



## Clinical trial results:

### A randomised phase II trial of imatinib alternating with regorafenib compared to imatinib alone for the first line treatment of advanced gastrointestinal stromal tumour (GIST)

#### Summary

EudraCT number	2015-001298-42
Trial protocol	SK ES NO FI GB NL FR DK IT
Global end of trial date	08 May 2024

#### Results information

Result version number	v1 (current)
This version publication date	01 August 2025
First version publication date	01 August 2025

#### Trial information

##### Trial identification

Sponsor protocol code	1321
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02365441
WHO universal trial number (UTN)	-
Other trial identifiers	NHMRC CTC Protocol number: CTC 0122/AGITG AG1013GST, SSG: ALT-GIST/SSG XXIII

Notes:

#### Sponsors

Sponsor organisation name	EORTC
Sponsor organisation address	Avenue E. Mounier 83, Bruxelles, Belgium,
Public contact	Head of Clinical Operations, EORTC, +32 27741035, regulatory@eortc.be
Scientific contact	Head of Clinical Operations, EORTC, +32 27741035, regulatory@eortc.be

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	28 July 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2020
Global end of trial reached?	Yes
Global end of trial date	08 May 2024
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To determine if an alternating regimen of imatinib and regorafenib has sufficient activity and safety to warrant further evaluation as a first line treatment for metastatic GIST.

Protection of trial subjects:

The study investigator ensured that the study was conducted in agreement with the Declaration of Helsinki and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The study was conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice, and the study protocol was approved by the competent authorities and ethics committee(s) as required by the applicable national legislation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2015
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	United Kingdom: 4
Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Norway: 9
Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Italy: 3
Worldwide total number of subjects	78
EEA total number of subjects	53

Notes:

<b>Subjects enrolled per age group</b>	
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)	45
From 65 to 84 years	33
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study originally aimed to recruit 240 patients. However, due to resource and study constraints, the design was amended to target a sample size of 76 patients. Between June 2015 and September 2018, a total of 76 eligible patients were recruited from 11 countries, including 8 in Europe.

### Pre-assignment

Screening details:

Adults (over 18 years) with histologically confirmed, measurable metastatic GIST, who have received no prior treatment for metastatic disease. Patients who were taking, and did not have longer than 21 days of continuous treatment immediately prior to randomisation with 400mg daily of imatinib were eligible to participate in this study.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Imatinib

Arm description:

Imatinib 400mg daily ongoing until progression.

Arm type	Standard of Care
Investigational medicinal product name	Imatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

400mg orally daily as standard of care

<b>Arm title</b>	Alternating
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Arm description:

Imatinib 400mg for 21 to 25 days with a 37 day washout period followed by Regorafenib 160mg for 21 days followed by a 7 day washout period.

Ongoing treatment until progression.

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

Dosage and administration details:

400mg orally daily as standard of care

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

Dosage and administration details:

Imatinib 400mg for 21 to 25 days with a 37 day washout period followed by Regorafenib 160mg for

21 days followed by a 7 day washout period.

<b>Number of subjects in period 1<sup>[1]</sup></b>	Imatinib	Alternating
Started	36	40
Completed	10	9
Not completed	26	31
Treatment discontinuation	26	31

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Some randomized patients did not start the study treatment

## Baseline characteristics

### Reporting groups

Reporting group title	Imatinib
Reporting group description: Imatinib 400mg daily ongoing until progression.	
Reporting group title	Alternating
Reporting group description: Imatinib 400mg for 21 to 25 days with a 37 day washout period followed by Regorafenib 160mg for 21 days followed by a 7 day washout period. Ongoing treatment until progression.	

Reporting group values	Imatinib	Alternating	Total
Number of subjects	36	40	76
Age categorical			
Units: Subjects			
Adults (18-64 years)	17	26	43
From 65-84 years	19	14	33
Age continuous			
Units: years			
median	65.4	58.4	
full range (min-max)	35.0 to 81.8	23.7 to 81.0	-
Gender categorical			
Units: Subjects			
Female	16	9	25
Male	20	31	51
Primary tumour site			
Units: Subjects			
Colon/Rectum	3	1	4
Not possible to define	7	6	13
Pelvis	1	1	2
Peritoneum/Omentum/Mesentery	2	2	4
Small intestine	9	16	25
Stomach	14	14	28
Prior adjuvant Imatinib			
Units: Subjects			
No	26	28	54
Yes	10	12	22
Commenced Imatinib for Prior to Randomisation			
Units: Subjects			
No	23	25	48
Yes	13	15	28

## End points

### End points reporting groups

Reporting group title	Imatinib
Reporting group description: Imatinib 400mg daily ongoing until progression.	
Reporting group title	Alternating
Reporting group description: Imatinib 400mg for 21 to 25 days with a 37 day washout period followed by Regorafenib 160mg for 21 days followed by a 7 day washout period. Ongoing treatment until progression.	

### Primary: Objective Tumour Response Rate (OTRR) at or before 9 months

End point title	Objective Tumour Response Rate (OTRR) at or before 9 months
End point description: Objective Tumour Response (OTRR) was defined as the proportion of patients exhibiting complete or partial response (CR or PR) at or before 9 months as per the RECIST v1.1. The Objective Tumour Response Rate (OTRR) will be calculated by summing the number of participants assessed as having a complete or partial response within the first 9 months from the time from either: (i) Randomisation (if patients have not yet commenced treatment), or (ii) Commencement of therapy (if patients are randomized during the first cycle of Imatinib), and dividing this by the total number of participants evaluable for response.	
End point type	Primary
End point timeframe: Imaging assessment was done every 8 weeks during the first 12 months	

End point values	Imatinib	Alternating		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	40		
Units: % at 9 months				
number (confidence interval 95%)	61 (45 to 75)	60 (45 to 74)		

### Statistical analyses

Statistical analysis title	Objective Tumour Response Rate (OTRR)
Comparison groups	Alternating v Imatinib
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
P-value	= 0.92
Method	Chi-squared
Parameter estimate	Difference in proportions

Notes:

[1] - Non-comparative

## Secondary: Progression-free survival

End point title	Progression-free survival
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End point description:

Progression-free survival (PFS) was measured from date of patient randomisation to the study [or commencement of therapy if patients are randomized during the first cycle of Imatinib] to date of first evidence of disease progression or patient death from any cause. PFS will be reported in months from the date of randomisation.

In patients who received study treatment without a progression date or death, PFS will be censored on the date of last clinical assessment or registration, whichever is later.

Patients who do not receive study treatment and who have neither progressed nor died will be considered to be censored on the date of their last assessment.

End point type	Secondary
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End point timeframe:

Imaging assessment was performed every 8 weeks for the first year on trial, and then every 12 weeks until disease progression or death.

End point values	Imatinib	Alternating		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	40		
Units: PFS proportion at 12 months				
number (confidence interval 95%)	83 (67 to 92)	88 (73 to 95)		

## Statistical analyses

Statistical analysis title	Progression-free survival
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Comparison groups	Imatinib v Alternating
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Number of subjects included in analysis	76
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Analysis specification	Pre-specified
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Analysis type	other <sup>[2]</sup>
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P-value	= 0.71
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Method	Regression, Cox
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Notes:

[2] - Non-comparative

## Secondary: Overall Survival

End point title	Overall Survival
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End point description:

Overall survival (OS) is measured from the date a patient is randomized to the study [or commencement of therapy if patients are randomized during the first cycle of Imatinib] to the date of death from any cause. Patients remaining alive or lost to follow-up will be censored at the date of last follow-up.

End point type	Secondary
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End point timeframe:

From randomization until the end of the study.



End point values	Imatinib	Alternating		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	40		
Units: OS proportion at 12 months				
number (confidence interval 95%)	97 (82 to 100)	98 (84 to 100)		

## Statistical analyses

Statistical analysis title	Overall Survival
Comparison groups	Imatinib v Alternating
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other <sup>[3]</sup>
P-value	= 0.31
Method	Regression, Cox

Notes:

[3] - Non-comparative

## Secondary: Time to treatment failure

End point title	Time to treatment failure
End point description:	
Treatment failure is defined as treatment discontinuation for any reason, including disease progression, treatment toxicity, patient/investigator's preference, non-protocol treatment or death. Only events in the first 12 months are considered. Patients not experiencing a treatment failure within 12 months were censored at 12 months.	
End point type	Secondary
End point timeframe:	
From the start to the end of the protocol treatment	

End point values	Imatinib	Alternating		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	40		
Units: Failure proportion at 12 months				
number (confidence interval 95%)	83 (67 to 92)	75 (59 to 86)		

## Statistical analyses

Statistical analysis title	Time to Treatment Failure
Comparison groups	Imatinib v Alternating

Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other <sup>[4]</sup>
P-value	= 0.83
Method	Regression, Cox

Notes:

[4] - Non-comparative

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The number of patients who experience specific adverse events in the period between randomization and 30 days (+7 days) after the last dose of study treatment were reported.

Adverse event reporting additional description:

The NCI Common Terminology Criteria for Adverse Events version 4 (NCI CTCAE v4.03) was used to classify and grade the intensity of adverse events after each treatment cycle.

Assessment type	Systematic
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### Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

### Reporting groups

Reporting group title	Imatinib only
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Reporting group description:

All patients randomized to the Imatinib alone arm and received at least one dose of chemotherapy

Reporting group title	imatinib alternating with regorafenib
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Reporting group description:

All patients randomized to receive imatinib alternating with regorafenib and received at least one dose of chemotherapy

Serious adverse events	Imatinib only	imatinib alternating with regorafenib	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 36 (36.11%)	14 / 40 (35.00%)	
number of deaths (all causes)	11	8	
number of deaths resulting from adverse events	0	1	
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	0 / 36 (0.00%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic reaction			

subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Left ventricular systolic dysfunction			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders - Other			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spleen disorder			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 36 (2.78%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic obstruction			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea			
subjects affected / exposed	3 / 36 (8.33%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric hemorrhage			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders - Other			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal fistula			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jejunal perforation			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			

subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 36 (2.78%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder obstruction			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalized muscle weakness			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Muscle weakness lower limb subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal infection subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations - Other subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection subjects affected / exposed	0 / 36 (0.00%)	4 / 40 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory infection subjects affected / exposed	0 / 36 (0.00%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hyponatremia			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Imatinib only	imatinib alternating with regorafenib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 36 (100.00%)	40 / 40 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other			
subjects affected / exposed	3 / 36 (8.33%)	1 / 40 (2.50%)	
occurrences (all)	3	18	
Vascular disorders			
Hot flashes			
subjects affected / exposed	1 / 36 (2.78%)	2 / 40 (5.00%)	
occurrences (all)	6	10	
Hypertension			
subjects affected / exposed	7 / 36 (19.44%)	24 / 40 (60.00%)	
occurrences (all)	50	152	
Hypotension			
subjects affected / exposed	2 / 36 (5.56%)	2 / 40 (5.00%)	
occurrences (all)	3	2	
Lymphedema			
subjects affected / exposed	2 / 36 (5.56%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Lymphocele			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Thromboembolic event			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Surgical and medical procedures			



Surgical and medical procedures - Other			
subjects affected / exposed	4 / 36 (11.11%)	1 / 40 (2.50%)	
occurrences (all)	7	2	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	2 / 36 (5.56%)	3 / 40 (7.50%)	
occurrences (all)	2	3	
Edema face			
subjects affected / exposed	5 / 36 (13.89%)	1 / 40 (2.50%)	
occurrences (all)	20	2	
Edema limbs			
subjects affected / exposed	8 / 36 (22.22%)	7 / 40 (17.50%)	
occurrences (all)	13	25	
Edema trunk			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	3	
Fatigue			
subjects affected / exposed	23 / 36 (63.89%)	30 / 40 (75.00%)	
occurrences (all)	175	193	
Fever			
subjects affected / exposed	2 / 36 (5.56%)	6 / 40 (15.00%)	
occurrences (all)	2	9	
Flu like symptoms			
subjects affected / exposed	2 / 36 (5.56%)	5 / 40 (12.50%)	
occurrences (all)	2	10	
Irritability			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	7	
Localized edema			
subjects affected / exposed	4 / 36 (11.11%)	1 / 40 (2.50%)	
occurrences (all)	36	1	
Non-cardiac chest pain			
subjects affected / exposed	1 / 36 (2.78%)	1 / 40 (2.50%)	
occurrences (all)	1	1	
Pain			

subjects affected / exposed	5 / 36 (13.89%)	3 / 40 (7.50%)	
occurrences (all)	7	8	
General disorders and administration site conditions - Other			
subjects affected / exposed	1 / 36 (2.78%)	2 / 40 (5.00%)	
occurrences (all)	20	2	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	1 / 36 (2.78%)	2 / 40 (5.00%)	
occurrences (all)	2	2	
Reproductive system and breast disorders			
Penile pain			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Reproductive system and breast disorders - Other			
subjects affected / exposed	0 / 36 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Testicular pain			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Uterine hemorrhage			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Vaginal discharge			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Allergic rhinitis			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	2 / 36 (5.56%)	5 / 40 (12.50%)	
occurrences (all)	5	12	
Dyspnea			

subjects affected / exposed	1 / 36 (2.78%)	8 / 40 (20.00%)
occurrences (all)	2	18
Hoarseness		
subjects affected / exposed	1 / 36 (2.78%)	9 / 40 (22.50%)
occurrences (all)	14	89
Laryngeal inflammation		
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	2
Nasal congestion		
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	1
Pharyngeal mucositis		
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	2
Pharyngolaryngeal pain		
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	1
Pleural effusion		
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	3	0
Pleuritic pain		
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	2
Respiratory failure		
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	1	0
Respiratory, thoracic and mediastinal disorders - Other		
subjects affected / exposed	1 / 36 (2.78%)	4 / 40 (10.00%)
occurrences (all)	8	6
Sore throat		
subjects affected / exposed	0 / 36 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	3
Voice alteration		
subjects affected / exposed	0 / 36 (0.00%)	5 / 40 (12.50%)
occurrences (all)	0	13

Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 36 (8.33%)	1 / 40 (2.50%)	
occurrences (all)	24	2	
Delirium			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	2 / 36 (5.56%)	0 / 40 (0.00%)	
occurrences (all)	6	0	
Insomnia			
subjects affected / exposed	4 / 36 (11.11%)	3 / 40 (7.50%)	
occurrences (all)	31	3	
Psychiatric disorders - Other			
subjects affected / exposed	3 / 36 (8.33%)	0 / 40 (0.00%)	
occurrences (all)	3	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 36 (11.11%)	8 / 40 (20.00%)	
occurrences (all)	9	27	
Alkaline phosphatase increased			
subjects affected / exposed	2 / 36 (5.56%)	6 / 40 (15.00%)	
occurrences (all)	2	21	
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 36 (22.22%)	7 / 40 (17.50%)	
occurrences (all)	20	19	
Blood bilirubin increased			
subjects affected / exposed	1 / 36 (2.78%)	6 / 40 (15.00%)	
occurrences (all)	22	15	
CPK increased			
subjects affected / exposed	2 / 36 (5.56%)	0 / 40 (0.00%)	
occurrences (all)	3	0	
Cholesterol high			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Creatinine increased			

subjects affected / exposed	7 / 36 (19.44%)	1 / 40 (2.50%)	
occurrences (all)	77	3	
GGT increased			
subjects affected / exposed	2 / 36 (5.56%)	2 / 40 (5.00%)	
occurrences (all)	2	22	
INR increased			
subjects affected / exposed	0 / 36 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Investigations - Other			
subjects affected / exposed	1 / 36 (2.78%)	4 / 40 (10.00%)	
occurrences (all)	1	8	
Lipase increased			
subjects affected / exposed	2 / 36 (5.56%)	7 / 40 (17.50%)	
occurrences (all)	19	28	
Lymphocyte count decreased			
subjects affected / exposed	2 / 36 (5.56%)	3 / 40 (7.50%)	
occurrences (all)	5	8	
Neutrophil count decreased			
subjects affected / exposed	5 / 36 (13.89%)	2 / 40 (5.00%)	
occurrences (all)	17	7	
Platelet count decreased			
subjects affected / exposed	1 / 36 (2.78%)	2 / 40 (5.00%)	
occurrences (all)	2	4	
Weight gain			
subjects affected / exposed	3 / 36 (8.33%)	0 / 40 (0.00%)	
occurrences (all)	38	0	
Weight loss			
subjects affected / exposed	2 / 36 (5.56%)	5 / 40 (12.50%)	
occurrences (all)	2	9	
White blood cell decreased			
subjects affected / exposed	1 / 36 (2.78%)	1 / 40 (2.50%)	
occurrences (all)	14	1	
Injury, poisoning and procedural complications			
Bruising			

subjects affected / exposed	1 / 36 (2.78%)	1 / 40 (2.50%)	
occurrences (all)	1	1	
Fall			
subjects affected / exposed	2 / 36 (5.56%)	0 / 40 (0.00%)	
occurrences (all)	5	0	
Injury, poisoning and procedural complications - Other			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	14	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	2	
Atrial fibrillation			
subjects affected / exposed	1 / 36 (2.78%)	2 / 40 (5.00%)	
occurrences (all)	1	12	
Cardiac arrest			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Chest pain - cardiac			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	2	
Heart failure			
subjects affected / exposed	1 / 36 (2.78%)	1 / 40 (2.50%)	
occurrences (all)	1	2	
Palpitations			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Sinus bradycardia			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	3	
Sinus tachycardia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			

Amnesia		
subjects affected / exposed	0 / 36 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	2
Cognitive disturbance		
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	14	0
Concentration impairment		
subjects affected / exposed	1 / 36 (2.78%)	1 / 40 (2.50%)
occurrences (all)	8	2
Dizziness		
subjects affected / exposed	5 / 36 (13.89%)	6 / 40 (15.00%)
occurrences (all)	12	15
Dysesthesia		
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	1
Dysgeusia		
subjects affected / exposed	4 / 36 (11.11%)	3 / 40 (7.50%)
occurrences (all)	12	10
Headache		
subjects affected / exposed	6 / 36 (16.67%)	13 / 40 (32.50%)
occurrences (all)	13	34
Memory impairment		
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	2
Nervous system disorders - Other		
subjects affected / exposed	2 / 36 (5.56%)	1 / 40 (2.50%)
occurrences (all)	3	1
Neuralgia		
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	30
Paresthesia		
subjects affected / exposed	0 / 36 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	5
Peripheral motor neuropathy		
subjects affected / exposed	0 / 36 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	3

Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	4 / 40 (10.00%) 8	
Presyncope subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	0 / 40 (0.00%) 0	
Somnolence subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	1 / 40 (2.50%) 2	
Tremor subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 2	0 / 40 (0.00%) 0	
Vasovagal reaction subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	1 / 40 (2.50%) 1	
Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all)	14 / 36 (38.89%) 96	13 / 40 (32.50%) 39	
Blood and lymphatic system disorders - Other subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 10	1 / 40 (2.50%) 1	
Lymph node pain subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	1 / 40 (2.50%) 1	
Ear and labyrinth disorders Ear and labyrinth disorders - Other subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	2 / 40 (5.00%) 3	
Ear pain subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	2 / 40 (5.00%) 2	
External ear pain subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	1 / 40 (2.50%) 1	
Hearing impaired			



subjects affected / exposed	1 / 36 (2.78%)	1 / 40 (2.50%)	
occurrences (all)	10	3	
Vertigo			
subjects affected / exposed	4 / 36 (11.11%)	0 / 40 (0.00%)	
occurrences (all)	4	0	
Eye disorders			
Blurred vision			
subjects affected / exposed	2 / 36 (5.56%)	0 / 40 (0.00%)	
occurrences (all)	8	0	
Conjunctivitis			
subjects affected / exposed	2 / 36 (5.56%)	0 / 40 (0.00%)	
occurrences (all)	6	0	
Dry eye			
subjects affected / exposed	3 / 36 (8.33%)	2 / 40 (5.00%)	
occurrences (all)	22	4	
Eye disorders - Other			
subjects affected / exposed	6 / 36 (16.67%)	1 / 40 (2.50%)	
occurrences (all)	27	1	
Eye pain			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Papilledema			
subjects affected / exposed	2 / 36 (5.56%)	1 / 40 (2.50%)	
occurrences (all)	3	1	
Retinal detachment			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Scleral disorder			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences (all)	3	0	
Watering eyes			
subjects affected / exposed	4 / 36 (11.11%)	0 / 40 (0.00%)	
occurrences (all)	7	0	
Gastrointestinal disorders			
Abdominal distension			

subjects affected / exposed	5 / 36 (13.89%)	1 / 40 (2.50%)
occurrences (all)	9	2
Abdominal pain		
subjects affected / exposed	15 / 36 (41.67%)	17 / 40 (42.50%)
occurrences (all)	40	62
Anal fistula		
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	1
Anal hemorrhage		
subjects affected / exposed	1 / 36 (2.78%)	1 / 40 (2.50%)
occurrences (all)	2	1
Anal mucositis		
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	1
Anal pain		
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	10	0
Anal ulcer		
subjects affected / exposed	1 / 36 (2.78%)	1 / 40 (2.50%)
occurrences (all)	2	1
Ascites		
subjects affected / exposed	1 / 36 (2.78%)	1 / 40 (2.50%)
occurrences (all)	7	1
Bloating		
subjects affected / exposed	7 / 36 (19.44%)	1 / 40 (2.50%)
occurrences (all)	13	1
Cheilitis		
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	4	0
Colitis		
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	1	0
Constipation		
subjects affected / exposed	8 / 36 (22.22%)	9 / 40 (22.50%)
occurrences (all)	23	28
Diarrhea		

subjects affected / exposed	21 / 36 (58.33%)	19 / 40 (47.50%)
occurrences (all)	128	87
Dry mouth		
subjects affected / exposed	2 / 36 (5.56%)	9 / 40 (22.50%)
occurrences (all)	4	18
Dyspepsia		
subjects affected / exposed	3 / 36 (8.33%)	3 / 40 (7.50%)
occurrences (all)	19	6
Flatulence		
subjects affected / exposed	2 / 36 (5.56%)	2 / 40 (5.00%)
occurrences (all)	7	3
Gastric fistula		
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	1	0
Gastric hemorrhage		
subjects affected / exposed	1 / 36 (2.78%)	1 / 40 (2.50%)
occurrences (all)	3	1
Gastritis		
subjects affected / exposed	2 / 36 (5.56%)	1 / 40 (2.50%)
occurrences (all)	6	1
Gastroesophageal reflux disease		
subjects affected / exposed	3 / 36 (8.33%)	3 / 40 (7.50%)
occurrences (all)	3	5
Gastrointestinal disorders - Other		
subjects affected / exposed	3 / 36 (8.33%)	5 / 40 (12.50%)
occurrences (all)	18	9
Gastrointestinal fistula		
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	3	0
Gastrointestinal pain		
subjects affected / exposed	3 / 36 (8.33%)	3 / 40 (7.50%)
occurrences (all)	5	4
Gastroparesis		
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)
occurrences (all)	4	0
Hemorrhoids		

subjects affected / exposed	2 / 36 (5.56%)	1 / 40 (2.50%)	
occurrences (all)	2	1	
Mucositis oral			
subjects affected / exposed	4 / 36 (11.11%)	20 / 40 (50.00%)	
occurrences (all)	7	98	
Nausea			
subjects affected / exposed	23 / 36 (63.89%)	17 / 40 (42.50%)	
occurrences (all)	69	69	
Oral hemorrhage			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Oral pain			
subjects affected / exposed	0 / 36 (0.00%)	5 / 40 (12.50%)	
occurrences (all)	0	39	
Proctitis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Rectal pain			
subjects affected / exposed	0 / 36 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Stomach pain			
subjects affected / exposed	1 / 36 (2.78%)	5 / 40 (12.50%)	
occurrences (all)	2	18	
Toothache			
subjects affected / exposed	0 / 36 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	3	
Upper gastrointestinal hemorrhage			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	11 / 36 (30.56%)	5 / 40 (12.50%)	
occurrences (all)	37	33	
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences (all)	1	0	

Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 36 (8.33%)	7 / 40 (17.50%)	
occurrences (all)	8	28	
Bullous dermatitis			
subjects affected / exposed	1 / 36 (2.78%)	1 / 40 (2.50%)	
occurrences (all)	1	1	
Dry skin			
subjects affected / exposed	4 / 36 (11.11%)	11 / 40 (27.50%)	
occurrences (all)	11	47	
Erythema multiforme			
subjects affected / exposed	1 / 36 (2.78%)	3 / 40 (7.50%)	
occurrences (all)	1	3	
Erythroderma			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Hyperhidrosis			
subjects affected / exposed	1 / 36 (2.78%)	2 / 40 (5.00%)	
occurrences (all)	5	4	
Hypohidrosis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Nail ridging			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Pain of skin			
subjects affected / exposed	0 / 36 (0.00%)	4 / 40 (10.00%)	
occurrences (all)	0	31	
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	1 / 36 (2.78%)	31 / 40 (77.50%)	
occurrences (all)	4	288	
Periorbital edema			
subjects affected / exposed	13 / 36 (36.11%)	10 / 40 (25.00%)	
occurrences (all)	117	44	
Pruritus			

subjects affected / exposed	5 / 36 (13.89%)	6 / 40 (15.00%)	
occurrences (all)	14	28	
Rash acneiform			
subjects affected / exposed	4 / 36 (11.11%)	3 / 40 (7.50%)	
occurrences (all)	8	9	
Rash maculo-papular			
subjects affected / exposed	6 / 36 (16.67%)	9 / 40 (22.50%)	
occurrences (all)	12	23	
Scalp pain			
subjects affected / exposed	0 / 36 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders - Other			
subjects affected / exposed	7 / 36 (19.44%)	11 / 40 (27.50%)	
occurrences (all)	14	18	
Skin ulceration			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	0 / 36 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	7	
Renal and urinary disorders			
Hematuria			
subjects affected / exposed	3 / 36 (8.33%)	0 / 40 (0.00%)	
occurrences (all)	7	0	
Proteinuria			
subjects affected / exposed	1 / 36 (2.78%)	1 / 40 (2.50%)	
occurrences (all)	1	1	
Renal and urinary disorders - Other			
subjects affected / exposed	2 / 36 (5.56%)	1 / 40 (2.50%)	
occurrences (all)	3	1	
Renal calculi			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences (all)	3	0	
Renal colic			

subjects affected / exposed	2 / 36 (5.56%)	0 / 40 (0.00%)	
occurrences (all)	3	0	
Urinary retention			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Urinary tract pain			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	2 / 36 (5.56%)	2 / 40 (5.00%)	
occurrences (all)	5	4	
Hypothyroidism			
subjects affected / exposed	1 / 36 (2.78%)	2 / 40 (5.00%)	
occurrences (all)	2	4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 36 (19.44%)	5 / 40 (12.50%)	
occurrences (all)	35	12	
Back pain			
subjects affected / exposed	7 / 36 (19.44%)	5 / 40 (12.50%)	
occurrences (all)	13	12	
Bone pain			
subjects affected / exposed	0 / 36 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	3	
Buttock pain			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Chest wall pain			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Flank pain			
subjects affected / exposed	0 / 36 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	3	
Generalized muscle weakness			

subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorder - Other			
subjects affected / exposed	14 / 36 (38.89%)	18 / 40 (45.00%)	
occurrences (all)	60	69	
Myalgia			
subjects affected / exposed	4 / 36 (11.11%)	4 / 40 (10.00%)	
occurrences (all)	28	16	
Neck pain			
subjects affected / exposed	1 / 36 (2.78%)	1 / 40 (2.50%)	
occurrences (all)	6	1	
Pain in extremity			
subjects affected / exposed	5 / 36 (13.89%)	5 / 40 (12.50%)	
occurrences (all)	11	12	
Infections and infestations			
Bladder infection			
subjects affected / exposed	4 / 36 (11.11%)	1 / 40 (2.50%)	
occurrences (all)	5	1	
Enterocolitis infectious			
subjects affected / exposed	1 / 36 (2.78%)	1 / 40 (2.50%)	
occurrences (all)	1	1	
Infections and infestations - Other			
subjects affected / exposed	7 / 36 (19.44%)	6 / 40 (15.00%)	
occurrences (all)	10	6	
Lip infection			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Lung infection			
subjects affected / exposed	2 / 36 (5.56%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Mucosal infection			
subjects affected / exposed	2 / 36 (5.56%)	1 / 40 (2.50%)	
occurrences (all)	2	1	
Otitis externa			



subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Sepsis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Skin infection			
subjects affected / exposed	2 / 36 (5.56%)	1 / 40 (2.50%)	
occurrences (all)	2	1	
Tooth infection			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Upper respiratory infection			
subjects affected / exposed	3 / 36 (8.33%)	4 / 40 (10.00%)	
occurrences (all)	8	7	
Urinary tract infection			
subjects affected / exposed	2 / 36 (5.56%)	2 / 40 (5.00%)	
occurrences (all)	2	4	
Vaginal infection			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	3	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	6 / 36 (16.67%)	11 / 40 (27.50%)	
occurrences (all)	14	21	
Dehydration			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Hyperglycemia			
subjects affected / exposed	0 / 36 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	3	
Hyperkalemia			
subjects affected / exposed	2 / 36 (5.56%)	1 / 40 (2.50%)	
occurrences (all)	3	1	

Hypermagnesemia			
subjects affected / exposed	0 / 36 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	4	
Hyponatremia			
subjects affected / exposed	0 / 36 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Hypoalbuminemia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences (all)	9	0	
Hypocalcemia			
subjects affected / exposed	5 / 36 (13.89%)	6 / 40 (15.00%)	
occurrences (all)	37	9	
Hypoglycemia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Hypokalemia			
subjects affected / exposed	3 / 36 (8.33%)	0 / 40 (0.00%)	
occurrences (all)	6	0	
Hypomagnesemia			
subjects affected / exposed	5 / 36 (13.89%)	5 / 40 (12.50%)	
occurrences (all)	26	17	
Hyponatremia			
subjects affected / exposed	2 / 36 (5.56%)	1 / 40 (2.50%)	
occurrences (all)	3	3	
Hypophosphatemia			
subjects affected / exposed	6 / 36 (16.67%)	10 / 40 (25.00%)	
occurrences (all)	27	35	

**More information**

**Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 August 2017	Change in study design including primary endpoint and sample size

Notes:

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**Interruptions (globally)**

Were there any global interruptions to the trial? No

**Limitations and caveats**

None reported