Clinical trial results:
EFFICACY AND SAFETY OF LANREOTIDE ATG 120 MG IN COMBINATION WITH TMZ IN SUBJECTS WITH PROGRESSIVE WELL DIFFERENTIATED THORACIC NEUROENDOCRINE TUMOURS

Summary

EudraCT number	2014-005579-10
Trial protocol	IT
Global end of trial date	18 June 2019

Results information

Result version number	v1 (current)
This version publication date	20 August 2020
First version publication date	20 August 2020

Trial information

Trial identification

Sponsor protocol code	A-93-52030-325

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02698410
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ipsen SpA
Sponsor organisation address	Via del Bosco Rinnovato n. 6, Milanofiori Nord - Palazzo U7, Assago, Italy, 20090
Public contact	Medical Director, Ipsen SpA, clinical.trials@ipsen.com
Scientific contact	Medical Director, Ipsen SpA, clinical.trials@ipsen.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	18 June 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of lanreotide autogel (ATG) 120 milligrams (mg) in combination with temozolomide (TMZ) in participants with unresectable advanced neuroendocrine tumours (NET) of the lung (typical and atypical carcinoids according to the WHO 2004 criteria) or thymus as disease control rate (DCR), defined as complete response (CR), partial response (PR) and stable disease (SD) at 9 months, according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria v 1.1.

Protection of trial subjects:

The study was conducted under the provisions of the Declaration of Helsinki (version 2013), in accordance with the International Conference on Harmonisation Consolidated Guideline on Good Clinical Practice and in compliance with independent ethics committees and informed consent regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 July 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	14
From 65 to 84 years	26

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This pilot study was conducted at 11 investigational sites in Italy between 06 July 2016 and 18 June 2019.

Pre-assignment

Screening details:

The study consisted of a screening period (maximum 4 weeks), followed by an open label treatment period of up to a maximum of 52 weeks or until disease progression, death or unacceptable toxicity, or subject/physician decision.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Lanreotide ATG plus Temozolomide

Arm description:

Lanreotide ATG 120 mg was administered by deep subcutaneous injection on Day 1 (baseline) and every 28 days for up to 52 weeks. Participants also received temozolomide 250 mg capsule orally once daily for 5 consecutive days every 28 days for up to 52 weeks. The dose of temozolomide could subsequently be reduced to 180 mg daily for 5 consecutive days every 28 days in case of bone marrow toxicity.

Arm type	Experimental
Investigational medicinal product name	Lanreotide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A dose of lanreotide ATG 120 mg was provided in a pre-filled syringe at baseline and every 28 days for a maximum of 48 weeks of treatment (total number of 13 injections), and a maximum delay of 4 weeks in lanreotide administration was allowed.

Investigational medicinal product name	Temozolomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

A starting dose of temozolomide 250 mg/day was administered in the fasting state for 5 consecutive days every 28 days for a maximum of 48 weeks or until progression/death or toxicity. In case of bone marrow toxicity the dose could subsequently be reduced to 180 mg daily for 5 consecutive days of each month.

Number of subjects in period 1	Lanreotide ATG plus Temozolomide
Started	40
Completed	36
Not completed	4
Consent withdrawn by subject	1
Adverse event, non-fatal	2
Unspecified	1

Baseline characteristics

Reporting groups	
Reporting group title	Lanreotide ATG plus Temozolomide
Reporting group description:	
Lanreotide ATG 120 mg was administered by deep subcutaneous injection on Day 1 (baseline) and every 28 days for up to 52 weeks. Participants also received temozolomide 250 mg capsule orally once daily for 5 consecutive days every 28 days for up to 52 weeks. The dose of temozolomide could subsequently be reduced to 180 mg daily for 5 consecutive days every 28 days in case of bone marrow toxicity.	

Reporting group values	Lanreotide ATG plus Temozolomide	Total	
Number of subjects	40	40	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	64.9		
standard deviation	± 11.8	-	
Gender categorical Units: Subjects			
Female	16	16	
Male	24	24	
Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	40	40	
More than one race	0	0	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Lanreotide ATG plus Temozolomide

Reporting group description:

Lanreotide ATG 120 mg was administered by deep subcutaneous injection on Day 1 (baseline) and every 28 days for up to 52 weeks. Participants also received temozolomide 250 mg capsule orally once daily for 5 consecutive days every 28 days for up to 52 weeks. The dose of temozolomide could subsequently be reduced to 180 mg daily for 5 consecutive days every 28 days in case of bone marrow toxicity.

Primary: DCR Assessed Locally at Month 9

End point title	DCR Assessed Locally at Month 9[1]

End point description:

Responders were participants who showed disease control according to RECIST criteria v 1.1 assessed locally by the investigator. DCR was defined as CR, PR or SD according to RECIST criteria v1.1. A sensitivity analysis-1 of local DCR was performed excluding participants withdrawn before 9 months with reason other than progressive disease (PD) or missing assessment and considering participants with PD prior or at 9 months as failures. A sensitivity analysis-2 was performed to consider assessments done between 7.5 and 10.5 months as 9 months assessments when 9-month assessment was missing using same methodology of sensitivity analysis-1. P-value for DCR to 30% and 10% clinically relevant threshold was 0.2968 and <0.0001, respectively. P-value for sensitivity analysis-1 DCR to 30% and 10% clinically relevant threshold was 0.0534 and <0.0001, respectively. P-value for sensitivity analysis-2 DCR to 30% and 10% clinically relevant threshold was 0.032 and <0.0001, respectively.

End point type	Primary

End point timeframe:

Up to Month 9; for sensitivity analysis-2, up to 10.5 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As data is presented for a single reporting arm, the analysis of the comparison of DCR to the clinically relevant threshold of 30% and 10% is reported within the end point description.

End point values	Lanreotide ATG plus Temozolomide			
Subject group type	Reporting group			
Number of subjects analysed	40[2]			
Units: percentage of participants				
number (confidence interval 95%)				
DCR at Month 9 (n=40)	35.0 (20.63 to 51.68)			
Sensitivity analysis-1 (n=31)	45.2 (27.32 to 63.97)			
Sensitivity analysis-2 (n=40)	45.0 (29.26 to 61.51)			

Notes:

[2] - The ITT/Safety population. Here, n = number of participants analysed for each time point.

Statistical analyses

No statistical analyses for this end point

Secondary: DCR Assessed Centrally at Month 9

End point title	DCR Assessed Centrally at Month 9

End point description:

The DCR was defined as SD, PR or CR according to RECIST criteria v1.1. A second set of the original computed tomography (CT) scan images were used for a centralized RECIST v1.1 assessment by an independent radiologist. The ITT/Safety population included all participants who received at least 1 dose of study medication (either lanreotide ATG 120 mg or temozolomide).

End point type	Secondary

End point timeframe:

Up to Month 9

End point values	Lanreotide ATG plus Temozolomide			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percentage of participants				
number (confidence interval 95%)	28.2 (15.00 to 44.87)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Progression Free Survival (PFS) Assessed Locally and Centrally

End point title	Median Progression Free Survival (PFS) Assessed Locally and Centrally

End point description:

The PFS was defined as the time from the first treatment administration to disease progression according to RECIST criteria v 1.1 or death from any cause. The PFS was assessed locally by the investigator and centrally by an independent radiologist. The distribution of PFS times was estimated using the Kaplan-Meier method. The PFS of participants who were lost to follow-up and those who had not progressed at end of study were censored at the date of the last disease assessment. The ITT/Safety population included all participants who received at least 1 dose of study medication (either lanreotide ATG 120 mg or temozolomide).

End point type	Secondary

End point timeframe:

From Day 1 up to end of study, 52 weeks

End point values	Lanreotide ATG plus Temozolomide			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: weeks				
median (confidence interval 95%)				
Local assessment	37.1 (24.1 to 52.9)			

Central assessment	37.1 (24.1 to 56.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Time to Response (TTR) Assessed Locally and Centrally

End point title	Median Time to Response (TTR) Assessed Locally and Centrally

End point description:

The TTR was defined as the time from first treatment administration to the first objective tumour response (PR or CR according to RECIST criteria v 1.1). The TTR was assessed locally by the investigator and centrally by an independent radiologist. The distribution of TTR was estimated using the Kaplan-Meier method. The TTR of participants who were lost to follow-up or died prior to any objective tumour response were censored at the date of the last disease assessment. The ITT/Safety population included all participants who received at least 1 dose of study medication (either lanreotide ATG 120 mg or temozolomide). -9999 and 9999 = Not computed as the median TTR could not be estimated due to the low number of participants with an objective response (OR).

End point type	Secondary

End point timeframe:

From Day 1 up to end of study, 52 weeks

End point values	Lanreotide ATG plus Temozolomide			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: weeks				
median (confidence interval 95%)				
Local assessment	9999 (-9999 to 9999)			
Central assessment	9999 (-9999 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Duration of Response (DOR) Assessed Locally and Centrally

End point title	Median Duration of Response (DOR) Assessed Locally and Centrally

End point description:

The DOR was defined as the time from onset of the first objective tumour response (PR or CR) to objective tumour progression (PD) according to RECIST criteria v 1.1. The DOR was assessed locally by the investigator and centrally by an independent radiologist. The ITT/Safety population included all participants who received at least 1 dose of study medication (either lanreotide ATG 120 mg or temozolomide). -9999 and 9999 = The median DOR could not be estimated due to the low number of participants with an OR with no documented PD.

End point type	Secondary

End point timeframe:

From Day 1 up to end of study, 52 weeks

End point values	Lanreotide ATG plus Temozolomide			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: weeks				
median (confidence interval 95%)				
Local assessment	9999 (-9999 to 9999)			
Central assessment	9999 (-9999 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Time to Progression (TTP) Assessed Locally and Centrally

End point title	Median Time to Progression (TTP) Assessed Locally and Centrally

End point description:

The TTP was defined as the time from first treatment administration to the first objective tumour progression (PD) according to RECIST criteria v 1.1. The TTP was assessed locally by the investigator and centrally by an independent radiologist. The distribution of TTP times was estimated using the Kaplan-Meier method. The TTP of participants who were lost to follow-up, and those who had not progressed at end of study were censored at the date of the last disease assessment. The ITT/Safety population included all participants who received at least 1 dose of study medication (either lanreotide ATG 120 mg or temozolomide).

End point type	Secondary

End point timeframe:

From Day 1 up to end of study, 52 weeks

End point values	Lanreotide ATG plus Temozolomide			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: weeks				
median (confidence interval 95%)				
Local assessment	37.1 (26.4 to 55.1)			
Central assessment	37.1 (24.1 to 56.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response (BOR) Assessed Locally and Centrally

End point title	Best Overall Response (BOR) Assessed Locally and Centrally

End point description:

The BOR was defined as the highest OR achieved by the participant from the time of first treatment until disease progression/recurrence or the end of study according to RECIST criteria v1.1 and was classified as: CR > PR > Non-CR/Non-progressive disease (NCR/NPD) > SD > PD > ND > not evaluable (NE). The BOR was assessed locally by the investigator and centrally by an independent radiologist. Percentages are based on the number of participants in the ITT/Safety population with non-missing observations. The ITT/Safety population included all participants who received at least 1 dose of study medication (either lanreotide ATG 120 mg or temozolomide). Here, 'n' is defined as number of participants analysed at each assessments.

End point type	Secondary

End point timeframe:

From Day 1 up to end of study, 52 weeks

End point values	Lanreotide ATG plus Temozolomide			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percentage of participants				
number (not applicable)				
Local assessment: CR (n=39)	0			
Local assessment: PR (n=39)	7.7			
Local assessment: SD (n=39)	71.8			
Local assessment: NCR/NPD (n=39)	0			
Local assessment: PD (n=39)	20.5			
Local assessment: NE (n=39)	0			
Local assessment: not applicable (n=39)	0			
Central assessment: CR (n=38)	0			
Central assessment: PR (n=38)	13.2			
Central assessment: SD (n=38)	65.8			
Central assessment: NCR/NPD (n=38)	2.6			
Central assessment: PD (n=38)	15.8			
Central assessment: NE (n=38)	0			
Central assessment: not applicable (n=38)	2.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) Assessed Locally and Centrally at Months 9 and 12

End point title	Objective Response Rate (ORR) Assessed Locally and Centrally at Months 9 and 12

End point description:

The ORR was defined as the percentage of participants with CR or PR according to RECIST criteria v1.1. The ORR was assessed locally by the investigator and centrally by an independent radiologist. The ORR was based on the participants with PD prior to 9 and 12 months with respectively PD at 9 and 12 months, and participants withdrawn before the assessment for reason other than PD or missing as failures. The ITT/Safety population included all participants who received at least 1 dose of study medication (either lanreotide ATG 120 mg or temozolomide).

End point type	Secondary

End point timeframe:

Months 9 and 12

End point values	Lanreotide ATG plus Temozolomide			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percentage of participants				
number (confidence interval 95%)				
Local assessment: Month 9	2.5 (0.06 to 13.16)			
Local assessment: Month 12	2.5 (0.06 to 13.16)			
Central assessment: Month 9	5.1 (0.63 to 17.32)			
Central assessment: Month 12	2.6 (0.06 to 13.48)			

Statistical analyses

No statistical analyses for this end point

Secondary: DCR Assessed Locally and Centrally at Month 12

End point title	DCR Assessed Locally and Centrally at Month 12

End point description:

The DCR was defined as SD, PR or CR according to RECIST criteria v1.1. The DCR was assessed locally by the investigator and centrally by an independent radiologist. The ITT/Safety population included all participants who received at least 1 dose of study medication (either lanreotide ATG 120 mg or temozolomide).

End point type	Secondary

End point timeframe:

Month 12

End point values	Lanreotide ATG plus Temozolomide			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percentage of participants				
number (confidence interval 95%)				
Local assessment	17.5 (7.34 to 32.78)			
Central assessment	15.4 (5.86 to 30.53)			

Statistical analyses

No statistical analyses for this end point

Secondary: DCR Assessed Locally and Centrally at Month 9 by Carcinoid Type

End point title	DCR Assessed Locally and Centrally at Month 9 by Carcinoid Type

End point description:

The influence of type of carcinoid (typical, atypical and undetermined carcinoid NET) on the local and central DCR at 9 months was analysed. Typical carcinoids were defined with absent foci of necrosis and mitotic count < 2 mitoses/2 millimeters^2 (mm^2); atypical carcinoids were defined with presence of foci of necrosis and/or 2 mitoses/2 mm^2 <= mitotic count <= 10 mitoses/2 mm^2; and carcinoid NET were defined as confirmed carcinoid without foci of necrosis and/or mitotic count reported. The DCR was assessed locally by the investigator and centrally by an independent radiologist. The ITT/Safety population included all participants who received at least 1 dose of study medication (either lanreotide ATG 120 mg or temozolomide). Here, 'n' is defined as number of participants analysed for each carcinoid type. -9999 and 9999 = The confidence interval could not be calculated due to no events.

End point type	Secondary

End point timeframe:

Up to Month 9

End point values	Lanreotide ATG plus Temozolomide			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percentage of participants				
number (confidence interval 95%)				
Local: Typical carcinoid (n=8)	12.5 (0.32 to 52.65)			
Local: Atypical carcinoid (n=21)	47.6 (25.71 to 70.22)			
Local: Carcinoid NET (n=11)	27.3 (6.02 to 60.97)			
Central: Typical carcinoid (n=8)	0 (-9999 to 9999)			

Central: Atypical carcinoid (n=21)	35.0 (15.39 to 59.22)			
Central: Carcinoid NET (n=11)	36.4 (10.93 to 69.21)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Biochemical Responders According to Chromogranin A (CgA) Plasma Levels

End point title	Percentage of Biochemical Responders According to Chromogranin A (CgA) Plasma Levels

End point description:

Participants with baseline CgA plasma levels greater than the upper limit of normal (ULN) were assessed for a biochemical response. A biochemical responder was defined as a participant who had a decrease of CgA >= 50% compared to baseline, while biochemical SD was defined as a decrease < 50% or an increase <= 25% compared to baseline. Biochemical non-responders had an increase >25% compared to baseline. Baseline was defined as value at Day 1. The ITT/Safety population included all participants who received at least 1 dose of study medication (either lanreotide ATG 120 mg or temozolomide). Only participants with baseline CgA levels greater than ULN were analysed. Here, 'n' is defined as number of participants analysed at specific time point.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 4, 12, 24, 36 and 52

End point values	Lanreotide ATG plus Temozolomide			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: percentage of participants				
number (confidence interval 95%)				
Week 4: Responders (n=22)	27.3 (9.36 to 45.13)			
Week 4: SD (n=22)	59.1 (31.31 to 72.2)			
Week 4: Non-responders (n=22)	13.6 (2.55 to 31.22)			
Week 12: Responders (n=16)	37.5 (11.89 to 54.28)			
Week 12: SD (n=16)	37.5 (11.89 to 54.28)			
Week 12: Non-responders (n=16)	25.0 (5.73 to 43.66)			
Week 24: Responders (n=13)	23.1 (5.04 to 53.81)			
Week 24: SD (n=13)	30.8 (9.09 to 61.43)			
Week 24: Non-responders (n=13)	46.2 (19.22 to 74.87)			
Week 36: Responders (n=11)	36.4 (9.09 to 61.43)			

Week 36: SD (n=11)	27.3 (5.04 to 53.81)			
Week 36: Non-responders (n=11)	36.4 (9.09 to 61.43)			
Week 52: Responders (n=8)	12.5 (0.28 to 48.25)			
Week 52: SD (n=8)	50.0 (13.7 to 78.8)			
Week 52: Non-responders (n=8)	37.5 (7.49 to 70.07)			

Statistical analyses

No statistical analyses for this end point

Secondary: Neuron-Specific Enolase (NSE) and CgA Biomarker Levels

End point title	Neuron-Specific Enolase (NSE) and CgA Biomarker Levels

End point description:

The NSE and CgA levels were classified according to ULN as follows: < 1 ULN, 1-2 ULN and > 2 ULN. Baseline was defined as value at Day 1. Percentages are based on the number of participants in the ITT/Safety population who attended the visit with non-missing observations. The ITT/Safety population included all participants who received at least 1 dose of study medication (either lanreotide ATG 120 mg or temozolomide). Here, 'n' is defined as number of participants analysed at specific time point.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 12, 24, 36 and 52

End point values	Lanreotide ATG plus Temozolomide			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percentage of participants				
number (not applicable)				
CgA: Baseline: <1 ULN (n=40)	40.0			
CgA: Baseline: 1-2 ULN (n=40)	15.0			
CgA: Baseline: >2 ULN (n=40)	45.0			
CgA: Week 4: <1 ULN (n=35)	34.3			
CgA: Week 4: 1-2 ULN (n=35)	22.9			
CgA: Week 4: >2 ULN (n=35)	42.9			
CgA: Week 12: <1 ULN (n=28)	46.4			
CgA: Week 12: 1-2 ULN (n=28)	17.9			
CgA: Week 12: >2 ULN (n=28)	35.7			
CgA: Week 24: <1 ULN (n=20)	30.0			
CgA: Week 24: 1-2 ULN (n=20)	25.0			
CgA: Week 24: >2 ULN (n=20)	45.0			
CgA: Week 36: <1 ULN (n=16)	31.3			
CgA: Week 36: 1-2 ULN (n=16)	12.5			
CgA: Week 36: >2 ULN (n=16)	56.3			
CgA: Week 52: <1 ULN (n=11)	27.3			

CgA: Week 52: 1-2 ULN (n=11)	9.1			
CgA: Week 52: >2 ULN (n=11)	63.6			
NSE: Baseline: <1 ULN (n=40)	65.0			
NSE: Baseline: 1-2 ULN (n=40)	25.0			
NSE: Baseline: >2 ULN (n=40)	10.0			
NSE: Week 4: <1 ULN (n=35)	62.9			
NSE: Week 4: 1-2 ULN (n=35)	25.7			
NSE: Week 4: >2 ULN (n=35)	11.4			
NSE: Week 12: <1 ULN (n=28)	78.6			
NSE: Week 12: 1-2 ULN (n=28)	17.9			
NSE: Week 12: >2 ULN (n=28)	3.6			
NSE: Week 24: <1 ULN (n=20)	80.0			
NSE: Week 24: 1-2 ULN (n=20)	10.0			
NSE: Week 24: >2 ULN (n=20)	10.0			
NSE: Week 36: <1 ULN (n=16)	87.5			
NSE: Week 36: 1-2 ULN (n=16)	6.3			
NSE: Week 36: >2 ULN (n=16)	6.3			
NSE: Week 52: <1 ULN (n=11)	63.6			
NSE: Week 52: 1-2 ULN (n=11)	18.2			
NSE: Week 52: >2 ULN (n=11)	18.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Influence of Biomarkers Expression on Locally and Centrally Assessed PFS

End point title	Influence of Biomarkers Expression on Locally and Centrally Assessed PFS

End point description:

The following biomarkers were investigated: Immunohistochemistry assay human somatostatin receptors 2 (SSTR2) including human epidermal growth factor receptor 2 (HER-2) score [0, 1+, 2+, 3+ and positive (+ve) versus negative (-ve)]; hormone receptor score (H-score) (from 0 to 300 as quantitative variable and +ve versus -ve); immunoreactive score (IRS) score (from 0 to 12 and reference for hazard ratio was 0-1). Ki67 index (from 0% to 100% and reference for hazard ratio was 4%-25%). O^6-methylguanine-DNA methyltransferase (MGMT) expression including percentage of +ve nuclei stained and methylated sites and H-score (from 0 to 300 as quantitative variable). For all these categories, higher score indicates a higher expression of biomarkers. Carcinoid type (typical or NET) was also investigated. Prognostic value of biomarkers expression at screening on PFS were assessed locally and centrally using univariate cox proportional hazard models. 9999= not calculated due to low number of events.

End point type	Secondary

End point timeframe:

From Screening period (-4 weeks) up to Week 52

End point values	Lanreotide ATG plus Temozolomide			
Subject group type	Reporting group			
Number of subjects analysed	40[3]			
Units: hazard ratio				
number (confidence interval 95%)				
Local: SSTR2: HER-2 score; +ve (2+, 3+) (n=26)	0.71 (0.26 to 1.92)			
Local: SSTR2: H-score; +ve (>= 50) (n=26)	0.66 (0.25 to 1.71)			
Local: SSTR2: IRS score; 2-3 (n=26)	0.31 (0.04 to 2.61)			
Local: SSTR2: IRS score; 4-8 (n=26)	0.90 (0.31 to 2.61)			
Local: SSTR2: IRS score; 9-12 (n=26)	0.12 (0.01 to 0.99)			
Local: Ki67: <4 (n=20)	1.08 (0.13 to 8.93)			
Local: Ki67: >=25 (n=20)	1.68 (0.37 to 7.70)			
Local: MGMT: +ve nuclei stained; +ve (>=5%) (n=26)	2.06 (0.27 to 15.69)			
Local: MGMT: Methylated sites; +ve (>10%) (n=24)	0.41 (0.05 to 3.20)			
Local: MGMT: H-score (n=26)	1.00 (1.00 to 1.01)			
Local: Carcinoid type: Typical (n=40)	1.05 (0.36 to 3.07)			
Local: Carcinoid type: Carcinoid NET (n=40)	1.59 (0.64 to 3.93)			
Central: SSTR2: HER-2 score; +ve (2+, 3+) (n=26)	0.50 (0.18 to 1.39)			
Central: SSTR2: H-score; +ve (>= 50) (n=26)	0.36 (0.12 to 1.04)			
Central: SSTR2: IRS score; 2-3 (n=26)	0.78 (0.16 to 3.92)			
Central: SSTR2: IRS score; 4-8 (n=26)	0.88 (0.28 to 2.76)			
Central: SSTR2: IRS score; 9-12 (n=26)	0.10 (0.01 to 0.89)			
Central: Ki67: <4 (n=20)	0.00 (0.00 to 9999)			
Central: Ki67: >=25 (n=20)	2.75 (0.55 to 13.76)			
Central:MGMT: +ve nuclei stained; +ve(>=5%) (n=26)	2.11 (0.27 to 16.34)			
Central: MGMT: Methylated sites; +ve (>10%) (n=24)	0.73 (0.16 to 3.33)			
Central: MGMT: H-score (n=26)	1.00 (0.99 to 1.01)			
Central: Carcinoid type: Typical (n=40)	0.99 (0.35 to 2.82)			
Central: Carcinoid type: Carcinoid NET (n=40)	0.61 (0.20 to 1.89)			

Notes:

[3] - The ITT/Safety population. n = number of participants analysed in a specific model.

Statistical analyses

No statistical analyses for this end point

Secondary: Influence of Biomarkers Expression on Locally and Centrally Assessed ORR at Months 9 and 12

End point title	Influence of Biomarkers Expression on Locally and Centrally Assessed ORR at Months 9 and 12

End point description:

The following biomarkers were investigated: Immunohistochemistry assay SSTR2 including HER-2 score (0, 1+, 2+, 3+); H-score (from 0 to 300 as quantitative variable); IRS score (from 0 to 12). Ki67 index (from 0% to 100%). MGMT expression including percentage of +ve nuclei stained and methylated sites and H-score (from 0 to 300 as quantitative variable). For all these categories, higher score indicates a higher expression of biomarkers. The ITT/Safety population included all participants who received at least 1 dose of study medication (either lanreotide ATG 120 mg or temozolomide). Less than 5 OR (CR or PR) events were reported, therefore this analysis was not performed.

End point type	Secondary

End point timeframe:

Screening period, Months 9 and 12

End point values	Lanreotide ATG plus Temozolomide			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: odds ratio				
number (confidence interval 95%)	(to)			

Notes:

[4] - Less than 5 OR (CR or PR) events were reported, therefore this analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Influence of Biomarkers Expression on Locally and Centrally Assessed DCR at Months 9 and 12

End point title	Influence of Biomarkers Expression on Locally and Centrally Assessed DCR at Months 9 and 12

End point description:

The following biomarkers were investigated: Immunohistochemistry assay SSTR2 including HER-2 score (0, 1+, 2+, 3+ and +ve versus -ve); H-score (from 0 to 300 as quantitative variable and +ve versus -ve); IRS score (from 0 to 12 and reference for odds ratio was 0-1). Ki67 index (from 0% to 100% and reference for odds ratio was 4%-25%). MGMT expression including percentage of +ve nuclei stained and methylated sites and H-score (from 0 to 300 as quantitative variable). For all these categories, higher score indicates a higher expression of biomarkers. Carcinoid type (typical or NET) was also investigated. Prognostic value of biomarkers expression at screening on DCR were assessed locally and centrally using univariate logistic regression models. M9= Month 9; M12= Month 12; Loc= Local assessment; Cntl= central assessment; -9999 and 9999= not calculated due to low number of events; -99999 and 99999= confidence interval could not be computed as odds ratio is <0.001.

End point type	Secondary

End point timeframe:

Screening period, Months 9 and 12

End point values	Lanreotide ATG plus Temozolomide			
Subject group type	Reporting group			
Number of subjects analysed	40[5]			
Units: odds ratio				
number (confidence interval 95%)				
M9: Loc: SSTR2: HER-2 score; +ve (2+, 3+) (n=26)	0.90 (0.18 to 4.55)			
M9: Loc: SSTR2: H-score; +ve (>= 50) (n=26)	0.78 (0.16 to 3.79)			
M9: Loc: SSTR2: IRS score; 2-3 (n=26)	9999 (-9999 to 9999)			
M9: Loc: SSTR2: IRS score; 4-8 (n=26)	0.67 (0.07 to 6.11)			
M9: Loc: SSTR2: IRS score; 9-12 (n=26)	12.00 (0.80 to 180.97)			
M9: Loc: Ki67: <4 (n=20)	99999 (-99999 to 99999)			
M9: Loc: Ki67: >=25 (n=20)	1.67 (0.09 to 31.87)			
M9: Loc:MGMT: +ve nuclei stained; +ve(>=5%) (n=26)	99999 (-99999 to 99999)			
M9: Loc: MGMT: Methylated sites; +ve (>10%) (n=24)	3.25 (0.25 to 41.91)			
M9: Loc: MGMT: H-score (n=26)	0.99 (0.98 to 1.00)			
M9: Loc: Carcinoid type: Typical (n=40)	0.16 (0.02 to 1.51)			
M9: Loc: Carcinoid type: Carcinoid NET (n=40)	0.41 (0.09 to 2.00)			
M9: Cntl: SSTR2: HER-2 score; +ve (2+, 3+) (n=26)	1.40 (0.26 to 7.58)			
M9: Cntl: SSTR2: H-score; +ve (>= 50) (n=26)	2.25 (0.42 to 12.09)			
M9: Cntl: SSTR2: IRS score; 2-3 (n=26)	3.00 (0.12 to 73.64)			
M9: Cntl: SSTR2: IRS score; 4-8 (n=26)	0.67 (0.07 to 6.11)			
M9: Cntl: SSTR2: IRS score; 9-12 (n=26)	12.00 (0.80 to 180.97)			
M9: Cntl: Ki67: <4 (n=20)	99999 (-99999 to 99999)			
M9: Cntl: Ki67: >=25 (n=20)	99999 (-99999 to 99999)			
M9: Cntl:MGMT: +ve nuclei stained;+ve(>=5%) (n=26)	0.50 (0.03 to 9.08)			
M9: Cntl:MGMT: Methylated sites; +ve (>10%) (n=24)	5.00 (0.38 to 66.01)			
M9: Cntl: MGMT: H-score (n=26)	1.00 (0.99 to 1.01)			
M9: Cntl: Carcinoid type: Typical (n=40)	99999 (-99999 to 99999)			
M9: Cntl: Carcinoid type: Carcinoid NET (n=40)	1.06 (0.23 to 4.92)			
M12: Loc: SSTR2: HER-2 score; +ve (2+, 3+) (n=26)	3.00 (0.28 to 31.63)			
M12: Loc: SSTR2: H-score; +ve (>= 50) (n=26)	4.40 (0.42 to 46.24)			
M12: Loc: SSTR2: IRS score; 2-3 (n=26)	99999 (-99999 to 99999)			

M12: Loc: SSTR2: IRS score; 4-8 (n=26)	0.70 (0.04 to 13.18)			
M12: Loc: SSTR2: IRS score; 9-12 (n=26)	10.50 (0.67 to 165.11)			
M12: Loc: Ki67: <4 (n=20)	9999 (-9999 to 9999)			
M12: Loc: Ki67: >=25 (n=20)	9999 (-9999 to 9999)			
M12: Loc:MGMT:+ve nuclei stained; +ve(>=5%) (n=26)	0.20 (0.01 to 3.91)			
M12: Loc: MGMT: Methylated sites; +ve(>10%) (n=24)	2.13 (0.15 to 29.66)			
M12: Loc: MGMT: H-score (n=26)	0.99 (0.96 to 1.01)			
M12: Loc: Carcinoid type: Typical (n=40)	0.46 (0.04 to 4.67)			
M12: Loc: Carcinoid type: Carcinoid NET (n=40)	0.32 (0.03 to 3.15)			
M12: Cntl: SSTR2: HER-2 score; +ve (2+, 3+) (n=26)	2.08 (0.19 to 23.30)			
M12: Cntl: SSTR2: H-score; +ve (>= 50) (n=26)	3.00 (0.27 to 33.49)			
M12: Cntl: SSTR2: IRS score; 2-3 (n=26)	99999 (-99999 to 99999)			
M12: Cntl: SSTR2: IRS score; 4-8 (n=26)	99999 (-99999 to 99999)			
M12: Cntl: SSTR2: IRS score; 9-12 (n=26)	10.50 (0.67 to 165.11)			
M12: Cntl: Ki67: <4 (n=20)	99999 (-99999 to 99999)			
M12: Cntl: Ki67: >=25 (n=20)	99999 (-99999 to 99999)			
M12: Cntl:MGMT:+ve nuclei stained;+ve(>=5%) (n=26)	0.14 (0.01 to 2.94)			
M12: Cntl:MGMT: Methylated sites; +ve(>10%) (n=24)	3.00 (0.20 to 44.36)			
M12: Cntl: MGMT: H-score (n=26)	0.99 (0.96 to 1.01)			
M12: Cntl: Carcinoid type: Typical (n=40)	0.57 (0.05 to 6.08)			
M12: Cntl: Carcinoid type: Carcinoid NET (n=40)	0.40 (0.04 to 4.11)			

Notes:

[5] - The ITT/Safety population. n = number of participants analysed in a specific model.

Statistical analyses

No statistical analyses for this end point

Secondary: Coefficient of Agreement Between Central and Local Assessment of Tumour Radiological Response at Month 9

End point title	Coefficient of Agreement Between Central and Local Assessment of Tumour Radiological Response at Month 9

End point description:

Differences between central radiology review and local investigator review were assessed according to the DCR status and the number of agreements and disagreements between the evaluators (central versus local) along with the p-values from the kappa test. A kappa statistic was used to evaluate the concordance between the central and the local review. The ITT/Safety population included all participants who received at least 1 dose of study medication (either lanreotide ATG 120 mg or temozolomide).

End point type	Secondary

End point timeframe:

Month 9

End point values	Lanreotide ATG plus Temozolomide			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: kappa coefficient				
number (confidence interval 95%)	0.71 (0.48 to 0.94)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events were collected from the start of the first treatment (Day 1) until 4 weeks after the end of the last study treatment, up to a maximum of 52 weeks.

Adverse event reporting additional description:

The ITT/Safety population included all participants who received at least 1 dose of study medication (either lanreotide ATG 120 mg or temozolomide). Number of deaths (all causes) occurred in both treatment period and follow-up period were reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Lanreotide ATG plus Temozolomide

Reporting group description:

Lanreotide ATG 120 mg was administered by deep subcutaneous injection on Day 1 (baseline) and every 28 days for up to 52 weeks. Participants also received temozolomide 250 mg capsule orally once daily for 5 consecutive days every 28 days for up to 52 weeks. The dose of temozolomide could subsequently be reduced to 180 mg daily for 5 consecutive days every 28 days in case of bone marrow toxicity.

Serious adverse events	Lanreotide ATG plus Temozolomide		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 40 (22.50%)		
number of deaths (all causes)	9		
number of deaths resulting from adverse events	2		
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Non-cardiac chest pain			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Lanreotide ATG plus Temozolomide		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 40 (95.00%)		
Vascular disorders			
Flushing			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Hypertension			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	3		
Hypotension			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	8 / 40 (20.00%)		
occurrences (all)	8		
Pyrexia			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	6		
Pain			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
Influenza like illness			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Fatigue			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	4		
Chest pain			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		

Reproductive system and breast disorders			
Breast mass			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	6		
Dyspnoea			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Dyspnoea exertional			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Haemoptysis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Pleural thickening			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Pneumonitis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		

Investigations			
Weight decreased			
subjects affected / exposed	7 / 40 (17.50%)		
occurrences (all)	7		
Blood cholesterol increased			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	5		
Platelet count decreased			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	7		
Blood creatinine increased			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Blood triglycerides increased			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Lymphocyte count decreased			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	5		
White blood cell count decreased			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	3		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Blood thyroid stimulating hormone			

increased			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Glucose tolerance decreased			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Glycosylated haemoglobin increased			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Neutrophil count decreased			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Transaminases increased			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Vitamin b12 decreased			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Tachyarrhythmia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	5		
Sciatica			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Dysgeusia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Paraesthesia			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Lymphopenia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Eye disorders			
Visual acuity reduced			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	21 / 40 (52.50%)		
occurrences (all)	42		
Vomiting			
subjects affected / exposed	13 / 40 (32.50%)		
occurrences (all)	24		
Diarrhoea			
subjects affected / exposed	12 / 40 (30.00%)		
occurrences (all)	36		
Constipation			
subjects affected / exposed	8 / 40 (20.00%)		
occurrences (all)	26		
Abdominal pain			

subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Dry mouth subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Haematochezia subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Stomatitis subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Toothache subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Hepatobiliary disorders Cholelithiasis subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 3		
Bile duct obstruction subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Hepatic steatosis subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 5		
Pruritus subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Erythema			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	5		
Musculoskeletal pain			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
Arthralgia			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	4		
Musculoskeletal chest pain			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	4		
Pain in jaw			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Angular cheilitis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Bacteriuria			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Ear infection			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Fungal infection			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Oral herpes			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	6		
Hypocalcaemia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Type 2 diabetes mellitus			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Vitamin d deficiency			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Decreased appetite			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		

Hypercalcaemia subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Hypercholesterolaemia subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Hyperkalaemia subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Hyperuricaemia subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 October 2016	A detailed description of optional sub study procedures (MGMT methylation and blood samples) was added. As consequence, the number and volume of blood samples to be collected was reduced. The analysis of MGMT methylation on tissue samples was added. This had no further impact on the participants and was to provide stronger data to the study. Participants with asymptomatic cholilithiasis, previously excluded from the study, could be enrolled. This was to guarantee as many participants as possible access to the study treatment.
16 November 2017	Amended to specify the timelines for adverse events collection, end of study visit and to specify a maximum delay for investigational medicinal product administration. Addition of specifications related to direct bilirubin assessment and specification that the description of the sub-study analysis will be performed through a separate statistical analysis plan and that the results will be reported separately.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported