



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
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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/m²) 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
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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/m² 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			
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			
Units: Years			
arithmetic mean	57.4	55.9	
standard deviation	± 10.07	± 9.08	-
Sex: Female, Male			
Units: Subjects			
Female	30	32	62
Male	0	0	0
Race/Ethnicity, Customized			
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
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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/m²) 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
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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/m² 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
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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
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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: 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: Duration of diarrhoea of any grade of severity

End point title	Duration of diarrhoea of any grade of severity
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End point description:

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

End point type	Secondary
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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: 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
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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
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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
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End point description:

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

End point type	Secondary
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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
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End point description:

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

End point type	Secondary
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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
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End point description:

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

End point type	Secondary
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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
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End point description:

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

End point type	Secondary
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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
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End point description:

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

End point type	Secondary
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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
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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
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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) \geq 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)
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	No Octreotide treatment
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Reporting group description:

Lap+Cap

Reporting group title	All Patients
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Reporting group description:

All Patients

Reporting group title	Octreotide treatment
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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 occurrences (all)	2 / 33 (6.06%) 2	6 / 62 (9.68%) 7	4 / 29 (13.79%) 5
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	5 / 62 (8.06%) 5	4 / 29 (13.79%) 4
Bilirubin conjugated increased subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	2 / 62 (3.23%) 3	2 / 29 (6.90%) 3
Blood bilirubin increased subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3	7 / 62 (11.29%) 10	4 / 29 (13.79%) 7
Vascular disorders			
Lymphoedema subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	3 / 62 (4.84%) 3	1 / 29 (3.45%) 1
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	6 / 33 (18.18%) 10	7 / 62 (11.29%) 11	1 / 29 (3.45%) 1
Neutropenia subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 7	5 / 62 (8.06%) 8	1 / 29 (3.45%) 1
Thrombocytopenia subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3	6 / 62 (9.68%) 6	3 / 29 (10.34%) 3
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	7 / 33 (21.21%) 7	9 / 62 (14.52%) 10	2 / 29 (6.90%) 3
Fatigue			

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 August 2014	<ul style="list-style-type: none">- Prior treatment with lapatinib was added as an exclusion criterion- Additional detail was provided for dermatological monitoring- Secondary endpoints related to patient reported outcomes were updated- The schedule for completion of the DMD and FACIT-D was clarified- The schedule of study visits relative to the week numbers and cycles of treatment with lapatinib and capecitabine was clarified- The use of octreotide sc within the diarrhea management guidelines was clarified
11 September 2015	<ul style="list-style-type: none">- Details of planned interim analysis included in Protocol Summary, Study Assessments, for early assessment of the primary endpoint- Recruitment Plan Section was included as an interim analysis was being incorporated- Blinding Section was updated with further clarification to support addition of an interim analysis- Number of subjects undergoing formal review of safety data was updated to reflect consistency with planned interim analysis- Details of tertiary Sponsor Medical Monitor Contact Information added. Author list, Sponsor Signatory, address and telephone numbers of medical monitors updated- Instructive text presented in Appendix for Country Specific Requirements deleted- 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