Clinical trial results:
Phase 1/2 Study of BMS-986310 Administered Alone and in Combination with Nivolumab in Participants with Advanced Solid Tumors

Summary

EudraCT number	2018-002108-15
Trial protocol	BE IT
Global end of trial date	29 December 2020

Results information

Result version number	v1 (current)
This version publication date	23 December 2021
First version publication date	23 December 2021

Trial information

Trial identification

Sponsor protocol code	CA044-001

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	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, 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	21 April 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability, and to determine the MTD or MAAD and RP2D of BMS-986310 when administered in combination with nivolumab in subjects with select advanced solid tumors.

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 participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 September 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	Belgium: 6
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	25
EEA total number of subjects	6

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)	19
From 65 to 84 years	6

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

25 participants were treated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1

Arm description:

BMS-986310 2 mg QD + Nivolumab 480 mg Q4W

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	BMS-986558
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

480 mg Q4W

Investigational medicinal product name	BMS-986310
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg QD

Arm title	Cohort 2

Arm description:

BMS-986310 6 mg QD + Nivolumab 480 mg Q4W

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	BMS-986558
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

480 mg Q4W

Investigational medicinal product name	BMS-986310
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details: 6 mg QD	

Arm title	Cohort 3
Arm description: BMS-986310 12 mg QD + Nivolumab 480 mg Q4W	
Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	BMS-986558
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 480 mg Q4W	
Investigational medicinal product name	BMS-986310
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 12 mg QD	
Arm title	Cohort 4
Arm description: BMS-986310 20 mg QD + Nivolumab 480 mg Q4W	
Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	BMS-986558
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 480 mg Q4W	
Investigational medicinal product name	BMS-986310
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 20 mg QD	
Arm title	Cohort 5
Arm description: BMS-986310 30 mg QD + Nivolumab 480 mg Q4W	
Arm type	Experimental
Investigational medicinal product name	BMS-986310
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details: 20 mg QD	
Investigational medicinal product name	BMS-986310
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 30 mg QD	
Arm title	Food Effect
Arm description: Single dose of BMS-986310 under fasting conditions, followed by a second single dose of BMS-986310 7 days later with a high fat meal	
Arm type	Experimental
Investigational medicinal product name	BMS-986310
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 6 mg single dose (fasting/with food)	

Number of subjects in period 1	Cohort 1	Cohort 2	Cohort 3
Started	3	4	3
Completed	0	0	0
Not completed	3	4	3
Adverse event, serious fatal	-	3	2
Consent withdrawn by subject	3	-	1
Other reasons	-	1	-
Follow-up no longer required per protocol	-	-	-

Number of subjects in period 1	Cohort 4	Cohort 5	Food Effect
Started	4	5	6
Completed	0	0	0
Not completed	4	5	6
Adverse event, serious fatal	2	4	3
Consent withdrawn by subject	1	1	1
Other reasons	-	-	1
Follow-up no longer required per protocol	1	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1
Reporting group description:	
BMS-986310 2 mg QD + Nivolumab 480 mg Q4W	
Reporting group title	Cohort 2
Reporting group description:	
BMS-986310 6 mg QD + Nivolumab 480 mg Q4W	
Reporting group title	Cohort 3
Reporting group description:	
BMS-986310 12 mg QD + Nivolumab 480 mg Q4W	
Reporting group title	Cohort 4
Reporting group description:	
BMS-986310 20 mg QD + Nivolumab 480 mg Q4W	
Reporting group title	Cohort 5
Reporting group description:	
BMS-986310 30 mg QD + Nivolumab 480 mg Q4W	
Reporting group title	Food Effect
Reporting group description:	
Single dose of BMS-986310 under fasting conditions, followed by a second single dose of BMS-986310 7 days later with a high fat meal	

Reporting group values	Cohort 1	Cohort 2	Cohort 3
Number of subjects	3	4	3
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)	2	3	2
From 65-84 years	1	1	1
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	60.3	56.3	56.0
standard deviation	± 8.1	± 10.2	± 9.2
Gender Categorical Units: Subjects			
Female	1	3	2
Male	2	1	1

Reporting group values	Cohort 4	Cohort 5	Food Effect
Number of subjects	4	5	6

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)	3	5	4
From 65-84 years	1	0	2
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	57.8	47.8	61.0
standard deviation	± 10.1	± 7.3	± 12.8
Gender Categorical Units: Subjects			
Female	3	5	4
Male	1	0	2

Reporting group values	Total		
Number of subjects	25		
Age Categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	19		
From 65-84 years	6		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical Units: Subjects			
Female	18		
Male	7		

End points

End points reporting groups

Reporting group title	Cohort 1
Reporting group description:	
BMS-986310 2 mg QD + Nivolumab 480 mg Q4W	
Reporting group title	Cohort 2
Reporting group description:	
BMS-986310 6 mg QD + Nivolumab 480 mg Q4W	
Reporting group title	Cohort 3
Reporting group description:	
BMS-986310 12 mg QD + Nivolumab 480 mg Q4W	
Reporting group title	Cohort 4
Reporting group description:	
BMS-986310 20 mg QD + Nivolumab 480 mg Q4W	
Reporting group title	Cohort 5
Reporting group description:	
BMS-986310 30 mg QD + Nivolumab 480 mg Q4W	
Reporting group title	Food Effect
Reporting group description:	
Single dose of BMS-986310 under fasting conditions, followed by a second single dose of BMS-986310 7 days later with a high fat meal	

Primary: Number of Participants Experiencing Adverse Events

End point title	Number of Participants Experiencing Adverse Events[1]
End point description:	
Number of participants experiencing different types of adverse events	
End point type	Primary
End point timeframe:	
From first dose to 100 days following last dose	

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 have been performed for this endpoint

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	3	4
Units: Participants				
Any type Adverse Event (any grade)	3	4	3	4
Serious Adverse Events (SAEs)	2	3	2	1
Adverse events meeting DLT criteria	0	0	0	0
AEs leading to dose delay	2	1	1	1
AEs leading to discontinuation	0	1	0	2
Deaths	0	4	2	2

End point values	Cohort 5	Food Effect		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	6		
Units: Participants				
Any type Adverse Event (any grade)	5	6		
Serious Adverse Events (SAEs)	3	5		
Adverse events meeting DLT criteria	0	0		
AEs leading to dose delay	1	1		
AEs leading to discontinuation	1	1		
Deaths	4	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

ORR is defined as the proportion of participants whose Best Overall Response (BOR) is either Complete Response (CR) or Partial Response (PR), as assessed by Investigator per RECIST v1.1 criteria

End point type	Secondary

End point timeframe:

From first dose to study completion

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	3	4
Units: Percent of Participants				
arithmetic mean (confidence interval 95%)	0 (0.0 to 70.8)	0 (0.0 to 60.2)	0 (0.0 to 70.8)	0 (0.0 to 60.2)

End point values	Cohort 5	Food Effect		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	6		
Units: Percent of Participants				
arithmetic mean (confidence interval 95%)	0 (0.0 to 52.2)	0 (0.0 to 45.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR for a participant with a BOR of CR or PR is defined as the time between the date of first response and the date of the first objectively documented tumor progression per RECIST v1.1 or death, whichever occurs first.

End point type	Secondary

End point timeframe:

From first dose to study completion

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[2]	0[3]	0[4]	0[5]
Units: Months				
median (full range (min-max))	(to)	(to)	(to)	(to)

Notes:

[2] - No BOR of CR or PR were observed

[3] - No BOR of CR or PR were observed

[4] - No BOR of CR or PR were observed

[5] - No BOR of CR or PR were observed

End point values	Cohort 5	Food Effect		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: Months				
median (full range (min-max))	(to)	(to)		

Notes:

[6] - No BOR of CR or PR were observed

[7] - No BOR of CR or PR were observed

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival Rates (PFSR)

End point title	Progression Free Survival Rates (PFSR)

End point description:

PFS for a participant is defined as the time from the first dosing date to the date of first objectively documented disease progression or death due to any cause, whichever occurs first.

End point type	Secondary

End point timeframe:

From first dose to 3,6,9,12 and 24 months after first dose

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	3	4
Units: Percent of Participants				
number (confidence interval 95%)				
3 month	50.0 (0.6 to 91.0)	0 (0 to 0)	50.0 (0.6 to 91.0)	25.0 (0.9 to 66.5)
6 month	0 (0 to 0)	0 (0 to 0)	50.0 (0.6 to 91.0)	99999 (99999 to 99999)
9 month	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	99999 (99999 to 99999)
12 month	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	99999 (99999 to 99999)
24 month	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	99999 (99999 to 99999)

End point values	Cohort 5	Food Effect		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	6		
Units: Percent of Participants				
number (confidence interval 95%)				
3 month	20.0 (0.8 to 58.2)	0 (0 to 0)		
6 month	20.0 (0.8 to 58.2)	0 (0 to 0)		
9 month	20.0 (0.8 to 58.2)	0 (0 to 0)		
12 month	99999 (99999 to 99999)	0 (0 to 0)		
24 month	99999 (99999 to 99999)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Concentration (Cmax) of BMS-986310

End point title	Maximum Observed Concentration (Cmax) of BMS-986310

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 Day 1, Cycle 2 Day 2 (Cycle 0 Day 1 - fasting, Cycle 1 Day 8-fed for Food Effect Cohort)

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	3	3
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
C1D1	82.4 (± 20)	218 (± 35)	317 (± 19)	644 (± 12)
C2D1	211 (± 99999)	593 (± 27)	869 (± 50)	1160 (± 99999)

End point values	Cohort 5	Food Effect		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	6		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
C1D1	1215 (± 12)	1149 (± 64)		
C2D1	3394 (± 37)	1045 (± 53)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve From Time Zero to the Time of the Last Quantifiable Concentration - AUC(0-T) of BMS-986310

End point title	Area Under the Concentration-Time Curve From Time Zero to the Time of the Last Quantifiable Concentration - AUC(0-T) of BMS-986310

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 Day 1, Cycle 2 Day 2 (Cycle 0 Day 1 - fasting, Cycle 1 Day 8-fed for Food Effect Cohort)

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	3	3
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)				
C1D1	1069 (± 20)	2005 (± 57)	5459 (± 18)	8322 (± 34)
C2D1	3802 (± 99999)	7310 (± 36)	15390 (± 58)	20030 (± 99999)

End point values	Cohort 5	Food Effect		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	6		
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)				
C1D1	14716 (± 46)	47398 (± 47)		
C2D1	43142 (± 71)	34576 (± 58)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve in One Dosing Interval - AUC(TAU) of BMS-986310

End point title	Area Under the Concentration-Time Curve in One Dosing Interval - AUC(TAU) of BMS-986310[8]

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 Day 1, Cycle 2 Day 2

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No analysis performed for this endpoint for the Food Effect cohort

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	3
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)				
C1D1	1069 (± 20)	3144 (± 21)	5459 (± 18)	8322 (± 34)
C2D1	3802 (± 99999)	8372 (± 34)	15390 (± 58)	20030 (± 99999)

End point values	Cohort 5			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)				
C1D1	19966 (± 17)			

C2D1	83395 (± 15)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Total Body Clearance (CLT/F) of BMS-986310

End point title	Apparent Total Body Clearance (CLT/F) of BMS-986310

End point description:

End point type	Secondary

End point timeframe:

Cycle 2 Day 1 (Cycle 0 Day 8 - Fed for Food Effect cohort)

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	2	2	1
Units: mL/min				
geometric mean (geometric coefficient of variation)	8.77 (± 99999)	11.9 (± 34)	13.0 (± 58)	16.6 (± 99999)

End point values	Cohort 5	Food Effect		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	6		
Units: mL/min				
geometric mean (geometric coefficient of variation)	6.00 (± 15)	9.45 (± 68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Ratio of AUC(TAU) at Steady State to AUC(TAU) After the First Dose - AI_AUC of BMS-986310

End point title	Ratio of AUC(TAU) at Steady State to AUC(TAU) After the First Dose - AI_AUC of BMS-986310[9]

End point description:

End point type	Secondary

End point timeframe:

From Cycle 1 Day 1 to Cycle 2 Day 1

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No analysis performed for this endpoint for the Food Effect cohort

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	2	2	1
Units: Ratio				
geometric mean (geometric coefficient of variation)	2.94 (± 99999)	2.94 (± 15)	2.76 (± 37)	2.86 (± 99999)

End point values	Cohort 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Ratio				
geometric mean (geometric coefficient of variation)	3.10 (± 141)			

Statistical analyses

No statistical analyses for this end point

Secondary: Half Life of BMS-986310 - T-Half

End point title	Half Life of BMS-986310 - T-Half[10]

End point description:

End point type	Secondary

End point timeframe:

Cycle 2 Day 1

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No analysis performed for this endpoint for the Food Effect cohort

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	2	2	1
Units: Hours				
arithmetic mean (standard deviation)	40.1 (± 99999)	36.3 (± 13.76)	39.0 (± 17.47)	36.8 (± 99999)

End point values	Cohort 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Hours				
arithmetic mean (standard deviation)	21.4 (± 30.30)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve From Time Zero Extrapolated to Infinite Time - AUC(INF) of BMS-986310

End point title	Area Under the Concentration-Time Curve From Time Zero Extrapolated to Infinite Time - AUC(INF) of BMS-986310[11]

End point description:

End point type	Secondary

End point timeframe:

Cycle 0 Day 8 - Fed

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis performed for this endpoint only in the Food Effect cohort

End point values	Food Effect			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)	52898 (± 52)			

Statistical analyses

No statistical analyses for this end point

Secondary: Fold Change From Baseline in Urinary Prostaglandin E Metabolite (PGEM/PGAM)

End point title	Fold Change From Baseline in Urinary Prostaglandin E Metabolite (PGEM/PGAM)[12]

End point description:

Fold change in urinary Prostaglandin E metabolite (PGEM/PGAM), normalized by urinary creatinine. Measurements were collected at Cycle 1 Day 1, Cycle 1 Day 2, Cycle 1 Day 8, Cycle 1 day 15, Cycle 2 Day 1, Cycle 2 Day 15, and Cycle 3 Day 1. Results of fold change from baseline for Cycle 3 Day 1 are reported here.

End point type	Secondary

End point timeframe:

From baseline to Cycle 3 Day 1 (approximately 8 weeks)

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No analysis performed for this endpoint for the Food Effect cohort

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	1	1	2
Units: Fold change				
geometric mean (geometric coefficient of variation)				
PGEM	1.02 (± 99999)	7.71 (± 99999)	4.83 (± 99999)	2.00 (± 7.01)
PGAM	0.85 (± 99999)	4.01 (± 99999)	5.74 (± 99999)	2.00 (± 54.95)

End point values	Cohort 5			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Fold change				
geometric mean (geometric coefficient of variation)				
PGEM	5.98 (± 114.42)			
PGAM	7.27 (± 106.30)			

Statistical analyses

No statistical analyses for this end point

Secondary: Fold Change From Baseline in Tumor Necrosis Factor Alpha (TNF-alpha)

End point title	Fold Change From Baseline in Tumor Necrosis Factor Alpha (TNF-alpha)[13]

End point description:

Fold change from baseline in TNF-alpha in lipopolysaccharide (LPS)-stimulated whole blood. Measurements were collected at multiple timepoints. Results for fold change from baseline to Cycle 2 Day 15 are reported here.

End point type	Secondary

End point timeframe:

From baseline to Cycle 2 Day 15 (approximately 6 weeks)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No analysis performed for this endpoint for the Food Effect cohort

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	2	2	1
Units: Fold change				
geometric mean (geometric coefficient of variation)	2.76 (± 99999)	2.89 (± 24.37)	3.65 (± 24.38)	1.05 (± 99999)

End point values	Cohort 5			
Subject group type	Reporting group			
Number of subjects analysed	0[14]			
Units: Fold change				
geometric mean (geometric coefficient of variation)	()			

Notes:

[14] - No measurements were available at the specified timepoint for this cohort.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
AEs collected were reported between first dose and 100 days after last dose of study therapy	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups	
Reporting group title	All Cohorts
Reporting group description:	
All participants receiving at least 1 dose of study drug	

Serious adverse events	All Cohorts		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 25 (64.00%)		
number of deaths (all causes)	16		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	7 / 25 (28.00%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Metastases to central nervous system			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour haemorrhage			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour pain			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric stenosis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites			

subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Biliary obstruction				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic haemorrhage				
subjects affected / exposed	1 / 25 (4.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infective myositis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All Cohorts		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 25 (96.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 25 (28.00%)		
occurrences (all)	9		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	11 / 25 (44.00%)		
occurrences (all)	14		
Gait disturbance			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	3		
Non-cardiac chest pain			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	3		
Oedema peripheral			
subjects affected / exposed	5 / 25 (20.00%)		
occurrences (all)	7		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Dysphonia			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	3		
Dyspnoea			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	9		
Pleural effusion			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	6		

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	6		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	13		
Blood bilirubin increased			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	8		
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	7		
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	3		
Lymphocyte count decreased			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	10		
Platelet count decreased			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	8		
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	4		
Lipase increased			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Infusion related reaction			

subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2		
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all) Palpitations subjects affected / exposed occurrences (all)	 4 / 25 (16.00%) 4 2 / 25 (8.00%) 2		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	 2 / 25 (8.00%) 3 5 / 25 (20.00%) 9		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 9 / 25 (36.00%) 31		
Eye disorders Cataract subjects affected / exposed occurrences (all) Vision blurred subjects affected / exposed occurrences (all)	 2 / 25 (8.00%) 2 3 / 25 (12.00%) 4		
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain lower subjects affected / exposed occurrences (all)	 3 / 25 (12.00%) 3 8 / 25 (32.00%) 15 2 / 25 (8.00%) 3		

Abdominal pain upper				
subjects affected / exposed	3 / 25 (12.00%)			
occurrences (all)	5			
Ascites				
subjects affected / exposed	4 / 25 (16.00%)			
occurrences (all)	7			
Constipation				
subjects affected / exposed	5 / 25 (20.00%)			
occurrences (all)	7			
Duodenal ulcer				
subjects affected / exposed	2 / 25 (8.00%)			
occurrences (all)	2			
Dyspepsia				
subjects affected / exposed	2 / 25 (8.00%)			
occurrences (all)	2			
Dry mouth				
subjects affected / exposed	2 / 25 (8.00%)			
occurrences (all)	2			
Diarrhoea				
subjects affected / exposed	4 / 25 (16.00%)			
occurrences (all)	5			
Dysphagia				
subjects affected / exposed	2 / 25 (8.00%)			
occurrences (all)	4			
Gastrooesophageal reflux disease				
subjects affected / exposed	2 / 25 (8.00%)			
occurrences (all)	2			
Oral pain				
subjects affected / exposed	2 / 25 (8.00%)			
occurrences (all)	2			
Vomiting				
subjects affected / exposed	7 / 25 (28.00%)			
occurrences (all)	9			
Nausea				
subjects affected / exposed	8 / 25 (32.00%)			
occurrences (all)	10			

Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	4		
Pruritus			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	5		
Rash			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	5		
Rash maculo-papular			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Dysuria			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 25 (20.00%)		
occurrences (all)	6		
Back pain			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	5		
Pain in extremity			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	4		
Myalgia			
subjects affected / exposed	5 / 25 (20.00%)		
occurrences (all)	12		
Muscular weakness			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	4		

Infections and infestations			
Candida infection			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Pneumonia			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 25 (24.00%)		
occurrences (all)	6		
Hypoalbuminaemia			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	9		
Hypocalcaemia			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	4		
Dehydration			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Hypomagnesaemia			
subjects affected / exposed	6 / 25 (24.00%)		
occurrences (all)	9		
Hypophosphataemia			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	5		
Hyponatraemia			
subjects affected / exposed	5 / 25 (20.00%)		
occurrences (all)	14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 August 2018	- Endpoints listed by study parts - Updates to criteria for discontinuation
07 March 2019	- Study design changes
10 May 2019	- Revision of eligibility criteria - Changes to exploratory endpoints

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.

The study was terminated for reasons not related to safety.

Notes: