# Clinical trial results:
# A multi-center, randomized, open-label, Phase IV study to investigate the management of pasireotide-induced hyperglycemia with incretin based therapy or insulin in adult patients with Cushing's disease or acromegaly

## Summary

| | |
|---|---|
| EudraCT number | 2012-002916-16 |
| Trial protocol | DE DK PL BE |
| Global end of trial date | 26 March 2018 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 16 March 2019 |
| First version publication date | 16 March 2019 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | CSOM230B2219 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02060383 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Novartis Pharma, AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Clinical Disclosure Manager, Novartis Pharma, AG, +41 613241111, novartis.email@novartis.com |
| Scientific contact | Clinical Disclosure Manager, Novartis Pharma, AG, +41 613241111, novartis.email@novartis.com |

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| 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 | 26 March 2018 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 26 March 2018 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the effect of treatment with incretin based therapy vs. insulin on the 16-week glycemic control in patients with Cushing's disease or acromegaly who develop or worsen hyperglycemia on pasireotide, and cannot be controlled by metformin alone or other background anti-diabetic treatments

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 23 May 2014 |
| 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 | Belgium: 10 |
| Country: Number of subjects enrolled | Brazil: 25 |
| Country: Number of subjects enrolled | China: 60 |
| Country: Number of subjects enrolled | Denmark: 8 |
| Country: Number of subjects enrolled | Germany: 3 |
| Country: Number of subjects enrolled | India: 21 |
| Country: Number of subjects enrolled | Peru: 11 |
| Country: Number of subjects enrolled | Poland: 38 |
| Country: Number of subjects enrolled | Russian Federation: 10 |
| Country: Number of subjects enrolled | Thailand: 23 |
| Country: Number of subjects enrolled | Turkey: 6 |
| Country: Number of subjects enrolled | United States: 34 |
| Worldwide total number of subjects | 249 |
| EEA total number of subjects | 59 |

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) | 0 |
| Adults (18-64 years) | 234 |
| From 65 to 84 years | 15 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

A total of 68 randomized evaluable participants with at least 8 weeks of randomized treatment without any rescue anti-diabetic medication was required. Approximately 79 participants were planned to be randomized.

### Pre-assignment

Screening details:

A total of 249 participants were included in the study & treated with pasireotide s.c. (59 participants with Cushing's disease) or pasireotide LAR (190 participants with acromegaly). 81 participants were randomized to either incretin-based therapy or insulin (with 72 evaluable for the primary analysis) & 168 who did not qualify for randomization.

### Period 1

| | |
|---|---|
| Period 1 title | Core Phase |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Incretin based therapy (randomized group) |

Arm description:

Participants randomized to the incretin based arm started with sitagliptin once daily. If sitagliptin did not control the participant's hyperglycemia, sitagliptin was stopped and participants switched to liraglutide once daily. If despite treatment with liraglutide, hyperglycemia was not controlled then the participant was eligible for rescue therapy with addition of insulin

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Pasireotide s.c. |
| Investigational medicinal product code | SOM230 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Pasireotide s.c. was provided as solution for injection in individual one-point-cut 1 mL ampule, containing 900, 600, and 300 µg pasireotide per 1 mL of solution, b.i.d. which was self-injected by the patients. Starting dose = 600 µg b.i.d.

| | |
|---|---|
| Investigational medicinal product name | Pasireotide i.m. long acting release (LAR) |
| Investigational medicinal product code | SOM230 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Pasireotide i.m. LAR was provided as 20 mg, 40 mg, 60 mg every 28 days (q28d); Starting dose = 40 mg q28d

| | |
|---|---|
| Investigational medicinal product name | Metformin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Individual doses starting from 1000 mg/day to maximum dose according to the approved package insert and depending on the patient tolerability

| | |
|---|---|
| Investigational medicinal product name | Sitagliptin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

50 or 100 mg administered orally once a day

| | |
|---|---|
| Investigational medicinal product name | Liraglutide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Administered s.c. once a day according to package insert

| | |
|---|---|
| Investigational medicinal product name | Insulin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Administered s.c. according to package insert, per investigator discretion. Insulin was only given as rescue therapy in the Incretin arm if required.

| | |
|---|---|
| **Arm title** | Insulin (randomized group) |

Arm description:

Participants randomized to the insulin arm started with once daily dose of basal insulin. The dose was up or down titrated at the discretion of the investigator. If blood glucose levels remained uncontrolled on basal insulin, participant switched to basal insulin plus prandial insulin

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Pasireotide s.c. |
| Investigational medicinal product code | SOM230 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Pasireotide s.c. was provided as solution for injection in individual one-point-cut 1 mL ampule, containing 900, 600, and 300 µg pasireotide per 1 mL of solution, b.i.d. which was self-injected by the patients. Starting dose = 600 µg b.i.d.

| | |
|---|---|
| Investigational medicinal product name | Pasireotide i.m. long acting release (LAR) |
| Investigational medicinal product code | SOM230 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Pasireotide i.m. LAR was provided as 20 mg, 40 mg, 60 mg every 28 days (q28d); Starting dose = 40 mg q28d

| | |
|---|---|
| Investigational medicinal product name | Metformin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Individual doses starting from 1000 mg/day to maximum dose according to the approved package insert and depending on the patient tolerability

| | |
|---|---|
| Investigational medicinal product name | Insulin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Administered s.c. according to package insert, per investigator discretion

| **Arm title** | Baseline Insulin (BL) (non-randomized group) |
|---|---|

Arm description:

This group included participants who were receiving insulin at study entry

| | |
|---|---|
| Arm type | This was an Observational arm |
| Investigational medicinal product name | Pasireotide s.c. |
| Investigational medicinal product code | SOM230 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Pasireotide s.c. was provided as solution for injection in individual one-point-cut 1 mL ampule, containing 900, 600, and 300 µg pasireotide per 1 mL of solution, b.i.d. which was self-injected by the patients. Starting dose = 600 µg b.i.d.

| | |
|---|---|
| Investigational medicinal product name | Pasireotide i.m. long acting release (LAR) |
| Investigational medicinal product code | SOM230 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Pasireotide i.m. LAR was provided as 20 mg, 40 mg, 60 mg every 28 days (q28d); Starting dose = 40

| | |
|---|---|
| Investigational medicinal product name | Pasireotide s.c. |
| Investigational medicinal product code | SOM230 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Pasireotide s.c. was provided as solution for injection in individual one-point-cut 1 mL ampule, containing 900, 600, and 300 µg pasireotide per 1 mL of solution, b.i.d. which was self-injected by the patients. Starting dose = 600 µg b.i.d.

| | |
|---|---|
| Investigational medicinal product name | Pasireotide i.m. long acting release (LAR) |
| Investigational medicinal product code | SOM230 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Pasireotide i.m. LAR was provided as 20 mg, 40 mg, 60 mg every 28 days (q28d); Starting dose = 40 mg q28d

| | |
|---|---|
| Investigational medicinal product name | Metformin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Metformin treatment was not required for the OAD group but may have been prescribed at the discretion of the investigator.

| | |
|---|---|
| **Arm title** | No OAD (non-randomized group) |

Arm description:

This group included participants who did not receive any anti-diabetic medication during the Core Phase of the study

| | |
|---|---|
| Arm type | This was an Observational arm |
| Investigational medicinal product name | Pasireotide i.m. long acting release (LAR) |
| Investigational medicinal product code | SOM230 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Pasireotide i.m. LAR was provided as 20 mg, 40 mg, 60 mg every 28 days (q28d); Starting dose = 40 mg q28d

| | |
|---|---|
| Investigational medicinal product name | Pasireotide s.c. |
| Investigational medicinal product code | SOM230 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Pasireotide s.c. was provided as solution for injection in individual one-point-cut 1 mL ampule, containing 900, 600, and 300 µg pasireotide per 1 mL of solution, b.i.d. which was self-injected by the patients. Starting dose = 600 µg b.i.d.

| Number of subjects in period 1 | Incretin based therapy (randomized group) | Insulin (randomized group) | Baseline Insulin (BL) (non-randomized group) |
|---|---|---|---|
| Started | 38 | 43 | 19 |
| Completed Core/Entered Extension | 17 [1] | 17 [2] | 10 [3] |
| Completed Core/Did not enter Extension | 18 [4] | 20 [5] | 9 [6] |
| Completed | 35 | 37 | 19 |
| Not completed | 3 | 6 | 0 |
| Consent withdrawn by subject | - | - | - |
| Adverse event, non-fatal | 2 | - | - |
| Unsatisfactory therapeutic effect | 1 | 5 | - |
| Administrative problems | - | 1 | - |
| Protocol deviation | - | - | - |

| Number of subjects in period 1 | Oral antidiabetic drugs (OAD) (non-randomized group) | No OAD (non-randomized group) |
|---|---|---|
| Started | 46 | 103 |
| Completed Core/Entered Extension | 21 [7] | 53 [8] |
| Completed Core/Did not enter Extension | 18 [9] | 42 [10] |
| Completed | 39 | 95 |
| Not completed | 7 | 8 |
| Consent withdrawn by subject | 4 | 2 |
| Adverse event, non-fatal | 2 | 6 |
| Unsatisfactory therapeutic effect | - | - |
| Administrative problems | - | - |
| Protocol deviation | 1 | - |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Not everyone who completed the Core phase entered the extension phase of the study.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Not everyone who completed the Core phase entered the extension phase of the study.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Not everyone who completed the Core phase entered the extension phase of the study.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Not everyone who completed the Core phase entered the extension phase of the study.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Not everyone who completed the Core phase entered the extension phase of the study.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the

arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Not everyone who completed the Core phase entered the extension phase of the study.

[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Not everyone who completed the Core phase entered the extension phase of the study.

[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Not everyone who completed the Core phase entered the extension phase of the study.

[9] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Not everyone who completed the Core phase entered the extension phase of the study.

[10] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Not everyone who completed the Core phase entered the extension phase of the study.

## Period 2

| | |
|---|---|
| Period 2 title | Extension Phase |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Incretin based therapy (randomized group) |

Arm description:

Participants randomized to the incretin based arm started with sitagliptin once daily. If sitagliptin did not control the participant's hyperglycemia, sitagliptin was stopped and participants switched to liraglutide once daily. If despite treatment with liraglutide, hyperglycemia was not controlled then the participant was eligible for rescue therapy with addition of insulin

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Pasireotide s.c. |
| Investigational medicinal product code | SOM230 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Pasireotide s.c. was provided as solution for injection in individual one-point-cut 1 mL ampule, containing 900, 600, and 300 µg pasireotide per 1 mL of solution, b.i.d. which was self-injected by the patients. Starting dose = 600 µg b.i.d.

| | |
|---|---|
| Investigational medicinal product name | Pasireotide i.m. long acting release (LAR) |
| Investigational medicinal product code | SOM230 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Pasireotide i.m. LAR was provided as 20 mg, 40 mg, 60 mg every 28 days (q28d); Starting dose = 40 mg q28d

| | |
|---|---|
| Investigational medicinal product name | Metformin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Metformin may have been continued in the Extension phase at the discretion of the investigator; however, it was not provided by Novartis unless required by local regulations.

| | |
|---|---|
| Investigational medicinal product name | Sitagliptin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Sitagliptin may have been continued in the Extension phase at the discretion of the investigator; however, it was not provided by Novartis unless required by local regulations.

| | |
|---|---|
| Investigational medicinal product name | Liraglutide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Liraglutide may have been continued in the Extension phase at the discretion of the investigator; however, it was not provided by Novartis unless required by local regulations.

| | |
|---|---|
| Investigational medicinal product name | Insulin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Insulin may have been continued in the Extension phase at the discretion of the investigator; however, it was not provided by Novartis unless required by local regulations.

| | |
|---|---|
| **Arm title** | Insulin (randomized group) |

Arm description:

Participants randomized to the insulin arm started with once daily dose of basal insulin. The dose was up or down titrated at the discretion of the investigator. If blood glucose levels remained uncontrolled on basal insulin, participant switched to basal insulin plus prandial insulin.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Pasireotide s.c. |
| Investigational medicinal product code | SOM230 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Pasireotide s.c. was provided as solution for injection in individual one-point-cut 1 mL ampule, containing 900, 600, and 300 µg pasireotide per 1 mL of solution, b.i.d. which was self-injected by the patients. Starting dose = 600 µg b.i.d.

| | |
|---|---|
| Investigational medicinal product name | Pasireotide i.m. long acting release (LAR) |
| Investigational medicinal product code | SOM230 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Pasireotide i.m. LAR was provided as 20 mg, 40 mg, 60 mg every 28 days (q28d); Starting dose = 40 mg q28d

| | |
|---|---|
| Investigational medicinal product name | Metformin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |

| | |
|---|---|
| Routes of administration | Oral use |

Dosage and administration details:

Metformin may have been continued in the Extension phase at the discretion of the investigator; however, it was not provided by Novartis unless required by local regulations.

| | |
|---|---|
| Investigational medicinal product name | Insulin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Insulin may have been continued in the Extension phase at the discretion of the investigator; however, it was not provided by Novartis unless required by local regulations.

| | |
|---|---|
| **Arm title** | Baseline Insulin (BL) (non-randomized group) |

Arm description:

This group included participants who were receiving insulin at study entry and thus were not eligible for randomization.

| | |
|---|---|
| Arm type | This was an Observational arm |
| Investigational medicinal product name | Pasireotide s.c. |
| Investigational medicinal product code | SOM230 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Pasireotide s.c. was provided as solution for injection in individual one-point-cut 1 mL ampule, containing 900, 600, and 300 µg pasireotide per 1 mL of solution, b.i.d. which was self-injected by the patients. Starting dose = 600 µg b.i.d.

| | |
|---|---|
| Investigational medicinal product name | Pasireotide i.m. long acting release (LAR) |
| Investigational medicinal product code | SOM230 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Pasireotide i.m. LAR was provided as 20 mg, 40 mg, 60 mg every 28 days (q28d); Starting dose = 40 mg q28d

| | |
|---|---|
| Investigational medicinal product name | Metformin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Metformin may have been continued in the Extension phase at the discretion of the investigator; however, it was not provided by Novartis unless required by local regulations.

| | |
|---|---|
| Investigational medicinal product name | Insulin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Insulin may have been continued in the Extension phase at the discretion of the investigator; however, it was not provided by Novartis unless required by local regulations.

| | |
|---|---|
| **Arm title** | Oral antidiabetic drugs (OAD) (non-randomized group) |

Arm description:

This group included participants who developed hyperglycemia that was controlled by metformin and/or other background anti-diabetic treatment and thus were not randomized.

| | |
|---|---|
| Arm type | This was an Observational arm |
| Investigational medicinal product name | Pasireotide s.c. |
| Investigational medicinal product code | SOM230 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Pasireotide s.c. was provided as solution for injection in individual one-point-cut 1 mL ampule, containing 900, 600, and 300 µg pasireotide per 1 mL of solution, b.i.d. which was self-injected by the patients. Starting dose = 600 µg b.i.d.

| | |
|---|---|
| Investigational medicinal product name | Pasireotide i.m. long acting release (LAR) |
| Investigational medicinal product code | SOM230 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Pasireotide i.m. LAR was provided as 20 mg, 40 mg, 60 mg every 28 days (q28d); Starting dose = 40 mg q28d

| | |
|---|---|
| Investigational medicinal product name | Metformin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Metformin may have been continued in the Extension phase at the discretion of the investigator; however, it was not provided by Novartis unless required by local regulations.

| | |
|---|---|
| **Arm title** | No OAD (non-randomized group) |

Arm description:

This group included participants who did not receive any anti-diabetic medication during the Core Phase of the study and thus were not randomized.

| | |
|---|---|
| Arm type | This was an Observational arm |
| Investigational medicinal product name | Pasireotide i.m. long acting release (LAR) |
| Investigational medicinal product code | SOM230 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Pasireotide i.m. LAR was provided as 20 mg, 40 mg, 60 mg every 28 days (q28d); Starting dose = 40 mg q28d

| | |
|---|---|
| Investigational medicinal product name | Pasireotide s.c. |
| Investigational medicinal product code | SOM230 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Pasireotide s.c. was provided as solution for injection in individual one-point-cut 1 mL ampule, containing 900, 600, and 300 µg pasireotide per 1 mL of solution, b.i.d. which was self-injected by the patients. Starting dose = 600 µg b.i.d.

| **Number of subjects in period 2[11]** | Incretin based therapy (randomized group) | Insulin (randomized group) | Baseline Insulin (BL) (non-randomized group) |
|---|---|---|---|
| Started | 17 | 17 | 10 |
| Completed | 14 | 14 | 7 |
| Not completed | 3 | 3 | 3 |
| Adverse event, serious fatal | - | - | 1 |
| Consent withdrawn by subject | - | 1 | - |
| Adverse event, non-fatal | 1 | 1 | 2 |
| Unsatisfactory therapeutic effect | 1 | 1 | - |
| Administrative problems | 1 | - | - |
| Protocol deviation | - | - | - |

| **Number of subjects in period 2[11]** | Oral antidiabetic drugs (OAD) (non-randomized group) | No OAD (non-randomized group) |
|---|---|---|
| Started | 21 | 53 |
| Completed | 19 | 46 |
| Not completed | 2 | 7 |
| Adverse event, serious fatal | - | 1 |
| Consent withdrawn by subject | - | 2 |
| Adverse event, non-fatal | - | 1 |
| Unsatisfactory therapeutic effect | 2 | 2 |
| Administrative problems | - | - |
| Protocol deviation | - | 1 |

Notes:

[11] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Not everyone who completed the Core phase entered the extension phase of the study.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Incretin based therapy (randomized group) |
| Reporting group description: | |
| Participants randomized to the incretin based arm started with sitagliptin once daily. If sitagliptin did not control the participant's hyperglycemia, sitagliptin was stopped and participants switched to liraglutide once daily. If despite treatment with liraglutide, hyperglycemia was not controlled then the participant was eligible for rescue therapy with addition of insulin | |
| Reporting group title | Insulin (randomized group) |
| Reporting group description: | |
| Participants randomized to the insulin arm started with once daily dose of basal insulin. The dose was up or down titrated at the discretion of the investigator. If blood glucose levels remained uncontrolled on basal insulin, participant switched to basal insulin plus prandial insulin | |
| Reporting group title | Baseline Insulin (BL) (non-randomized group) |
| Reporting group description: | |
| This group included participants who were receiving insulin at study entry | |
| Reporting group title | Oral antidiabetic drugs (OAD) (non-randomized group) |
| Reporting group description: | |
| This group included participants who developed hyperglycemia that was controlled by metformin and/or other background anti-diabetic treatment | |
| Reporting group title | No OAD (non-randomized group) |
| Reporting group description: | |
| This group included participants who did not receive any anti-diabetic medication during the Core Phase of the study | |

| Reporting group values | Incretin based therapy (randomized group) | Insulin (randomized group) | Baseline Insulin (BL) (non-randomized group) |
|---|---|---|---|
| Number of subjects | 38 | 43 | 19 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 32 | 40 | 18 |
| From 65-84 years | 6 | 3 | 1 |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 50.6 | 46.4 | 46.7 |
| standard deviation | ± 11.76 | ± 12.90 | ± 12.54 |
| Sex: Female, Male<br>Units: Subjects | | | |
| Female | 22 | 27 | 10 |
| Male | 16 | 16 | 9 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| Other | 22 | 24 | 11 |
| Chinese | 5 | 9 | 1 |
| Hispanic/Latino | 7 | 2 | 5 |
| Indian (Indian subcontinent) | 4 | 8 | 2 |
| Japanese | 0 | 0 | 0 |

| Reporting group values | Oral antidiabetic drugs (OAD) (non-randomized group) | No OAD (non-randomized group) | Total |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Number of subjects | 46 | 103 | 249 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 43 | 101 | 234 |
| From 65-84 years | 3 | 2 | 15 |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 40.2 | 37.8 | |
| standard deviation | ± 13.80 | ± 11.17 | - |
| Sex: Female, Male<br>Units: Subjects | | | |
| Female | 31 | 47 | 137 |
| Male | 15 | 56 | 112 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| Other | 25 | 43 | 125 |
| Chinese | 13 | 33 | 61 |
| Hispanic/Latino | 6 | 19 | 39 |
| Indian (Indian subcontinent) | 2 | 7 | 23 |
| Japanese | 0 | 1 | 1 |

## End points

### End points reporting groups

| Reporting group title | Incretin based therapy (randomized group) |
|---|---|
| Reporting group description: | |
| Participants randomized to the incretin based arm started with sitagliptin once daily. If sitagliptin did not control the participant's hyperglycemia, sitagliptin was stopped and participants switched to liraglutide once daily. If despite treatment with liraglutide, hyperglycemia was not controlled then the participant was eligible for rescue therapy with addition of insulin | |
| Reporting group title | Insulin (randomized group) |
| Reporting group description: | |
| Participants randomized to the insulin arm started with once daily dose of basal insulin. The dose was up or down titrated at the discretion of the investigator. If blood glucose levels remained uncontrolled on basal insulin, participant switched to basal insulin plus prandial insulin | |
| Reporting group title | Baseline Insulin (BL) (non-randomized group) |
| Reporting group description: | |
| This group included participants who were receiving insulin at study entry | |
| Reporting group title | Oral antidiabetic drugs (OAD) (non-randomized group) |
| Reporting group description: | |
| This group included participants who developed hyperglycemia that was controlled by metformin and/or other background anti-diabetic treatment | |
| Reporting group title | No OAD (non-randomized group) |
| Reporting group description: | |
| This group included participants who did not receive any anti-diabetic medication during the Core Phase of the study | |
| Reporting group title | Incretin based therapy (randomized group) |
| Reporting group description: | |
| Participants randomized to the incretin based arm started with sitagliptin once daily. If sitagliptin did not control the participant's hyperglycemia, sitagliptin was stopped and participants switched to liraglutide once daily. If despite treatment with liraglutide, hyperglycemia was not controlled then the participant was eligible for rescue therapy with addition of insulin | |
| Reporting group title | Insulin (randomized group) |
| Reporting group description: | |
| Participants randomized to the insulin arm started with once daily dose of basal insulin. The dose was up or down titrated at the discretion of the investigator. If blood glucose levels remained uncontrolled on basal insulin, participant switched to basal insulin plus prandial insulin. | |
| Reporting group title | Baseline Insulin (BL) (non-randomized group) |
| Reporting group description: | |
| This group included participants who were receiving insulin at study entry and thus were not eligible for randomization. | |
| Reporting group title | Oral antidiabetic drugs (OAD) (non-randomized group) |
| Reporting group description: | |
| This group included participants who developed hyperglycemia that was controlled by metformin and/or other background anti-diabetic treatment and thus were not randomized. | |
| Reporting group title | No OAD (non-randomized group) |
| Reporting group description: | |
| This group included participants who did not receive any anti-diabetic medication during the Core Phase of the study and thus were not randomized. | |

## Primary: Change in HbA1c from randomization to approximately 16 weeks

| End point title | Change in HbA1c from randomization to approximately 16 weeks[1] |
|---|---|

End point description:

Absolute change in HbA1c from randomization to end of core phase (16 weeks) in incretin based therapy arm and insulin arm, and mean difference of change in HbA1c between the two treatment groups based on an ANOVA model using treatment (Incretin, Insulin) and the two randomization stratification factors (Disease: Cushing's disease vs Acromegaly; Baseline glycemic status: HbA1c <7% vs HbA1c ≥ 7%) as fixed effects. For Participants who discontinued the study or required rescue treatment before the time of assessing the primary endpoint, the last HbA1c assessment collected 8 weeks (56 days) after randomization (and prior to or on the date of start of rescue treatment) was carried forward. If the participant discontinued the study or used rescue treatment within 8 weeks after randomization, it was considered missing.

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

End point timeframe:

Randomization, 16 weeks

Notes:

[1] - 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: Statistics analysis was done only within these 3 groups

| **End point values** | Incretin based therapy (randomized group) | Insulin (randomized group) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 38 | 43 | | |
| Units: HbA1c percentage | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| All Patients (n = 31, 41) | -0.12 (-0.36 to 0.13) | 0.26 (-0.01 to 0.53) | | |
| Cushing's Disease (n = 7, 11) | 0.33 (-0.41 to 1.07) | 0.45 (-0.20 to 1.09) | | |
| Acromegaly (n = 24, 30) | -0.25 (-0.49 to -0.00) | 0.19 (-0.12 to 0.49) | | |

## Statistical analyses

| **Statistical analysis title** | All Patients |
|---|---|

Statistical analysis description:

Incretin based therapy (randomized group) vs.
Insulin (randomized group)

| Comparison groups | Incretin based therapy (randomized group) v Insulin (randomized group) |
|---|---|
| Number of subjects included in analysis | 81 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.63 |
| upper limit | 0.08 |

| | |
|---|---|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.18 |

| **Statistical analysis title** | Cushing's Disease |
|---|---|
| Statistical analysis description:<br>Incretin based therapy (randomized group) vs.<br>Insulin (randomized group) | |
| Comparison groups | Incretin based therapy (randomized group) v Insulin (randomized group) |
| Number of subjects included in analysis | 81 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.96 |
| upper limit | 0.95 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.45 |

| **Statistical analysis title** | Acromegaly |
|---|---|
| Statistical analysis description:<br>Incretin based therapy (randomized group) vs.<br>Insulin (randomized group) | |
| Comparison groups | Incretin based therapy (randomized group) v Insulin (randomized group) |
| Number of subjects included in analysis | 81 |
| | Pre-specified |

| | |
|---|---|
| End point description: | |
| Absolute change in HbA1c overtime from randomization to end of core phase per randomized arm | |
| End point type | Secondary |
| End point timeframe: | |
| R, R - Week 4, R - Week 8, R - Week 12, R - Week 16, end of Core phase | |
| Notes: | |
| [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: No statistical analysis was planned for this endpoint. | |

| **End point values** | Incretin based therapy (randomized group) | Insulin (randomized group) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 38 | 43 | | |
| Units: HbA1c percentage | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (Randomization) | 7.1 (± 1.00) | 7.1 (± 0.75) | | |
| Change at RW4 D29 (n = 37, 43) | 0.5 (± 0.73) | 0.5 (± 0.60) | | |
| Change at RW8 D57 (n = 37, 43) | 0.3 (± 0.98) | 0.5 (± 0.86) | | |
| Change at RW12 D85 (n = 37, 40) | 0.2 (± 1.03) | 0.4 (± 0.85) | | |
| Change at RW16 D113 (n = 35, 37) | 0.0 (± 0.93) | 0.3 (± 0.87) | | |
| End of Core Phase (n = 37, 42) | 0.0 (± 0.92) | 0.3 (± 0.84) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change in FPG (Fasting Plasma Glucose) from randomization until end of Core phase

| | |
|---|---|
| End point title | Change in FPG (Fasting Plasma Glucose) from randomization until end of Core phase[3] |
| End point description: | |
| Absolute change in fasting glucose overtime from randomization to end of core phase per randomized arm | |
| End point type | Secondary |
| End point timeframe: | |
| Randomization, R(randomization) Week 2, R-Week 4, R-Week 6, R-Week 8, R-Week 10, R-Week 12, R-Week 14, R-Week 16, end of Core phase | |
| Notes: | |
| [3] - 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: No statistical analysis was planned for this endpoint. | |

| **End point values** | Incretin based therapy (randomized group) | Insulin (randomized group) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 38 | 43 | | |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | | | | |

| | | | | |
|---|---|---|---|---|
| Baseline (Randomization) | 172.2 (± 60.78) | 167.9 (± 40.77) | | |
| Change at RW2 D15 (n = 36, 42) | 4.6 (± 51.01) | -31.1 (± 41.19) | | |
| Change at RW4 D29 (n = 38, 43) | -15.0 (± 47.95) | -28.3 (± 41.14) | | |
| Change at RW6 D43 (n = 36, 41) | -17.7 (± 57.97) | -37.5 (± 52.39) | | |
| Change at RW8 D57 (n = 36, 42) | -25.7 (± 53.32) | -38.3 (± 44.10) | | |
| Change at RW10 D71 (n = 37, 37) | -28.8 (± 61.14) | -36.9 (± 50.82) | | |
| Change at RW12 D85 (n = 37, 40) | -33.4 (± 50.17) | -41.1 (± 51.68) | | |
| Change at RW14 D99 (n = 36, 36) | -35.1 (± 55.83) | -35.6 (± 47.43) | | |
| Change at RW16 D113 (n = 35, 34) | -38.8 (± 53.69) | -33.4 (± 47.63) | | |
| End of Core Phase (n = 37, 41) | -40.1 (± 56.35) | -36.0 (± 46.90) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of participants in the incretin-based arm who required anti-diabetic rescue therapy with insulin

| | |
|---|---|
| End point title | Percentage of participants in the incretin-based arm who required anti-diabetic rescue therapy with insulin[4] |

End point description:

The percentage of participants who received anti-diabetic rescue therapy in incretin based therapy is summarized.

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

End point timeframe:

Randomization to up to 16 weeks

Notes:

[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: No statistical analysis was planned for this endpoint.

| **End point values** | Incretin based therapy (randomized group) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 38 | | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 31.6 (17.5 to 48.7) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute change in HbA1c from baseline to end of Core phase

| End point title | Absolute change in HbA1c from baseline to end of Core phase |
|---|---|
| End point description: | |
| Absolute change in HbA1c from baseline to end of core phase in the incretin based therapy arm and the insulin arm | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, up to 32 weeks (end of Core phase) | |

| **End point values** | Incretin based therapy (randomized group) | Insulin (randomized group) | Baseline Insulin (BL) (non-randomized group) | Oral antidiabetic drugs (OAD) (non-randomized group) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 38 | 43 | 19 | 46 |
| Units: HbA1c percentage | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline: All Patients (n = 38, 43, 19, 46,102) | 6.3 (± 0.80) | 6.3 (± 0.63) | 7.7 (± 1.51) | 5.7 (± 0.41) |
| Change at EOP: All Patients (n = 37,42, 19,45,100) | 0.8 (± 0.97) | 1.1 (± 0.94) | 1.3 (± 1.40) | 0.8 (± 0.64) |
| Baseline: Cushing's (n = 12, 13, 6, 13, 15) | 6.6 (± 0.87) | 6.5 (± 0.58) | 6.9 (± 0.92) | 5.9 (± 0.49) |
| Change at EOP: Cushing's (n = 12, 13, 6, 13, 14) | 1.3 (± 1.19) | 1.7 (± 1.05) | 1.4 (± 1.58) | 0.9 (± 0.95) |
| Baseline: Acromegaly (n = 26, 30, 13, 33, 87) | 6.1 (± 0.71) | 6.3 (± 0.65) | 8.0 (± 1.61) | 5.6 (± 0.36) |
| Change at EOP: Acromegaly (n = 25, 29, 13, 32, 86) | 0.6 (± 0.78) | 0.8 (± 0.78) | 1.2 (± 1.37) | 0.7 (± 0.47) |

| **End point values** | No OAD (non-randomized group) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 103 | | | |
| Units: HbA1c percentage | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline: All Patients (n = 38, 43, 19, 46,102) | 5.4 (± 0.33) | | | |
| Change at EOP: All Patients (n = 37,42, 19,45,100) | 0.4 (± 0.32) | | | |
| Baseline: Cushing's (n = 12, 13, 6, 13, 15) | 5.5 (± 0.41) | | | |
| Change at EOP: Cushing's (n = 12, 13, 6, 13, 14) | 0.5 (± 0.51) | | | |
| Baseline: Acromegaly (n = 26, 30, 13, 33, 87) | 5.4 (± 0.32) | | | |

| | | | | |
|---|---|---|---|---|
| Change at EOP: Acromegaly (n = 25, 29, 13, 32, 86) | 0.4 (± 0.28) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute change in FPG from baseline to end of Core Phase

| | |
|---|---|
| End point title | Absolute change in FPG from baseline to end of Core Phase |

End point description:

Absolute change in FPG from baseline to end of core phase in the incretin based therapy arm and the insulin arm.

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

End point timeframe:

Baseline, Up to 32 weeks (end of Core Phase)

| **End point values** | Incretin based therapy (randomized group) | Insulin (randomized group) | Baseline Insulin (BL) (non-randomized group) | Oral antidiabetic drugs (OAD) (non-randomized group) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 38 | 43 | 19 | 46 |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline: All Patients (n = 38, 43, 19, 46, 103) | 111.1 (± 18.95) | 111.8 (± 18.20) | 157.7 (± 66.50) | 97.2 (± 14.24) |
| Change at EOP: All Patients (n = 37,41,19,45,101) | 22.2 (± 31.67) | 22.5 (± 34.05) | 9.8 (± 75.67) | 22.9 (± 23.40) |
| Baseline: Cushing's (n = 12, 13, 6, 13, 15) | 117.9 (± 20.99) | 106.3 (± 15.71) | 147.2 (± 68.38) | 93.3 (± 10.98) |
| Change at EOP: Cushing's (n = 12, 12, 6, 13, 14) | 13.4 (± 34.92) | 36.4 (± 33.11) | 21.3 (± 72.01) | 15.8 (± 18.43) |
| Baseline: Acromegaly (n = 26, 30, 13, 33, 88) | 107.9 (± 17.46) | 114.2 (± 18.91) | 162.5 (± 67.85) | 98.8 (± 15.20) |
| Change at EOP: Acromegaly (n = 25, 29, 13, 32, 87) | 26.5 (± 29.79) | 16.7 (± 33.29) | 4.6 (± 79.57) | 25.8 (± 24.82) |

| **End point values** | No OAD (non-randomized group) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 103 | | | |
| Units: mg/dL | | | | |
| arithmetic mean (standard deviation) | | | | |

| | | | | |
|---|---|---|---|---|
| Baseline: All Patients (n = 38, 43, 19, 46, 103) | 92.2 (± 8.58) | | | |
| Change at EOP: All Patients (n = 37,41,19,45,101) | 16.3 (± 13.63) | | | |
| Baseline: Cushing's (n = 12, 13, 6, 13, 15) | 85.5 (± 6.92) | | | |
| Change at EOP: Cushing's (n = 12, 12, 6, 13, 14) | 11.7 (± 22.11) | | | |
| Baseline: Acromegaly (n = 26, 30, 13, 33, 88) | 93.4 (± 8.32) | | | |
| Change at EOP: Acromegaly (n = 25, 29, 13, 32, 87) | 17.0 (± 11.75) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of participants with ≤ 0.3% HbA1c increase to end of Core Phase

| | |
|---|---|
| End point title | Percentage of participants with ≤ 0.3% HbA1c increase to end of Core Phase[5] |

End point description:

Percentage of participants with ≤ 0.3% HbA1c increase in the incretin based therapy arm and the insulin arm.

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

End point timeframe:

Randomization, up to 16 weeks

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: No statistical analysis was planned for this endpoint.

| **End point values** | Incretin based therapy (randomized group) | Insulin (randomized group) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 38 | 43 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 73.7 (56.9 to 86.6) | 65.1 (49.1 to 79.0) | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse Events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit up to approximately 46 months.

Adverse event reporting additional description:

There are different safety follow-up period for Cushing's and for acromegaly patients: On-treatment period: from day of first dose of study medication to 28 days after last dose of pasireotide s.c. and 84 days after last dose of pasireotide long acting, or the follow-up visit, whichever comes later.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Incretin based therapy (randomized group) |

Reporting group description:

Participants randomized to the incretin based arm started with sitagliptin once daily. If sitagliptin did not control the participant's hyperglycemia, sitagliptin was stopped and participants switched to liraglutide once daily. If despite treatment with liraglutide, hyperglycemia was not controlled then the participant was eligible for rescue therapy with addition of insulin

| | |
|---|---|
| Reporting group title | Insulin (randomized group) |

Reporting group description:

Participants randomized to the insulin arm started with once daily dose of basal insulin. The dose was up or down titrated at the discretion of the investigator. If blood glucose levels remained uncontrolled on basal insulin, participant switched to basal insulin plus prandial insulin.

| | |
|---|---|
| Reporting group title | Baseline Insulin (BL) (non-randomized group) |

Reporting group description:

This group included participants who were receiving insulin at study entry and thus were not eligible for randomization.

| | |
|---|---|
| Reporting group title | Oral antidiabetic drugs (OAD) (non-randomized group) |

Reporting group description:

This group included participants who developed hyperglycemia that was controlled by metformin and/or other background antidiabetic treatment and thus were not randomized.

| | |
|---|---|
| Reporting group title | No OAD (non-randomized group) |

Reporting group description:

This group included participants who did not receive any antidiabetic medication during the Core Phase of the study and thus were not randomized.

| **Serious adverse events** | Incretin based therapy (randomized group) | Insulin (randomized group) | Baseline Insulin (BL) (non-randomized group) |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 38 (15.79%) | 3 / 43 (6.98%) | 4 / 19 (21.05%) |
| number of deaths (all causes) | 0 | 0 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |

| | | | |
|---|---|---|---|
| Papillary thyroid cancer | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pituitary tumour benign | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tubular breast carcinoma | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Shock | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 43 (2.33%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Mental status changes | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Glycosylated haemoglobin increased | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 43 (2.33%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Seizure | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 43 (2.33%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 43 (2.33%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal injury | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Cushing's syndrome | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Breast abscess | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 43 (2.33%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epiglottitis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paronychia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 43 (2.33%) | 1 / 19 (5.26%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypovolaemia | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lactic acidosis | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Oral antidiabetic drugs (OAD) (non-randomized group) | No OAD (non-randomized group) | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 7 / 103 (6.80%) | |
| number of deaths (all causes) | 0 | 1 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Papillary thyroid cancer | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pituitary tumour benign | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tubular breast carcinoma | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Shock | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 2 / 103 (1.94%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Mental status changes | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Glycosylated haemoglobin increased | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Wound | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Seizure | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal injury | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Cushing's syndrome | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Breast abscess | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epiglottitis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 103 (0.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paronychia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypovolaemia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lactic acidosis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | Incretin based therapy (randomized group) | Insulin (randomized group) | Baseline Insulin (BL) (non-randomized group) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 37 / 38 (97.37%) | 40 / 43 (93.02%) | 18 / 19 (94.74%) |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 2 | 0 | 1 |

| | | | |
|---|---|---|---|
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | 4 / 43 (9.30%) | 0 / 19 (0.00%) |
| occurrences (all) | 4 | 4 | 0 |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 1 | 0 | 1 |
| Reproductive system and breast disorders | | | |
| Amenorrhoea | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 43 (2.33%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 1 | 1 |
| Polycystic ovaries | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 2 / 43 (4.65%) | 1 / 19 (5.26%) |
| occurrences (all) | 4 | 4 | 1 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 3 / 43 (6.98%) | 1 / 19 (5.26%) |
| occurrences (all) | 2 | 4 | 1 |
| Bacterial test positive | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood creatine phosphokinase increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 3 | 0 | 3 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Blood glucose increased | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 1 / 43 (2.33%) | 0 / 19 (0.00%) |
| occurrences (all) | 2 | 5 | 0 |
| Blood insulin increased | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 1 | 0 | 1 |
| Blood urea increased | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 1 | 0 | 1 |
| Blood uric acid increased | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 43 (4.65%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 2 | 1 |
| Carbon dioxide decreased | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 4 / 43 (9.30%) | 0 / 19 (0.00%) |
| occurrences (all) | 2 | 6 | 0 |
| Glycosylated haemoglobin increased | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 1 / 43 (2.33%) | 0 / 19 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Lipase increased | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 2 / 43 (4.65%) | 0 / 19 (0.00%) |
| occurrences (all) | 4 | 2 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 10 / 38 (26.32%) | 4 / 43 (9.30%) | 0 / 19 (0.00%) |
| occurrences (all) | 11 | 5 | 0 |
| Weight increased | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 43 (2.33%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 1 | 1 |

| | | | |
|---|---|---|---|
| Injury, poisoning and procedural complications | | | |
| Laceration | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Cardiac disorders | | | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Sinus bradycardia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 5 / 38 (13.16%) | 5 / 43 (11.63%) | 0 / 19 (0.00%) |
| occurrences (all) | 5 | 5 | 0 |
| Dysgeusia | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Headache | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | 4 / 43 (9.30%) | 0 / 19 (0.00%) |
| occurrences (all) | 5 | 4 | 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 43 (4.65%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 2 | 1 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 2 / 19 (10.53%) |
| occurrences (all) | 0 | 0 | 3 |
| Ear and labyrinth disorders | | | |

| | | | |
|---|---|---|---|
| Vertigo | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 2 / 43 (4.65%) | 0 / 19 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Abdominal distension | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 1 / 43 (2.33%) | 0 / 19 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 2 / 43 (4.65%) | 1 / 19 (5.26%) |
| occurrences (all) | 1 | 2 | 1 |
| Constipation | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 11 / 38 (28.95%) | 12 / 43 (27.91%) | 2 / 19 (10.53%) |
| occurrences (all) | 14 | 17 | 3 |
| Erosive duodenitis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Gingival hypertrophy | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Nausea | | | |
| subjects affected / exposed | 13 / 38 (34.21%) | 7 / 43 (16.28%) | 0 / 19 (0.00%) |
| occurrences (all) | 15 | 7 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 5 / 38 (13.16%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 6 | 0 | 0 |
| Hepatobiliary disorders | | | |

| | | | |
|---|---|---|---|
| Cholelithiasis | | | |
| subjects affected / exposed | 5 / 38 (13.16%) | 8 / 43 (18.60%) | 0 / 19 (0.00%) |
| occurrences (all) | 5 | 9 | 0 |
| Hepatic steatosis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 43 (2.33%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 1 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 1 / 43 (2.33%) | 0 / 19 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Pruritus generalised | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 1 / 43 (2.33%) | 0 / 19 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Rash | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 2 / 43 (4.65%) | 1 / 19 (5.26%) |
| occurrences (all) | 3 | 2 | 1 |
| Rash generalised | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Renal and urinary disorders | | | |
| Glycosuria | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 43 (2.33%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 1 | 1 |
| Haematuria | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 43 (2.33%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 2 | 1 |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Hypothyroidism | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 43 (2.33%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Back pain | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 3 / 43 (6.98%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 2 / 43 (4.65%) | 0 / 19 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 2 / 43 (4.65%) | 1 / 19 (5.26%) |
| occurrences (all) | 1 | 2 | 1 |
| Osteopenia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Infections and infestations | | | |
| Bone abscess | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 4 / 43 (9.30%) | 0 / 19 (0.00%) |
| occurrences (all) | 3 | 6 | 0 |
| Onychomycosis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 43 (2.33%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 1 | 2 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Respiratory tract infection viral | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 43 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 43 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 3 / 43 (6.98%) | 3 / 19 (15.79%) |
| occurrences (all) | 2 | 6 | 3 |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 5 / 43 (11.63%) | 1 / 19 (5.26%) |
| occurrences (all) | 6 | 9 | 1 |

| | | | |
|---|---|---|---|
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 1 / 43 (2.33%) | 0 / 19 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |

| **Non-serious adverse events** | Oral antidiabetic drugs (OAD) (non-randomized group) | No OAD (non-randomized group) | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 38 / 46 (82.61%) | 87 / 103 (84.47%) | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 2 / 103 (1.94%) | |
| occurrences (all) | 1 | 3 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 5 / 103 (4.85%) | |
| occurrences (all) | 1 | 5 | |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 1 / 103 (0.97%) | |
| occurrences (all) | 2 | 1 | |
| Reproductive system and breast disorders | | | |
| Amenorrhoea | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Polycystic ovaries | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 103 (0.97%) | |
| occurrences (all) | 0 | 1 | |
| Investigations | | | |

| | | | |
|---|---|---|---|
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 2 / 103 (1.94%) | |
| occurrences (all) | 1 | 2 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 2 / 103 (1.94%) | |
| occurrences (all) | 1 | 2 | |
| Bacterial test positive | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 5 / 103 (4.85%) | |
| occurrences (all) | 1 | 5 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood glucose increased | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 9 / 103 (8.74%) | |
| occurrences (all) | 3 | 11 | |
| Blood insulin increased | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 103 (0.97%) | |
| occurrences (all) | 0 | 1 | |
| Blood urea increased | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood uric acid increased | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Carbon dioxide decreased | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 0 / 103 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Glycosylated haemoglobin increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 103 (0.97%) | |
| occurrences (all) | 0 | 1 | |
| Lipase increased | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 5 / 103 (4.85%) | |
| occurrences (all) | 1 | 6 | |
| Weight decreased | | | |
| subjects affected / exposed | 5 / 46 (10.87%) | 2 / 103 (1.94%) | |
| occurrences (all) | 5 | 2 | |
| Weight increased | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 0 / 103 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Laceration | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Cardiac disorders | | | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 103 (0.97%) | |
| occurrences (all) | 0 | 1 | |
| Sinus bradycardia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 6 / 103 (5.83%) | |
| occurrences (all) | 1 | 6 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 6 / 103 (5.83%) | |
| occurrences (all) | 3 | 6 | |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Headache | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 12 / 103 (11.65%) | |
| occurrences (all) | 2 | 29 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|---|---|---|
| Anaemia | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 3 / 103 (2.91%) | |
| occurrences (all) | 2 | 3 | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 3 / 103 (2.91%) | |
| occurrences (all) | 1 | 3 | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 103 (0.97%) | |
| occurrences (all) | 0 | 1 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 4 / 103 (3.88%) | |
| occurrences (all) | 1 | 4 | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 1 / 103 (0.97%) | |
| occurrences (all) | 2 | 1 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 2 / 103 (1.94%) | |
| occurrences (all) | 1 | 2 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 3 / 103 (2.91%) | |
| occurrences (all) | 0 | 3 | |
| Diarrhoea | | | |
| subjects affected / exposed | 10 / 46 (21.74%) | 21 / 103 (20.39%) | |
| occurrences (all) | 13 | 49 | |
| Erosive duodenitis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Gingival hypertrophy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nausea | | | |
| subjects affected / exposed | 5 / 46 (10.87%) | 11 / 103 (10.68%) | |
| occurrences (all) | 7 | 12 | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 1 / 103 (0.97%) | |
| occurrences (all) | 4 | 1 | |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 4 / 46 (8.70%) | 9 / 103 (8.74%) | |
| occurrences (all) | 5 | 9 | |
| Hepatic steatosis | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 1 / 103 (0.97%) | |
| occurrences (all) | 3 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 3 / 103 (2.91%) | |
| occurrences (all) | 0 | 3 | |
| Pruritus generalised | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rash | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 2 / 103 (1.94%) | |
| occurrences (all) | 1 | 2 | |
| Rash generalised | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Renal and urinary disorders | | | |
| Glycosuria | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Haematuria | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 103 (0.97%) | |
| occurrences (all) | 0 | 1 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 1 / 103 (0.97%) | |
| occurrences (all) | 1 | 1 | |
| Hypothyroidism | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 1 / 103 (0.97%) | |
| occurrences (all) | 3 | 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 8 / 103 (7.77%) | |
| occurrences (all) | 1 | 17 | |
| Back pain | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 5 / 103 (4.85%) | |
| occurrences (all) | 2 | 6 | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Myalgia | | | |
| subjects affected / exposed | 4 / 46 (8.70%) | 1 / 103 (0.97%) | |
| occurrences (all) | 4 | 1 | |
| Osteopenia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Infections and infestations | | | |
| Bone abscess | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 16 / 103 (15.53%) | |
| occurrences (all) | 3 | 27 | |
| Onychomycosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 4 / 103 (3.88%) | |
| occurrences (all) | 0 | 5 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 103 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 103 (0.97%) | |
| occurrences (all) | 0 | 1 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 6 / 46 (13.04%) | 15 / 103 (14.56%) | |
| occurrences (all) | 9 | 16 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 4 / 103 (3.88%) | |
| occurrences (all) | 0 | 4 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 2 / 103 (1.94%) | |
| occurrences (all) | 1 | 2 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 14 / 46 (30.43%) | 4 / 103 (3.88%) | |
| occurrences (all) | 14 | 4 | |
| Dyslipidaemia | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 2 / 103 (1.94%) | |
| occurrences (all) | 3 | 2 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 9 / 46 (19.57%) | 13 / 103 (12.62%) | |
| occurrences (all) | 10 | 13 | |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 103 (0.97%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|---|---|---|---|
| Hypoglycaemia | | | |
| subjects affected / exposed | 5 / 46 (10.87%) | 4 / 103 (3.88%) | |
| occurrences (all) | 7 | 7 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 0 / 103 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Impaired fasting glucose | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 14 / 103 (13.59%) | |
| occurrences (all) | 2 | 16 | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 1 / 103 (0.97%) | |
| occurrences (all) | 1 | 1 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 08 August 2014 | Changes were introduced upon Health Authorities (HA) request: An additional LFT monitoring at Week 1 for the cohort of patients with Cushing's disease (pasireotide s.c. formulation) was included in line with the approved Signifor SmPC; Additional ECG monitoring at Week 1 in line with the approved Signifor SmPC for the cohort of patients on the s.c. formulation of pasireotide; and at Week 3 in line with the proposed EU SmPC for pasireotide LAR in Acromegaly were included; In line with the Adverse Drug Report profile described in the approved labels of anti-diabetic medications used in this study, the following changes were implemented: Exclusion #13 to exclude patients with cholelithiasis and acute and chronic pancreatitis; A new exclusion criterion for patients with a family history of MTC or MEN2 was added; Exclusion #18 to exclude patients with renal dysfunction as defined by local metformin label (e.g. As per SmPC, creatinine clearance < 60 mL/min); Additional pancreatic safety monitoring (lipase and amylase) was added for all patients; Patients in Denmark on pasireotide long acting were to participate in the overall study for up to a maximum of 1 year; To ensure that patients were followed for at least 5 times the t1/2 of study drug, the safety follow-up monitoring was extended to 84 days in patients who received the pasireotide LAR; To account for gender differences in QTcF as acknowledged by HA, the exclusion criterion at screening was modified to QTcF > 450 ms for males and > 460 ms for females; To clarify the washout period for other SSAs, 8 weeks washout for octreotide long acting and lanreotide autogel was specified; Wash-out period for previous exposure to pasireotide s.c. has been updated to 1 week to minimize unnecessary interruption of pasireotide based on the 16-hour t1/2 of pasireotide s.c.; The suggested insulin titration schedule was updated to align with the study defined glycemic control (mean -consecutive daily SMBG < 126 mg/dL). |
| 29 September 2016 | The rationale of amendment 2 was to remove the protocol requirement to randomize the equal number of patients with Cushing's disease and Acromegaly (a total of 79 patients).<br>In protocol amendment 1, the target was to randomize 79 patients (42 in Cushing's disease and 37 in acromegaly) to obtain 68 randomized patients (34 with Cushing's disease and 34 with acromegaly, who completed at least 8-week randomized treatment without any rescue medication). |
| 17 March 2017 | Clarification regarding the protocol visits included in the 28-day Safety follow-up for Cushing's disease patients who received pasireotide s.c and the 84-day Safety follow-up<br>for acromegaly patients who received pasireotide long acting as follows: Eligible patients as per protocol who are transitioning to a roll-over study or local access program were not be required to perform the safety follow-up visit (779) as patients were continued to be monitored for safety; Eligible patients as per protocol who were transitioning to commercial drug were required to perform the safety follow-up visit (779); Re-insertion of the missing figure related to QT Prolongation Safety Management; Allow a ± 3 day visit window for Cushing's patients. Visit windows for Acromegaly patients remained unchanged. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported