



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

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|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| 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

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|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| 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

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|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|
| 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

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|-----------------|--------------------------------------------------------------|
| 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).

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

End point timeframe:

From Day 1 up to end of study, 52 weeks

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|----------------------------------|----------------------------------|--|--|--|
| 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

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|-----------------|------------------------------------------------------------------|
| 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.

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|-----------------------------------------|-----------|
| 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

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|-----------------|-----------------------------------------------------------------|
| 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

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|-----------------|------------------------------------------------------------|
| 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

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|-----------------|---------------------------------------------------------------------------------|
| 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).

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|----------------|-----------|
| 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

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|-----------------|------------------------------------------------|
| 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

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|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| 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

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|-----------------|--------------------------------------------------------------------------------------|
| 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 $\geq 50\%$ compared to baseline, while biochemical SD was defined as a decrease $< 50\%$ or an increase $\leq 25\%$ 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

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|-----------------|--------------------------------------------------------|
| 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%). O⁶-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 ($\geq 5\%$) (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($\geq 5\%$) (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

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

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|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| 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

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|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| 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 | | |

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

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

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

| | | | |
|------------------------------------|-----------------|--|--|
| 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 | 1 / 40 (2.50%) | | |
| occurrences (all) | 1 | | |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences (all) | 1 | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences (all) | 1 | | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences (all) | 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 cholelithiasis, 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