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 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 BL Insulin group but may have been prescribed at the discretion of the investigator.

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	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

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 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 Units: Subjects			
Adults (18-64 years)	32	40	18
From 65-84 years	6	3	1
Age Continuous Units: Years			
arithmetic mean	50.6	46.4	46.7
standard deviation	± 11.76	± 12.90	± 12.54
Sex: Female, Male Units: Subjects			
Female	22	27	10
Male	16	16	9
Race/Ethnicity, Customized 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 Units: Subjects			
Adults (18-64 years)	43	101	234
From 65-84 years	3	2	15
Age Continuous Units: Years			
arithmetic mean	40.2	37.8	
standard deviation	± 13.80	± 11.17	-
Sex: Female, Male Units: Subjects			
Female	31	47	137
Male	15	56	112
Race/Ethnicity, Customized 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: 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	-0.01
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: 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	-0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.74
upper limit	0.02
Variability estimate	Standard error of the mean
Dispersion value	0.19

Secondary: Change in HbA1c from randomization over time per randomized arm

End point title	Change in HbA1c from randomization over time per randomized arm[2]

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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 38 (7.89%)	3 / 43 (6.98%)	0 / 19 (0.00%)
occurrences (all)	3	3	0
Diabetes mellitus			
subjects affected / exposed	5 / 38 (13.16%)	9 / 43 (20.93%)	2 / 19 (10.53%)
occurrences (all)	5	9	2
Dyslipidaemia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 43 (2.33%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Hyperglycaemia			
subjects affected / exposed	14 / 38 (36.84%)	11 / 43 (25.58%)	6 / 19 (31.58%)
occurrences (all)	51	21	34
Hypertriglyceridaemia			
subjects affected / exposed	3 / 38 (7.89%)	1 / 43 (2.33%)	0 / 19 (0.00%)
occurrences (all)	3	1	0
Hypoglycaemia			
subjects affected / exposed	5 / 38 (13.16%)	10 / 43 (23.26%)	8 / 19 (42.11%)
occurrences (all)	8	25	32
Hypokalaemia			
subjects affected / exposed	3 / 38 (7.89%)	0 / 43 (0.00%)	1 / 19 (5.26%)
occurrences (all)	3	0	1
Impaired fasting glucose			
subjects affected / exposed	0 / 38 (0.00%)	2 / 43 (4.65%)	0 / 19 (0.00%)
occurrences (all)	0	2	0

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). 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 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