Clinical trial results:
A Phase 4 Multicenter, Randomized, Open-label, Efficacy Assessor-blinded Study of Risankizumab Compared to Apremilast for the Treatment of Adult Subjects With Moderate Plaque Psoriasis Who Are Candidates for Systemic Therapy

Summary

EudraCT number	2020-005512-21
Trial protocol	DE
Global end of trial date	20 April 2023

Results information

Result version number	v1 (current)
This version publication date	20 April 2024
First version publication date	20 April 2024

Trial information

Trial identification

Sponsor protocol code	M20-326

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04908475
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co. KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6 4UB
Public contact	Global Medical Services, Abbvie, 001 8006339110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, Abbvie, 001 8006339110, abbvieclinicaltrials@abbvie.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	20 April 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 April 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the study is to evaluate the efficacy and safety of risankizumab versus apremilast for the treatment of adult subjects with moderate plaque PsO who are candidates for systemic therapy.

Protection of trial subjects:

Subject and/or legal guardian read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 June 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 77
Country: Number of subjects enrolled	Germany: 94
Country: Number of subjects enrolled	Israel: 14
Country: Number of subjects enrolled	Poland: 47
Country: Number of subjects enrolled	United States: 120
Worldwide total number of subjects	352
EEA total number of subjects	141

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)	314
From 65 to 84 years	38

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 352 participants were enrolled from 48 sites across 5 countries including Canada, Germany, Israel, Poland, and the United States.

Pre-assignment

Screening details:

Period A: participants were randomized in a 1:2 ratio to risankizumab (RZB) or apremilast (APR). Period B: participants receiving RZB were continued up to Week 52; participants receiving APR were re-randomized (stratified by PASI 75 response) in a 1:1 ratio to receive either RZB or APR (with the option to receive RZB as rescue) up to Week 52.

Period 1

Period 1 title	Period A (Baseline to Week 16)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Blinded Efficacy Assessor: A qualified physician (may be a non-dermatologist) or designee (may be a non-physician) from the site was responsible for performing the efficacy assessments, including PASI, BSA, and sPGA at all appropriate study visits. The efficacy assessor remained blinded to patient's treatment, clinical laboratory results, and all subject safety data during the course of the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Period A: APR

Arm description:

Apremilast 30 mg orally twice daily (BID) up to Week 16

Arm type	Active comparator
Investigational medicinal product name	apremilast
Investigational medicinal product code	
Other name	Otezla
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Study drug administration for apremilast began at Baseline (Day 1) based on the dose titration schedule from Day 1 to Day 5 and continued with 30 mg BID until the day prior to the Week 16 visit where re-randomization occurred.

Arm title	Period A: RZB

Arm description:

Risankizumab 150 mg as a single subcutaneous (SC) injection at Baseline (Day 1) and Week 4.

Arm type	Experimental
Investigational medicinal product name	risankizumab
Investigational medicinal product code	ABBV-066
Other name	Skyrizi
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Study drug administration for risankizumab will occur at Baseline (Day 1) and Week 4.

Number of subjects in period 1	Period A: APR	Period A: RZB
Started	234	118
Completed	216	118
Not completed	18	0
Consent withdrawn by subject	9	-
Lost to follow-up	3	-
Other, Not Specified	6	-

Period 2

Period 2 title	Period B (Week 16 to Week 52)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Blinded Efficacy Assessor: A qualified physician (may be a non-dermatologist) or designee (may be a non-physician) from the site was responsible for performing the efficacy assessments, including PASI, BSA, and sPGA at all appropriate study visits. The efficacy assessor remained blinded to patient's treatment, clinical laboratory results, and all subject safety data during the course of the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Period B: RZB/RZB

Arm description:

Risankizumab 150 mg as a single SC injection at Weeks 16, 28, and 40.

Arm type	Experimental
Investigational medicinal product name	risankizumab
Investigational medicinal product code	ABBV-066
Other name	Skyrizi
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received risankizumab 150 mg as a single SC injection at Weeks 16, 28, and 40.

Arm title	Period B: APR/APR, NR

Arm description:

Participants who were randomized to apremilast in Period A, failed to achieve PASI 75 at Week 16 (non-responders [NR]) and were re-randomized to apremilast 30 mg orally BID up to Week 52.

Arm type	Active comparator
Investigational medicinal product name	apremilast
Investigational medicinal product code	
Other name	Otezla
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received apremilast 30 mg orally BID up to Week 52.

Investigational medicinal product name	risankizumab
Investigational medicinal product code	ABBV-066
Other name	Skyrizi
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Rescue risankizumab was offered to participants re-randomized to apremilast who were PASI 50 nonresponders at Week 28 (rescue risankizumab administered at Weeks 28, 32, and 44) or Week 40 (rescue risankizumab administered at Weeks 40 and 44).

Arm title	Period B: APR/RZB, NR

Arm description:

Participants who were randomized to apremilast in Period A, failed to achieve PASI 75 at Week 16 (NR) and were re-randomized to risankizumab 150 mg as a single SC injection at Weeks 16, 20, 32, and 44.

Arm type	Experimental
Investigational medicinal product name	risankizumab
Investigational medicinal product code	ABBV-066
Other name	Skyrizi
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received risankizumab 150 mg as a single SC injection at Weeks 16, 20, 32, and 44.

Arm title	Period B: APR/APR, R

Arm description:

Participants who were randomized to apremilast in Period A, achieved PASI 75 at Week 16 (responders [R]) and were re-randomized to apremilast 30 mg orally BID up to Week 52.

Arm type	Active comparator
Investigational medicinal product name	apremilast
Investigational medicinal product code	
Other name	Otezla
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received apremilast 30 mg orally BID up to Week 52.

Investigational medicinal product name	risankizumab
Investigational medicinal product code	ABBV-066
Other name	Skyrizi
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Rescue risankizumab was offered to participants re-randomized to apremilast who were PASI 50 nonresponders at Week 28 (rescue risankizumab administered at Weeks 28, 32, and 44) or Week 40 (rescue risankizumab administered at Weeks 40 and 44).

Arm title	Period B: APR/RZB, R

Arm description:

Participants who were randomized to apremilast in Period A, achieved PASI 75 at Week 16 (R) and were re-randomized to risankizumab 150 mg as a single SC injection at Weeks 16, 20, 32, and 44.

Arm type	Experimental
Investigational medicinal product name	risankizumab
Investigational medicinal product code	ABBV-066
Other name	Skyrizi
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received risankizumab 150 mg as a single SC injection at Weeks 16, 20, 32, and 44.

Number of subjects in period 2[1]	Period B: RZB/RZB	Period B: APR/APR, NR	Period B: APR/RZB, NR
Started	118	78	83
Received ≥1 Dose of Study Drug	116	75	82
Received RZB as Rescue Medication	0 [2]	47	0 [3]
Completed	69	42	57
Not completed	49	36	26
Consent withdrawn by subject	5	13	2
Lost to follow-up	6	4	6
Other, Not Specified	38	19	18

Number of subjects in period 2[1]	Period B: APR/APR, R	Period B: APR/RZB, R
Started	22	20
Received ≥1 Dose of Study Drug	22	20
Received RZB as Rescue Medication	1 [4]	0 [5]
Completed	15	13
Not completed	7	7
Consent withdrawn by subject	3	-
Lost to follow-up	-	-
Other, Not Specified	4	7

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Only participants re-randomized for Part B are included.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Milestones are correct as presented.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Only participants re-randomized for Part B are included.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Milestones are correct as presented.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestones are correct as presented.

Baseline characteristics

Reporting groups	
Reporting group title	Period A: APR
Reporting group description:	
Apremilast 30 mg orally twice daily (BID) up to Week 16	
Reporting group title	Period A: RZB
Reporting group description:	
Risankizumab 150 mg as a single subcutaneous (SC) injection at Baseline (Day 1) and Week 4.	

Reporting group values	Period A: APR	Period A: RZB	Total
Number of subjects	234	118	352
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	46.2	45.5	
standard deviation	± 14.27	± 13.63	-
Gender categorical Units: Subjects			
Female	79	42	121
Male	155	76	231
Ethnicity Units: Subjects			
Hispanic or Latino	23	7	30
Not Hispanic or Latino	211	111	322
Race Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	14	12	26
Native Hawaiian or Other Pacific Islander	1	2	3
Black or African American	9	5	14
White	209	98	307
More Than One Race	0	1	1

End points

End points reporting groups

Reporting group title	Period A: APR
Reporting group description: Apremilast 30 mg orally twice daily (BID) up to Week 16	
Reporting group title	Period A: RZB
Reporting group description: Risankizumab 150 mg as a single subcutaneous (SC) injection at Baseline (Day 1) and Week 4.	
Reporting group title	Period B: RZB/RZB
Reporting group description: Risankizumab 150 mg as a single SC injection at Weeks 16, 28, and 40.	
Reporting group title	Period B: APR/APR, NR
Reporting group description: Participants who were randomized to apremilast in Period A, failed to achieve PASI 75 at Week 16 (non-responders [NR]) and were re-randomized to apremilast 30 mg orally BID up to Week 52.	
Reporting group title	Period B: APR/RZB, NR
Reporting group description: Participants who were randomized to apremilast in Period A, failed to achieve PASI 75 at Week 16 (NR) and were re-randomized to risankizumab 150 mg as a single SC injection at Weeks 16, 20, 32, and 44.	
Reporting group title	Period B: APR/APR, R
Reporting group description: Participants who were randomized to apremilast in Period A, achieved PASI 75 at Week 16 (responders [R]) and were re-randomized to apremilast 30 mg orally BID up to Week 52.	
Reporting group title	Period B: APR/RZB, R
Reporting group description: Participants who were randomized to apremilast in Period A, achieved PASI 75 at Week 16 (R) and were re-randomized to risankizumab 150 mg as a single SC injection at Weeks 16, 20, 32, and 44.	

Primary: Percentage of Participants Achieving Psoriasis Area Severity Index (PASI) 90 (Defined as at Least 90% Improvement in PASI From Baseline) in Intent to Treat Population at Week 16 (ITT_A)

End point title	Percentage of Participants Achieving Psoriasis Area Severity Index (PASI) 90 (Defined as at Least 90% Improvement in PASI From Baseline) in Intent to Treat Population at Week 16 (ITT_A)

End point description:

The PASI is used to evaluate a participant's overall psoriasis disease state that includes the percent of surface area of skin that is affected and the severity of erythema, induration, and desquamation over four body regions (head, upper extremities, trunk, and lower extremities). Scores range from 0 to 72, with higher scores indicating more severe disease.

ITT_A Population: all participants randomized in Period A

End point type	Primary

End point timeframe:

Week 16

End point values	Period A: APR	Period A: RZB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	234	118		
Units: percentage of participants				
number (confidence interval 95%)	5.1 (2.3 to 8.0)	55.9 (47.0 to 64.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Period A: APR v Period A: RZB
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	50.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	41.3
upper limit	60.1

Notes:

[1] - Adjusted for strata (baseline body weight [≤100 kg, > 100 kg] and prior exposure to any systemic and/or biologic treatment for psoriasis [0, ≥1]) for the comparison of 2 treatment groups.

Primary: Percentage of Participants Achieving Static Physician Global Assessment (sPGA) 0 or 1 With at least 2-grade Improvement From Baseline in Intent to Treat Population at Week 16 (ITT_A)

End point title	Percentage of Participants Achieving Static Physician Global Assessment (sPGA) 0 or 1 With at least 2-grade Improvement From Baseline in Intent to Treat Population at Week 16 (ITT_A)

End point description:

The sPGA is the physician's current assessment of the average thickness, erythema, and scaling of all psoriatic lesions. Scores range from 0 (clear) to 4 (severe).

ITT_A Population: all participants randomized in Period A.

End point type	Primary

End point timeframe:

Week 16

End point values	Period A: APR	Period A: RZB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	234	118		
Units: percentage of participants				
number (confidence interval 95%)	18.4 (13.4 to 23.3)	75.4 (67.7 to 83.2)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Period A: APR v Period A: RZB
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	56.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	47.7
upper limit	66

Notes:

[2] - Adjusted for strata (baseline body weight [≤100 kg, > 100 kg] and prior exposure to any systemic and/or biologic treatment for psoriasis [0, ≥1]) for the comparison of 2 treatment groups.

Primary: Percentage of Participants Achieving PASI 90 in Intent to Treat Population for Apremilast Non-Responders at Week 52 (ITT_B_NR)

End point title	Percentage of Participants Achieving PASI 90 in Intent to Treat Population for Apremilast Non-Responders at Week 52 (ITT_B_NR)

End point description:

The PASI is used to evaluate a participant's overall psoriasis disease state that includes the percent of surface area of skin that is affected and the severity of erythema, induration, and desquamation over four body regions (head, upper extremities, trunk, and lower extremities). Scores range from 0 to 72, with higher scores indicating more severe disease.

ITT_B_NR Population: participants randomized to APR at Baseline who failed to achieve PASI 75 at Week 16 and were re-randomized to APR or RZB in Period B.

End point type	Primary

End point timeframe:

Week 52

End point values	Period B: APR/APR, NR	Period B: APR/RZB, NR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	83		
Units: percentage of participants				
number (confidence interval 95%)	2.6 (0.0 to 6.1)	72.3 (62.7 to 81.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Period B: APR/APR, NR v Period B: APR/RZB, NR
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Chi-squared
Parameter estimate	Difference
Point estimate	69.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	59.5
upper limit	80

Secondary: Percentage of Participants Achieving Static Physician Global Assessment (sPGA) 0 or 1 With at least 2-grade Improvement From Baseline in Intent to Treat Population for Apremilast Non-Responders at Week 52 (ITT_B_NR)

End point title	Percentage of Participants Achieving Static Physician Global Assessment (sPGA) 0 or 1 With at least 2-grade Improvement From Baseline in Intent to Treat Population for Apremilast Non-Responders at Week 52 (ITT_B_NR)

End point description:

The sPGA is the physician's current assessment of the average thickness, erythema, and scaling of all psoriatic lesions. Scores range from 0 (clear) to 4 (severe).

ITT_B_NR Population: participants randomized to APR at Baseline who failed to achieve PASI 75 at Week 16 and were re-randomized to APR or RZB in Period B.

End point type	Secondary

End point timeframe:

Week 52

End point values	Period B: APR/APR, NR	Period B: APR/RZB, NR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	83		
Units: percentage of participants				
number (confidence interval 95%)	7.7 (1.8 to 13.6)	77.1 (68.1 to 86.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Period B: APR/APR, NR v Period B: APR/RZB, NR
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Chi-squared
Parameter estimate	Difference
Point estimate	69.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	58.6
upper limit	80.2

Secondary: Percentage of Participants Achieving PASI 75 (Defined as at Least 75% Improvement in PASI From Baseline) in Intent to Treat Population at Week 16 (ITT_A)

End point title	Percentage of Participants Achieving PASI 75 (Defined as at Least 75% Improvement in PASI From Baseline) in Intent to Treat Population at Week 16 (ITT_A)

End point description:

The PASI is used to evaluate a participant's overall psoriasis disease state that includes the percent of surface area of skin that is affected and the severity of erythema, induration, and desquamation over four body regions (head, upper extremities, trunk, and lower extremities). Scores range from 0 to 72, with higher scores indicating more severe disease.

ITT_A Population: all participants randomized in Period A

End point type	Secondary

End point timeframe:

Week 16

End point values	Period A: APR	Period A: RZB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	234	118		
Units: percentage of participants				
number (confidence interval 95%)	18.8 (13.8 to 23.8)	84.7 (78.3 to 91.2)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Period A: APR v Period A: RZB
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Difference
Point estimate	65.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	57.6
upper limit	73.9

Notes:

[3] - Adjusted for strata (baseline body weight [≤100 kg, > 100 kg] and prior exposure to any systemic and/or biologic treatment for psoriasis [0, ≥1] for the comparison of 2 treatment groups.

Secondary: Percentage of Participants Achieving PASI 75 in Intent to Treat Population for Apremilast Non-Responders at Week 52 (ITT_B_NR)

End point title	Percentage of Participants Achieving PASI 75 in Intent to Treat Population for Apremilast Non-Responders at Week 52 (ITT_B_NR)

End point description:

The PASI is used to evaluate a participant's overall psoriasis disease state that includes the percent of surface area of skin that is affected and the severity of erythema, induration, and desquamation over four body regions (head, upper extremities, trunk, and lower extremities). Scores range from 0 to 72, with higher scores indicating more severe disease.

ITT_B_NR Population: participants randomized to APR at Baseline who failed to achieve PASI 75 at Week 16 and were re-randomized to APR or RZB in Period B.

End point type	Secondary

End point timeframe:

Week 52

End point values	Period B: APR/APR, NR	Period B: APR/RZB, NR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	83		
Units: percentage of participants				
number (confidence interval 95%)	11.5 (4.4 to 18.6)	83.1 (75.1 to 91.2)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Period B: APR/APR, NR v Period B: APR/RZB, NR
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Chi-squared
Parameter estimate	Difference
Point estimate	71.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	60.9
upper limit	82.3

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug through approximately 20 weeks (140 days) after administration of the last dose of RZB (Week 40 or Week 44) or approximately 4 weeks (28 days) after the last dose of APR (Week 52).

Adverse event reporting additional description:

Safety Population: participants who received ≥1 dose of study drug. Note: Response at Week 16 was not
applicable to the Safety Reporting Groups.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Period A: APR

Reporting group description:

Apremilast 30 mg orally BID up to Week 16

Reporting group title	Period B: APR/APR/RZB

Reporting group description:

Participants who received apremilast in Period A who were re-randomized to receive apremilast 30 mg orally BID and received rescue medication with risankizumab.

Reporting group title	Period B: APR/RZB

Reporting group description:

Participants who received apremilast in Period A who were re-randomized to receive risankizumab 150 mg as a single SC injection at Weeks 16, 20, 32 and 44.

Reporting group title	Period B: RZB/RZB

Reporting group description:

Participants who received risankizumab 150 mg as a single subcutaneous (SC) injection at Day 1 and continued on risankizumab at Weeks 16, 28, and 40

Reporting group title	Period A: RZB

Reporting group description:

Risankizumab 150 mg as a single SC injection at Day 1 and Week 4

Reporting group title	Period B: APR/APR

Reporting group description:

Participants who received apremilast in Period A who were re-randomized to receive apremilast 30 mg orally BID up to Week 52.

Serious adverse events	Period A: APR	Period B: APR/APR/RZB	Period B: APR/RZB
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 234 (1.71%)	0 / 48 (0.00%)	3 / 102 (2.94%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
PROSTATE CANCER			

subjects affected / exposed	0 / 234 (0.00%)	0 / 48 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	0 / 234 (0.00%)	0 / 48 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOWER LIMB FRACTURE			
subjects affected / exposed	0 / 234 (0.00%)	0 / 48 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 234 (0.43%)	0 / 48 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CORONARY ARTERY DISEASE			
subjects affected / exposed	0 / 234 (0.00%)	0 / 48 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
CAROTID ARTERY STENOSIS			
subjects affected / exposed	1 / 234 (0.43%)	0 / 48 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SCIATICA			
subjects affected / exposed	0 / 234 (0.00%)	0 / 48 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GENERALISED TONIC-CLONIC SEIZURE			

subjects affected / exposed	0 / 234 (0.00%)	0 / 48 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
HYPERSENSITIVITY			
subjects affected / exposed	0 / 234 (0.00%)	0 / 48 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 234 (0.00%)	0 / 48 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OBSTRUCTIVE PANCREATITIS			
subjects affected / exposed	0 / 234 (0.00%)	0 / 48 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 234 (0.00%)	0 / 48 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UMBILICAL HERNIA			
subjects affected / exposed	0 / 234 (0.00%)	0 / 48 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
NASAL INFLAMMATION			
subjects affected / exposed	0 / 234 (0.00%)	0 / 48 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 234 (0.00%)	0 / 48 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Skin and subcutaneous tissue disorders			
URTICARIA			
subjects affected / exposed	0 / 234 (0.00%)	0 / 48 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
OSTEOCHONDROSIS			
subjects affected / exposed	1 / 234 (0.43%)	0 / 48 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOARTHRITIS			
subjects affected / exposed	0 / 234 (0.00%)	0 / 48 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
APPENDICITIS PERFORATED			
subjects affected / exposed	0 / 234 (0.00%)	0 / 48 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPSIS			
subjects affected / exposed	1 / 234 (0.43%)	0 / 48 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
HYPONATRAEMIA			
subjects affected / exposed	0 / 234 (0.00%)	0 / 48 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Period B: RZB/RZB	Period A: RZB	Period B: APR/APR
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 116 (6.90%)	1 / 118 (0.85%)	2 / 97 (2.06%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

PROSTATE CANCER			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOWER LIMB FRACTURE			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CORONARY ARTERY DISEASE			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
CAROTID ARTERY STENOSIS			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SCIATICA			
subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GENERALISED TONIC-CLONIC SEIZURE			

subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
HYPERSENSITIVITY			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OBSTRUCTIVE PANCREATITIS			
subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UMBILICAL HERNIA			
subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
NASAL INFLAMMATION			
subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY EMBOLISM			
subjects affected / exposed	2 / 116 (1.72%)	0 / 118 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Skin and subcutaneous tissue disorders			
URTICARIA			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
OSTEOCHONDROSIS			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOARTHRITIS			
subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
APPENDICITIS PERFORATED			
subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPSIS			
subjects affected / exposed	0 / 116 (0.00%)	0 / 118 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
HYPONATRAEMIA			
subjects affected / exposed	1 / 116 (0.86%)	0 / 118 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Period A: APR	Period B: APR/APR/RZB	Period B: APR/RZB
Total subjects affected by non-serious adverse events			
subjects affected / exposed	101 / 234 (43.16%)	15 / 48 (31.25%)	31 / 102 (30.39%)

Vascular disorders HYPERTENSION subjects affected / exposed occurrences (all)	3 / 234 (1.28%) 3	3 / 48 (6.25%) 3	1 / 102 (0.98%) 1
Nervous system disorders HEADACHE subjects affected / exposed occurrences (all)	27 / 234 (11.54%) 28	1 / 48 (2.08%) 1	5 / 102 (4.90%) 6
Gastrointestinal disorders DIARRHOEA subjects affected / exposed occurrences (all)	47 / 234 (20.09%) 50	0 / 48 (0.00%) 0	1 / 102 (0.98%) 1
NAUSEA subjects affected / exposed occurrences (all)	41 / 234 (17.52%) 45	0 / 48 (0.00%) 0	0 / 102 (0.00%) 0
Infections and infestations COVID-19 subjects affected / exposed occurrences (all)	16 / 234 (6.84%) 16	6 / 48 (12.50%) 6	12 / 102 (11.76%) 12
NASOPHARYNGITIS subjects affected / exposed occurrences (all)	10 / 234 (4.27%) 13	5 / 48 (10.42%) 6	10 / 102 (9.80%) 11
UPPER RESPIRATORY TRACT INFECTION subjects affected / exposed occurrences (all)	2 / 234 (0.85%) 2	1 / 48 (2.08%) 1	6 / 102 (5.88%) 8

Non-serious adverse events	Period B: RZB/RZB	Period A: RZB	Period B: APR/APR
Total subjects affected by non-serious adverse events subjects affected / exposed	36 / 116 (31.03%)	24 / 118 (20.34%)	27 / 97 (27.84%)
Vascular disorders HYPERTENSION subjects affected / exposed occurrences (all)	6 / 116 (5.17%) 6	2 / 118 (1.69%) 2	0 / 97 (0.00%) 0
Nervous system disorders HEADACHE subjects affected / exposed occurrences (all)	1 / 116 (0.86%) 1	3 / 118 (2.54%) 3	4 / 97 (4.12%) 4
Gastrointestinal disorders			

DIARRHOEA			
subjects affected / exposed	0 / 116 (0.00%)	1 / 118 (0.85%)	1 / 97 (1.03%)
occurrences (all)	0	1	1
NAUSEA			
subjects affected / exposed	2 / 116 (1.72%)	0 / 118 (0.00%)	3 / 97 (3.09%)
occurrences (all)	2	0	3
Infections and infestations			
COVID-19			
subjects affected / exposed	19 / 116 (16.38%)	13 / 118 (11.02%)	14 / 97 (14.43%)
occurrences (all)	20	13	14
NASOPHARYNGITIS			
subjects affected / exposed	11 / 116 (9.48%)	4 / 118 (3.39%)	8 / 97 (8.25%)
occurrences (all)	14	5	10
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	5 / 116 (4.31%)	3 / 118 (2.54%)	3 / 97 (3.09%)
occurrences (all)	5	3	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 November 2022	- Text was updated throughout the Protocol to align with revisions in the protocol template and changes due to new safety information available. Protocol sections include: Section 2.2, Section 4.1, Section 5.1, Section 5.4, Section 5.5, Section 5.6, Section 6.1, Section 9, Section 11, Appendix B, Appendix C, Appendix D, and Appendix E. - Protocol Section 7.1: added the interim lock for primary analysis for Period B. - Administrative Change 2: Update the Sponsor/Emergency Medical Contact information

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported