

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

y	
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 Yes Is this the baseline period? 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	ı 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 i	nsert, per investigator discretion. Insulin was only given as
rescue therapy in the Incretin arm if req	
Arm title	Insulin (randomized group)
Arm description:	
Darticipants randomized to the inculin or	
	m 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
or down titrated at the discretion of the basal insulin, participant switched to bas	investigator. If blood glucose levels remained uncontrolled on al insulin plus prandial insulin
or down titrated at the discretion of the basal insulin, participant switched to bas	investigator. If blood glucose levels remained uncontrolled on sal insulin plus prandial insulin Experimental
or down titrated at the discretion of the basal insulin, participant switched to bas Arm type Investigational medicinal product name	investigator. If blood glucose levels remained uncontrolled on sal insulin plus prandial insulin Experimental Pasireotide s.c.
or down titrated at the discretion of the basal insulin, participant switched to bas Arm type Investigational medicinal product name Investigational medicinal product code	investigator. If blood glucose levels remained uncontrolled on sal insulin plus prandial insulin Experimental
or down titrated at the discretion of the basal insulin, participant switched to bas Arm type Investigational medicinal product name Investigational medicinal product code Other name	investigator. If blood glucose levels remained uncontrolled on sal insulin plus prandial insulin Experimental Pasireotide s. c. SOM230
or down titrated at the discretion of the basal insulin, participant switched to base. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms.	investigator. If blood glucose levels remained uncontrolled on sal insulin plus prandial insulin Experimental Pasireotide s.c. SOM230 Injection
or down titrated at the discretion of the basal insulin, participant switched to bas Arm type Investigational medicinal product name Investigational medicinal product code Other name Pharmaceutical forms Routes of administration	investigator. If blood glucose levels remained uncontrolled on sal insulin plus prandial insulin Experimental Pasireotide s. c. SOM230
or down titrated at the discretion of the basal insulin, participant switched to base. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details:	investigator. If blood glucose levels remained uncontrolled on sal insulin plus prandial insulin Experimental Pasireotide s.c. SOM230 Injection Subcutaneous use
or down titrated at the discretion of the basal insulin, participant switched to base. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide s.c. was provided as solution.	investigator. If blood glucose levels remained uncontrolled on sal insulin plus prandial insulin Experimental Pasireotide s.c. SOM230 Injection Subcutaneous use for injection in individual one-point-cut 1 mL ampule,
or down titrated at the discretion of the basal insulin, participant switched to base. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide s.c. was provided as solution.	investigator. If blood glucose levels remained uncontrolled on sal insulin plus prandial insulin Experimental Pasireotide s.c. SOM230 Injection Subcutaneous use
or down titrated at the discretion of the basal insulin, participant switched to base. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide s.c. was provided as solution containing 900, 600, and 300 µg pasired.	investigator. If blood glucose levels remained uncontrolled on sal insulin plus prandial insulin Experimental Pasireotide s.c. SOM230 Injection Subcutaneous use for injection in individual one-point-cut 1 mL ampule,
or down titrated at the discretion of the basal insulin, participant switched to base. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide s.c. was provided as solution containing 900, 600, and 300 µg pasired patients. Starting dose = 600 µg b.i.d.	investigator. If blood glucose levels remained uncontrolled on sal insulin plus prandial insulin Experimental Pasireotide s. c. SOM230 Injection Subcutaneous use for injection in individual one-point-cut 1 mL ampule, bide per 1 mL of solution, b.i.d. which was self-injected by the
or down titrated at the discretion of the basal insulin, participant switched to base. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide s.c. was provided as solution containing 900, 600, and 300 µg pasired patients. Starting dose = 600 µg b.i.d. Investigational medicinal product name.	investigator. If blood glucose levels remained uncontrolled on all insulin plus prandial insulin Experimental Pasireotide s.c. SOM230 Injection Subcutaneous use for injection in individual one-point-cut 1 mL ampule, otide per 1 mL of solution, b.i.d. which was self-injected by the Pasireotide i.m. long acting release (LAR)
or down titrated at the discretion of the basal insulin, participant switched to base. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration. Dosage and administration details: Pasireotide s.c. was provided as solution containing 900, 600, and 300 µg pasireotic patients. Starting dose = 600 µg b.i.d. Investigational medicinal product code.	investigator. If blood glucose levels remained uncontrolled on all insulin plus prandial insulin Experimental Pasireotide s.c. SOM230 Injection Subcutaneous use for injection in individual one-point-cut 1 mL ampule, otide per 1 mL of solution, b.i.d. which was self-injected by the Pasireotide i.m. long acting release (LAR)
or down titrated at the discretion of the basal insulin, participant switched to base. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide s.c. was provided as solution containing 900, 600, and 300 µg pasired patients. Starting dose = 600 µg b.i.d. Investigational medicinal product name. Investigational medicinal product code. Other name.	investigator. If blood glucose levels remained uncontrolled on sal insulin plus prandial insulin Experimental Pasireotide s.c. SOM230 Injection Subcutaneous use for injection in individual one-point-cut 1 mL ampule, otide per 1 mL of solution, b.i.d. which was self-injected by the Pasireotide i.m. long acting release (LAR) SOM230
or down titrated at the discretion of the basal insulin, participant switched to base. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration. Dosage and administration details: Pasireotide s.c. was provided as solution containing 900, 600, and 300 µg pasired patients. Starting dose = 600 µg b.i.d. Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms.	investigator. If blood glucose levels remained uncontrolled on sal insulin plus prandial insulin Experimental Pasireotide s.c. SOM230 Injection Subcutaneous use for injection in individual one-point-cut 1 mL ampule, otide per 1 mL of solution, b.i.d. which was self-injected by the Pasireotide i.m. long acting release (LAR) SOM230 Injection
or down titrated at the discretion of the basal insulin, participant switched to base. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide s.c. was provided as solution containing 900, 600, and 300 µg pasired patients. Starting dose = 600 µg b.i.d. Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details:	investigator. If blood glucose levels remained uncontrolled on sal insulin plus prandial insulin Experimental Pasireotide s.c. SOM230 Injection Subcutaneous use for injection in individual one-point-cut 1 mL ampule, otide per 1 mL of solution, b.i.d. which was self-injected by the Pasireotide i.m. long acting release (LAR) SOM230 Injection
or down titrated at the discretion of the basal insulin, participant switched to base. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide s.c. was provided as solution containing 900, 600, and 300 µg pasired patients. Starting dose = 600 µg b.i.d. Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide i.m. LAR was provided as 20.	investigator. If blood glucose levels remained uncontrolled on sal insulin plus prandial insulin Experimental Pasireotide s.c. SOM230 Injection Subcutaneous use for injection in individual one-point-cut 1 mL ampule, stide per 1 mL of solution, b.i.d. which was self-injected by the Pasireotide i.m. long acting release (LAR) SOM230 Injection Intramuscular use
or down titrated at the discretion of the basal insulin, participant switched to base. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide s.c. was provided as solution containing 900, 600, and 300 µg pasired patients. Starting dose = 600 µg b.i.d. Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide i.m. LAR was provided as 20 mg q28d.	investigator. If blood glucose levels remained uncontrolled on sal insulin plus prandial insulin Experimental Pasireotide s.c. SOM230 Injection Subcutaneous use for injection in individual one-point-cut 1 mL ampule, stide per 1 mL of solution, b.i.d. which was self-injected by the Pasireotide i.m. long acting release (LAR) SOM230 Injection Intramuscular use omg, 40 mg, 60 mg every 28 days (q28d); Starting dose = 40
or down titrated at the discretion of the basal insulin, participant switched to base. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide s.c. was provided as solution containing 900, 600, and 300 µg pasired patients. Starting dose = 600 µg b.i.d. Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide i.m. LAR was provided as 20 mg q28d. Investigational medicinal product name.	investigator. If blood glucose levels remained uncontrolled on sal insulin plus prandial insulin Experimental Pasireotide s.c. SOM230 Injection Subcutaneous use for injection in individual one-point-cut 1 mL ampule, stide per 1 mL of solution, b.i.d. which was self-injected by the Pasireotide i.m. long acting release (LAR) SOM230 Injection Intramuscular use omg, 40 mg, 60 mg every 28 days (q28d); Starting dose = 40
or down titrated at the discretion of the basal insulin, participant switched to base. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide s.c. was provided as solution containing 900, 600, and 300 µg pasired patients. Starting dose = 600 µg b.i.d. Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide i.m. LAR was provided as 20 mg q28d. Investigational medicinal product name. Investigational medicinal product name. Investigational medicinal product name. Investigational medicinal product code.	investigator. If blood glucose levels remained uncontrolled on sal insulin plus prandial insulin Experimental Pasireotide s.c. SOM230 Injection Subcutaneous use for injection in individual one-point-cut 1 mL ampule, stide per 1 mL of solution, b.i.d. which was self-injected by the Pasireotide i.m. long acting release (LAR) SOM230 Injection Intramuscular use omg, 40 mg, 60 mg every 28 days (q28d); Starting dose = 40
or down titrated at the discretion of the basal insulin, participant switched to base Arm type Investigational medicinal product name Investigational medicinal product code Other name Pharmaceutical forms Routes of administration Dosage and administration details: Pasireotide s.c. was provided as solution containing 900, 600, and 300 µg pasired patients. Starting dose = 600 µg b.i.d. Investigational medicinal product name Investigational medicinal product code Other name Pharmaceutical forms Routes of administration Dosage and administration Dosage and administration details: Pasireotide i.m. LAR was provided as 20 mg q28d Investigational medicinal product name Investigational medicinal product code Other name	investigator. If blood glucose levels remained uncontrolled on al insulin plus prandial insulin Experimental Pasireotide s.c. SOM230 Injection Subcutaneous use for injection in individual one-point-cut 1 mL ampule, atide per 1 mL of solution, b.i.d. which was self-injected by the Pasireotide i.m. long acting release (LAR) SOM230 Injection Intramuscular use Omg, 40 mg, 60 mg every 28 days (q28d); Starting dose = 40 Metformin

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 i	nsert, per investigator discretion	
Arm title	Baseline Insulin (BL) (non-randomized group)	
Arm description:	<u> </u>	
This group included participants who we	re 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 μ g pasireotide per 1 mL of solution, b.i.d. which was self-injected by the patients. Starting dose = 600 μ g 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

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

Intramuscular use

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:	
containing 900, 600, and 300 µg pasireo	for injection in individual one-point-cut 1 mL ampule, otide per 1 mL of solution, b.i.d. which was self-injected by the
containing 900, 600, and 300 μg pasired patients. Starting dose = 600 μg b.i.d.	
containing 900, 600, and 300 µg pasireo patients. Starting dose = 600 µg b.i.d. Investigational medicinal product name	otide per 1 mL of solution, b.i.d. which was self-injected by the
containing 900, 600, and 300 µg pasired patients. Starting dose = 600 µg b.i.d. Investigational medicinal product name Investigational medicinal product code	Pasireotide i.m. long acting release (LAR)
	Pasireotide i.m. long acting release (LAR)

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 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 μ g pasireotide per 1 mL of solution, b.i.d. which was self-injected by the patients. Starting dose = 600 μ g 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 μ g pasireotide per 1 mL of solution, b.i.d. which was self-injected by the patients. Starting dose = 600 μ g 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 however, it was not provided by Novartis	he Extension phase at the discretion of the investigator; 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 t however, it was not provided by Novartis	he Extension phase at the discretion of the investigator; sunless 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 however, it was not provided by Novartis	the Extension phase at the discretion of the investigator; sunless 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:	
· ·	Extension phase at the discretion of the investigator; however, equired by local regulations.
Arm title	Insulin (randomized group)
Arm description:	
	m started with once daily dose of basal insulin. The dose was up investigator. If blood glucose levels remained uncontrolled on al insulin plus prandial insulin.
Participants randomized to the insulin ar or down titrated at the discretion of the i	investigator. If blood glucose levels remained uncontrolled on
Participants randomized to the insulin ar or down titrated at the discretion of the basal insulin, participant switched to bas	investigator. If blood glucose levels remained uncontrolled on al insulin plus prandial insulin.
Participants randomized to the insulin ar or down titrated at the discretion of the basal insulin, participant switched to bas Arm type	nvestigator. If blood glucose levels remained uncontrolled on al insulin plus prandial insulin. Experimental
Participants randomized to the insulin ar or down titrated at the discretion of the basal insulin, participant switched to bas Arm type Investigational medicinal product name	nvestigator. If blood glucose levels remained uncontrolled on al insulin plus prandial insulin. Experimental Pasireotide s.c.
Participants randomized to the insulin ar or down titrated at the discretion of the basal insulin, participant switched to base Arm type Investigational medicinal product name Investigational medicinal product code	nvestigator. If blood glucose levels remained uncontrolled on al insulin plus prandial insulin. Experimental Pasireotide s. c. SOM230
Participants randomized to the insulin ar or down titrated at the discretion of the ibasal insulin, participant switched to base. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name.	nvestigator. If blood glucose levels remained uncontrolled on al insulin plus prandial insulin. Experimental Pasireotide s. c. SOM230 Injection
Participants randomized to the insulin ar or down titrated at the discretion of the insulin, participant switched to base Arm type Investigational medicinal product name Investigational medicinal product code Other name Pharmaceutical forms	nvestigator. If blood glucose levels remained uncontrolled on al insulin plus prandial insulin. Experimental Pasireotide s. c. SOM230
Participants randomized to the insulin ar or down titrated at the discretion of the insulin, participant switched to base. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide s.c. was provided as solution.	nvestigator. If blood glucose levels remained uncontrolled on al insulin plus prandial insulin. Experimental Pasireotide s. c. SOM230 Injection
Participants randomized to the insulin ar or down titrated at the discretion of the insulin, participant switched to base. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide s.c. was provided as solution containing 900, 600, and 300 µg pasireotide.	nvestigator. If blood glucose levels remained uncontrolled on al insulin plus prandial insulin. Experimental Pasireotide s. c. SOM230 Injection Subcutaneous use for injection in individual one-point-cut 1 mL ampule,
Participants randomized to the insulin ar or down titrated at the discretion of the insulin, participant switched to base. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide s.c. was provided as solution containing 900, 600, and 300 µg pasireo patients. Starting dose = 600 µg b.i.d.	nvestigator. If blood glucose levels remained uncontrolled on al insulin plus prandial insulin. Experimental Pasireotide s.c. SOM230 Injection Subcutaneous use for injection in individual one-point-cut 1 mL ampule, tide per 1 mL of solution, b.i.d. which was self-injected by the
Participants randomized to the insulin ar or down titrated at the discretion of the inbasal insulin, participant switched to base. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration. Dosage and administration details: Pasireotide s.c. was provided as solution containing 900, 600, and 300 µg pasireo patients. Starting dose = 600 µg b.i.d. Investigational medicinal product name.	Investigator. If blood glucose levels remained uncontrolled on al insulin plus prandial insulin. Experimental Pasireotide s.c. SOM230 Injection Subcutaneous use for injection in individual one-point-cut 1 mL ampule, tide per 1 mL of solution, b.i.d. which was self-injected by the Pasireotide i.m. long acting release (LAR)
Participants randomized to the insulin ar or down titrated at the discretion of the insulin, participant switched to base. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide s.c. was provided as solution containing 900, 600, and 300 µg pasireot patients. Starting dose = 600 µg b.i.d. Investigational medicinal product code.	Investigator. If blood glucose levels remained uncontrolled on al insulin plus prandial insulin. Experimental Pasireotide s.c. SOM230 Injection Subcutaneous use for injection in individual one-point-cut 1 mL ampule, tide per 1 mL of solution, b.i.d. which was self-injected by the Pasireotide i.m. long acting release (LAR)
Participants randomized to the insulin ar or down titrated at the discretion of the insulin, participant switched to base. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration. Dosage and administration details: Pasireotide s.c. was provided as solution containing 900, 600, and 300 µg pasireo patients. Starting dose = 600 µg b.i.d. Investigational medicinal product name. Investigational medicinal product code. Other name.	nvestigator. If blood glucose levels remained uncontrolled on al insulin plus prandial insulin. Experimental Pasireotide s.c. SOM230 Injection Subcutaneous use for injection in individual one-point-cut 1 mL ampule, tide per 1 mL of solution, b.i.d. which was self-injected by the Pasireotide i.m. long acting release (LAR) SOM230
Participants randomized to the insulin ar or down titrated at the discretion of the insulin, participant switched to base. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide s.c. was provided as solution containing 900, 600, and 300 µg pasireo patients. Starting dose = 600 µg b.i.d. Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms	Investigator. If blood glucose levels remained uncontrolled on al insulin plus prandial insulin. Experimental Pasireotide s.c. SOM230 Injection Subcutaneous use for injection in individual one-point-cut 1 mL ampule, tide per 1 mL of solution, b.i.d. which was self-injected by the Pasireotide i.m. long acting release (LAR) SOM230 Injection
Participants randomized to the insulin ar or down titrated at the discretion of the ibasal insulin, participant switched to bass. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide s.c. was provided as solution containing 900, 600, and 300 µg pasireo patients. Starting dose = 600 µg b.i.d. Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details:	Investigator. If blood glucose levels remained uncontrolled on al insulin plus prandial insulin. Experimental Pasireotide s.c. SOM230 Injection Subcutaneous use for injection in individual one-point-cut 1 mL ampule, tide per 1 mL of solution, b.i.d. which was self-injected by the Pasireotide i.m. long acting release (LAR) SOM230 Injection
Participants randomized to the insulin ar or down titrated at the discretion of the insulin, participant switched to base. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide s.c. was provided as solution containing 900, 600, and 300 µg pasireous patients. Starting dose = 600 µg b.i.d. Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide i.m. LAR was provided as 20.	Investigator. If blood glucose levels remained uncontrolled on al insulin plus prandial insulin. Experimental Pasireotide s.c. SOM230 Injection Subcutaneous use for injection in individual one-point-cut 1 mL ampule, tide per 1 mL of solution, b.i.d. which was self-injected by the Pasireotide i.m. long acting release (LAR) SOM230 Injection Intramuscular use
Participants randomized to the insulin ar or down titrated at the discretion of the insulin, participant switched to base. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide s.c. was provided as solution containing 900, 600, and 300 µg pasireous patients. Starting dose = 600 µg b.i.d. Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide i.m. LAR was provided as 20 mg q28d.	nvestigator. If blood glucose levels remained uncontrolled on al insulin plus prandial insulin. Experimental Pasireotide s.c. SOM230 Injection Subcutaneous use for injection in individual one-point-cut 1 mL ampule, tide per 1 mL of solution, b.i.d. which was self-injected by the Pasireotide i.m. long acting release (LAR) SOM230 Injection Intramuscular use mg, 40 mg, 60 mg every 28 days (q28d); Starting dose = 40
Participants randomized to the insulin ar or down titrated at the discretion of the insulin, participant switched to base. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide s.c. was provided as solution containing 900, 600, and 300 µg pasireo patients. Starting dose = 600 µg b.i.d. Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide i.m. LAR was provided as 20 mg q28d. Investigational medicinal product name.	nvestigator. If blood glucose levels remained uncontrolled on al insulin plus prandial insulin. Experimental Pasireotide s.c. SOM230 Injection Subcutaneous use for injection in individual one-point-cut 1 mL ampule, tide per 1 mL of solution, b.i.d. which was self-injected by the Pasireotide i.m. long acting release (LAR) SOM230 Injection Intramuscular use mg, 40 mg, 60 mg every 28 days (q28d); Starting dose = 40
Participants randomized to the insulin ar or down titrated at the discretion of the insulin, participant switched to base. Arm type Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration details: Pasireotide s.c. was provided as solution containing 900, 600, and 300 µg pasireous patients. Starting dose = 600 µg b.i.d. Investigational medicinal product name. Investigational medicinal product code. Other name. Pharmaceutical forms. Routes of administration. Dosage and administration. Dosage and administration details: Pasireotide i.m. LAR was provided as 20 mg q28d. Investigational medicinal product name. Investigational medicinal product code.	nvestigator. If blood glucose levels remained uncontrolled on al insulin plus prandial insulin. Experimental Pasireotide s.c. SOM230 Injection Subcutaneous use for injection in individual one-point-cut 1 mL ampule, tide per 1 mL of solution, b.i.d. which was self-injected by the Pasireotide i.m. long acting release (LAR) SOM230 Injection Intramuscular use mg, 40 mg, 60 mg every 28 days (q28d); Starting dose = 40

Routes of administration	Oral use
Dosage and administration details:	
Metformin may have been continued in the however, it was not provided by Novartis	he Extension phase at the discretion of the investigator; sunless 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 I it was not provided by Novartis unless re	Extension phase at the discretion of the investigator; however, quired by local regulations.
Arm title	Baseline Insulin (BL) (non-randomized group)
Arm description:	
This group included participants who wer randomization.	re receiving insulin at study entry and thus were not eligible for
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:	
	for injection in individual one-point-cut 1 mL ampule, tide per 1 mL of solution, b.i.d. which was self-injected by the
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 q28d	mg, 40 mg, 60 mg every 28 days (q28d); Starting dose = 40
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 however, it was not provided by Novartis	he Extension phase at the discretion of the investigator; sunless 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 lit was not provided by Novartis unless re	Extension phase at the discretion of the investigator; however, quired 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

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

<u> </u>	
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 μ g pasireotide per 1 mL of solution, b.i.d. which was self-injected by the patients. Starting dose = 600 μ g b.i.d.

Number of subjects in period 2 ^[11]	Incretin based therapy (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 aroub true	HIICIEUH DASEU HIELADV HAHUOHIIZEU ULUUD)

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	3 () (No OAD (non- randomized group)	Total
	randomized group)		

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:	•
control the participant's hyperglycemia	based arm started with sitagliptin once daily. If sitagliptin did not a, sitagliptin was stopped and participants switched to liraglutide raglutide, hyperglycemia was not controlled then the participant dition of insulin
Reporting group title	Insulin (randomized group)
Reporting group description:	
	arm started with once daily dose of basal insulin. The dose was up e investigator. If blood glucose levels remained uncontrolled on asal insulin plus prandial insulin
Reporting group title	Baseline Insulin (BL) (non-randomized group)
Reporting group description:	·
This group included participants who w	vere receiving insulin at study entry
Reporting group title	Oral antidiabetic drugs (OAD) (non-randomized group)
Reporting group description:	•
This group included participants who dother background anti-diabetic treatme	eveloped hyperglycemia that was controlled by metformin and/or ent
Reporting group title	No OAD (non-randomized group)
Reporting group description:	
This group included participants who d of the study	id not receive any anti-diabetic medication during the Core Phase
Reporting group title	Incretin based therapy (randomized group)
Reporting group description:	
control the participant's hyperglycemia	based arm started with sitagliptin once daily. If sitagliptin did not a, sitagliptin was stopped and participants switched to liraglutide raglutide, hyperglycemia was not controlled then the participant dition of insulin
Reporting group title	Insulin (randomized group)
Reporting group description:	
	arm started with once daily dose of basal insulin. The dose was up e investigator. If blood glucose levels remained uncontrolled on asal insulin plus prandial insulin.
Reporting group title	Baseline Insulin (BL) (non-randomized group)
Reporting group description:	
This group included participants who wrandomization.	vere receiving insulin at study entry and thus were not eligible for
Reporting group title	Oral antidiabetic drugs (OAD) (non-randomized group)
Reporting group description:	
This group included participants who dother background anti-diabetic treatme	eveloped hyperglycemia that was controlled by metformin and/or ent and thus were not randomized.

Reporting group description:

Reporting group title

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

No OAD (non-randomized group)

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

<u> </u>		
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 grou Insulin (randomized group)	up) vs.
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 grou Insulin (randomized group)	up) vs.
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 grou Insulin (randomized group)	up) vs.
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)	O.4 (± 0.85)	
Change at RW16 D113 (n = 35, 37)	0.0 (± 0.93)	O.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

Randomization to up to 16 weeks

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

diabetic rescue therapy	With mount
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 summarized.	s who received anti-diabetic rescue therapy in incretin based therapy is
End point type	Secondary
End point timeframe:	

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

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)	O.7 (± O.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,	0.4 (± 0.28)		
29, 13, 32, 86)			

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 \leq 0.3% HbA1c increase to end of Core Phase

riidse	
	Percentage of participants with 0.3% HbA1c increase to end of Core Phase ^[5]
End point description:	
Percentage of participants with 0.3% Farm.	HbA1c increase in the incretin based therapy arm and the insulin
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.

С
(

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 description:

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

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			

	1 / 38 (2.63%)	0 / 43 (0.00%)	0 / 19 (0.00%)
occurrences causally related to	0 / 1	0/0	0/0
treatment / all			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			

Occurrences causally related to treatment / all O/O O/O O/O O/O	subjects affected / exposed	1 / 38 (2.63%)	1 / 43 (2.33%)	0 / 19 (0.00%)
treatment / all deaths causally related to deaths ca	occurrences causally related to			· · · · · · · · · · · · · · · · · · ·
Treatment / ali				
Subjects affected / exposed		0/0	0/0	0/0
Occurrences causally related to treatment / all deaths causally related to deaths causally				
treatment / all deaths causally related to treatment / all	subjects affected / exposed	0 / 38 (0.00%)	1 / 43 (2.33%)	0 / 19 (0.00%)
treatment / ali		0/0	1 / 1	0/0
Subjects affected / exposed 1 / 38 (2.63%) 0 / 43 (0.00%) 0 / 19 (0.00%)		0/0	0/0	0/0
Occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all O / O O / O O / O	Vomiting			
treatment / all deaths causally related to treatment / all	subjects affected / exposed	1 / 38 (2.63%)	0 / 43 (0.00%)	0 / 19 (0.00%)
treatment / ali		0 / 1	0/0	0/0
Cholecystitis acute		0/0	0/0	0/0
Subjects affected / exposed 1 / 38 (2.63%) 0 / 43 (0.00%) 0 / 19 (0.00%)	Hepatobiliary disorders			
Occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all	1			
treatment / all deaths causally related to treatment / all o/0 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%) 0 ccurrences causally related to treatment / all deaths causally related to death	subjects affected / exposed	1 / 38 (2.63%)	0 / 43 (0.00%)	0 / 19 (0.00%)
treatment / all		1 / 1	0/0	0/0
Acute kidney injury subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all o/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0		0/0	0/0	0/0
subjects affected / exposed 1 / 38 (2.63%) 0 / 43 (0.00%) 0 / 19 (0.00%) occurrences causally related to treatment / all deaths causally related to treatment / all subjects affected / exposed 0 / 1 0 / 0 0 / 0 Renal injury subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all 0 / 38 (0.00%) 0 / 43 (0.00%) 0 / 19 (0.00%) Endocrine disorders Cushing's syndrome subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all 0 / 0	Renal and urinary disorders			
occurrences causally related to treatment / all deaths causally related to treatment / all 0/0 0/0 0/0 0/0 Renal injury subjects affected / exposed 0/38 (0.00%) 0/43 (0.00%) 0/19 (0.00%) 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/	Acute kidney injury			
treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Renal injury subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all O/0 Endocrine disorders Cushing's syndrome subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all O/0 O/43 (0.00%) O/43 (0.00%) O/43 (0.00%) O/19 (0.00%) O/0 O/0 Infections and infestations	subjects affected / exposed	1 / 38 (2.63%)	0 / 43 (0.00%)	0 / 19 (0.00%)
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%) 0 / 0 0 / 0 occurrences causally related to treatment / all 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%) 0 / 0 / 0 / 0 / 0 / 0 / 0 / 0 / 0 / 0	•	0 / 1	0/0	0/0
subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Dodo Oncorrences causally related to treatment / all Dodo Oncorrences causally related to treatment / all Oncorrences causally related to treatment / all Oncorrences causally related to treatment / all Dodo Oncorrences causally related to treatment / all		0/0	0/0	0/0
occurrences causally related to treatment / all deaths causally related to treatment / all Dodo occurrences causally related to treatment / all Endocrine disorders Cushing's syndrome subjects affected / exposed Occurrences causally related to treatment / all deaths causally related to treatment / all Dodo occurrences causally related to treatment / all	Renal injury			
treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Endocrine disorders Cushing's syndrome subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all o/0 O/0 O/0 O/0 O/0 O/0 O/0 O/0	subjects affected / exposed	0 / 38 (0.00%)	0 / 43 (0.00%)	0 / 19 (0.00%)
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 deaths causally related to treatment / all 0 / 0 0 / 0 Infections and infestations		0/0	0/0	0/0
Cushing's syndrome subjects affected / exposed 0 / 38 (0.00%) 0 / 43 (0.00%) 0 / 19 (0.00%) 0 / 0 0 /		0/0	0/0	0/0
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 Infections and infestations	Endocrine disorders			
occurrences causally related to treatment / all deaths causally related to treatment / all 0 / 0 0 / 0 0 / 0 Infections and infestations	Cushing's syndrome			
treatment / all deaths causally related to treatment / all O / O O / O Infections and infestations	subjects affected / exposed	0 / 38 (0.00%)	0 / 43 (0.00%)	0 / 19 (0.00%)
treatment / all 0 / 0 0 / 0 Infections and infestations		0/0	0/0	0/0
		0/0	0/0	0/0
Breast abscess	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 / 4/ (0 00%)	0 / 103 / 0 009/)	1
	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			
•	•	•	•

Occurrences causally related to treatment / all deaths causally related to do / 0 / 0 / 0 / 0 / 0 / 0 / 0 / 0 / 0 /	subjects affected / exposed	0 / 46 (0.00%)	0 / 103 (0.00%)	1
deaths causally related to treatment / all			, i	
Treatment / ali				
subjects affected / exposed occurrences causally related to treatment / all deaths causally related to decourrences cau		0/0	0/0	
occurrences causally related to treatment / all deaths causally related to treatment ment / all o/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0 0/0				
treatment / all deaths causally related to treatment / all Vomiting subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Death causally related to death causally related to treatment / all Death causally related to death causally related to treatment / all Death causally related to death causally related to treatment / all Death causally related to	subjects affected / exposed	0 / 46 (0.00%)	0 / 103 (0.00%)	
treatment / all		0/0	0/0	
subjects affected / exposed occurrences causally related to treatment / all deaths causally related to o/0 0/0 Hepatobiliary disorders Cholecystitis acute subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all		0/0	0/0	
occurrences causally related to treatment / all deaths causally related to treatment / all o/0 0/0 0/0 Hepatobiliary disorders Cholecystitis acute subjects affected / exposed occurrences causally related to treatment / all deaths causally related to deaths causal	Vomiting			
treatment / all deaths causally related to treatment / all Hepatobiliary disorders Cholecystitis acute subjects affected / exposed occurrences causally related to treatment / all deaths causally related to	subjects affected / exposed	0 / 46 (0.00%)	0 / 103 (0.00%)	
Hepatobiliary disorders Cholecystitis acute subjects affected / exposed		0/0	0/0	
Cholecystitis acute subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all occurrences causally related to occurrences causally related to treatment / all occurrences causally related to occ		0/0	0/0	
subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Renal injury subjects affected / exposed occurrences causally related to treatment / all deaths causally related to	Hepatobiliary disorders			
occurrences causally related to treatment / all deaths causally related to treatment / all o/ 0 0/0 Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all o/ 0 0/0 Renal injury subjects affected / exposed o/ 46 (0.00%) 0/0 Renal injury subjects affected / exposed o/ 46 (0.00%) 1/103 (0.09%) occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all o/ 0 0/0 Endocrine disorders Cushing's syndrome subjects affected / exposed occurrences causally related to treatment / all deaths causally related to	•			
treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Renal injury subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all D/O I/103 (0.00%) 1 / 103 (0.97%) O/O I/1 Endocrine disorders Cushing's syndrome subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to	subjects affected / exposed	0 / 46 (0.00%)	0 / 103 (0.00%)	
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all occurrences causally related to treatment / all deaths causally related to		0/0	0/0	
Acute kidney injury subjects affected / exposed		0/0	0/0	
subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all occurrences causally related to treatment / all occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Endocrine disorders Cushing's syndrome subjects affected / exposed occurrences causally related to treatment / all deaths causally related to	Renal and urinary disorders			
occurrences causally related to treatment / all deaths causally related to treatment / all				
treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Renal injury subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Endocrine disorders Cushing's syndrome subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to	subjects affected / exposed	0 / 46 (0.00%)	0 / 103 (0.00%)	
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 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 deaths causally related to	•	0/0	0/0	
subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Endocrine disorders Cushing's syndrome subjects affected / exposed occurrences causally related to treatment / all occurrences causally related to treatment / all deaths causally related to deaths causally related to		0/0	0/0	
occurrences causally related to treatment / all deaths causally related to treatment / all Dodo 1 / 1 Description of the control of the con	Renal injury			
treatment / all deaths causally related to treatment / all O/O Endocrine disorders Cushing's syndrome subjects affected / exposed occurrences causally related to treatment / all deaths causally related to	subjects affected / exposed	0 / 46 (0.00%)	1 / 103 (0.97%)	
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 deaths causally related to		0/0	1 / 1	
Cushing's syndrome subjects affected / exposed occurrences causally related to treatment / all deaths causally related to		0/0	0/0	
subjects affected / exposed 1 / 46 (2.17%) 0 / 103 (0.00%) 0 / 103 (0.00%) 0 / 103 (0.00%) 1 / 46 (2.17%) 0 / 103 (0.00%)	Endocrine disorders			
occurrences causally related to treatment / all deaths causally related to	Cushing's syndrome			
treatment / all deaths causally related to	subjects affected / exposed	1 / 46 (2.17%)	0 / 103 (0.00%)	
		0 / 1	0/0	
Heatment / all U/U U/U	deaths causally related to treatment / all	0/0	0/0	
Infections and infestations	Infections and infestations			
Breast abscess	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	
etabolism 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)			
occurrences (aii)	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
	_	S	
Blood glucose increased subjects affected / exposed	0 / 00 / 5 0 / 0 /	1 / 10 / 0 000/)	0 / 10 / 0 000/)
occurrences (all)	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 Headache			
subjects affected / exposed	4 / 38 (10.53%)	4 / 43 (9.30%)	0 / 19 (0.00%)
occurrences (all)	5	4	0
(3.0)	3	4	U
Syncope			
subjects affected / exposed	0 / 38 (0.00%)	0 / 43 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	О	1
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed	0 / 20 / 0 00%)	2 / 42 / 4 / 50/)	1 /10 /5 2/0/)
	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	О	0
Abdominal pain			
subjects affected / exposed	2 / 38 (5.26%)	1 / 43 (2.33%)	0 / 19 (0.00%)
occurrences (all)	2	1	О
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	О
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
Drumitus manaralised			
Pruritus generalised subjects affected / exposed	2 / 38 (5.26%)	1 / 43 (2.33%)	0 / 19 (0.00%)
occurrences (all)			
occurrences (un)	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 / 20 / 0 00%	0 / 42 /0 00%	1 /10 /5 2/0/)
occurrences (all)	0 / 38 (0.00%)	0 / 43 (0.00%)	1 / 19 (5.26%)
occurrences (aii)	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)	О	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
Ostoponia			
Osteopenia subjects affected / exposed	0 / 38 (0.00%)	0 / 43 (0.00%)	1 / 19 (5.26%)
occurrences (all)			_
occurrences (an)	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)			
555411 511565 (ull)	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

		I	<u> </u>
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	
	'	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)		1 / 103 (0. // ///)	
occurrences (an)	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			
	•	•	•

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)	О	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)	О	1
Blood urea increased		
subjects affected / exposed	0 / 46 (0.00%)	0 / 103 (0.00%)
occurrences (all)	О	0
Blood uric acid increased		
subjects affected / exposed	0 / 46 (0.00%)	0 / 103 (0.00%)
occurrences (all)	О	0
Carbon dioxide decreased		
subjects affected / exposed	0 / 46 (0.00%)	0 / 103 (0.00%)
occurrences (all)	О	0
Gamma-glutamyItransferase increased		
subjects affected / exposed	2 / 46 (4.35%)	0 / 103 (0.00%)
	İ	1

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 / 4/ (0 00%)	0 (100 (0.00%)	
	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	О	
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			
, , , , , , , , , , , , , , , , , , ,	ı	ı	ı

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)	О	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	
		1	

subjects affected / exposed	0 / 46 (0.00%)	0 / 103 (0.00%)	
occurrences (all)	0	О	
Nausea Nausea			
subjects affected / exposed	5 / 46 (10.87%)	11 / 103 (10.68%)	
occurrences (all)	7	12	
Vomiting subjects affected / exposed	2 / 4/ /4 250/)	1 / 102 (0.07%)	
occurrences (all)	2 / 46 (4.35%)	1 / 103 (0.97%)	
occurrences (un)	4	1	
Hepatobiliary disorders			
Cholelithiasis subjects affected / exposed	4 / 44 (0.700/)	9 / 103 (8.74%)	
occurrences (all)	4 / 46 (8.70%)		
33333303 (411)	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 / 1/ (0 00%)	0 / 100 / 0 000/)	
occurrences (all)	0 / 46 (0.00%)	0 / 103 (0.00%)	
occurrences (an)	0	0	
Skin ulcer			
subjects affected / exposed	0 / 46 (0.00%)	0 / 103 (0.00%)	
occurrences (all)	О	0	
Renal and urinary disorders			
Glycosuria			
subjects affected / exposed	0 / 46 (0.00%)	0 / 103 (0.00%)	
occurrences (all)	0	0	
Haematuria			

Nephrolithiasis Subjects affected / exposed O / 46 (0.00%) O / 103 (0.00%) O O	subjects affected / exposed	0 / 46 (0.00%)	1 / 103 (0.97%)	
Nephrolithiasis Subjects affected / exposed O / 46 (0.00%) O / 103 (0.00%) O O	occurrences (all)	0		
Subjects affected / exposed occurrences (all)		_	·	
Endocrine disorders	l ·			
Endocrine disorders Adrenal insufficiency subjects affected / exposed occurrences (all) Hypothyroidism subjects affected / exposed occurrences (all) 1 Hypothyroidism subjects affected / exposed occurrences (all) 3 1 Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) 1 17 Back pain subjects affected / exposed occurrences (all) 2 6 Muscular weakness subjects affected / exposed occurrences (all) 0 0 Myalgia subjects affected / exposed occurrences (all) 0 Osteopenia subjects affected / exposed occurrences (all) 0 Osteopenia subjects affected / exposed occurrences (all) 0 Oiteopenia subjects affected / exposed occurrences (all)	subjects affected / exposed	0 / 46 (0.00%)	0 / 103 (0.00%)	
Adrenal insufficiency subjects affected / exposed occurrences (all) Hypothyroidism subjects affected / exposed occurrences (all) Ausculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) 1	occurrences (all)	0	0	
subjects affected / exposed occurrences (all) 1 / 46 (2.17%) 1 / 103 (0.97%) Hypothyroidism subjects affected / exposed occurrences (all) 3 / 46 (6.52%) 1 / 103 (0.97%) Musculoskeletal and connective tissue disorders 1 1 Arthralgia subjects affected / exposed occurrences (all) 1 / 46 (2.17%) 8 / 103 (7.77%) Back pain subjects affected / exposed occurrences (all) 2 / 46 (4.35%) 5 / 103 (4.85%) Occurrences (all) 2 6 Muscular weakness subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 0 / 103 (0.00%) Occurrences (all) 4 / 46 (8.70%) 1 / 103 (0.97%) Occurrences (all) 4 1 Osteopenia subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 0 / 103 (0.00%) Occurrences (all) 0 0 Infections and infestations Bone abscess subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 0 / 103 (0.00%) Nasopharyngitis subjects affected / exposed occurrences (all) 3 / 46 (6.52%) 16 / 103 (15.53%) Occurrences (all) 3 / 46 (6.52%) 3 / 46 (6.52%) 3 / 46 (6.52%)	Endocrine disorders			
Section 1	Adrenal insufficiency			
Hypothyroidism subjects affected / exposed 3 / 46 (6.52%) 1 / 103 (0.97%)	subjects affected / exposed	1 / 46 (2.17%)	1 / 103 (0.97%)	
Subjects affected / exposed occurrences (all) 3 1 1 1 1 1 1 1 1 1	occurrences (all)	1	1	
Subjects affected / exposed occurrences (all) 3 1 1 1 1 1 1 1 1 1	Hypothyroidism			
Musculoskeletal and connective tissue disorders		3 / 46 (6.52%)	1 / 103 (0.97%)	
disorders Arthralgia subjects affected / exposed	occurrences (all)			
disorders Arthralgia subjects affected / exposed	Mucoulogkolotel and command:			
subjects affected / exposed 1 / 46 (2.17%) 8 / 103 (7.77%) occurrences (all) 1 17 Back pain subjects affected / exposed occurrences (all) 2 / 46 (4.35%) 5 / 103 (4.85%) occurrences (all) 2 6 Muscular weakness subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 0 / 103 (0.00%) occurrences (all) 4 4 (8.70%) 1 / 103 (0.97%) occurrences (all) 4 1 Osteopenia subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 0 / 103 (0.00%) occurrences (all) 0 0 Infections and infestations Bone abscess subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 0 / 103 (0.00%) Nasopharyngitis subjects affected / exposed occurrences (all) 3 / 46 (6.52%) 16 / 103 (15.53%) occurrences (all) 3 27				
Description	Arthralgia			
Back pain subjects affected / exposed	subjects affected / exposed	1 / 46 (2.17%)	8 / 103 (7.77%)	
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 4 / 46 (8.70%) 1 / 103 (0.97%) occurrences (all) 4 1 Osteopenia 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 3 / 46 (6.52%) 16 / 103 (15.53%) occurrences (all) 3 27	occurrences (all)	1	17	
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 4 / 46 (8.70%) 1 / 103 (0.97%) occurrences (all) 4 1 Osteopenia 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 3 / 46 (6.52%) 16 / 103 (15.53%) occurrences (all) 3 27	Back pain			
Occurrences (all) 2		2 / 46 (4.35%)	5 / 103 (4.85%)	
subjects affected / exposed	occurrences (all)			
subjects affected / exposed				
occurrences (all) Myalgia subjects affected / exposed				
Myalgia subjects affected / exposed	subjects affected / exposed	0 / 46 (0.00%)	0 / 103 (0.00%)	
subjects affected / exposed	occurrences (all)	О	0	
occurrences (all) 4 1 Osteopenia subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 0 / 103 (0.00%) occurrences (all) 0 0 Infections and infestations Bone abscess subjects affected / exposed occurrences (all) O	Myalgia			
Osteopenia subjects affected / exposed occurrences (all) Infections and infestations Bone abscess subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) 3 / 46 (6.52%) occurrences (all) 3 27	subjects affected / exposed	4 / 46 (8.70%)	1 / 103 (0.97%)	
subjects affected / exposed	occurrences (all)	4	1	
subjects affected / exposed	Ostasmania			
occurrences (all) O Infections and infestations Bone abscess subjects affected / exposed O / 46 (0.00%) Occurrences (all) Nasopharyngitis subjects affected / exposed 3 / 46 (6.52%) Occurrences (all) 3 27	· ·	0 / 4/ (0 00%)	0 / 102 / 0 009/)	
Infections and infestations Bone abscess subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) 3 / 46 (6.52%) occurrences (all) 3 27				
Bone abscess subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) 3 / 46 (6.52%) occurrences (all) 3 / 27	occurrences (all)	0	0	
subjects affected / exposed 0 / 46 (0.00%) 0 / 103 (0.00%) occurrences (all) 0 0 Nasopharyngitis subjects affected / exposed occurrences (all) 3 / 46 (6.52%) 16 / 103 (15.53%) occurrences (all) 3 27	Infections and infestations			
occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) 3 / 46 (6.52%) 3 / 46 (6.52%) 27				
Nasopharyngitis subjects affected / exposed occurrences (all) 3 / 46 (6.52%) 16 / 103 (15.53%) 27	subjects affected / exposed	0 / 46 (0.00%)	0 / 103 (0.00%)	
subjects affected / exposed 3 / 46 (6.52%) 16 / 103 (15.53%) occurrences (all) 3	occurrences (all)	О	0	
subjects affected / exposed 3 / 46 (6.52%) 16 / 103 (15.53%) occurrences (all) 3	Nasopharyngitis			
occurrences (all) 3 27	1	3 / 46 (6.52%)	16 / 103 (15.53%)	
Onychomycosis	occurrences (all)			
	Onychomycosis			

Pharyngitis Subjects affected / exposed occurrences (all) O	subjects affected / exposed	0 / 46 (0.00%)	0 / 103 (0.00%)
subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 4 / 103 (3.88%) Pneumonia subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 0 / 103 (0.00%) Respiratory tract infection viral subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 0 / 103 (0.00%) Subcutaneous abscess subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 1 / 103 (0.97%) Upper respiratory tract infection subjects affected / exposed occurrences (all) 6 / 46 (13.04%) 15 / 103 (14.56%) Urinary tract infection subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 4 / 103 (3.88%) Decreased appetite subjects affected / exposed occurrences (all) 1 / 46 (2.17%) 2 / 103 (1.94%) Diabetes mellitus subjects affected / exposed occurrences (all) 1 / 46 (30.43%) 4 / 103 (3.88%) Dyslipidaemia subjects affected / exposed occurrences (all) 3 / 46 (6.52%) 2 / 103 (1.94%) Hyperglycaemia subjects affected / exposed occurrences (all) 10 / 46 (19.57%) 13 / 103 (12.62%) Hypertriglyceridaemia subjects affected / exposed 0 / 46 (0.00%) 1 / 103 (0.97%)	occurrences (all)	0	О
subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 4 / 103 (3.88%) Pneumonia subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 0 / 103 (0.00%) Respiratory tract infection viral subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 0 / 103 (0.00%) Subcutaneous abscess subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 1 / 103 (0.97%) Upper respiratory tract infection subjects affected / exposed occurrences (all) 6 / 46 (13.04%) 15 / 103 (14.56%) Urinary tract infection subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 4 / 103 (3.88%) Decreased appetite subjects affected / exposed occurrences (all) 1 / 46 (2.17%) 2 / 103 (1.94%) Diabetes mellitus subjects affected / exposed occurrences (all) 1 / 46 (30.43%) 4 / 103 (3.88%) Dyslipidaemia subjects affected / exposed occurrences (all) 3 / 46 (6.52%) 2 / 103 (1.94%) Hyperglycaemia subjects affected / exposed occurrences (all) 10 / 46 (19.57%) 13 / 103 (12.62%) Hypertriglyceridaemia subjects affected / exposed 0 / 46 (0.00%) 1 / 103 (0.97%)	Di		
Preumonia Subjects affected / exposed occurrences (all)		0 / 46 (0 00%)	4 / 102 (2 99%)
Pneumonia subjects affected / exposed occurrences (all) 0 0 0 Respiratory tract infection viral subjects affected / exposed occurrences (all) 0 0 0 Subcutaneous abscess subjects affected / exposed occurrences (all) 0 1 Upper respiratory tract infection subjects affected / exposed occurrences (all) 0 1 Upper respiratory tract infection subjects affected / exposed occurrences (all) 9 16 Urinary tract infection subjects affected / exposed occurrences (all) 9 16 Urinary tract infection subjects affected / exposed occurrences (all) 0 4 Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) 1 2 Diabetes mellitus subjects affected / exposed occurrences (all) 1 2 Dyslipidaemia subjects affected / exposed occurrences (all) 3 4 / 103 (3.88%) occurrences (all) 14 4 Dyslipidaemia subjects affected / exposed occurrences (all) 3 2 Hyperglycaemia subjects affected / exposed occurrences (all) 10 13 Hypertriglycaemia subjects affected / exposed occurrences (all) 10 13 Hypertriglycaemia subjects affected / exposed occurrences (all) 10 13 Hypertriglycaemia subjects affected / exposed occurrences (all) 10 13			
subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 0 / 103 (0.00%) Respiratory tract infection viral subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 0 / 103 (0.00%) Subcutaneous abscess subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 1 / 103 (0.97%) Upper respiratory tract infection subjects affected / exposed occurrences (all) 6 / 46 (13.04%) 15 / 103 (14.56%) Urinary tract infection subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 4 / 103 (3.88%) Decreased appetite subjects affected / exposed occurrences (all) 1 / 46 (2.17%) 2 / 103 (1.94%) Diabetes mellitus subjects affected / exposed occurrences (all) 14 / 46 (30.43%) 4 / 103 (3.88%) Dyslipidaemia subjects affected / exposed occurrences (all) 3 / 46 (6.52%) 2 / 103 (1.94%) Atyperglycaemia subjects affected / exposed occurrences (all) 9 / 46 (19.57%) 13 / 103 (12.62%) Atypertriglyceridaemia subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 1 / 103 (0.97%)	occurrences (any	U	5
Occurrences (all)	Pneumonia		
Respiratory tract infection viral subjects affected / exposed occurrences (all) Subcutaneous abscess subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) O	subjects affected / exposed	0 / 46 (0.00%)	0 / 103 (0.00%)
subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 0 / 103 (0.00%) Subcutaneous abscess subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 1 / 103 (0.97%) Upper respiratory tract infection subjects affected / exposed occurrences (all) 6 / 46 (13.04%) 15 / 103 (14.56%) Urinary tract infection subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 4 / 103 (3.88%) Decreased appetite subjects affected / exposed occurrences (all) 1 / 46 (2.17%) 2 / 103 (1.94%) Diabetes mellitus subjects affected / exposed occurrences (all) 14 / 46 (30.43%) 4 / 103 (3.88%) Dyslipidaemia subjects affected / exposed occurrences (all) 3 / 46 (6.52%) 2 / 103 (1.94%) Hyperglycaemia subjects affected / exposed occurrences (all) 9 / 46 (19.57%) 13 / 103 (12.62%) Hypertriglyceridaemia subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 1 / 103 (0.97%)	occurrences (all)	0	0
subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 0 / 103 (0.00%) Subcutaneous abscess subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 1 / 103 (0.97%) Upper respiratory tract infection subjects affected / exposed occurrences (all) 6 / 46 (13.04%) 15 / 103 (14.56%) Urinary tract infection subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 4 / 103 (3.88%) Decreased appetite subjects affected / exposed occurrences (all) 1 / 46 (2.17%) 2 / 103 (1.94%) Diabetes mellitus subjects affected / exposed occurrences (all) 14 / 46 (30.43%) 4 / 103 (3.88%) Dyslipidaemia subjects affected / exposed occurrences (all) 3 / 46 (6.52%) 2 / 103 (1.94%) Hyperglycaemia subjects affected / exposed occurrences (all) 9 / 46 (19.57%) 13 / 103 (12.62%) Hypertriglyceridaemia subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 1 / 103 (0.97%)	Respiratory tract infection viral		
Subcutaneous abscess subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) O	-	0 / 46 (0.00%)	0 / 103 (0.00%)
subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 1 / 103 (0.97%) Upper respiratory tract infection subjects affected / exposed occurrences (all) 6 / 46 (13.04%) 15 / 103 (14.56%) Urinary tract infection subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 4 / 103 (3.88%) Decreased appetite subjects affected / exposed occurrences (all) 1 / 46 (2.17%) 2 / 103 (1.94%) Diabetes mellitus subjects affected / exposed occurrences (all) 14 / 46 (30.43%) 4 / 103 (3.88%) Dyslipidaemia subjects affected / exposed occurrences (all) 3 / 46 (6.52%) 2 / 103 (1.94%) Hyperglycaemia subjects affected / exposed occurrences (all) 9 / 46 (19.57%) 13 / 103 (12.62%) Hypertriglyceridaemia subjects affected / exposed 0 / 46 (0.00%) 1 / 103 (0.97%)	occurrences (all)	0	0
subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 1 / 103 (0.97%) Upper respiratory tract infection subjects affected / exposed occurrences (all) 6 / 46 (13.04%) 15 / 103 (14.56%) Urinary tract infection subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 4 / 103 (3.88%) Decreased appetite subjects affected / exposed occurrences (all) 1 / 46 (2.17%) 2 / 103 (1.94%) Diabetes mellitus subjects affected / exposed occurrences (all) 14 / 46 (30.43%) 4 / 103 (3.88%) Dyslipidaemia subjects affected / exposed occurrences (all) 3 / 46 (6.52%) 2 / 103 (1.94%) Hyperglycaemia subjects affected / exposed occurrences (all) 9 / 46 (19.57%) 13 / 103 (12.62%) Hypertriglyceridaemia subjects affected / exposed 0 / 46 (0.00%) 1 / 103 (0.97%)			
Occurrences (all)		0 / 46 (0 00%)	1 / 102 (0.07%)
Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Diabetes mellitus subjects affected / exposed occurrences (all) Dyslipidaemia subjects affected / exposed occurrences (all) All pysripidaemia subjects affected / exposed occurrences (all) Hyperglycaemia subjects affected / exposed occurrences (all) Dyslipidaemia subjects affected / exposed occurrences (all) Oliabetes mellitus occurrences (all) Dyslipidaemia subjects affected / exposed occurrences (all) Oliabetes mellitus occurrences (all) Dyslipidaemia occurrences (all) Dyslipidaemia occurrences (all) Oliabetes mellitus occurre			
subjects affected / exposed occurrences (all) 6 / 46 (13.04%) 15 / 103 (14.56%) Urinary tract infection subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 4 / 103 (3.88%) Occurrences (all) 0 4 Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) 1 / 46 (2.17%) 2 / 103 (1.94%) Diabetes mellitus subjects affected / exposed occurrences (all) 14 / 46 (30.43%) 4 / 103 (3.88%) Dyslipidaemia subjects affected / exposed occurrences (all) 3 / 46 (6.52%) 2 / 103 (1.94%) Hyperglycaemia subjects affected / exposed occurrences (all) 9 / 46 (19.57%) 13 / 103 (12.62%) Hypertriglyceridaemia subjects affected / exposed 0 / 46 (0.00%) 1 / 103 (0.97%)	cocan enecs (any	0	'
occurrences (all) 9 16 Urinary tract infection subjects affected / exposed occurrences (all) 0 / 46 (0.00%) 4 / 103 (3.88%) Occurrences (all) 0 4 Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) 1 / 46 (2.17%) 2 / 103 (1.94%) Diabetes mellitus subjects affected / exposed occurrences (all) 14 / 46 (30.43%) 4 / 103 (3.88%) Dyslipidaemia subjects affected / exposed occurrences (all) 3 / 46 (6.52%) 2 / 103 (1.94%) Dyslipidaemia subjects affected / exposed occurrences (all) 9 / 46 (19.57%) 13 / 103 (12.62%) Hyperglycaemia subjects affected / exposed occurrences (all) 9 / 46 (19.57%) 13 / 103 (12.62%) Hypertriglyceridaemia subjects affected / exposed 0 / 46 (0.00%) 1 / 103 (0.97%)			
Urinary tract infection subjects affected / exposed occurrences (all) Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Diabetes mellitus subjects affected / exposed occurrences (all) Dyslipidaemia subjects affected / exposed occurrences (all) Dyslipidaemia subjects affected / exposed occurrences (all) All pyperglycaemia subjects affected / exposed occurrences (all) Hyperglycaemia subjects affected / exposed occurrences (all) O / 46 (0.00%) 4 / 103 (3.88%) 2 / 103 (1.94%) 3 / 46 (6.52%) 2 / 103 (1.94%) 3 / 46 (19.57%) 13 / 103 (12.62%) 14 / 46 (19.57%) 15 / 103 (12.62%) 16 / 17 / 103 (12.62%) 17 / 103 (0.97%)		6 / 46 (13.04%)	15 / 103 (14.56%)
subjects affected / exposed occurrences (all) Retabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Diabetes mellitus subjects affected / exposed occurrences (all) Dyslipidaemia subjects affected / exposed occurrences (all) A Dyslipidaemia subjects affected / exposed occurrences (all) A Dyslipidaemia subjects affected / exposed occurrences (all) A Hyperglycaemia subjects affected / exposed occurrences (all) O / 46 (0.00%) A / 103 (3.88%)	occurrences (all)	9	16
occurrences (all) O Aetabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Diabetes mellitus subjects affected / exposed occurrences (all) Dyslipidaemia subjects affected / exposed occurrences (all) Au Dyslipidaemia subjects affected / exposed occurrences (all) Au Dyslipidaemia subjects affected / exposed occurrences (all) Au Au Au Au Au Au Au Au Au A	Urinary tract infection		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Diabetes mellitus subjects affected / exposed occurrences (all) 1	subjects affected / exposed	0 / 46 (0.00%)	4 / 103 (3.88%)
Decreased appetite subjects affected / exposed occurrences (all) Diabetes mellitus subjects affected / exposed occurrences (all) Dyslipidaemia subjects affected / exposed occurrences (all) Dyslipidaemia subjects affected / exposed occurrences (all) A Dyslipidaemia subjects affected / exposed occurrences (all) A Hyperglycaemia subjects affected / exposed occurrences (all) Dyslipidaemia subjects affected / exposed Occurrences (all) Dyslipidaemia subjects affected / exposed Occurrences (all)	occurrences (all)	0	4
Decreased appetite subjects affected / exposed occurrences (all) Diabetes mellitus subjects affected / exposed occurrences (all) Dyslipidaemia subjects affected / exposed occurrences (all) Dyslipidaemia subjects affected / exposed occurrences (all) A Dyslipidaemia subjects affected / exposed Occurrences (all)	Matabalism and nutrition disorders		
subjects affected / exposed occurrences (all) Diabetes mellitus subjects affected / exposed occurrences (all) Dyslipidaemia subjects affected / exposed occurrences (all) Augustia affected / exposed occurrences (all) Hyperglycaemia subjects affected / exposed occurrences (all) Augustia affected / expos			
Diabetes mellitus subjects affected / exposed occurrences (all) Dyslipidaemia subjects affected / exposed occurrences (all) A Dyslipidaemia subjects affected / exposed occurrences (all) A A A A A A A A A B Dyslipidaemia subjects affected / exposed occurrences (all) A B A A A A A A A A B A A	• •	1 / 46 (2.17%)	2 / 103 (1.94%)
subjects affected / exposed occurrences (all) Dyslipidaemia subjects affected / exposed occurrences (all) A Dyslipidaemia subjects affected / exposed occurrences (all) A 3 / 46 (6.52%) 2 / 103 (1.94%) 2 Hyperglycaemia subjects affected / exposed occurrences (all) 10 13 Hypertriglyceridaemia subjects affected / exposed O / 46 (0.00%) 1 / 103 (0.97%)	occurrences (all)	1	2
subjects affected / exposed occurrences (all) Dyslipidaemia subjects affected / exposed occurrences (all) A Dyslipidaemia subjects affected / exposed occurrences (all) A 3 / 46 (6.52%) 2 / 103 (1.94%) 2 Hyperglycaemia subjects affected / exposed occurrences (all) 10 13 Hypertriglyceridaemia subjects affected / exposed O / 46 (0.00%) 1 / 103 (0.97%)	B: 1 1 1 11 11 11 11 11 11 11 11 11 11 11		
occurrences (all) 14 4 Dyslipidaemia subjects affected / exposed occurrences (all) 3 / 46 (6.52%) 2 / 103 (1.94%) 2 Hyperglycaemia subjects affected / exposed occurrences (all) 9 / 46 (19.57%) 13 / 103 (12.62%) 10 13 Hypertriglyceridaemia subjects affected / exposed 0 / 46 (0.00%) 1 / 103 (0.97%)		14 / 46 (20 42%)	4 / 102 (2 99%)
Dyslipidaemia subjects affected / exposed occurrences (all) Hyperglycaemia subjects affected / exposed occurrences (all) 10 13 Hypertriglyceridaemia subjects affected / exposed occurrences (all) 10 13 11 11 12 13 146 (6.52%) 2 / 103 (1.94%) 2 13 / 103 (12.62%) 10 13 14 15 16 17 17 18 18 18 18 18 18 18 18			
subjects affected / exposed 3 / 46 (6.52%) 2 / 103 (1.94%) occurrences (all) 3 2 Hyperglycaemia subjects affected / exposed occurrences (all) 9 / 46 (19.57%) 13 / 103 (12.62%) hypertriglyceridaemia subjects affected / exposed 0 / 46 (0.00%) 1 / 103 (0.97%)	(4)	14	4
occurrences (all) Hyperglycaemia subjects affected / exposed occurrences (all) 10 13 Hypertriglyceridaemia subjects affected / exposed 0 / 46 (0.00%) 1 / 103 (0.97%)	•		
Hyperglycaemia subjects affected / exposed occurrences (all) Hypertriglyceridaemia subjects affected / exposed 0 / 46 (0.00%) 13 / 103 (12.62%) 13 / 103 (12.62%) 14 / 103 (0.97%)		3 / 46 (6.52%)	2 / 103 (1.94%)
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)	3	2
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%)	Hyperglycaemia		
Hypertriglyceridaemia subjects affected / exposed 0 / 46 (0.00%) 1 / 103 (0.97%)		9 / 46 (19.57%)	13 / 103 (12.62%)
subjects affected / exposed 0 / 46 (0.00%) 1 / 103 (0.97%)	occurrences (all)	10	13
subjects affected / exposed 0 / 46 (0.00%) 1 / 103 (0.97%)	Llup ortrigly ocalida casia		
(11)		0 / 46 (0 00%)	1 / 103 (0 07%)
· · · · · · · · · · · · · · · · · · ·	courrented (un)	l o	1

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