Clinical trial results:
COMBI-Aplus: Open-label, phase IIIb study of dabrafenib in COMBInation with trametinib in the Adjuvant treatment of stage III BRAF V600 mutation-positive melanoma after complete resection to evaluate the impact on pyrexia related outcomes of an adapted pyrexia AE-management algorithm

Summary

EudraCT number	2018-000168-27
Trial protocol	NO FI GB LT GR SI SK BE LV HU PT PL IT
Global end of trial date	16 September 2021

Results information

Result version number	v1 (current)
This version publication date	04 October 2022
First version publication date	04 October 2022

Trial information

Trial identification

Sponsor protocol code	CDRB436F2410

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03551626
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 September 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study was to evaluate the impact on pyrexia-related outcomes of an adapted pyrexia adverse event (AE)-management algorithm

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 August 2018
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	Argentina: 7
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Brazil: 10
Country: Number of subjects enrolled	Canada: 32
Country: Number of subjects enrolled	Czechia: 32
Country: Number of subjects enrolled	Finland: 16
Country: Number of subjects enrolled	France: 176
Country: Number of subjects enrolled	Greece: 23
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Italy: 112
Country: Number of subjects enrolled	Japan: 3
Country: Number of subjects enrolled	Latvia: 3
Country: Number of subjects enrolled	Lithuania: 4
Country: Number of subjects enrolled	Norway: 11
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Portugal: 5
Country: Number of subjects enrolled	Russian Federation: 18
Country: Number of subjects enrolled	Slovakia: 9

Country: Number of subjects enrolled	Slovenia: 5
Country: Number of subjects enrolled	Sweden: 9
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	United Kingdom: 35
Worldwide total number of subjects	552
EEA total number of subjects	428

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)	430
From 65 to 84 years	122
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients in this study were enrolled at 103 centers across 23 countries

Pre-assignment

Screening details:

A total of 748 patients were screened. Of the screened patients, 552 patients were treated.

Period 1

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

Arms

Arm title	Dabrafenib+trametinib

Arm description:

Subjects received dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) orally for up to 12 months.

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

Dosage and administration details:

Trametinib 2mg once daily provided as 0.5mg and 2.0mg tablets for oral administration

Investigational medicinal product name	Dabrafenib
Investigational medicinal product code	DRB436
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dabrafenib 150mg twice daily provided as 50 mg and 75 mg capsules for oral administration

Number of subjects in period 1	Dabrafenib+trametinib
Started	552
Completed	425
Not completed	127
Patient decision	5
Physician decision	4
Adverse event, non-fatal	88
Technical problems	1
Protocol deviation	1

Disease relapse	18
Pregnancy	1
Withdrawal of informed consent	6
Lost to follow-up	3

Baseline characteristics

Reporting groups	
Reporting group title	Dabrafenib+trametinib
Reporting group description:	
Subjects received dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) orally for up to 12 months.	

Reporting group values	Dabrafenib+trametinib	Total	
Number of subjects	552	552	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	430	430	
From 65-84 years	122	122	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	53.4		
standard deviation	± 13.09	-	
Sex: Female, Male Units: Participants			
Female	255	255	
Male	297	297	
Race/Ethnicity, Customized Units: Subjects			
White	377	377	
Asian	3	3	
Missing	172	172	

End points

End points reporting groups

Reporting group title	Dabrafenib+trametinib

Reporting group description:

Subjects received dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) orally for up to 12 months.

Primary: Composite rate of pyrexia related events

End point title	Composite rate of pyrexia related events[1]

End point description:

The composite rate of pyrexia related events was calculated as the total number of participants experiencing at least one of the three components of the composite endpoint (i.e., grade 3/4 pyrexia, hospitalization due to pyrexia, or permanent treatment discontinuation due to pyrexia), divided by the total number of participants treated in the study and multiplied by 100. Pyrexia is defined as fever ≥ 38 °C.
Pyrexia events were graded by the investigator using Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (Life-threatening) and Grade 5 (Death)

End point type	Primary

End point timeframe:

Baseline up to 12 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 statistical analyses were planned for this endpoint

End point values	Dabrafenib+trametinib			
Subject group type	Reporting group			
Number of subjects analysed	552			
Units: Percentage of participants				
number (confidence interval 95%)	7.6 (5.5 to 10.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse free survival (RFS) rate

End point title	Relapse free survival (RFS) rate

End point description:

RFS is defined as the time from the date of first dose of the study treatment to the date of the first documented disease recurrence or death due to any cause whichever comes first. Treatment emergent malignancies other than second melanomas were not considered as events.
RFS rate is the estimated percent probability that a patient will remain event-free up to the specified time point. RFS rate was obtained from the Kaplan-Meier survival estimates. RFS was censored if no RFS event was observed before the first to occur between: (i) the analysis cut-off date, and (ii) the date when a new anti-cancer therapy is started. The censoring date was the date of the last adequate tumor assessment prior to data cut-off date/start of new anti-cancer therapy date.

End point type	Secondary

End point timeframe:

At 12 and 24 months

End point values	Dabrafenib+trametinib			
Subject group type	Reporting group			
Number of subjects analysed	552			
Units: Percent probability				
number (confidence interval 95%)				
12 months	91.7 (89.0 to 93.8)			
24 months	57.5 (48.9 to 65.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) rate

End point title	Overall Survival (OS) rate

End point description:

OS is defined as the time from date of the first dose of study medication to date of death due to any cause, whichever comes first. If a patient was not known to have died, then
OS rate is the estimated probability that a patient will remain event-free up to the specified time point. OS rate was obtained from the Kaplan-Meier survival estimates. OS was censored at the last contact date when the patient was known to be alive (on or before the cut-off date).

End point type	Secondary

End point timeframe:

At 12 and 24 months

End point values	Dabrafenib+trametinib			
Subject group type	Reporting group			
Number of subjects analysed	552			
Units: Percent probability				
number (confidence interval 95%)				
12 months	99.1 (97.8 to 99.6)			
24 months	92.6 (90.0 to 94.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who required management of pyrexia

End point title	Percentage of participants who required management of pyrexia

End point description:

Percentage of patients who experienced pyrexia and required intervention including hospitalizations, concomitant medications, and study treatment modifications (dose reductions, permanent discontinuations and/or interruptions) due to pyrexia. Pyrexia is defined as fever ≥ 38 °C

End point type	Secondary

End point timeframe:

Baseline up to 12 months

End point values	Dabrafenib+trametinib			
Subject group type	Reporting group			
Number of subjects analysed	552			
Units: Participants				
Hospitalizations	24			
Concomitant medications	210			
Permanent discontinuation of study treatment	13			
Reduction of study treatment	29			
Interruption of study treatment	339			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who permanently discontinued treatment due to any adverse event (AE)

End point title	Percentage of participants who permanently discontinued treatment due to any adverse event (AE)

End point description:

Percentage of participants who permanently discontinued treatment due to any AE during treatment. An AE is any untoward medical occurrence (e.g., any unfavorable and unintended sign, symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study.

End point type	Secondary

End point timeframe:

Baseline up to 12 months

End point values	Dabrafenib+trametinib			
Subject group type	Reporting group			
Number of subjects analysed	552			
Units: Participants	87			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Subject-reported Quality of Life (QoL) Assessed by Functional Assessment Cancer Therapy - Melanoma subscale Score (FACT-M MS)

End point title	Change From Baseline in Subject-reported Quality of Life (QoL) Assessed by Functional Assessment Cancer Therapy - Melanoma subscale Score (FACT-M MS)

End point description:

The FACT-M is a questionnaire that assesses participant health-related quality of life. It includes a melanoma specific (FACT-M MS) subscale that consists in 16 items related to signs, symptoms, physical/social activities most relevant to participants with advanced-stage melanoma. Each item ranges from 0 (not at all) to 4 (very much). FACT-M MS score ranges from 0 to 64, with higher score indicating better quality of life. If a patient discontinued the study treatment at Month 1 or Month 2, then the follow-up assessments started at Month 3 follow-up and continued until Month 24 follow-up or at withdrawal, lost to follow-up, death, or end of study. If a patient discontinued the study treatment from Month 3 through Month 5, the follow-up assessments started at Month 6 follow-up. If a patient discontinued from Month 6 through Month 11, the follow-up assessments started from Month 12 follow-up.

End point type	Secondary

End point timeframe:

Baseline up to 24 months

End point values	Dabrafenib+trametinib			
Subject group type	Reporting group			
Number of subjects analysed	552			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Month 1	-2.46 (± 5.488)			
Month 2	-2.42 (± 4.892)			
Month 3	-2.26 (± 4.789)			
Month 4	-2.34 (± 5.297)			
Month 5	-2.03 (± 5.278)			
Month 6	-2.19 (± 5.494)			
Month 7	-2.39 (± 5.873)			
Month 8	-2.32 (± 5.609)			

Month 9	-2.06 (± 5.534)			
Month 10	-2.15 (± 5.743)			
Month 11	-2.05 (± 5.578)			
Month 12	-1.96 (± 5.757)			
End of treatment	-3.36 (± 5.944)			
Follow-up Month 3	2.43 (± 4.685)			
Follow-up Month 6	-0.33 (± 4.915)			
Follow-up Month 12	-1.71 (± 5.671)			
Follow-up Month 15	-0.60 (± 6.018)			
Follow-up Month 18	-0.09 (± 4.948)			
Follow-up Month 24	-0.75 (± 5.406)			

Statistical analyses

No statistical analyses for this end point

Post-hoc: All collected deaths

End point title	All collected deaths

End point description:

On treatment deaths were collected from date of first administration of study treatment to 30 days after date of last administration of any study treatment (dabrafenib or trametinib).
Deaths post-treatment follow-up were collected after the on-treatment period.
All deaths refer to the sum of on-treatment and post-treatment deaths

End point type	Post-hoc

End point timeframe:

On-treatment: from first study treatment to 30 days after last dose of study treatment, up to 13 months. Post-treatment: From day 31 after last study treatment up to approximately 39 months

End point values	Dabrafenib+trametinib			
Subject group type	Reporting group			
Number of subjects analysed	552			
Units: Participants				
On-treatment deaths	1			
Post-treatment deaths	47			
All deaths	48			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of first administration of study treatment to 30 days after date of last actual administration of any study treatment: dabrafenib or trametinib (including start and stop date), up to approximately 13 months.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	All subjects

Reporting group description:

All subjects

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	121 / 552 (21.92%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	4 / 552 (0.72%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma in situ			
subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			

subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uterine leiomyoma			
subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Lymphoedema			
subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Venous thrombosis			
subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	28 / 552 (5.07%)		
occurrences causally related to treatment / all	29 / 31		
deaths causally related to treatment / all	0 / 0		
Chills			
subjects affected / exposed	2 / 552 (0.36%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Influenza like illness			
subjects affected / exposed	3 / 552 (0.54%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Fatigue				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperthermia				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Granuloma				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Ovarian cyst				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pulmonary embolism				
subjects affected / exposed	3 / 552 (0.54%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Major depression				

subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Ejection fraction decreased				
subjects affected / exposed	19 / 552 (3.44%)			
occurrences causally related to treatment / all	23 / 23			
deaths causally related to treatment / all	0 / 0			
Alanine aminotransferase increased				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic enzyme increased				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General physical condition abnormal				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lipase increased				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lymphocyte morphology abnormal				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neutrophil count decreased				

subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Seroma			
subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 552 (0.54%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Left ventricular dysfunction			
subjects affected / exposed	2 / 552 (0.36%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Focal dyscognitive seizures			
subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Headache				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Loss of consciousness				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple sclerosis				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Polyneuropathy				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Radicular pain				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Febrile neutropenia				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lymphadenopathy				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenia				

subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal vein occlusion			
subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Detachment of retinal pigment epithelium			
subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Scleritis			
subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Uveitis			
subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Diarrhoea				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholestasis				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatotoxicity				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertransaminasaemia				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				

Erythema nodosum			
subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Erythema multiforme			
subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	2 / 552 (0.36%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Panniculitis			
subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash maculo-papular			
subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin mass			
subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vasculitic rash			
subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin ulcer			
subjects affected / exposed	1 / 552 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Nephrolithiasis				
subjects affected / exposed	2 / 552 (0.36%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haematuria				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal colic				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthralgia				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Cellulitis				
subjects affected / exposed	5 / 552 (0.91%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	3 / 552 (0.54%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			

Bacterial infection				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia legionella				
subjects affected / exposed	2 / 552 (0.36%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Complicated appendicitis				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Groin infection				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				

subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prostate infection				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Soft tissue infection				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Systemic candida				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hypokalaemia				
subjects affected / exposed	2 / 552 (0.36%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hypophosphataemia				
subjects affected / exposed	1 / 552 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	All subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	526 / 552 (95.29%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	75 / 552 (13.59%)		
occurrences (all)	97		
Amylase increased			
subjects affected / exposed	35 / 552 (6.34%)		
occurrences (all)	40		
Aspartate aminotransferase increased			
subjects affected / exposed	74 / 552 (13.41%)		
occurrences (all)	91		
Blood alkaline phosphatase increased			
subjects affected / exposed	37 / 552 (6.70%)		
occurrences (all)	46		
Blood creatine phosphokinase increased			
subjects affected / exposed	168 / 552 (30.43%)		
occurrences (all)	231		
Lipase increased			
subjects affected / exposed	72 / 552 (13.04%)		
occurrences (all)	96		
Vascular disorders			
Hypertension			
subjects affected / exposed	41 / 552 (7.43%)		
occurrences (all)	51		
Nervous system disorders			
Dizziness			
subjects affected / exposed	31 / 552 (5.62%)		
occurrences (all)	35		
Headache			
subjects affected / exposed	174 / 552 (31.52%)		
occurrences (all)	436		
Blood and lymphatic system disorders			

Neutropenia			
subjects affected / exposed	44 / 552 (7.97%)		
occurrences (all)	69		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	146 / 552 (26.45%)		
occurrences (all)	356		
Fatigue			
subjects affected / exposed	142 / 552 (25.72%)		
occurrences (all)	264		
Pain			
subjects affected / exposed	28 / 552 (5.07%)		
occurrences (all)	45		
Oedema peripheral			
subjects affected / exposed	66 / 552 (11.96%)		
occurrences (all)	80		
Influenza like illness			
subjects affected / exposed	65 / 552 (11.78%)		
occurrences (all)	149		
Asthenia			
subjects affected / exposed	131 / 552 (23.73%)		
occurrences (all)	203		
Pyrexia			
subjects affected / exposed	374 / 552 (67.75%)		
occurrences (all)	1911		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	44 / 552 (7.97%)		
occurrences (all)	60		
Abdominal pain upper			
subjects affected / exposed	30 / 552 (5.43%)		
occurrences (all)	39		
Constipation			
subjects affected / exposed	46 / 552 (8.33%)		
occurrences (all)	51		
Diarrhoea			

subjects affected / exposed	149 / 552 (26.99%)		
occurrences (all)	281		
Nausea			
subjects affected / exposed	128 / 552 (23.19%)		
occurrences (all)	276		
Vomiting			
subjects affected / exposed	84 / 552 (15.22%)		
occurrences (all)	139		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	29 / 552 (5.25%)		
occurrences (all)	32		
Dyspnoea			
subjects affected / exposed	36 / 552 (6.52%)		
occurrences (all)	45		
Cough			
subjects affected / exposed	79 / 552 (14.31%)		
occurrences (all)	99		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	33 / 552 (5.98%)		
occurrences (all)	40		
Rash			
subjects affected / exposed	116 / 552 (21.01%)		
occurrences (all)	209		
Erythema			
subjects affected / exposed	38 / 552 (6.88%)		
occurrences (all)	42		
Pruritus			
subjects affected / exposed	29 / 552 (5.25%)		
occurrences (all)	33		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	116 / 552 (21.01%)		
occurrences (all)	207		
Back pain			

subjects affected / exposed	39 / 552 (7.07%)		
occurrences (all)	60		
Muscle spasms			
subjects affected / exposed	42 / 552 (7.61%)		
occurrences (all)	68		
Myalgia			
subjects affected / exposed	85 / 552 (15.40%)		
occurrences (all)	148		
Pain in extremity			
subjects affected / exposed	48 / 552 (8.70%)		
occurrences (all)	72		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	38 / 552 (6.88%)		
occurrences (all)	39		
Hyperglycaemia			
subjects affected / exposed	31 / 552 (5.62%)		
occurrences (all)	37		
Hypophosphataemia			
subjects affected / exposed	38 / 552 (6.88%)		
occurrences (all)	48		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 December 2018	The primary purpose of this protocol amendment is to implement clinically relevant feedback received from the Health Authorities and participating center's Ethics Committees upon review of the protocol. In addition, clarifications and corrections are made throughout the protocol as well as editorial change to improve flow and consistency.
12 March 2019	The primary purpose of this protocol amendment is to implement clinically relevant feedback received from the Health Authorities and participating center's Ethics Committees upon reviewof the protocol. In addition, study population inclusion criteria was expanded, clarifications and corrections are made throughout the protocol, as well as editorial change to improve flow and consistency.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Most patients remained relapse-free at the end of the study. Due to the design of the study, RFS and OS data consisted of a majority of censored data, the 24-months RFS rate and OS rate could not be estimated meaningfully.

Notes: