Clinical trial results:
PHASE IIIB, RANDOMIZED STUDY OF MULTIPLE ADMINISTRATION REGIMENS FOR NIVOLUMAB PLUS IPILIMUMAB IN SUBJECTS WITH PREVIOUSLY UNTREATED UNRESECTABLE OR METASTATIC MELANOMA

Summary

EudraCT number	2016-001941-26
Trial protocol	ES IT
Global end of trial date	25 October 2019

Results information

Result version number	v1 (current)
This version publication date	07 November 2020
First version publication date	07 November 2020

Trial information

Trial identification

Sponsor protocol code	CA209-742

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.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	23 December 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the difference in safety between co-administered BMS-986214 fixed ratio combination (FRC) (nivolumab 1 mg/kg and ipilimumab 3 mg/kg) relative to sequentially administered nivolumab (1 mg/kg) and ipilimumab (3 mg/kg) as measured by the incidence of AEs in the Broad Scope MedDRA Anaphylactic Reaction SMQ occurring within 2 days after dosing during the combination, Part 1 period in subjects with previously untreated, unresectable or metastatic melanoma.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 October 2016
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	Australia: 28
Country: Number of subjects enrolled	France: 42
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Spain: 20
Worldwide total number of subjects	106
EEA total number of subjects	78

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)	67
From 65 to 84 years	38
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

106 participants were randomized and treated.

Period 1

Period 1 title	Treatment Phase Part 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Concomitant administration of Nivolumab and Ipilimumab every 3 weeks for 4 doses followed by Nivolumab flat dose in the Maintenance Phase

Arm type	Experimental
Investigational medicinal product name	Nivolumab/Ipilimumab FRC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

40 mg Nivolumab/ 120 mg Ipilimumab - every 3 weeks for 4 doses

Arm title	Arm B

Arm description:

Sequential administration of Nivolumab and Ipilimumab every 3 weeks for 4 doses followed by Nivolumab flat dose in the Maintenance Phase

Arm type	Experimental
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

3 mg/Kg every 3 weeks for 4 doses

Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1 mg/kg very 3 weeks for 4 doses

Number of subjects in period 1	Arm A	Arm B
Started	53	53
Completed	24	30
Not completed	29	23
Study Drug Toxicity	22	16
Participant Withdrew Consent	1	-
Disease Progression	6	7

Period 2

Period 2 title	Transition from Part 1 to Part 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Concomitant administration of Nivolumab and Ipilimumab every 3 weeks for 4 doses followed by Nivolumab flat dose in the Maintenance Phase

Arm type	Experimental
Investigational medicinal product name	Nivolumab/Ipilimumab FRC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

40 mg Nivolumab/ 120 mg Ipilimumab every 3 weeks for 4 doses

Arm title	Arm B

Arm description:

Sequential administration of Nivolumab and Ipilimumab every 3 weeks for 4 doses followed by Nivolumab flat dose in the Maintenance Phase

Arm type	Experimental
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

3 mg/Kg every 3 weeks for 4 doses

Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection

Routes of administration	Intravenous use

Dosage and administration details:

1 mg/kg every 3 weeks for 4 doses

Number of subjects in period 2	Arm A	Arm B
Started	24	30
Completed	20	22
Not completed	4	8
Adverse event, serious fatal	-	1
Adverse event, non-fatal	1	1
Adverse event unrelated to study drug	1	-
Study Drug Toxicity	-	4
Participant Withdrew Consent	-	1
Disease Progression	2	1

Period 3

Period 3 title	Maintenance Phase Part 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Concomitant administration of Nivolumab and Ipilimumab every 3 weeks for 4 doses followed by Nivolumab flat dose in the Maintenance Phase

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

480 mg every 4 weeks

Arm title	Arm B

Arm description:

Sequential administration of Nivolumab and Ipilimumab every 3 weeks for 4 doses followed by Nivolumab flat dose in the Maintenance Phase

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

480 mg every 4 weeks

Number of subjects in period 3	Arm A	Arm B
Started	20	22
Completed	8	14
Not completed	12	8
Maximum Clinical Benefit	-	2
Study Drug Toxicity	3	4
Disease Progression	9	2

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
Concomitant administration of Nivolumab and Ipilimumab every 3 weeks for 4 doses followed by Nivolumab flat dose in the Maintenance Phase	
Reporting group title	Arm B
Reporting group description:	
Sequential administration of Nivolumab and Ipilimumab every 3 weeks for 4 doses followed by Nivolumab flat dose in the Maintenance Phase	

Reporting group values	Arm A	Arm B	Total
Number of subjects	53	53	106
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	32	35	67
From 65-84 years	20	18	38
85 years and over	1	0	1
Age Continuous Units: years			
arithmetic mean	58.1	56.3	
standard deviation	± 14.5	± 14.6	-
Sex: Female, Male Units: Participants			
Female	18	26	44
Male	35	27	62
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	48	50	98
More than one race	0	0	0
Unknown or Not Reported	4	3	7
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	1	2
Not Hispanic or Latino	26	28	54
Unknown or Not Reported	26	24	50

End points

End points reporting groups

Reporting group title	Arm A

Reporting group description:

Concomitant administration of Nivolumab and Ipilimumab every 3 weeks for 4 doses followed by Nivolumab flat dose in the Maintenance Phase

Reporting group title	Arm B

Reporting group description:

Sequential administration of Nivolumab and Ipilimumab every 3 weeks for 4 doses followed by Nivolumab flat dose in the Maintenance Phase

Reporting group title	Arm A

Reporting group description:

Concomitant administration of Nivolumab and Ipilimumab every 3 weeks for 4 doses followed by Nivolumab flat dose in the Maintenance Phase

Reporting group title	Arm B

Reporting group description:

Sequential administration of Nivolumab and Ipilimumab every 3 weeks for 4 doses followed by Nivolumab flat dose in the Maintenance Phase

Reporting group title	Arm A

Reporting group description:

Concomitant administration of Nivolumab and Ipilimumab every 3 weeks for 4 doses followed by Nivolumab flat dose in the Maintenance Phase

Reporting group title	Arm B

Reporting group description:

Sequential administration of Nivolumab and Ipilimumab every 3 weeks for 4 doses followed by Nivolumab flat dose in the Maintenance Phase

Primary: Percentage of participants affected by Adverse Events (AEs) in the Broad Scope MedDRA Anaphylactic Reaction standardized MedDRA queries (SMQ)

End point title	Percentage of participants affected by Adverse Events (AEs) in the Broad Scope MedDRA Anaphylactic Reaction standardized MedDRA queries (SMQ)

End point description:

This outcome describes the proportion of participants experiencing at least 1 AE in the MedDRA Anaphylactic Reaction broad scope SMQ. Such AEs include any acute systemic reaction characterized by a large list of terms, including (but not limited to) pruritus, urticaria, flushing, hypotension, respiratory distress, and vascular insufficiency. It also includes other signs and symptoms such as asthma, choking sensation, coughing, sneezing, and difficulty breathing due to laryngeal spasm and/or bronchospasm. Less frequent clinical presentations are also captured and include hyperventilation, sensation of foreign body, and ocular edema.

End point type	Primary

End point timeframe:

Within 2 days of dose in part 1 period (assessed up to June 2018, approximately 19 months)

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	53		
Units: Percent of Participants				
number (confidence interval 95%)	15.1 (6.7 to 27.6)	18.9 (9.4 to 32.0)		

Statistical analyses

Statistical analysis title	AEs in the Broad Scope Anaphylactic Reaction SMQ
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Cochran-Mantel-Haenszel Odds Ratio
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	2.13

Statistical analysis title	AEs in the Broad Scope Anaphylactic Reaction SMQ
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Percent difference in incidence rates
Point estimate	-3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.3
upper limit	10.7

Secondary: Percentage of participants affected by AEs in the Narrow Scope MedDRA Anaphylactic Reaction SMQ

End point title	Percentage of participants affected by AEs in the Narrow Scope MedDRA Anaphylactic Reaction SMQ

End point description:

This outcome describes the proportion of participants experiencing at least 1 AE in the MedDRA Anaphylactic Reaction narrow scope SMQ. The narrow scope SMQ is composed of a large list of terms, including (but not limited to) anaphylactic shock and reaction, shock and shock symptoms, and circulatory collapse, among the others.

End point type	Secondary

End point timeframe:

Within 2 days of dose in Part 1 period (assessed up to June 2018, approximately 19 months)

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	53		
Units: Percent of Participants				
number (confidence interval 95%)	0.0 (0.0 to 6.7)	0.0 (0.0 to 6.7)		

Statistical analyses

Statistical analysis title	AEs in the Narrow Scope Anaphylactic Reaction SMQ
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Percent Difference in incidence rates
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Secondary: Percentage of Participants Affected by Hypersensitivity/Infusion Reaction Select AEs

End point title	Percentage of Participants Affected by Hypersensitivity/Infusion Reaction Select AEs

End point description:

This outcome describes the proportion of participants experiencing at least 1 AE in the Hypersensitivity/Infusion select AEs category. The select AEs consist of a list of preferred terms defined by the Sponsor and represent AEs with a potential immune-mediated etiology. The following 5 MedDRA preferred terms are included in the hypersensitivity/infusion reaction select AE category: Anaphylactic Reaction, Anaphylactic Shock, Bronchospasm, Hypersensitivity, and Infusion Related Reaction

End point type	Secondary

End point timeframe:

Within 2 days of dose in part 1 period (assessed up to December 2019, approximately 37 months)

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	53		
Units: Percent of Participants				
number (not applicable)	7.5	9.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants affected by All Causality Grade 3 - 5 AEs

End point title	Percentage of participants affected by All Causality Grade 3 - 5 AEs

End point description:

This outcome describes the proportion of participants who experienced at least 1 AE of Grade 3 or higher defined using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 criteria

End point type	Secondary

End point timeframe:

From initial dose of study treatment and within 30 days of the last dose of study treatment (assessed up to December 2019, approximately 37 months)

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	53		
Units: Percent of participants				
number (not applicable)	69.8	56.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants affected by Drug-related Grade 3 - 5 AEs

End point title	Percentage of participants affected by Drug-related Grade 3 - 5 AEs

End point description:

This outcome describes the proportion of participants who experienced at least 1 Drug-related AE of Grade 3 or higher defined using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 criteria

End point type	Secondary

End point timeframe:

From initial dose of study treatment and within 30 days of the last dose of study treatment (assessed up to December 2019, approximately 37 months)

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	53		
Units: Percent of participants				
number (not applicable)	58.5	47.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Concentration of Ipilimumab at End of Infusion (EOI)

End point title	Geometric Mean Concentration of Ipilimumab at End of Infusion (EOI)

End point description:

End point type	Secondary

End point timeframe:

From Cycle 1, Day 1 to Cycle 4, Day 1 (approximately 9 weeks). Each cycle lasts 3 weeks. Cycle 1 day 1, Cycle 2 day 1 and Cycle 4 day 1 values reported.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	53		
Units: micrograms per milliliter (ug/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1	60.4 (± 93.0)	61.5 (± 72.3)		
Cycle 2 Day 1	66.8 (± 134)	72.1 (± 71.8)		
Cycle 4 Day 1	77.9 (± 94.2)	84.6 (± 104)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Concentration of Nivolumab at End of Infusion (EOI)

End point title	Geometric Mean Concentration of Nivolumab at End of Infusion (EOI)

End point description:

End point type	Secondary

End point timeframe:

From Cycle 1, Day 1 to Cycle 4, Day 1 (approximately 9 weeks). Each cycle lasts 3 weeks. Cycle 1 day 1, Cycle 2 day 1 and Cycle 4 day 1 values reported

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	53		
Units: micrograms per milliliter (ug/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1	20.9 (± 77.3)	21.8 (± 117)		
Cycle 2 Day 1	24.2 (± 122)	22.4 (± 101)		
Cycle 4 Day 1	27.9 (± 79.8)	27.4 (± 79.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Trough Concentration of Ipilimumab

End point title	Geometric Mean Trough Concentration of Ipilimumab

End point description:

End point type	Secondary

End point timeframe:

From Cycle 2, Day 1 to Cycle 4, Day 1 (approximately 6 weeks). Each cycle lasts 3 weeks.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	53		
Units: micrograms per milliliter (ug/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 2 Day 1	10.8 (± 30.2)	9.94 (± 38.9)		
Cycle 4 Day 1	16.5 (± 36.9)	13.7 (± 46.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Trough Concentration of Nivolumab

End point title	Geometric Mean Trough Concentration of Nivolumab

End point description:

End point type	Secondary

End point timeframe:

From Cycle 2, Day 1 to Cycle 4, Day 1 (approximately 6 weeks). Each cycle lasts 3 weeks.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	53		
Units: micrograms per milliliter (ug/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 2 Day 1	3.94 (± 56.6)	2.75 (± 65.9)		
Cycle 4 Day 1	6.50 (± 44.6)	4.05 (± 75.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

The ORR is defined as the proportion of participants with a Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR). The BOR is defined as the best response designation, as determined by the investigator, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anti-cancer therapy, whichever occurs first.

End point type	Secondary

End point timeframe:

Week 12 following randomization, every 8 weeks for the first 12 months and then every 12 weeks until disease progression

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	53		
Units: Percentage of Participants				
number (confidence interval 95%)	52.8 (38.6 to 66.7)	60.4 (46.0 to 73.5)		

Statistical analyses

Statistical analysis title	ORR
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference of ORRs
Point estimate	-7.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.1
upper limit	11

Statistical analysis title	ORR
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	1.58

Secondary: Progression Free Survival (PFS)	
End point title	Progression Free Survival (PFS)
End point description:	
PFS is defined as the time between the date of randomization and the first date of documented progression, as determined by the investigator, or death due to any cause, whichever occurs first.	
End point type	Secondary
End point timeframe:	
From the date of randomization to the first date of documented progression (assessed up to December 2019, approximately 37 months)	

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	53		
Units: Months				
median (confidence interval 95%)	10.25 (2.96 to 9999)	9999 (4.96 to 9999)		

Statistical analyses

Statistical analysis title	PFS
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	2.37

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from start of treatment up to 30 days after last treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Fixed Ratio Combination

Reporting group description:

Subjects were infused with a fixed dose of BMS-986214 for 60 minutes for 6 weeks in Part 1 followed by nivolumab flat dose (480 mg, 30 minute infusion) in Part 2 until progression or unacceptable toxicity.

Reporting group title	Sequential Combination

Reporting group description:

Subjects were administered nivolumab and ipilimumab sequentially, as two separate infusions, one 60 minute nivolumab infusion and one 90 minute ipilimumab infusion with a 30 minute break between each infusion for 6 weeks in Part 1 followed by nivolumab flat dose (480 mg, 30 minute infusion) in Part 2 until progression or unacceptable toxicity.

Serious adverse events	Fixed Ratio Combination	Sequential Combination	
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 53 (54.72%)	26 / 53 (49.06%)	
number of deaths (all causes)	14	14	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	2 / 53 (3.77%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Thrombosis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
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			
Adverse drug reaction			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	7 / 53 (13.21%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	5 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Autoimmune disorder			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	0 / 53 (0.00%)	3 / 53 (5.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 53 (1.89%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 53 (1.89%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic enzymes increased			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Facial paralysis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Motor neurone disease			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Iridocyclitis			

subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 53 (1.89%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune colitis			
subjects affected / exposed	2 / 53 (3.77%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Colitis			
subjects affected / exposed	3 / 53 (5.66%)	3 / 53 (5.66%)	
occurrences causally related to treatment / all	3 / 3	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyclic vomiting syndrome			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 53 (1.89%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erosive duodenitis			

subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 53 (5.66%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-Mediated enterocolitis			
subjects affected / exposed	1 / 53 (1.89%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune hepatitis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic function abnormal			

subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	2 / 53 (3.77%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	4 / 53 (7.55%)	2 / 53 (3.77%)	
occurrences causally related to treatment / all	5 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	2 / 53 (3.77%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypophysitis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroiditis			
subjects affected / exposed	1 / 53 (1.89%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	2 / 53 (3.77%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma muscle			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (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			
Lower respiratory tract infection			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 53 (1.89%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urosepsis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
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: 5 %

Non-serious adverse events	Fixed Ratio Combination	Sequential Combination	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 53 (86.79%)	50 / 53 (94.34%)	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	11 / 53 (20.75%)	15 / 53 (28.30%)	
occurrences (all)	12	17	
Chills			
subjects affected / exposed	3 / 53 (5.66%)	4 / 53 (7.55%)	
occurrences (all)	3	4	
Fatigue			
subjects affected / exposed	9 / 53 (16.98%)	8 / 53 (15.09%)	
occurrences (all)	9	9	
Influenza like illness			
subjects affected / exposed	2 / 53 (3.77%)	6 / 53 (11.32%)	
occurrences (all)	2	6	
Pyrexia			
subjects affected / exposed	14 / 53 (26.42%)	15 / 53 (28.30%)	
occurrences (all)	16	19	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 53 (13.21%)	3 / 53 (5.66%)	
occurrences (all)	7	3	

Dyspnoea			
subjects affected / exposed	2 / 53 (3.77%)	3 / 53 (5.66%)	
occurrences (all)	2	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 53 (3.77%)	3 / 53 (5.66%)	
occurrences (all)	2	3	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 53 (13.21%)	6 / 53 (11.32%)	
occurrences (all)	11	7	
Amylase increased			
subjects affected / exposed	4 / 53 (7.55%)	2 / 53 (3.77%)	
occurrences (all)	4	2	
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 53 (9.43%)	4 / 53 (7.55%)	
occurrences (all)	7	4	
Blood lactate dehydrogenase increased			
subjects affected / exposed	4 / 53 (7.55%)	3 / 53 (5.66%)	
occurrences (all)	5	3	
Lipase increased			
subjects affected / exposed	6 / 53 (11.32%)	3 / 53 (5.66%)	
occurrences (all)	6	4	
Gamma-Glutamyltransferase increased			
subjects affected / exposed	3 / 53 (5.66%)	1 / 53 (1.89%)	
occurrences (all)	4	1	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	4 / 53 (7.55%)	3 / 53 (5.66%)	
occurrences (all)	7	3	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 53 (3.77%)	3 / 53 (5.66%)	
occurrences (all)	2	4	
Headache			

subjects affected / exposed	8 / 53 (15.09%)	10 / 53 (18.87%)	
occurrences (all)	9	12	
Paraesthesia			
subjects affected / exposed	2 / 53 (3.77%)	4 / 53 (7.55%)	
occurrences (all)	2	4	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 53 (3.77%)	4 / 53 (7.55%)	
occurrences (all)	2	4	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 53 (7.55%)	3 / 53 (5.66%)	
occurrences (all)	4	3	
Abdominal pain upper			
subjects affected / exposed	2 / 53 (3.77%)	3 / 53 (5.66%)	
occurrences (all)	2	3	
Constipation			
subjects affected / exposed	8 / 53 (15.09%)	6 / 53 (11.32%)	
occurrences (all)	8	6	
Diarrhoea			
subjects affected / exposed	12 / 53 (22.64%)	22 / 53 (41.51%)	
occurrences (all)	17	28	
Dry mouth			
subjects affected / exposed	5 / 53 (9.43%)	1 / 53 (1.89%)	
occurrences (all)	5	1	
Nausea			
subjects affected / exposed	9 / 53 (16.98%)	11 / 53 (20.75%)	
occurrences (all)	12	11	
Vomiting			
subjects affected / exposed	6 / 53 (11.32%)	8 / 53 (15.09%)	
occurrences (all)	7	11	
Abdominal distension			
subjects affected / exposed	3 / 53 (5.66%)	1 / 53 (1.89%)	
occurrences (all)	3	1	
Colitis			

subjects affected / exposed	1 / 53 (1.89%)	3 / 53 (5.66%)	
occurrences (all)	1	3	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	4 / 53 (7.55%)	2 / 53 (3.77%)	
occurrences (all)	5	2	
Hepatocellular injury			
subjects affected / exposed	5 / 53 (9.43%)	1 / 53 (1.89%)	
occurrences (all)	5	1	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	3 / 53 (5.66%)	4 / 53 (7.55%)	
occurrences (all)	3	4	
Hyperhidrosis			
subjects affected / exposed	1 / 53 (1.89%)	3 / 53 (5.66%)	
occurrences (all)	1	3	
Lichenoid keratosis			
subjects affected / exposed	1 / 53 (1.89%)	3 / 53 (5.66%)	
occurrences (all)	1	3	
Night sweats			
subjects affected / exposed	2 / 53 (3.77%)	5 / 53 (9.43%)	
occurrences (all)	2	6	
Pruritus			
subjects affected / exposed	5 / 53 (9.43%)	11 / 53 (20.75%)	
occurrences (all)	5	11	
Rash			
subjects affected / exposed	13 / 53 (24.53%)	10 / 53 (18.87%)	
occurrences (all)	13	11	
Rash pruritic			
subjects affected / exposed	9 / 53 (16.98%)	6 / 53 (11.32%)	
occurrences (all)	10	7	
Vitiligo			
subjects affected / exposed	4 / 53 (7.55%)	3 / 53 (5.66%)	
occurrences (all)	4	3	
Endocrine disorders			

Hyperthyroidism			
subjects affected / exposed	8 / 53 (15.09%)	6 / 53 (11.32%)	
occurrences (all)	8	6	
Hypothyroidism			
subjects affected / exposed	8 / 53 (15.09%)	3 / 53 (5.66%)	
occurrences (all)	8	3	
Thyroiditis			
subjects affected / exposed	2 / 53 (3.77%)	3 / 53 (5.66%)	
occurrences (all)	2	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 53 (13.21%)	3 / 53 (5.66%)	
occurrences (all)	8	4	
Back pain			
subjects affected / exposed	3 / 53 (5.66%)	1 / 53 (1.89%)	
occurrences (all)	3	1	
Musculoskeletal pain			
subjects affected / exposed	3 / 53 (5.66%)	1 / 53 (1.89%)	
occurrences (all)	3	2	
Myalgia			
subjects affected / exposed	6 / 53 (11.32%)	7 / 53 (13.21%)	
occurrences (all)	6	7	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	3 / 53 (5.66%)	2 / 53 (3.77%)	
occurrences (all)	4	2	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 53 (16.98%)	6 / 53 (11.32%)	
occurrences (all)	9	7	
Hypokalaemia			
subjects affected / exposed	3 / 53 (5.66%)	2 / 53 (3.77%)	
occurrences (all)	3	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 August 2017	- changed the timing of primary endpoint analysis - study duration revised - other minor changes

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported