Clinical trial results:
A Phase 2, Randomized, Double-blind, Parallel Group, Placebo Controlled Study to Evaluate the Effect of Tezepelumab on Airway Inflammation in Adults with Inadequately Controlled Asthma on Inhaled Corticosteroids and at least one additional asthma controller (CASCADE)

Summary

EudraCT number	2018-002069-21
Trial protocol	DK GB DE
Global end of trial date	16 November 2020

Results information

Result version number	v1 (current)
This version publication date	26 November 2021
First version publication date	26 November 2021

Trial information

Trial identification

Sponsor protocol code	D5180C00013

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03688074
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	151 85, Södertälje, Sweden,
Public contact	AstraZeneca Clinical Study Information, AstraZeneca, information.center@astrazeneca.com
Scientific contact	Global Clinical Head, AstraZeneca, information.center@astrazeneca.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	11 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 November 2020
Global end of trial reached?	Yes
Global end of trial date	16 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To explore the airway anti-inflammatory effect of tezepelumab

Protection of trial subjects:

Data safety monitoring board is utilized for this study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 November 2018
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: 22
Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	Denmark: 34
Country: Number of subjects enrolled	United Kingdom: 29
Country: Number of subjects enrolled	Germany: 24
Worldwide total number of subjects	116
EEA total number of subjects	58

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)	100
From 65 to 84 years	16

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

116 subjects randomized to Tezepelumab 210 mg Q4W or Placebo in 1:1 treatment allocation. All randomized subjects were treated. 59 (50.9%) were randomized to Tezepelumab 210 mg Q4W, and 57 (49.1%) were randomized to Placebo.

Pre-assignment

Screening details:

The study randomized subjects across the spectrum of T2 status. Randomization was stratified by baseline blood eosinophil level (< 50 , 150 - <300, >= 300 cells/µL).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Teze 210 mg Q4W

Arm description:

Tezepelumab subcutaneous injection

Arm type	Experimental
Investigational medicinal product name	Tezepelumab
Investigational medicinal product code	MEDI9929 anti-TSLP mAb (AMG157)
Other name	AMG 157
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

210 mg

Arm title	Placebo

Arm description:

Placebo subcutaneous injection

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1

Number of subjects in period 1	Teze 210 mg Q4W	Placebo
Started	59	57
Completed	58	56
Not completed	1	1
Adverse event, non-fatal	-	1
Other	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Teze 210 mg Q4W
Reporting group description: Tezepelumab subcutaneous injection	
Reporting group title	Placebo
Reporting group description: Placebo subcutaneous injection	

Reporting group values	Teze 210 mg Q4W	Placebo	Total
Number of subjects	59	57	116
Age Categorical			
Full Analysis Set - Include all subjects randomised to study treatment who received at least one dose of IP, irrespective of their protocol adherence and continued participation in the study.			
Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	51	49	100
>=65 years	8	8	16
Age Continuous			
Full Analysis Set - Include all subjects randomised to study treatment who received at least one dose of IP, irrespective of their protocol adherence and continued participation in the study.			
Units: years			
arithmetic mean	50.4	50.4	
standard deviation	± 12.7	± 13.9	-
Sex: Female, Male			
Full Analysis Set - Include all subjects randomised to study treatment who received at least one dose of IP, irrespective of their protocol adherence and continued participation in the study.			
Units: Participants			
Female	39	26	65
Male	20	31	51
Race/Ethnicity, Customized			
Race - Full Analysis Set - Include all subjects randomised to study treatment who received at least one dose of IP, irrespective of their protocol adherence and continued participation in the study.			
Units: Subjects			
White	54	55	109
Black or African American	2	1	3
Asian	2	1	3
Other	1	0	1
Race/Ethnicity, Customized			
Ethnicity - Full Analysis Set - Include all subjects randomised to study treatment who received at least one dose of IP, irrespective of their protocol adherence and continued participation in the study.			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	59	57	116

End points

End points reporting groups	
Reporting group title	Teze 210 mg Q4W
Reporting group description: Tezepelumab subcutaneous injection	
Reporting group title	Placebo
Reporting group description: Placebo subcutaneous injection	

Primary: Airway submucosal inflammatory cells ratio change from baseline to EOT.	
End point title	Airway submucosal inflammatory cells ratio change from baseline to EOT.
End point description: The change from baseline to end of treatment (EOT) expressed as a ratio i.e. (EOT/baseline) in numbers of each of the airway submucosal inflammatory cells, determined by microscopic evaluation of bronchoscopic biopsies.	
End point type	Primary
End point timeframe: First dose of investigational product to end of treatment (EOT) at Week 28 (or up to Week 48 due to COVID19 pandemic).	

End point values	Teze 210 mg Q4W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	51		
Units: Ratio				
geometric mean (confidence interval 90%)				
Eosinophils	0.11 (0.06 to 0.21)	0.75 (0.41 to 1.38)		
Neutrophils	1.11 (0.88 to 1.39)	0.81 (0.66 to 1.01)		
T cells CD3+	0.91 (0.78 to 1.07)	0.81 (0.70 to 0.95)		
T cells CD4+	0.96 (0.82 to 1.14)	0.81 (0.70 to 0.95)		
Mast cells Tryptase+	0.84 (0.70 to 1.02)	1.01 (0.84 to 1.22)		
Mast cells Chymase+	1.07 (0.76 to 1.52)	0.90 (0.65 to 1.26)		

Statistical analyses

Statistical analysis title	Eosinophils (cells/mm2)
Statistical analysis description: All subjects randomised to study treatment who completed at least 20 weeks of study treatment and	

had a baseline assessment and an EOT assessment not greater than 8 weeks after date of last dose of IP.

Comparison groups	Teze 210 mg Q4W v Placebo
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.001 [2]
Method	ANCOVA
Parameter estimate	Ratio of Geometric LSMeans
Point estimate	0.15
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.06
upper limit	0.35

Notes:

[1] - Ratio change from baseline to EOT treatment comparison

[2] - Model includes treatment+log transformed baseline value+stratification factor (screening eos count [<150, 150-<300, >=300 cells/uL])

Statistical analysis title	Neutrophils (cells/mm2)

Statistical analysis description:

All subjects randomised to study treatment who completed at least 20 weeks of study treatment and had a baseline assessment and an EOT assessment not greater than 8 weeks after date of last dose of IP.

Comparison groups	Teze 210 mg Q4W v Placebo
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.106 [4]
Method	ANCOVA
Parameter estimate	Ratio of Geometric LSMeans
Point estimate	1.36
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.99
upper limit	1.86

Notes:

[3] - Ratio change from baseline to EOT treatment comparisons

[4] - Model includes treatment+log transformed baseline value+stratification factor (screening eos count [<150, 150-<300, >=300 cells/uL])

Statistical analysis title	T cells CD3+ (cells/mm2)

Statistical analysis description:

All subjects randomised to study treatment who completed at least 20 weeks of study treatment and had a baseline assessment and an EOT assessment not greater than 8 weeks after date of last dose of IP.

Comparison groups	Teze 210 mg Q4W v Placebo

Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.389 [6]
Method	ANCOVA
Parameter estimate	Ratio of Geometric LSMeans
Point estimate	1.12
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.9
upper limit	1.4

Notes:

[5] - Ratio change from baseline to EOT treatment comparisons

[6] - Model includes treatment+log transformed baseline value+stratification factor (screening eos count [<150, 150-<300, >=300 cells/uL])

Statistical analysis title	T cells CD4+ (cells/mm2)

Statistical analysis description:

All subjects randomised to study treatment who completed at least 20 weeks of study treatment and had a baseline assessment and an EOT assessment not greater than 8 weeks after date of last dose of IP.

Comparison groups	Teze 210 mg Q4W v Placebo
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.216 [8]
Method	ANCOVA
Parameter estimate	Ratio of Geometric LSMeans
Point estimate	1.18
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.94
upper limit	1.48

Notes:

[7] - Ratio change from baseline to EOT treatment comparisons

[8] - Model includes treatment+log transformed baseline value+stratification factor (screening eos count [<150, 150-<300, >=300 cells/uL])

Statistical analysis title	Mast cells Tryptase+ (cells/mm2)

Statistical analysis description:

All subjects randomised to study treatment who completed at least 20 weeks of study treatment and had a baseline assessment and an EOT assessment not greater than 8 weeks after date of last dose of IP.

Comparison groups	Teze 210 mg Q4W v Placebo
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.26 [10]
Method	ANCOVA
Parameter estimate	Ratio of Geometric LSMeans
Point estimate	0.83

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.64
upper limit	1.09

Notes:

[9] - Ratio change from baseline to EOT treatment comparisons

[10] - Model includes treatment+log transformed baseline value+stratification factor (screening eos count [<150, 150-<300, >=300 cells/uL])

Statistical analysis title	Mast cells Chymase+ (cells/mm2)

Statistical analysis description:

All subjects randomised to study treatment who completed at least 20 weeks of study treatment and had a baseline assessment and an EOT assessment not greater than 8 weeks after date of last dose of IP.

Comparison groups	Teze 210 mg Q4W v Placebo
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.546 [12]
Method	ANCOVA
Parameter estimate	Ratio of Geometric LSMeans
Point estimate	1.19
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.74
upper limit	1.92

Notes:

[11] - Ratio change from baseline to EOT treatment comparisons

[12] - Model includes treatment+log transformed baseline value+stratification factor (screening eos count [<150, 150-<300, >=300 cells/uL])

Secondary: Reticular basement membrane (RBM) thickness ratio change from baseline to EOT.

End point title	Reticular basement membrane (RBM) thickness ratio change from baseline to EOT.

End point description:

The change from baseline to EOT expressed as a ratio i.e. (EOT/baseline) in RBM thickness, determined by microscopic evaluation of bronchoscopic biopsies.

End point type	Secondary

End point timeframe:

First dose of investigational product to end of treatment (EOT) at Week 28 (or up to Week 48 due to COVID19 pandemic).

End point values	Teze 210 mg Q4W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	40		
Units: Ratio				
geometric mean (confidence interval 90%)	0.87 (0.79 to 0.95)	0.90 (0.81 to 0.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent (%) airway epithelial integrity ratio change from baseline to EOT.

End point title	Percent (%) airway epithelial integrity ratio change from baseline to EOT.

End point description:

The change from baseline to EOT expressed as a ratio i.e. (EOT/baseline) in % airway epithelial, determined by microscopic evaluation of bronchoscopic biopsies.

End point type	Secondary

End point timeframe:

First dose of investigational product to end of treatment (EOT) at Week 28 (or up to Week 48 due to COVID19 pandemic).

End point values	Teze 210 mg Q4W	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	46		
Units: Ratio				
geometric mean (confidence interval 90%)				
Intact epithelium	0.87 (0.61 to 1.23)	0.84 (0.59 to 1.19)		
Damaged epithelium	1.01 (0.92 to 1.12)	0.95 (0.86 to 1.04)		
Denuded epithelium	1.05 (0.83 to 1.31)	1.34 (1.07 to 1.68)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From first dose of investigational product till the end of the study.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.1
Reporting groups	
Reporting group title	Teze 210 mg Q4W
Reporting group description: Tezepelumab subcutaneous injection	
Reporting group title	Placebo
Reporting group description: Placebo subcutaneous injection	

Serious adverse events	Teze 210 mg Q4W	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 59 (5.08%)	7 / 57 (12.28%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningioma			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Post procedural complication			

subjects affected / exposed	0 / 59 (0.00%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocarditis			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Influenza			

subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Teze 210 mg Q4W	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 59 (81.36%)	45 / 57 (78.95%)	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 59 (3.39%)	0 / 57 (0.00%)	
occurrences (all)	5	0	
Fall			
subjects affected / exposed	2 / 59 (3.39%)	1 / 57 (1.75%)	
occurrences (all)	4	1	
Post procedural complication			
subjects affected / exposed	11 / 59 (18.64%)	10 / 57 (17.54%)	
occurrences (all)	11	12	
Post procedural fever			
subjects affected / exposed	4 / 59 (6.78%)	2 / 57 (3.51%)	
occurrences (all)	4	2	
Procedural pain			
subjects affected / exposed	3 / 59 (5.08%)	0 / 57 (0.00%)	
occurrences (all)	3	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 59 (1.69%)	2 / 57 (3.51%)	
occurrences (all)	1	2	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 59 (10.17%)	8 / 57 (14.04%)	
occurrences (all)	9	8	
General disorders and administration site conditions			

Influenza like illness			
subjects affected / exposed	3 / 59 (5.08%)	3 / 57 (5.26%)	
occurrences (all)	3	3	
Injection site erythema			
subjects affected / exposed	5 / 59 (8.47%)	2 / 57 (3.51%)	
occurrences (all)	14	12	
Injection site granuloma			
subjects affected / exposed	2 / 59 (3.39%)	0 / 57 (0.00%)	
occurrences (all)	2	0	
Injection site pruritus			
subjects affected / exposed	4 / 59 (6.78%)	1 / 57 (1.75%)	
occurrences (all)	5	1	
Oedema peripheral			
subjects affected / exposed	3 / 59 (5.08%)	0 / 57 (0.00%)	
occurrences (all)	3	0	
Pyrexia			
subjects affected / exposed	3 / 59 (5.08%)	0 / 57 (0.00%)	
occurrences (all)	3	0	
Eye disorders			
Dry eye			
subjects affected / exposed	2 / 59 (3.39%)	0 / 57 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 59 (8.47%)	0 / 57 (0.00%)	
occurrences (all)	6	0	
Vomiting			
subjects affected / exposed	2 / 59 (3.39%)	3 / 57 (5.26%)	
occurrences (all)	2	3	
Nausea			
subjects affected / exposed	2 / 59 (3.39%)	2 / 57 (3.51%)	
occurrences (all)	2	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 59 (10.17%)	4 / 57 (7.02%)	
occurrences (all)	9	5	

Dysphonia			
subjects affected / exposed	2 / 59 (3.39%)	2 / 57 (3.51%)	
occurrences (all)	2	2	
Oropharyngeal pain			
subjects affected / exposed	6 / 59 (10.17%)	2 / 57 (3.51%)	
occurrences (all)	6	2	
Nasal congestion			
subjects affected / exposed	1 / 59 (1.69%)	2 / 57 (3.51%)	
occurrences (all)	1	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 59 (5.08%)	3 / 57 (5.26%)	
occurrences (all)	3	4	
Back pain			
subjects affected / exposed	2 / 59 (3.39%)	2 / 57 (3.51%)	
occurrences (all)	2	2	
Bursitis			
subjects affected / exposed	0 / 59 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	2	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 59 (1.69%)	2 / 57 (3.51%)	
occurrences (all)	1	3	
Myalgia			
subjects affected / exposed	3 / 59 (5.08%)	1 / 57 (1.75%)	
occurrences (all)	3	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 59 (3.39%)	0 / 57 (0.00%)	
occurrences (all)	2	0	
Candida infection			
subjects affected / exposed	2 / 59 (3.39%)	0 / 57 (0.00%)	
occurrences (all)	2	0	
Chronic sinusitis			
subjects affected / exposed	0 / 59 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	2	
Conjunctivitis			

subjects affected / exposed	2 / 59 (3.39%)	0 / 57 (0.00%)		
occurrences (all)	2	0		
Gastroenteritis				
subjects affected / exposed	1 / 59 (1.69%)	2 / 57 (3.51%)		
occurrences (all)	1	2		
Lower respiratory tract infection				
subjects affected / exposed	2 / 59 (3.39%)	1 / 57 (1.75%)		
occurrences (all)	2	1		
Nasopharyngitis				
subjects affected / exposed	22 / 59 (37.29%)	21 / 57 (36.84%)		
occurrences (all)	28	22		
Lower respiratory tract infection bacterial				
subjects affected / exposed	1 / 59 (1.69%)	2 / 57 (3.51%)		
occurrences (all)	1	2		
Oral candidiasis				
subjects affected / exposed	2 / 59 (3.39%)	0 / 57 (0.00%)		
occurrences (all)	4	0		
Pneumonia				
subjects affected / exposed	2 / 59 (3.39%)	1 / 57 (1.75%)		
occurrences (all)	2	1		
Rhinitis				
subjects affected / exposed	1 / 59 (1.69%)	2 / 57 (3.51%)		
occurrences (all)	1	2		
Tonsillitis				
subjects affected / exposed	2 / 59 (3.39%)	0 / 57 (0.00%)		
occurrences (all)	2	0		
Sinusitis				
subjects affected / exposed	0 / 59 (0.00%)	2 / 57 (3.51%)		
occurrences (all)	0	2		
Upper respiratory tract infection				
subjects affected / exposed	3 / 59 (5.08%)	4 / 57 (7.02%)		
occurrences (all)	3	4		
Urinary tract infection				
subjects affected / exposed	3 / 59 (5.08%)	2 / 57 (3.51%)		
occurrences (all)	4	5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2018	Changes are summarized in the CSP version 2.0
03 May 2019	Changes are summarized in the CSP version 3.0
30 April 2020	Most of the changes to the trial due to COVID-19 and other changes are summarized in the CSP version 4.0

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported