 (± 1.39)   | -1.08 (± 1.84)       | 99999 (± 99999)      | 99999 (± 99999)      |
| Day 28 (n = 5, 0, 18, 0)             | 2.35 (± 2.27)   | 99999 (± 99999)      | -0.69 (± 2.76)       | 99999 (± 99999)      |
| Day 42 (n = 5, 0, 0, 18)             | 2.91 (± 3.71)   | 99999 (± 99999)      | 99999 (± 99999)      | -1.23 (± 2.11)       |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in 1-Hour Postprandial Plasma Glucose (1-Hour-PPG) at Day 14, Day 28 and Day 42

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in 1-Hour Postprandial Plasma Glucose (1-Hour-PPG) at Day 14, Day 28 and Day 42 <sup>[7]</sup> |
|-----------------|---|

End point description:

1-Hour PPG excursion was calculated as the difference between the plasma glucose value 1 hour post meal test (T1.5) and the plasma glucose value before time of injection (T0): 1-Hour-PPG excursion = PG-T1.5 - PG-T0. Baseline was defined as the last values done on Day -1 before first study drug administration. Analysis was performed on PD population. Here, 'n' = subjects with available data for each specified category and '99999' was used as a space filler and indicated that no subjects were involved in the PD analysis at the specified time points.

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

End point timeframe:

Baseline, Days 14, 28 and 42

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data were planned to be collected and analysed for specified arms only.

| End point values                     | Placebo         | Lixisenatide 5 mcg   | Lixisenatide 10 mcg  | Lixisenatide 20 mcg  |
|--------------------------------------|-----------------|----------------------|----------------------|----------------------|
| Subject group type                   | Reporting group | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed          | 5               | 18                   | 18                   | 18                   |
| Units: mmol/L                        |                 |                      |                      |                      |
| arithmetic mean (standard deviation) |                 |                      |                      |                      |
| Day 14 (n = 5, 17, 0, 0)             | 0.42 (± 2.12)   | -1.28 (± 2.36)       | 99999 (± 99999)      | 99999 (± 99999)      |
| Day 28 (n = 5, 0, 18, 0)             | -0.76 (± 3.45)  | 99999 (± 99999)      | -3.12 (± 2.24)       | 99999 (± 99999)      |
| Day 42 (n = 5, 0, 0, 16)             | 0.59 (± 2.33)   | 99999 (± 99999)      | 99999 (± 99999)      | -3.19 (± 3.12)       |

## Statistical analyses

**Secondary: Change From Baseline in 2-Hours Postprandial Plasma Glucose (2-Hours-PPG) at Day 14, Day 28 and Day 42**

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in 2-Hours Postprandial Plasma Glucose (2-Hours-PPG) at Day 14, Day 28 and Day 42 <sup>[8]</sup> |
|-----------------|---|

## End point description:

2-Hours PPG excursion was calculated as the difference between the plasma glucose value 2 hours post meal test (T2.5) and the plasma glucose value before time of injection (T0): 2-Hours-PPG excursion = PG-T2.5 - PG-T0. Baseline was defined as the last values done on Day -1 before first study drug administration. Analysis was performed on PD population. Here, 'n' = subjects with available data for each specified category and '99999' was used as a space filler at fields and indicated that no subjects were involved in the PD analysis at the specified time points.

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

## End point timeframe:

Baseline, Days 14, 28 and 42

## Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data were planned to be collected and analysed for specified arms only.

| End point values                     | Placebo         | Lixisenatide 5 mcg   | Lixisenatide 10 mcg  | Lixisenatide 20 mcg  |
|--------------------------------------|-----------------|----------------------|----------------------|----------------------|
| Subject group type                   | Reporting group | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed          | 5               | 18                   | 18                   | 18                   |
| Units: mmol/L                        |                 |                      |                      |                      |
| arithmetic mean (standard deviation) |                 |                      |                      |                      |
| Day 14 (n = 5, 17, 0, 0)             | -1.43 (± 2.24)  | -1.12 (± 1.73)       | 99999 (± 99999)      | 99999 (± 99999)      |
| Day 28 (n = 5, 0, 18, 0)             | -0.57 (± 2.36)  | 99999 (± 99999)      | -2.75 (± 2.09)       | 99999 (± 99999)      |
| Day 42 (n = 5, 0, 0, 17)             | -0.08 (± 1.17)  | 99999 (± 99999)      | 99999 (± 99999)      | -3.96 (± 3.17)       |

**Statistical analyses**

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AE data were collected from signature of the informed consent form up to end-of-study (i.e. up to Day 45)

Adverse event reporting additional description:

TEAEs were defined as AEs that occurred or worsened or became serious during the on-treatment phase (the time from the first study drug administration up to 3 days after last study drug administration [i.e. up to Day 45]). Analysis was performed on safety population.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects received a dose of placebo (matched to lixisenatide) as SC injection from Day 1 to Day 42.

|                       |              |
|-----------------------|--------------|
| Reporting group title | Lixisenatide |
|-----------------------|--------------|

Reporting group description:

Subjects received 3 doses of lixisenatide (5 mcg, 10 mcg and 20 mcg) as SC injection in incremental sequential dose escalation steps of 2 weeks from Day 1 to Day 42.

| Serious adverse events                            | Placebo       | Lixisenatide   |  |
|---|---------------|----------------|--|
| Total subjects affected by serious adverse events |               |                |  |
| subjects affected / exposed                       | 0 / 5 (0.00%) | 1 / 18 (5.56%) |  |
| number of deaths (all causes)                     | 0             | 0              |  |
| number of deaths resulting from adverse events    |               |                |  |
| Infections and infestations                       |               |                |  |
| Gastroenteritis Viral                             |               |                |  |
| subjects affected / exposed                       | 0 / 5 (0.00%) | 1 / 18 (5.56%) |  |
| occurrences causally related to treatment / all   | 0 / 0         | 0 / 1          |  |
| deaths causally related to treatment / all        | 0 / 0         | 0 / 0          |  |

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

| Non-serious adverse events                            | Placebo        | Lixisenatide    |  |
|---|----------------|-----------------|--|
| Total subjects affected by non-serious adverse events |                |                 |  |
| subjects affected / exposed                           | 3 / 5 (60.00%) | 7 / 18 (38.89%) |  |
| Investigations  |                |                 |  |

|  |                     |                      |  |
|--|---------------------|----------------------|--|
| Alanine Aminotransferase Increased<br>subjects affected / exposed<br>occurrences (all)   | 1 / 5 (20.00%)<br>1 | 0 / 18 (0.00%)<br>0  |  |
| Weight Increased<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Injury, poisoning and procedural complications<br>Limb Injury<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 5 (20.00%)<br>1 | 0 / 18 (0.00%)<br>0  |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 1 / 18 (5.56%)<br>3  |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| General disorders and administration site conditions<br>Influenza Like Illness<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Injection Site Pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Eye disorders<br>Chalazion<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Gastrointestinal disorders<br>Gastrooesophageal Reflux Disease<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 5 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)   | 1 / 5 (20.00%)<br>1 | 2 / 18 (11.11%)<br>8 |  |
| Vomiting   |                     |                      |  |

|   |                     |                       |  |
|---|---------------------|-----------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 2 / 18 (11.11%)<br>11 |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 1 / 5 (20.00%)<br>1 | 0 / 18 (0.00%)<br>0   |  |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                | 0 / 5 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1   |  |
| Upper Respiratory Tract Infection<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 5 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1   |  |
| Urinary Tract Infection Bacterial<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 5 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1   |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 15 September 2016 | Following changes were made:<br>-A part of the standard reporting text was deleted for unknown technical reasons in the finalisation procedure of the document. The reason for this Amendment was to re-include the standard reporting text.<br>-Guidelines for reporting SAEs was updated.  |
| 19 July 2017      | Following changes were made:<br>- Inclusion Criterion: In order to accommodate local medical paediatric practice and clinical guidelines the global protocol did not specify the exact metformin dose. The other aspects of the Inclusion Criterion would not be changed as they were requirements.<br>- Exclusion Criterion: Based on the local paediatric medical practice and clinical necessity, the utilisation of psychotropic agents would be accepted as long as the subjects were stabilised for at least three months on this therapy. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported