Clinical trial results:
An Open Label Study to Characterize the Incidence and Severity of Diarrhea in Patients with Early Stage HER2+ Breast Cancer Treated with Neratinib and Intensive Loperamide Prophylaxis

Summary

EudraCT number	2015-004374-15
Trial protocol	ES AT
Global end of trial date	22 April 2021

Results information

Result version number	v1 (current)
This version publication date	28 April 2022
First version publication date	28 April 2022

Trial information

Trial identification

Sponsor protocol code	PUMA-NER-6201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02400476
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Puma Biotechnology
Sponsor organisation address	10880 Wilshire Blvd, Suite 2150, Los Angeles, United States, 90024
Public contact	Clinical Trials Information Desk, Puma Biotechnology, Inc., +1 4242486500, clinicaltrials@pumabiotechnology.com
Scientific contact	Clinical Trials Information Desk, Puma Biotechnology, Inc., +1 4242486500, clinicaltrials@pumabiotechnology.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	10 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 April 2021
Global end of trial reached?	Yes
Global end of trial date	22 April 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To characterize the incidence and severity of diarrhea in patients with early stage HER2 overexpressed/amplified (HER2+) breast cancer treated with neratinib when administered with intensive loperamide prophylaxis, after prior treatment with trastuzumab.

Protection of trial subjects:

Study commencement required prior written approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Clinical trial data were monitored at regular intervals by the Sponsor or their representative throughout the study to verify compliance to study protocol, completeness, accuracy and consistency of the data and adherence to local regulations on the conduct of clinical research. Patients were discontinued from investigational product(s) (IP) in the following circumstances: disease recurrence (as determined by the Investigator), death, unacceptable toxicity, or other specified withdrawal criterion.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 February 2015
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	France: 6
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Spain: 25
Country: Number of subjects enrolled	Australia: 86
Country: Number of subjects enrolled	Canada: 27
Country: Number of subjects enrolled	United States: 413
Worldwide total number of subjects	563
EEA total number of subjects	37

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)	487
From 65 to 84 years	75
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The institutional review board/independent ethics committee must review and approve the protocol and informed consent form (ICF) before any subjects provide consent.

Pre-assignment

Screening details:

Each subject must participate in the informed consent process and sign and date an Informed Consent Form (ICF) for this protocol before any protocol-required procedures are performed.

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Loperamide

Arm description:

Patients in the Loperamide Arm were enrolled under the original protocol as well as patients enrolled under amendments 1 and 2.

Patients enrolled under Original Protocol received mandatory low dose loperamide prophylaxis for 2 cycles + neratinib 240 mg/day for all thirteen (13) 28-day cycles.

Patients enrolled under Amendment 1 or 2 received mandatory high dose loperamide prophylaxis for 2 cycles + neratinib 240 mg/day for all thirteen (13) 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	loperamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For patients enrolled under the Original Protocol:
Initial dose of 4 mg (2 tablets/capsules) with the first dose of neratinib, followed by 2 mg (1 tablet/capsule) every 4 hours for the first 3 days.

After the first 3 days, loperamide 2 mg every 6 to 8 hours through the first 2 cycles of therapy (56 days) from start of neratinib.

For patients enrolled under Amendment 1 and Amendment 2:
For the first 14 days, loperamide 4 mg (2 tablets/capsules) will be self-administered orally by patients 3 times a day (total 12 mg a day). The initial dose of loperamide 4 mg will be self-administered orally with the first dose of neratinib.

After the first 14 days, loperamide 4 mg (2 tablets/capsules) will be self-administered orally twice a day (total 8 mg a day) through the first 2 cycles of therapy (Day 56) from start of neratinib dosing.

Investigational medicinal product name	neratinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Neratinib (240 mg; provided as six 40-mg tablets) will be self-administered orally by patients on a daily

basis, starting with Cycle 1/Day 1. Neratinib must be taken with food, preferably in the morning; however, neratinib may be taken in the evening. Neratinib will be given continuously for one year (364 days) in thirteen (13) 28-day cycles, with no rest between cycles.

Arm title	Budesonide

Arm description:

Patients enrolled in the Budesonide Arm (under Amendment 3) received mandatory high dose loperamide prophylaxis for two (2) cycles + budesonide for one (1) cycle + neratinib 240 mg/day for all thirteen (13) 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	neratinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Neratinib (240 mg; provided as six 40-mg tablets) will be self-administered orally by patients on a daily basis, starting with Cycle 1/Day 1. Neratinib must be taken with food, preferably in the morning; however, neratinib may be taken in the evening. Neratinib will be given continuously for one year (364 days) in thirteen (13) 28-day cycles, with no rest between cycles.

Investigational medicinal product name	loperamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For the first 14 days, loperamide 4 mg (2 tablets/capsules) will be self-administered orally by patients 3 times a day (total 12 mg a day). The initial dose of loperamide 4 mg will be self-administered orally with the first dose of neratinib.

After the first 14 days, loperamide 4 mg (2 tablets/capsules) will be self-administered orally twice a day (total 8 mg a day) through the first 2 cycles of therapy (Day 56) from start of neratinib dosing.

Investigational medicinal product name	budesonide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For patients enrolled under Amendment 3 and who participate in the initial cohort that will evaluate budesonide, patients will self-administer oral budesonide at a dose of 9 mg once daily with or without food, for the first treatment cycle (28 days), to be taken with neratinib and intensive loperamide prophylaxis.

Arm title	Colestipol

Arm description:

Patients enrolled in the Colestipol Arm (under amendment 4) received mandatory high dose loperamide prophylaxis + colestipol for one (1) cycle + neratinib 240 mg/day for all thirteen (13) 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	neratinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Neratinib (240 mg; provided as six 40-mg tablets) will be self-administered orally by patients on a daily

basis, starting with Cycle 1/Day 1. Neratinib must be taken with food, preferably in the morning; however, neratinib may be taken in the evening. Neratinib will be given continuously for one year (364 days) in thirteen (13) 28-day cycles, with no rest between cycles.

Investigational medicinal product name	loperamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For the first 14 days, the initial dose of loperamide 4 mg will be self-administered orally with the first dose of neratinib, followed by loperamide 4 mg (2 tablets/capsules) self-administered orally by patients 3 times a day (total 12 mg a day).

After the first 14 days, loperamide 4 mg (2 tablets/capsules) will be self-administered orally twice a day (total 8 mg a day), for 1 cycle [28 days], and then as needed (PRN) (not to exceed 16 mg per day).

Investigational medicinal product name	colestipol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For patients who participate in the evaluation of colestipol, patients will self-administer colestipol at a dose of 2 g twice daily for the first treatment cycle, to be taken at least 2 hours after, but at least 4 hours before, neratinib and intensive loperamide prophylaxis.

Arm title	Colestipol + Loperamide PRN

Arm description:

Patients enrolled in the Colestipol + Loperamide PRN Arm (under amendment 5) received loperamide as needed + colestipol for 1 cycle + neratinib 240 mg/day all 13 cycles.

Arm type	Experimental
Investigational medicinal product name	neratinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Neratinib (240 mg; provided as six 40-mg tablets) will be self-administered orally by patients on a daily basis, starting with Cycle 1/Day 1. Neratinib must be taken with food, preferably in the morning; however, neratinib may be taken in the evening. Neratinib will be given continuously for one year (364 days) in thirteen (13) 28-day cycles, with no rest between cycles.

Investigational medicinal product name	loperamide PRN
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Loperamide 4 mg (2 tablets/capsules) will be self-administered orally by patients on a PRN (as needed) basis, from the start of neratinib dosing with a goal of titrating to 1-2 bowel movements a day (not to exceed 16 mg per day).

Investigational medicinal product name	colestipol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

For patients who participate in the evaluation of colestipol, patients will self-administer colestipol at a dose of 2 g twice daily for the first treatment cycle, to be taken at least 2 hours after, but at least 4

hours before, neratinib and loperamide.

Arm title	Neratinib Dose Escalation

Arm description:

Patients enrolled in the Neratinib Dose Escalation Arm (under Amendments 6 and 6.1) received 120 mg neratinib daily for Week 1 (C1D1 – C1D7), followed by 160 mg neratinib daily for Week 2 (C1D8 – C1D14), followed by 240 mg neratinib daily starting at Week 3 and thereafter (C1D15 to EOT). Loperamide was administered on an as-needed basis only.

Arm type	Experimental
Investigational medicinal product name	loperamide PRN
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Loperamide 4 mg (2 tablets/capsules) will be self-administered orally by patients on a PRN (as needed) basis, from the start of neratinib dosing with a goal of titrating to 1-2 bowel movements a day (not to exceed 16 mg per day).

Investigational medicinal product name	neratinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients enrolled under Amendment 6 and Amendment 6.1 will receive neratinib at a starting dose of 120 mg/day with dose escalation (ie, total dose 120 mg daily for Week 1, 160 mg daily for the Week 2, and 240 mg daily for Week 3 and thereafter, until End of Treatment, up to 364 days).

Arm title	Neratinib Dose Escalation Scheme 2

Arm description:

Patients enrolled in the Neratinib Dose Escalation Scheme 2 Arm (under Amendments 7 and 7.1) received 160 mg neratinib daily for Weeks 1 and 2 (C1D1 – C1D14), followed by 200 mg neratinib daily for Weeks 3 and 4 (C1D15 – C1D28), followed by 240 mg neratinib daily starting at Week 5 and thereafter (C2D1 to EOT). Loperamide was administered on an as-needed basis only.

Arm type	Experimental
Investigational medicinal product name	loperamide PRN
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Loperamide 4 mg (2 tablets/capsules) will be self-administered orally by patients on a PRN (as needed) basis, from the start of neratinib dosing with a goal of titrating to 1-2 bowel movements a day (not to exceed 16 mg per day).

Investigational medicinal product name	neratinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients enrolled starting with Amendment 7 will receive neratinib 160 mg neratinib for the first 2 weeks (Cycle 1, Day 1 through – Cycle 1 Day 14), followed by 200 mg neratinib for the next 2 weeks (Cycle 1 Day 15 through Cycle 1 Day 28), followed by 240 mg neratinib thereafter (Cycle 2 Day 1 to End of

Treatment, up to 364 days). Daily dosing should continue until a criterion for treatment withdrawal is met.

Number of subjects in period 1	Loperamide	Budesonide	Colestipol
Started	137	64	136
Completed	76	52	97
Not completed	61	12	39
Consent withdrawn by subject	2	-	11
Physician decision	-	-	1
Adverse event, non-fatal	55	11	21
Disease relapse	1	1	1
Non-compliance with study drug	-	-	1
Other reasons	3	-	4
Lost to follow-up	-	-	-

Number of subjects in period 1	Colestipol + Loperamide PRN	Neratinib Dose Escalation	Neratinib Dose Escalation Scheme 2
Started	104	60	62
Completed	75	47	46
Not completed	29	13	16
Consent withdrawn by subject	7	5	4
Physician decision	1	-	1
Adverse event, non-fatal	19	5	8
Disease relapse	1	2	1
Non-compliance with study drug	-	-	-
Other reasons	1	-	2
Lost to follow-up	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Loperamide
Reporting group description:	
Patients in the Loperamide Arm were enrolled under the original protocol as well as patients enrolled under amendments 1 and 2. Patients enrolled under Original Protocol received mandatory low dose loperamide prophylaxis for 2 cycles + neratinib 240 mg/day for all thirteen (13) 28-day cycles. Patients enrolled under Amendment 1 or 2 received mandatory high dose loperamide prophylaxis for 2 cycles + neratinib 240 mg/day for all thirteen (13) 28-day cycles.	
Reporting group title	Budesonide
Reporting group description:	
Patients enrolled in the Budesonide Arm (under Amendment 3) received mandatory high dose loperamide prophylaxis for two (2) cycles + budesonide for one (1) cycle + neratinib 240 mg/day for all thirteen (13) 28-day cycles.	
Reporting group title	Colestipol
Reporting group description:	
Patients enrolled in the Colestipol Arm (under amendment 4) received mandatory high dose loperamide prophylaxis + colestipol for one (1) cycle + neratinib 240 mg/day for all thirteen (13) 28-day cycles.	
Reporting group title	Colestipol + Loperamide PRN
Reporting group description:	
Patients enrolled in the Colestipol + Loperamide PRN Arm (under amendment 5) received loperamide as needed + colestipol for 1 cycle + neratinib 240 mg/day all 13 cycles.	
Reporting group title	Neratinib Dose Escalation
Reporting group description:	
Patients enrolled in the Neratinib Dose Escalation Arm (under Amendments 6 and 6.1) received 120 mg neratinib daily for Week 1 (C1D1 – C1D7), followed by 160 mg neratinib daily for Week 2 (C1D8 – C1D14), followed by 240 mg neratinib daily starting at Week 3 and thereafter (C1D15 to EOT). Loperamide was administered on an as-needed basis only.	
Reporting group title	Neratinib Dose Escalation Scheme 2
Reporting group description:	
Patients enrolled in the Neratinib Dose Escalation Scheme 2 Arm (under Amendments 7 and 7.1) received 160 mg neratinib daily for Weeks 1 and 2 (C1D1 – C1D14), followed by 200 mg neratinib daily for Weeks 3 and 4 (C1D15 – C1D28), followed by 240 mg neratinib daily starting at Week 5 and thereafter (C2D1 to EOT). Loperamide was administered on an as-needed basis only.	

Reporting group values	Loperamide	Budesonide	Colestipol
Number of subjects	137	64	136
Age categorical Units: Subjects			
Adults (18-64 years)	116	58	117
65 years and older	21	6	19
Age continuous Units: years			
arithmetic mean	53.4	49.1	52.5
standard deviation	± 11.1	± 10.6	± 11.1
Gender categorical Units: Subjects			
Female	137	64	133
Male	0	0	3

Reporting group values	Colestipol + Loperamide PRN	Neratinib Dose Escalation	Neratinib Dose Escalation Scheme 2
Number of subjects	104	60	62
Age categorical Units: Subjects			
Adults (18-64 years)	93	51	52
65 years and older	11	9	10
Age continuous Units: years			
arithmetic mean	52.0	51.9	53.8
standard deviation	± 10.2	± 10.7	± 10.2
Gender categorical Units: Subjects			
Female	104	60	62
Male	0	0	0

Reporting group values	Total		
Number of subjects	563		
Age categorical Units: Subjects			
Adults (18-64 years)	487		
65 years and older	76		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	560		
Male	3		

End points

End points reporting groups

Reporting group title	Loperamide

Reporting group description:

Patients in the Loperamide Arm were enrolled under the original protocol as well as patients enrolled under amendments 1 and 2.

Patients enrolled under Original Protocol received mandatory low dose loperamide prophylaxis for 2 cycles + neratinib 240 mg/day for all thirteen (13) 28-day cycles.

Patients enrolled under Amendment 1 or 2 received mandatory high dose loperamide prophylaxis for 2 cycles + neratinib 240 mg/day for all thirteen (13) 28-day cycles.

Reporting group title	Budesonide

Reporting group description:

Patients enrolled in the Budesonide Arm (under Amendment 3) received mandatory high dose loperamide prophylaxis for two (2) cycles + budesonide for one (1) cycle + neratinib 240 mg/day for all thirteen (13) 28-day cycles.

Reporting group title	Colestipol

Reporting group description:

Patients enrolled in the Colestipol Arm (under amendment 4) received mandatory high dose loperamide prophylaxis + colestipol for one (1) cycle + neratinib 240 mg/day for all thirteen (13) 28-day cycles.

Reporting group title	Colestipol + Loperamide PRN

Reporting group description:

Patients enrolled in the Colestipol + Loperamide PRN Arm (under amendment 5) received loperamide as needed + colestipol for 1 cycle + neratinib 240 mg/day all 13 cycles.

Reporting group title	Neratinib Dose Escalation

Reporting group description:

Patients enrolled in the Neratinib Dose Escalation Arm (under Amendments 6 and 6.1) received 120 mg neratinib daily for Week 1 (C1D1 – C1D7), followed by 160 mg neratinib daily for Week 2 (C1D8 – C1D14), followed by 240 mg neratinib daily starting at Week 3 and thereafter (C1D15 to EOT). Loperamide was administered on an as-needed basis only.

Reporting group title	Neratinib Dose Escalation Scheme 2

Reporting group description:

Patients enrolled in the Neratinib Dose Escalation Scheme 2 Arm (under Amendments 7 and 7.1) received 160 mg neratinib daily for Weeks 1 and 2 (C1D1 – C1D14), followed by 200 mg neratinib daily for Weeks 3 and 4 (C1D15 – C1D28), followed by 240 mg neratinib daily starting at Week 5 and thereafter (C2D1 to EOT). Loperamide was administered on an as-needed basis only.

Primary: Percentage of Patients with Grade 3 or Higher Diarrhoea

End point title	Percentage of Patients with Grade 3 or Higher Diarrhoea[1]

End point description:

The primary objective of this study is to characterize the percentage of patients with Grade 3 or higher diarrhoea in patients with early-stage HER2 overexpressed/amplified (HER2+) breast cancer treated with neratinib when administered with intensive loperamide prophylaxis, after prior treatment with trastuzumab. Grade 3: Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL. Grade 4: Life-threatening consequences; urgent intervention indicated. Grade 5: Death.

End point type	Primary

End point timeframe:

From first dose through 28 days after last dose, up to 15.5 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: No formal comparisons between treatment groups were specified by the protocol.

Descriptive statistics only are provided.

End point values	Loperamide	Budesonide	Colestipol	Colestipol + Loperamide PRN
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	137	64	136	104
Units: percentage of patients				
number (confidence interval 95%)	30.7 (23.1 to 39.1)	28.1 (17.6 to 40.8)	20.6 (14.1 to 28.4)	32.7 (23.8 to 42.6)

End point values	Neratinib Dose Escalation	Neratinib Dose Escalation Scheme 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	62		
Units: percentage of patients				
number (confidence interval 95%)	13.3 (5.9 to 24.6)	27.4 (16.9 to 40.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients With Diarrhoea by Grade, According to the National Cancer Institute Common Terminology Criteria (NCI CTCAE), Version 4.0.

End point title	Percentage of Patients With Diarrhoea by Grade, According to the National Cancer Institute Common Terminology Criteria (NCI CTCAE), Version 4.0.

End point description:

Assess the percentage of patients with diarrhoea after the administration of an anti-inflammatory agent, a bile acid sequestrant, or following two different dose-escalation regimens of neratinib, by maximum CTC grade. Grade 1: an increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline. Grade 2: Increase of 4 -6 stools per day over baseline; moderate increase in ostomy output compared to baseline. Grade 3: Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL. Grade 4: Life-threatening consequences; urgent intervention indicated. Grade 5: Death.

End point type	Secondary

End point timeframe:

From first dose through 28 days after last dose, up to 15.5 months.

End point values	Loperamide	Budesonide	Colestipol	Colestipol + Loperamide PRN
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	137	64	136	104
Units: percentage of patients				
number (not applicable)				
Grade 1	24.1	23.4	27.9	32.7
Grade 2	24.8	34.4	34.6	29.8
Grade 3	30.7	28.1	20.6	32.7

End point values	Neratinib Dose Escalation	Neratinib Dose Escalation Scheme 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	62		
Units: percentage of patients				
number (not applicable)				
Grade 1	40.0	37.1		
Grade 2	45.0	33.9		
Grade 3	13.3	27.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients With Serious Adverse Events and Other Adverse Events of Special Interest

End point title	Percentage of Patients With Serious Adverse Events and Other Adverse Events of Special Interest

End point description:

Assess the percentage of patients with serious adverse events (SAEs) and other adverse events of special interest (AESI). AESIs were selected based on the known safety profile of neratinib as well as typical key body system toxicity concerns generally reviewed for any new drug. These AESIs were grouped into the following categories: gastrointestinal toxicity (diarrhea and stomatitis), hepatotoxicity, pulmonary toxicity (interstitial lung disease), cardiac toxicity (LVEF decreased), and dermatologic toxicity (rash and nail disorders). The AESIs were analyzed by searching the clinical database for all TEAEs and SAEs using either Standardized MedDRA Queries(SMQs) or, if an applicable SMQ did not exist, a Sponsor-defined list of MedDRA Preferred Terms.

End point type	Secondary

End point timeframe:

From first dose of investigational product through 28 days after last dose, up to 15.5 months.

End point values	Loperamide	Budesonide	Colestipol	Colestipol + Loperamide PRN
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	137	64	136	104
Units: percentage of patients				
number (not applicable)				
% of patients with SAEs	6.57	6.25	6.62	2.88
% of patients with GI toxicities (broad)	81.75	87.5	83.82	96.15
% of patients with hepatotoxicities (broad)	12.41	7.81	4.41	4.81
% of patients with ILD (broad)	0	0	0	0
% of patients with cardiac toxicities (broad)	5.84	6.25	10.29	7.69
% of patients with dermatologic toxicities	12.41	37.5	23.53	18.27
% of patients with GI toxicities (narrow)	80.29	85.94	83.09	95.19
% of patients with hepatotoxicities (narrow)	10.95	7.81	3.68	3.85
% of patients with ILD (narrow)	0	0	0	0
% of patients with cardiac toxicites (narrow)	2.92	0	1.47	0.96

End point values	Neratinib Dose Escalation	Neratinib Dose Escalation Scheme 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	62		
Units: percentage of patients				
number (not applicable)				
% of patients with SAEs	8.33	8.06		
% of patients with GI toxicities (broad)	98.33	98.39		
% of patients with hepatotoxicities (broad)	8.33	4.84		
% of patients with ILD (broad)	0	0		
% of patients with cardiac toxicities (broad)	10.00	4.84		
% of patients with dermatologic toxicities	11.67	30.65		
% of patients with GI toxicities (narrow)	98.33	98.39		
% of patients with hepatotoxicities (narrow)	8.33	4.84		
% of patients with ILD (narrow)	0	0		
% of patients with cardiac toxicites (narrow)	1.67	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 1st dose through 28 days after last dose up to 15.5 months	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0
Reporting groups	
Reporting group title	Loperamide
Reporting group description: Loperamide	
Reporting group title	Budesonide
Reporting group description: Budesonide	
Reporting group title	Colestipol
Reporting group description: Colestipol	
Reporting group title	Colestipol+Loperamide PRN
Reporting group description: Colestipol+Loperamide PRN	
Reporting group title	Neratinib Dose Escalation
Reporting group description: Neratinib Dose Escalation	
Reporting group title	Neratinib Dose Escalation Scheme 2
Reporting group description: Neratinib Dose Escalation Scheme 2	

Serious adverse events	Loperamide	Budesonide	Colestipol
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 137 (6.57%)	4 / 64 (6.25%)	9 / 136 (6.62%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma in situ			
subjects affected / exposed	0 / 137 (0.00%)	0 / 64 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fat necrosis			

subjects affected / exposed	0 / 137 (0.00%)	0 / 64 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 137 (0.00%)	1 / 64 (1.56%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 137 (0.00%)	0 / 64 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 137 (0.00%)	0 / 64 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 137 (0.73%)	0 / 64 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 137 (0.00%)	0 / 64 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 137 (0.73%)	0 / 64 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Rib fracture			

subjects affected / exposed	0 / 137 (0.00%)	1 / 64 (1.56%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 137 (0.73%)	0 / 64 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 137 (0.00%)	0 / 64 (0.00%)	2 / 136 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 137 (0.00%)	0 / 64 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 137 (0.00%)	0 / 64 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 137 (0.00%)	0 / 64 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 137 (0.73%)	0 / 64 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 137 (1.46%)	0 / 64 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pancreatitis			
subjects affected / exposed	0 / 137 (0.00%)	0 / 64 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	1 / 137 (0.73%)	0 / 64 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 137 (0.00%)	0 / 64 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 137 (0.00%)	0 / 64 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 137 (0.00%)	1 / 64 (1.56%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 137 (0.00%)	1 / 64 (1.56%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash erythematous			
subjects affected / exposed	1 / 137 (0.73%)	0 / 64 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			

subjects affected / exposed	0 / 137 (0.00%)	0 / 64 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cellulitis			
subjects affected / exposed	0 / 137 (0.00%)	1 / 64 (1.56%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 137 (0.00%)	0 / 64 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 137 (0.73%)	0 / 64 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 137 (0.00%)	0 / 64 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 137 (0.73%)	0 / 64 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 137 (0.00%)	0 / 64 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 137 (0.00%)	0 / 64 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Listeriosis			

subjects affected / exposed	0 / 137 (0.00%)	0 / 64 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 137 (0.00%)	0 / 64 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	1 / 137 (0.73%)	0 / 64 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 137 (0.73%)	0 / 64 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 137 (0.73%)	0 / 64 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 137 (0.73%)	0 / 64 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 137 (0.00%)	0 / 64 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 137 (0.73%)	0 / 64 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			

subjects affected / exposed	1 / 137 (0.73%)	0 / 64 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 137 (0.73%)	0 / 64 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Colestipol+Loperamide PRN	Neratinib Dose Escalation	Neratinib Dose Escalation Scheme 2
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 104 (2.88%)	5 / 60 (8.33%)	5 / 62 (8.06%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma in situ			
subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fat necrosis			
subjects affected / exposed	0 / 104 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 104 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			

subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 104 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 104 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 104 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			

subjects affected / exposed	0 / 104 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			

subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash erythematous			
subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cellulitis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 104 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			

subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Listeriosis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 104 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			

subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 104 (0.96%)	1 / 60 (1.67%)	0 / 62 (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
Hypokalaemia			
subjects affected / exposed	0 / 104 (0.00%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Loperamide	Budesonide	Colestipol
Total subjects affected by non-serious adverse events			
subjects affected / exposed	137 / 137 (100.00%)	64 / 64 (100.00%)	136 / 136 (100.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	8 / 137 (5.84%)	6 / 64 (9.38%)	17 / 136 (12.50%)
occurrences (all)	8	7	17

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 137 (4.38%)	1 / 64 (1.56%)	1 / 136 (0.74%)
occurrences (all)	6	1	1
Fatigue			
subjects affected / exposed	73 / 137 (53.28%)	34 / 64 (53.13%)	65 / 136 (47.79%)
occurrences (all)	92	53	85
Pyrexia			
subjects affected / exposed	6 / 137 (4.38%)	2 / 64 (3.13%)	10 / 136 (7.35%)
occurrences (all)	6	4	11
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	4 / 137 (2.92%)	7 / 64 (10.94%)	8 / 136 (5.88%)
occurrences (all)	4	7	9
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 137 (5.11%)	7 / 64 (10.94%)	9 / 136 (6.62%)
occurrences (all)	8	9	9
Dyspnoea			
subjects affected / exposed	9 / 137 (6.57%)	4 / 64 (6.25%)	4 / 136 (2.94%)
occurrences (all)	10	4	5
Epistaxis			
subjects affected / exposed	2 / 137 (1.46%)	2 / 64 (3.13%)	9 / 136 (6.62%)
occurrences (all)	2	4	10
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 137 (4.38%)	8 / 64 (12.50%)	10 / 136 (7.35%)
occurrences (all)	6	9	10
Anxiety			
subjects affected / exposed	5 / 137 (3.65%)	4 / 64 (6.25%)	3 / 136 (2.21%)
occurrences (all)	5	4	4
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	9 / 137 (6.57%)	4 / 64 (6.25%)	4 / 136 (2.94%)
occurrences (all)	12	6	4
Aspartate aminotransferase increased			

subjects affected / exposed	4 / 137 (2.92%)	1 / 64 (1.56%)	3 / 136 (2.21%)
occurrences (all)	7	1	3
Weight decreased			
subjects affected / exposed	10 / 137 (7.30%)	4 / 64 (6.25%)	11 / 136 (8.09%)
occurrences (all)	13	5	11
Blood glucose increased			
subjects affected / exposed	0 / 137 (0.00%)	0 / 64 (0.00%)	0 / 136 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	19 / 137 (13.87%)	6 / 64 (9.38%)	21 / 136 (15.44%)
occurrences (all)	21	8	26
Headache			
subjects affected / exposed	26 / 137 (18.98%)	12 / 64 (18.75%)	20 / 136 (14.71%)
occurrences (all)	31	18	40
Neuropathy peripheral			
subjects affected / exposed	4 / 137 (2.92%)	3 / 64 (4.69%)	3 / 136 (2.21%)
occurrences (all)	4	4	3
Paraesthesia			
subjects affected / exposed	3 / 137 (2.19%)	1 / 64 (1.56%)	3 / 136 (2.21%)
occurrences (all)	4	1	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 137 (5.84%)	5 / 64 (7.81%)	1 / 136 (0.74%)
occurrences (all)	9	5	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 137 (0.00%)	4 / 64 (6.25%)	3 / 136 (2.21%)
occurrences (all)	0	5	3
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	7 / 137 (5.11%)	2 / 64 (3.13%)	7 / 136 (5.15%)
occurrences (all)	7	2	8
Abdominal distension			
subjects affected / exposed	21 / 137 (15.33%)	5 / 64 (7.81%)	22 / 136 (16.18%)
occurrences (all)	27	7	28
Abdominal pain			

subjects affected / exposed	36 / 137 (26.28%)	12 / 64 (18.75%)	26 / 136 (19.12%)
occurrences (all)	55	21	36
Constipation			
subjects affected / exposed	78 / 137 (56.93%)	48 / 64 (75.00%)	93 / 136 (68.38%)
occurrences (all)	180	391	773
Abdominal pain upper			
subjects affected / exposed	5 / 137 (3.65%)	7 / 64 (10.94%)	16 / 136 (11.76%)
occurrences (all)	5	8	20
Dry mouth			
subjects affected / exposed	18 / 137 (13.14%)	6 / 64 (9.38%)	12 / 136 (8.82%)
occurrences (all)	23	6	14
Diarrhoea			
subjects affected / exposed	109 / 137 (79.56%)	55 / 64 (85.94%)	113 / 136 (83.09%)
occurrences (all)	802	1159	2174
Dyspepsia			
subjects affected / exposed	12 / 137 (8.76%)	10 / 64 (15.63%)	16 / 136 (11.76%)
occurrences (all)	17	12	20
Flatulence			
subjects affected / exposed	5 / 137 (3.65%)	6 / 64 (9.38%)	5 / 136 (3.68%)
occurrences (all)	5	8	5
Nausea			
subjects affected / exposed	78 / 137 (56.93%)	32 / 64 (50.00%)	83 / 136 (61.03%)
occurrences (all)	115	52	130
Gastrooesophageal reflux disease			
subjects affected / exposed	10 / 137 (7.30%)	5 / 64 (7.81%)	10 / 136 (7.35%)
occurrences (all)	11	7	12
Stomatitis			
subjects affected / exposed	7 / 137 (5.11%)	4 / 64 (6.25%)	14 / 136 (10.29%)
occurrences (all)	9	13	15
Vomiting			
subjects affected / exposed	36 / 137 (26.28%)	16 / 64 (25.00%)	43 / 136 (31.62%)
occurrences (all)	47	21	55
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	2 / 137 (1.46%)	4 / 64 (6.25%)	5 / 136 (3.68%)
occurrences (all)	3	4	5

Dry skin			
subjects affected / exposed	6 / 137 (4.38%)	8 / 64 (12.50%)	7 / 136 (5.15%)
occurrences (all)	6	8	7
Onychoclasis			
subjects affected / exposed	5 / 137 (3.65%)	3 / 64 (4.69%)	6 / 136 (4.41%)
occurrences (all)	5	3	6
Rash			
subjects affected / exposed	7 / 137 (5.11%)	12 / 64 (18.75%)	15 / 136 (11.03%)
occurrences (all)	9	28	20
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 137 (7.30%)	14 / 64 (21.88%)	15 / 136 (11.03%)
occurrences (all)	11	17	18
Back pain			
subjects affected / exposed	10 / 137 (7.30%)	5 / 64 (7.81%)	9 / 136 (6.62%)
occurrences (all)	11	5	10
Muscle spasms			
subjects affected / exposed	15 / 137 (10.95%)	8 / 64 (12.50%)	14 / 136 (10.29%)
occurrences (all)	18	10	17
Myalgia			
subjects affected / exposed	3 / 137 (2.19%)	4 / 64 (6.25%)	6 / 136 (4.41%)
occurrences (all)	3	4	7
Pain in extremity			
subjects affected / exposed	7 / 137 (5.11%)	3 / 64 (4.69%)	7 / 136 (5.15%)
occurrences (all)	9	3	7
Infections and infestations			
Influenza			
subjects affected / exposed	2 / 137 (1.46%)	0 / 64 (0.00%)	3 / 136 (2.21%)
occurrences (all)	2	0	3
Cellulitis			
subjects affected / exposed	3 / 137 (2.19%)	1 / 64 (1.56%)	0 / 136 (0.00%)
occurrences (all)	3	1	0
Nasopharyngitis			
subjects affected / exposed	5 / 137 (3.65%)	4 / 64 (6.25%)	2 / 136 (1.47%)
occurrences (all)	6	5	2
Urinary tract infection			

subjects affected / exposed	10 / 137 (7.30%)	2 / 64 (3.13%)	8 / 136 (5.88%)
occurrences (all)	10	2	9
Upper respiratory tract infection			
subjects affected / exposed	5 / 137 (3.65%)	7 / 64 (10.94%)	7 / 136 (5.15%)
occurrences (all)	6	9	7
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	26 / 137 (18.98%)	11 / 64 (17.19%)	24 / 136 (17.65%)
occurrences (all)	26	11	29
Hypokalaemia			
subjects affected / exposed	4 / 137 (2.92%)	1 / 64 (1.56%)	8 / 136 (5.88%)
occurrences (all)	5	1	9
Dehydration			
subjects affected / exposed	7 / 137 (5.11%)	6 / 64 (9.38%)	5 / 136 (3.68%)
occurrences (all)	9	7	6

Non-serious adverse events	Colestipol+Loperamide PRN	Neratinib Dose Escalation	Neratinib Dose Escalation Scheme 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	104 / 104 (100.00%)	60 / 60 (100.00%)	62 / 62 (100.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	7 / 104 (6.73%)	7 / 60 (11.67%)	4 / 62 (6.45%)
occurrences (all)	7	7	6
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 104 (3.85%)	3 / 60 (5.00%)	2 / 62 (3.23%)
occurrences (all)	4	5	2
Fatigue			
subjects affected / exposed	41 / 104 (39.42%)	28 / 60 (46.67%)	19 / 62 (30.65%)
occurrences (all)	62	35	30
Pyrexia			
subjects affected / exposed	3 / 104 (2.88%)	2 / 60 (3.33%)	1 / 62 (1.61%)
occurrences (all)	4	2	1
Reproductive system and breast disorders			

Breast pain			
subjects affected / exposed	6 / 104 (5.77%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences (all)	6	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 104 (7.69%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences (all)	10	1	0
Dyspnoea			
subjects affected / exposed	4 / 104 (3.85%)	3 / 60 (5.00%)	1 / 62 (1.61%)
occurrences (all)	4	3	1
Epistaxis			
subjects affected / exposed	4 / 104 (3.85%)	3 / 60 (5.00%)	4 / 62 (6.45%)
occurrences (all)	5	3	4
Psychiatric disorders			
Insomnia			
subjects affected / exposed	8 / 104 (7.69%)	3 / 60 (5.00%)	4 / 62 (6.45%)
occurrences (all)	8	3	4
Anxiety			
subjects affected / exposed	3 / 104 (2.88%)	3 / 60 (5.00%)	2 / 62 (3.23%)
occurrences (all)	3	3	2
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 104 (2.88%)	4 / 60 (6.67%)	2 / 62 (3.23%)
occurrences (all)	3	5	3
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 104 (1.92%)	3 / 60 (5.00%)	2 / 62 (3.23%)
occurrences (all)	6	3	3
Weight decreased			
subjects affected / exposed	4 / 104 (3.85%)	1 / 60 (1.67%)	3 / 62 (4.84%)
occurrences (all)	4	1	3
Blood glucose increased			
subjects affected / exposed	0 / 104 (0.00%)	3 / 60 (5.00%)	0 / 62 (0.00%)
occurrences (all)	0	5	0
Nervous system disorders			
Dizziness			

subjects affected / exposed	20 / 104 (19.23%)	9 / 60 (15.00%)	8 / 62 (12.90%)
occurrences (all)	24	10	9
Headache			
subjects affected / exposed	24 / 104 (23.08%)	13 / 60 (21.67%)	8 / 62 (12.90%)
occurrences (all)	27	15	10
Neuropathy peripheral			
subjects affected / exposed	6 / 104 (5.77%)	0 / 60 (0.00%)	1 / 62 (1.61%)
occurrences (all)	7	0	1
Paraesthesia			
subjects affected / exposed	0 / 104 (0.00%)	5 / 60 (8.33%)	0 / 62 (0.00%)
occurrences (all)	0	5	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 104 (4.81%)	0 / 60 (0.00%)	0 / 62 (0.00%)
occurrences (all)	7	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 104 (0.00%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	5 / 104 (4.81%)	2 / 60 (3.33%)	0 / 62 (0.00%)
occurrences (all)	6	2	0
Abdominal distension			
subjects affected / exposed	15 / 104 (14.42%)	6 / 60 (10.00%)	10 / 62 (16.13%)
occurrences (all)	16	7	10
Abdominal pain			
subjects affected / exposed	27 / 104 (25.96%)	13 / 60 (21.67%)	15 / 62 (24.19%)
occurrences (all)	31	16	24
Constipation			
subjects affected / exposed	39 / 104 (37.50%)	22 / 60 (36.67%)	15 / 62 (24.19%)
occurrences (all)	392	271	126
Abdominal pain upper			
subjects affected / exposed	7 / 104 (6.73%)	3 / 60 (5.00%)	8 / 62 (12.90%)
occurrences (all)	8	3	9
Dry mouth			

subjects affected / exposed	5 / 104 (4.81%)	4 / 60 (6.67%)	3 / 62 (4.84%)
occurrences (all)	5	4	3
Diarrhoea			
subjects affected / exposed	99 / 104 (95.19%)	59 / 60 (98.33%)	61 / 62 (98.39%)
occurrences (all)	2843	1640	1821
Dyspepsia			
subjects affected / exposed	13 / 104 (12.50%)	7 / 60 (11.67%)	6 / 62 (9.68%)
occurrences (all)	16	16	6
Flatulence			
subjects affected / exposed	2 / 104 (1.92%)	1 / 60 (1.67%)	3 / 62 (4.84%)
occurrences (all)	2	1	4
Nausea			
subjects affected / exposed	64 / 104 (61.54%)	27 / 60 (45.00%)	28 / 62 (45.16%)
occurrences (all)	103	48	40
Gastrooesophageal reflux disease			
subjects affected / exposed	6 / 104 (5.77%)	2 / 60 (3.33%)	4 / 62 (6.45%)
occurrences (all)	6	2	4
Stomatitis			
subjects affected / exposed	13 / 104 (12.50%)	6 / 60 (10.00%)	6 / 62 (9.68%)
occurrences (all)	27	6	7
Vomiting			
subjects affected / exposed	25 / 104 (24.04%)	9 / 60 (15.00%)	5 / 62 (8.06%)
occurrences (all)	43	10	6
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	1 / 104 (0.96%)	1 / 60 (1.67%)	4 / 62 (6.45%)
occurrences (all)	1	1	5
Dry skin			
subjects affected / exposed	10 / 104 (9.62%)	4 / 60 (6.67%)	9 / 62 (14.52%)
occurrences (all)	10	4	9
Onychoclasis			
subjects affected / exposed	4 / 104 (3.85%)	3 / 60 (5.00%)	6 / 62 (9.68%)
occurrences (all)	4	3	6
Rash			
subjects affected / exposed	10 / 104 (9.62%)	1 / 60 (1.67%)	8 / 62 (12.90%)
occurrences (all)	16	2	11

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	13 / 104 (12.50%)	9 / 60 (15.00%)	4 / 62 (6.45%)
occurrences (all)	15	12	4
Back pain			
subjects affected / exposed	10 / 104 (9.62%)	4 / 60 (6.67%)	2 / 62 (3.23%)
occurrences (all)	11	5	2
Muscle spasms			
subjects affected / exposed	15 / 104 (14.42%)	12 / 60 (20.00%)	8 / 62 (12.90%)
occurrences (all)	17	17	9
Myalgia			
subjects affected / exposed	5 / 104 (4.81%)	2 / 60 (3.33%)	3 / 62 (4.84%)
occurrences (all)	6	2	4
Pain in extremity			
subjects affected / exposed	5 / 104 (4.81%)	2 / 60 (3.33%)	3 / 62 (4.84%)
occurrences (all)	6	2	3
Infections and infestations			
Influenza			
subjects affected / exposed	4 / 104 (3.85%)	3 / 60 (5.00%)	0 / 62 (0.00%)
occurrences (all)	4	3	0
Cellulitis			
subjects affected / exposed	2 / 104 (1.92%)	3 / 60 (5.00%)	0 / 62 (0.00%)
occurrences (all)	3	3	0
Nasopharyngitis			
subjects affected / exposed	3 / 104 (2.88%)	1 / 60 (1.67%)	1 / 62 (1.61%)
occurrences (all)	3	1	1
Urinary tract infection			
subjects affected / exposed	9 / 104 (8.65%)	6 / 60 (10.00%)	5 / 62 (8.06%)
occurrences (all)	12	9	6
Upper respiratory tract infection			
subjects affected / exposed	5 / 104 (4.81%)	6 / 60 (10.00%)	2 / 62 (3.23%)
occurrences (all)	5	6	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	26 / 104 (25.00%)	8 / 60 (13.33%)	8 / 62 (12.90%)
occurrences (all)	30	9	8

Hypokalaemia			
subjects affected / exposed	2 / 104 (1.92%)	1 / 60 (1.67%)	0 / 62 (0.00%)
occurrences (all)	2	1	0
Dehydration			
subjects affected / exposed	4 / 104 (3.85%)	2 / 60 (3.33%)	2 / 62 (3.23%)
occurrences (all)	4	3	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 May 2015	Amendment 1 changed the loperamide dosing schedule to regular daytime intervals of three times a day, with the intent of improving patient compliance.
06 November 2015	Amendment 2 added patient reported outcomes to the data collection performed. The number of assessments of left ventricular ejection fraction (LVEF) with ECHO or MUGA evaluations was also decreased from 6 to 2 (Screening Visit and End of Treatment Visit), based on echocardiogram results from study 3144A2-3004-WW, A Randomized, Double-Blind, Placebo-Controlled Trial of Neratinib (HKI-272) after Trastuzumab in Women with Early-Stage HER-2/neu Overexpressed/Amplified Breast Cancer, showing no LVEF change from baseline to Month 12. Patients enrolled under the Original Protocol, Amendment 1, and Amendment 2 comprised the Loperamide (L) cohort.
24 March 2016	Amendment 3 added anti-inflammatory treatment to neratinib and loperamide prophylaxis. Budesonide XR 9 mg tablets administered once daily for 1 cycle was added to the 2 cycles of loperamide prophylaxis during neratinib therapy. Two additional anti-inflammatory medication cohorts, mesalamine and bismuth subsalicylate, were also added by Amendment 3, but these cohorts were subsequently terminated in Amendment 5 without enrollment (new information was reviewed by the Sponsor, in addition to the availability of results from recent sets of preclinical data which were discussed with external expert consultants, which indicated that the bile acid sequestrant colestipol would be more effective in mitigating diarrhea than either bismuth subsalicylate or mesalamine). Patients enrolled under Amendment 3 comprised the Budesonide+Loperamide (BL) cohort.
19 August 2016	Amendment 4 added colestipol (a bile acid sequestrant), using a regimen of two 1 g tablets administered twice daily to neratinib and intensive loperamide prophylaxis for 1 cycle based on the results of preclinical rat model studies, which suggested the possible implication of bile acid malabsorption. Patients enrolled under Amendment 4 comprised the Colestipol+Loperamide (CL) cohort.
19 September 2017	Amendment 5 used the same colestipol treatment regimen as Amendment 4, but loperamide was to be taken on a PRN basis only. Patients enrolled under Amendment 5 comprised the Colestipol+Loperamide PRN (CL-PRN) cohort.
26 October 2017	Amendment 6 introduced a design to evaluate the effects of a more gradual neratinib titration regimen (ie, 120 mg daily from C1D1-C1D7, to 160 mg daily from C1D8-C1D14, then 240 mg daily on C1D15 thereafter) on the incidence of severe diarrhea. Amendment 6.1 (30-APR-2018) added another patient reported outcome to the data collection. Patients enrolled under Amendment 6 and 6.1 comprised the Dose Escalation (DE) cohort.
08 October 2018	Amendment 7 was designed to investigate the effect of a second dose escalation scheme on the incidence and severity of diarrhea. Patients in this cohort were started at 160 mg daily neratinib for the first 2 weeks of treatment followed by 200 mg daily neratinib for the subsequent 2 weeks of dosing, then reaching the full 240 mg daily dose of neratinib from Cycle 2 onwards. An inclusion criteria requirement was also added by this amendment to require documented hormone receptor (HR)-positive disease, defined as estrogen receptor (ER) positive and/or progesterone receptor (PR) positive disease; however, this requirement was later removed for North America and Australia in regional Amendment 7.1 (25-JUL-2019). Patients enrolled under Amendment 7 and 7.1 comprised the Dose Escalation 2 (DE2) cohort.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
23 March 2020	The study indefinitely paused screening and enrollment of new patients on 23-Mar-2020 in response to the global COVID-19 pandemic. In September 2020, enrollment was formally closed due to the study having achieved its scientific objective. There were sufficient data to analyze the primary endpoint of the study and other key variables. All remaining active ongoing patients continued to receive per protocol treatment and care according to study protocol, and relevant country and/or institutional COVID-19 pandemic guidelines.	-

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32464281