# Clinical trial results:
# A Randomised, Multicentre, Open Label, Phase II study of Prophylactic Octreotide to Prevent or Reduce the Frequency and Severity of Diarrhoea in Subjects Receiving Lapatinib with Capecitabine for the Treatment of Metastatic Breast Cancer

## Summary

| | |
|---|---|
| EudraCT number | 2014-000256-28 |
| Trial protocol | CZ GB IT GR PL FR |
| Global end of trial date | 19 October 2017 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 04 November 2018 |
| First version publication date | 04 November 2018 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | LAP117314 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02294786 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

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

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 19 October 2017 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 19 October 2017 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to determine the efficacy of prophylactic octreotide in reducing the proportion of subjects experiencing diarrhea with a severity of National Cancer Institute common terminology criteria for adverse events (NCI CTCAE) grade 2 and above.

Protection of trial subjects:

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

Background therapy:

All subjects received treatment with lapatinib 1250 mg orally once daily and capecitabine 1000 mg/m2 orally twice daily until disease progression. Lapatinib was given every day; capecitabine was given in 3 week cycles of two weeks treatment followed by one week off treatment.

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 17 December 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Israel: 1 |
| Country: Number of subjects enrolled | Czech Republic: 2 |
| Country: Number of subjects enrolled | Poland: 15 |
| Country: Number of subjects enrolled | Russian Federation: 35 |
| Country: Number of subjects enrolled | United Kingdom: 9 |
| Worldwide total number of subjects | 62 |
| EEA total number of subjects | 26 |

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 | 0 |

| | |
|---|---|
| months) | |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 48 |
| From 65 to 84 years | 14 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The study enrolled 62 women in 17 centers; Czech Republic (1), Israel (1), Poland (3), the United Kingdom (4) Russian Federation (8)

### Pre-assignment

Screening details:

The study was terminated early after 62 patients (out of 140 planned) were randomized as criteria for futility was met.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Octreotide treatment |

Arm description:

Subjects randomised to receive Octreotide were administered with Octreotide (Sandostatin LAR™) 40mg 7 days before the start of treatment with Lapatinib and Capecitabine and again 28 days later. All subjects received treatment with Lapatinib 1250milligram (mg) once daily and Capecitabine 1000 milligram/square meter (mg/m^2) twice daily until disease progression. Lapatinib was given every day; Capecitabine was given in 3 week cycles of two weeks treatment followed by one week off treatment. SANDOSTATIN™ is a trademark of Novartis.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Octreotide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

two doses of octreotide: one each on 7 days before the start of treatment with lapatinib and capecitabine, and Day 28 of the study, in addition to the doses of lapatinib and capecitabine mentioned above. The first dose was administered as a 0.1 mg sc injection, the second dose of 40 mg was administered as an intramuscular injection.

| | |
|---|---|
| **Arm title** | No Octreotide treatment |

Arm description:

Subjects randomised to receive no octreotide, treatment with Lapatinib and Capecitabine was initiated immediately following enrolment. All subjects received treatment with Lapatinib 1250mg once daily and Capecitabine 1000mg/m^2 twice daily until disease progression. Lapatinib was given every day; Capecitabine was given in 3 week cycles of two weeks treatment followed by one week off treatment

| | |
|---|---|
| Arm type | No intervention |

No investigational medicinal product assigned in this arm

| **Number of subjects in period 1** | Octreotide treatment | No Octreotide treatment |
|---|---|---|
| Started | 30 | 32 |
| ITT Population | 30 | 32 |
| Completed | 19 | 18 |
| Not completed | 11 | 14 |
| Adverse event, serious fatal | 2 | 3 |
| Physician decision | 6 | 7 |
| Consent withdrawn by subject | - | 1 |
| Adverse event, non-fatal | 1 | 1 |
| Lost to follow-up | 1 | 2 |
| Protocol deviation | 1 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Octreotide treatment |

Reporting group description:

Subjects randomised to receive Octreotide were administered with Octreotide (Sandostatin LAR™) 40mg 7 days before the start of treatment with Lapatinib and Capecitabine and again 28 days later. All subjects received treatment with Lapatinib 1250milligram (mg) once daily and Capecitabine 1000 milligram/square meter (mg/m^2) twice daily until disease progression. Lapatinib was given every day; Capecitabine was given in 3 week cycles of two weeks treatment followed by one week off treatment. SANDOSTATIN™ is a trademark of Novartis.

| Reporting group title | No Octreotide treatment |
|---|---|

Reporting group description:

Subjects randomised to receive no octreotide, treatment with Lapatinib and Capecitabine was initiated immediately following enrolment. All subjects received treatment with Lapatinib 1250mg once daily and Capecitabine 1000mg/m^2 twice daily until disease progression. Lapatinib was given every day; Capecitabine was given in 3 week cycles of two weeks treatment followed by one week off treatment

| Reporting group values | Octreotide treatment | No Octreotide treatment | Total |
|---|---|---|---|
| Number of subjects | 30 | 32 | 62 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 23 | 25 | 48 |
| From 65-84 years | 7 | 7 | 14 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 57.4 | 55.9 | |
| standard deviation | ± 10.07 | ± 9.08 | - |
| Sex: Female, Male<br>Units: Subjects | | | |
| Female | 30 | 32 | 62 |
| Male | 0 | 0 | 0 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| Hispanic or Latino | 0 | 1 | 1 |
| Not Hispanic or Latino | 30 | 31 | 61 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Octreotide treatment |

Reporting group description:

Subjects randomised to receive Octreotide were administered with Octreotide (Sandostatin LAR™) 40mg 7 days before the start of treatment with Lapatinib and Capecitabine and again 28 days later. All subjects received treatment with Lapatinib 1250milligram (mg) once daily and Capecitabine 1000 milligram/square meter (mg/m^2) twice daily until disease progression. Lapatinib was given every day; Capecitabine was given in 3 week cycles of two weeks treatment followed by one week off treatment. SANDOSTATIN™ is a trademark of Novartis.

| | |
|---|---|
| Reporting group title | No Octreotide treatment |

Reporting group description:

Subjects randomised to receive no octreotide, treatment with Lapatinib and Capecitabine was initiated immediately following enrolment. All subjects received treatment with Lapatinib 1250mg once daily and Capecitabine 1000mg/m^2 twice daily until disease progression. Lapatinib was given every day; Capecitabine was given in 3 week cycles of two weeks treatment followed by one week off treatment

### Primary: Proportion of Subjects experiencing diarrhoea of Grade 2 and above

| | |
|---|---|
| End point title | Proportion of Subjects experiencing diarrhoea of Grade 2 and above |

End point description:

Proportion of subjects experiencing at least one episode of diarrhoea with a severity of Grade 2 and above, as defined by the National Cancer Institute common terminology criteria for adverse events (NCI CTCAE) version 4.03, recorded as AEs in the Electronic case report form (eCRF). Subjects that withdrew from the study on or prior to the Cycle 4 visit date were assumed to have experienced diarrhoea.

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

End point timeframe:

9 weeks (first 3 cycles of treatment)

| End point values | Octreotide treatment | No Octreotide treatment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 32 | | |
| Units: Participants | 7 | 9 | | |

### Statistical analyses

| Statistical analysis title | Diarrhoea of Grade 2 and above |
|---|---|
| Comparison groups | No Octreotide treatment v Octreotide treatment |
| Number of subjects included in analysis | 62 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.775 |
| Method | Chi-squared |
| Parameter estimate | Difference in Percentages |
| Point estimate | -4.8 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -29.2 |
| upper limit | 20 |

## Secondary: Proportion of subjects experiencing diarrhoea of Grade 3 and above

| End point title | Proportion of subjects experiencing diarrhoea of Grade 3 and above |
|---|---|

End point description:

Proportion of subjects experiencing diarrhoea with a severity of Grade 3 and above, as defined by the NCI CTCAE, version 4.03 and recorded as AEs in the eCRF

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

End point timeframe:

Up to 24 weeks

| End point values | Octreotide treatment | No Octreotide treatment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 32 | | |
| Units: Participants | 2 | 0 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of diarrhoea of any grade of severity

| End point title | Duration of diarrhoea of any grade of severity |
|---|---|

End point description:

Duration of diarrhoea of any grade of severity, recorded as AEs in the eCRF

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

End point timeframe:

Up to 24 weeks

| End point values | Octreotide treatment | No Octreotide treatment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[1] | 0[2] | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[1] - Not analyzed as study was terminated early

[2] - Not analyzed as study was terminated early

## Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of subjects experiencing diarrhoea of any grade of severity

| End point title | Proportion of subjects experiencing diarrhoea of any grade of severity |
|---|---|

End point description:

Proportion of subjects experiencing diarrhoea of any grade of severity as defined by the NCI CTCAE, version 4.03 and recorded as AEs in the eCRF

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

End point timeframe:

Up to 24 weeks

| End point values | Octreotide treatment | No Octreotide treatment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 32 | | |
| Units: Participants | 18 | 14 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to onset of the first episode of diarrhoea of any grade of severity

| End point title | Time to onset of the first episode of diarrhoea of any grade of severity |
|---|---|

End point description:

Time to onset of the first episode of diarrhoea of any grade of severity, recorded as an AE in the eCRF

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

End point timeframe:

Up to 24 weeks

| End point values | Octreotide treatment | No Octreotide treatment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[3] | 0[4] | | |
| Units: Days | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[3] - Not analyzed as study was terminated early

[4] - Not analyzed as study was terminated early

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of subjects taking anti-diarrhoeal medication

| End point title | Proportion of subjects taking anti-diarrhoeal medication |
|---|---|

End point description:

Proportion of subjects taking anti-diarrhoeal medication as recorded in the eCRF

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

End point timeframe:

Up to 24 weeks

| End point values | Octreotide treatment | No Octreotide treatment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[5] | 0[6] | | |
| Units: Participants | | | | |

Notes:

[5] - Not analyzed as study was terminated early

[6] - Not analyzed as study was terminated early

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of subjects who had unscheduled visits to healthcare professionals due to diarrhoea

| End point title | Proportion of subjects who had unscheduled visits to healthcare professionals due to diarrhoea |
|---|---|

End point description:

Proportion of subjects making diarrhoea related unscheduled visits to healthcare professionals as recorded in the eCRF

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

End point timeframe:

Up to 24 weeks

| End point values | Octreotide treatment | No Octreotide treatment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[7] | 0[8] | | |
| Units: Participants | | | | |

Notes:

[7] - Not analyzed as study was terminated early

[8] - Not analyzed as study was terminated early

### Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of subjects requiring dose reduction in Lapatinib and Capecitabine

| End point title | Proportion of subjects requiring dose reduction in Lapatinib and Capecitabine |
|---|---|

End point description:

Proportion of subjects requiring diarrhoea related Lapatinib and Capecitabine dose reduction as recorded in the eCRF

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

End point timeframe:

Up to 24 weeks

| End point values | Octreotide treatment | No Octreotide treatment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[9] | 0[10] | | |
| Units: Participants | | | | |

Notes:

[9] - Not analyzed as study was terminated early

[10] - Not analyzed as study was terminated early

### Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of subjects requiring dose delay in Lapatinib and Capecitabine

| End point title | Proportion of subjects requiring dose delay in Lapatinib and Capecitabine |
|---|---|

End point description:

Proportion of subjects requiring diarrhoea related Lapatinib and Capecitabine dose delay as recorded in the eCRF

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

End point timeframe:

Up to 24 weeks

| End point values | Octreotide treatment | No Octreotide treatment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[11] | 0[12] | | |
| Units: Participants | | | | |

Notes:

[11] - Not analyzed as study was terminated early

[12] - Not analyzed as study was terminated early

### Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of subjects requiring treatment withdrawal in Lapatinib and Capecitabine

| End point title | Proportion of subjects requiring treatment withdrawal in Lapatinib and Capecitabine |
|---|---|

End point description:

Proportion of subjects requiring diarrhoea related Lapatinib and Capecitabine treatment withdrawal as recorded in the eCRF

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

End point timeframe:

Up to 24 weeks

| End point values | Octreotide treatment | No Octreotide treatment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[13] | 0[14] | | |
| Units: Participants | | | | |

Notes:

[13] - Not analyzed as study was terminated early

[14] - Not analyzed as study was terminated early

### Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of subjects requiring use of diarrhoea-related intravenous fluids

| End point title | Proportion of subjects requiring use of diarrhoea-related intravenous fluids |
|---|---|

End point description:

Proportion of subjects requiring use of diarrhoea-related intravenous fluids for rehydration as recorded in the eCRF

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

End point timeframe:

Up to 24 weeks

| End point values | Octreotide treatment | No Octreotide treatment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[15] | 0[16] | | |
| Units: Participants | | | | |

Notes:

[15] - Not analyzed as study was terminated early

[16] - Not analyzed as study was terminated early

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Lapatinib and Capecitabine tablets dispensed and returned

| End point title | Number of Lapatinib and Capecitabine tablets dispensed and returned |
|---|---|

End point description:

Number of Lapatinib and Capecitabine tablets dispensed and returned as recorded in the eCRF

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

End point timeframe:

Up to 24 weeks

| End point values | Octreotide treatment | No Octreotide treatment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[17] | 0[18] | | |
| Units: tablets | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[17] - Not analyzed as study was terminated early

[18] - Not analyzed as study was terminated early

### Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Response Rate

| End point title | Overall Response Rate |
|---|---|

End point description:

Overall response rate as measured in accordance with the Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1

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

End point timeframe:

Up to 24 weeks

| End point values | Octreotide treatment | No Octreotide treatment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 32 | | |
| Units: Participants | | | | |
| complete response (CR) | 0 | 2 | | |
| partial response (PR) | 6 | 4 | | |
| stable disease (SD) | 4 | 5 | | |
| Progressive Disease | 14 | 17 | | |
| Not Evaluable | 6 | 4 | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Clinical Benefit Response

| End point title | Clinical Benefit Response |
|---|---|

End point description:

Clinical benefit response as measured in accordance with the Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1

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

End point timeframe:

Up to 24 weeks

| End point values | Octreotide treatment | No Octreotide treatment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 32 | | |
| Units: Participants | | | | |
| complete response (CR) | 0 | 2 | | |
| partial response (PR) | 6 | 4 | | |
| stable disease (SD) >= 24 weeks | 1 | 3 | | |
| stable disease (SD) < 24 weeks | 3 | 2 | | |
| Progressive Disease | 14 | 17 | | |
| Not Evaluable | 6 | 4 | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of subjects reporting changes in bowel movements from baseline (frequency and/or consistency) as recorded in the Diarrhoea Management Diary (DMD)

| End point title | Proportion of subjects reporting changes in bowel movements from baseline (frequency and/or consistency) as recorded in the Diarrhoea Management Diary (DMD) |
|---|---|

End point description:

All subjects will complete the baseline DMD during the 3 days prior to randomisation, before any study-related treatment is administered. Subjects randomised to receive Octreotide will complete a second baseline DMD before starting the first cycle of treatment with Lapatinib and Capecitabine. The baseline DMD will comprise of 3 questions to record stool form and consistency. The DMD to be completed throughout the rest of the study will comprise of 3 questions in the baseline DMD and a further 5 questions and 6 sub-questions to evaluate the consequences and management of diarrhoea

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

End point timeframe:

Up to 24 weeks

| **End point values** | Octreotide treatment | No Octreotide treatment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[19] | 0[20] | | |
| Units: Participants | | | | |

Notes:

[19] - Not analyzed as study was terminated early

[20] - Not analyzed as study was terminated early

### Statistical analyses

No statistical analyses for this end point

## Secondary: Time to the first subject reported change in frequency and/or consistency of bowel movements from baseline as recorded in the DMD

| End point title | Time to the first subject reported change in frequency and/or consistency of bowel movements from baseline as recorded in the DMD |
|---|---|

End point description:

The time to onset of the first subject-reported increase in frequency and/or worsening of consistency of bowel movements will be summarised by treatment arm

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

End point timeframe:

Up to 24 weeks

| **End point values** | Octreotide treatment | No Octreotide treatment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[21] | 0[22] | | |
| Units: Days | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[21] - Not analyzed as study was terminated early

[22] - Not analyzed as study was terminated early

### Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of subjects taking anti-diarrhoeal medication as recorded in the DMD

| End point title | Proportion of subjects taking anti-diarrhoeal medication as recorded in the DMD |
|---|---|

End point description:

The proportion of subjects taking medication at least once as a result of diarrhoea will be summarised and analysed

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

End point timeframe:

Up to 24 weeks

| End point values | Octreotide treatment | No Octreotide treatment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[23] | 0[24] | | |
| Units: Participants | | | | |

Notes:

[23] - Not analyzed as study was terminated early

[24] - Not analyzed as study was terminated early

### Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of subjects making dietary changes due to diarrhoea as recorded in the DMD

| End point title | Proportion of subjects making dietary changes due to diarrhoea as recorded in the DMD |
|---|---|

End point description:

The proportion of subjects making dietary changes to help with the diarrhoea will be summarised and analysed using the Generalised Estimating Equations (GEE) analysis and plots

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

End point timeframe:

Up to 24 weeks

| End point values | Octreotide treatment | No Octreotide treatment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[25] | 0[26] | | |
| Units: Participants | | | | |

Notes:

[25] - Not analyzed as study was terminated early

[26] - Not analyzed as study was terminated early

### Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of subjects contacting other non-hospital healthcare professionals to discuss diarrhoea as recorded in the DMD

| End point title | Proportion of subjects contacting other non-hospital healthcare professionals to discuss diarrhoea as recorded in the DMD |
|---|---|

End point description:

The proportion of subjects contacting a health care professional other than the hospital doctors/nurses to discuss diarrhoea will be summarised and analysed using the GEE analysis and plots

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

End point timeframe:

Up to 24 weeks

| End point values | Octreotide treatment | No Octreotide treatment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[27] | 0[28] | | |
| Units: Participants | | | | |

Notes:

[27] - Not analyzed as study was terminated early

[28] - Not analyzed as study was terminated early

### Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of subjects reporting stopping completely or missing doses of anti-cancer tablets due to diarrhoea as recorded in the DMD

| End point title | Proportion of subjects reporting stopping completely or missing doses of anti-cancer tablets due to diarrhoea as recorded in the DMD |
|---|---|

End point description:

The proportion of subjects reducing or completely stopping the number of anti-cancer tablets to help with diarrhoea will be summarised and analysed using the GEE analysis and plots. Summaries will be performed separately for each type of change in anti-cancer tablets (i.e. reducing tablets and stopping completely) as well as overall

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

End point timeframe:

Up to 24 weeks

| End point values | Octreotide treatment | No Octreotide treatment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[29] | 0[30] | | |
| Units: Participants | | | | |

Notes:

[29] - Not analyzed as study was terminated early

[30] - Not analyzed as study was terminated early

### Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of Subjects experiencing diarrhoea of Grade 2 and above

| End point title | Proportion of Subjects experiencing diarrhoea of Grade 2 and above |
|---|---|

End point description:

Proportion of subjects experiencing at least one episode of diarrhoea with a severity of Grade 2 and above, as defined by the National Cancer Institute common terminology criteria for adverse events (NCI CTCAE) version 4.03, recorded as AEs in the Electronic case report form (eCRF). Subjects who did not have diarrhea event prior to the End of Study/Withdrawal visit date were not assumed to have experienced diarrhoea.

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

End point timeframe:

Up to 24 weeks

| End point values | Octreotide treatment | No Octreotide treatment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 32 | | |
| Units: Participants | 6 | 5 | | |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the SAE field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator. One patient randomized to Oct analyzed in non-Oct group (got only 0.1 mg dose).

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 19.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | No Octreotide treatment |

Reporting group description:

Lap+Cap

| | |
|---|---|
| Reporting group title | All Patients |

Reporting group description:

All Patients

| | |
|---|---|
| Reporting group title | Octreotide treatment |

Reporting group description:

Octreotide+Lap+Cap

| Serious adverse events | No Octreotide treatment | All Patients | Octreotide treatment |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | 8 / 62 (12.90%) | 5 / 29 (17.24%) |
| number of deaths (all causes) | 0 | 1 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 62 (1.61%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 62 (1.61%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |

| | | | |
|---|---|---|---|
| Paraparesis | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 1 / 62 (1.61%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 62 (1.61%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 1 / 62 (1.61%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 1 / 62 (1.61%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 62 (1.61%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vulvitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 62 (1.61%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | No Octreotide treatment | All Patients | Octreotide treatment |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 27 / 33 (81.82%) | 53 / 62 (85.48%) | 26 / 29 (89.66%) |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 6 / 62 (9.68%) | 4 / 29 (13.79%) |
| occurrences (all) | 2 | 7 | 5 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 5 / 62 (8.06%) | 4 / 29 (13.79%) |
| occurrences (all) | 1 | 5 | 4 |
| Bilirubin conjugated increased | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 62 (3.23%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 3 | 3 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | 7 / 62 (11.29%) | 4 / 29 (13.79%) |
| occurrences (all) | 3 | 10 | 7 |
| Vascular disorders | | | |
| Lymphoedema | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 3 / 62 (4.84%) | 1 / 29 (3.45%) |
| occurrences (all) | 2 | 3 | 1 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 6 / 33 (18.18%) | 7 / 62 (11.29%) | 1 / 29 (3.45%) |
| occurrences (all) | 10 | 11 | 1 |
| Neutropenia | | | |
| subjects affected / exposed | 4 / 33 (12.12%) | 5 / 62 (8.06%) | 1 / 29 (3.45%) |
| occurrences (all) | 7 | 8 | 1 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | 6 / 62 (9.68%) | 3 / 29 (10.34%) |
| occurrences (all) | 3 | 6 | 3 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 7 / 33 (21.21%) | 9 / 62 (14.52%) | 2 / 29 (6.90%) |
| occurrences (all) | 7 | 10 | 3 |
| Fatigue | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 33 (3.03%) | 4 / 62 (6.45%) | 3 / 29 (10.34%) |
| occurrences (all) | 1 | 4 | 3 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 62 (3.23%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 2 | 2 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 62 (3.23%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 3 | 3 |
| Diarrhoea | | | |
| subjects affected / exposed | 15 / 33 (45.45%) | 32 / 62 (51.61%) | 17 / 29 (58.62%) |
| occurrences (all) | 38 | 64 | 26 |
| Dry mouth | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 3 / 62 (4.84%) | 2 / 29 (6.90%) |
| occurrences (all) | 1 | 3 | 2 |
| Mouth ulceration | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 2 / 62 (3.23%) | 0 / 29 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Nausea | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 4 / 62 (6.45%) | 2 / 29 (6.90%) |
| occurrences (all) | 3 | 5 | 2 |
| Oral pain | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 2 / 62 (3.23%) | 0 / 29 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Stomatitis | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 4 / 62 (6.45%) | 2 / 29 (6.90%) |
| occurrences (all) | 2 | 4 | 2 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 3 / 62 (4.84%) | 2 / 29 (6.90%) |
| occurrences (all) | 1 | 4 | 3 |
| Hepatobiliary disorders | | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 4 / 62 (6.45%) | 2 / 29 (6.90%) |
| occurrences (all) | 4 | 6 | 2 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---|---|---|
| Cough | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | 5 / 62 (8.06%) | 2 / 29 (6.90%) |
| occurrences (all) | 3 | 6 | 3 |
| Epistaxis | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 2 / 62 (3.23%) | 0 / 29 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Blister | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 62 (3.23%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 2 | 2 |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 11 / 33 (33.33%) | 24 / 62 (38.71%) | 13 / 29 (44.83%) |
| occurrences (all) | 11 | 24 | 13 |
| Rash | | | |
| subjects affected / exposed | 7 / 33 (21.21%) | 11 / 62 (17.74%) | 4 / 29 (13.79%) |
| occurrences (all) | 11 | 16 | 5 |
| Skin fissures | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 4 / 62 (6.45%) | 2 / 29 (6.90%) |
| occurrences (all) | 3 | 5 | 2 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 2 / 62 (3.23%) | 0 / 29 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Bone pain | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 2 / 62 (3.23%) | 0 / 29 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 4 / 62 (6.45%) | 2 / 29 (6.90%) |
| occurrences (all) | 2 | 4 | 2 |
| Infections and infestations | | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 4 / 62 (6.45%) | 3 / 29 (10.34%) |
| occurrences (all) | 1 | 4 | 3 |
| Oral candidiasis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 62 (3.23%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 2 | 2 |
| Paronychia | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 4 / 62 (6.45%) | 2 / 29 (6.90%) |
| occurrences (all) | 2 | 4 | 2 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 3 / 62 (4.84%) | 1 / 29 (3.45%) |
| occurrences (all) | 2 | 3 | 1 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 11 August 2014 | - Prior treatment with lapatinib was added as an exclusion criterion<br>- Additional detail was provided for dermatological monitoring<br>- Secondary endpoints related to patient reported outcomes were updated<br>- The schedule for completion of the DMD and FACIT-D was clarified<br>- The schedule of study visits relative to the week numbers and cycles of treatment with lapatinib and capecitabine was clarified<br>- The use of octreotide sc within the diarrhea management guidelines was clarified |
| 11 September 2015 | - Details of planned interim analysis included in Protocol Summary, Study Assessments, for early assessment of the primary endpoint<br>- Recruitment Plan Section was included as an interim analysis was being incorporated<br>- Blinding Section was updated with further clarification to support addition of an interim analysis<br>- Number of subjects undergoing formal review of safety data was updated to reflect consistency with planned interim analysis<br>- Details of tertiary Sponsor Medical Monitor Contact Information added. Author list, Sponsor Signatory, address and telephone numbers of medical monitors updated<br>- Instructive text presented in Appendix for Country Specific Requirements deleted<br>- Statement regarding application of amendment 01 to all participating sites added to improve the quality of the protocol |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported