Clinical trial results:
PEANUT ALLERGY ORAL IMMUNOTHERAPY STUDY OF AR101 FOR DESENSITIZATION IN CHILDREN AND ADULTS (THE PALISADE STUDY)

Summary

EudraCT number	2015-004257-41
Trial protocol	SE DE GB DK IE NL ES IT
Global end of trial date	02 July 2018

Results information

Result version number	v1 (current)
This version publication date	11 July 2019
First version publication date	11 July 2019

Trial information

Trial identification

Sponsor protocol code	ARC003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02635776
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aimmune Therapeutics Inc.
Sponsor organisation address	8000 Marina Blvd, Suite 300, Brisbane, United States, 94005
Public contact	Clinical Operations, Aimmune Therapeutics, 001 6503963822, amarcantonio@aimmune.com
Scientific contact	Clinical Operations, Aimmune Therapeutics, 001 6503963822, amarcantonio@aimmune.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001734-PIP01-14
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	26 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 December 2017
Global end of trial reached?	Yes
Global end of trial date	02 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to demonstrate the efficacy of AR101, a pharmaceutical-grade peanut allergen formulation, through reduction in clinical reactivity to limited amounts of peanut allergen in peanut-allergic children (ages 4-17 years, inclusive).

Protection of trial subjects:

Education of patients to notify sites of allergic symptoms occuring at home. eDiary for completion at home by patients to measure IP compliance and alert sites of Adverse Events of Interest, including accidental exposure or Epi pen use.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 December 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	18 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	Sweden: 12
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	Germany: 27
Country: Number of subjects enrolled	Ireland: 16
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Canada: 39
Country: Number of subjects enrolled	United States: 399
Worldwide total number of subjects	555
EEA total number of subjects	117

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)	328
Adolescents (12-17 years)	171
Adults (18-64 years)	56
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 842 subjects between the ages of 4 and 55 with suspected peanut allergy were screened for inclusion, of which 555 subjects were randomized and enrolled in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	AR101

Arm description:

A peanut-derived oral immunotherapy drug

Arm type	Experimental
Investigational medicinal product name	AR101
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use

Dosage and administration details:

AR101 drug product was supplied in 2 presentations. These were pull-apart capsules containing 0.5, 1, 10, 20 and 100mg of peanut protein and sealed, foil-laminated sachets containing 300mg of peanut protein. The capsules were used during the Initial Escalation and Up-dosing phases of the study. The sachets were used during the Maintenance phase. These 3 phases are described below:

Initial Escalation: Comprised of dose-escalation (from 0.5mg to a maximum of 6 mg at 20 to 30-minute intervals) on Day 1 and confirmation of the tolerability of a single 3 mg dose on Day 2.

Up-dosing: Following initial escalation, subjects received daily doses of AR101 and are up-dosed every 2 weeks for approximately 20 weeks. Dosing commenced at 3mg and progressed to 300mg via 10 incremental dosing steps at 2 weekly intervals.

Maintenance: All subjects who reach and tolerate 300mg/d will continue to take a daily maintenance dose of 300mg/d for 24 weeks. Maintenance visits occur every 4 weeks.

Arm title	Placebo

Arm description:

Matching placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use

Dosage and administration details:

A Placebo matching the AR101 drug product was supplied in 2 presentations. These were pull-apart capsules matching the 0.5, 1, 10, 20 and 100mg peanut capsules but containing no peanut protein and

sealed, foil-laminated sachets matching the peanut protein sachets but without any peanut protein. The capsules were used during the Initial Escalation and Up-dosing phases of the study. The sachets were used during the Maintenance phase. These 3 phases are described as for AR101 drug product but utilising the placebo presentations.

Number of subjects in period 1	AR101	Placebo
Started	416	139
Completed	314	128
Not completed	102	11
Physician decision	1	-
Consent withdrawn by subject	41	7
Adverse event, non-fatal	51	3
Other reasons	5	1
Lost to follow-up	4	-

Baseline characteristics

Reporting groups	
Reporting group title	AR101
Reporting group description:	
A peanut-derived oral immunotherapy drug	
Reporting group title	Placebo
Reporting group description:	
Matching placebo	

Reporting group values	AR101	Placebo	Total
Number of subjects	416	139	555
Age categorical Units: Subjects			
Children (2-11 years)	238	90	328
Adolescents (12-17 years)	136	35	171
Adults (18-64 years)	42	14	56
Gender categorical Units: Subjects			
Female	181	56	237
Male	235	83	318

Subject analysis sets	
Subject analysis set title	AR101 ITT Population Ages 4-17
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The pre-specified primary efficacy population includes subjects Ages 4-17 in the ITT Population	

Subject analysis set title	Placebo ITT Population Ages 4-17
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The pre-specified primary efficacy population includes subjects Ages 4-17 in the ITT Population	

Reporting group values	AR101 ITT Population Ages 4-17	Placebo ITT Population Ages 4-17	
Number of subjects	372	124	
Age categorical Units: Subjects			
Children (2-11 years)	238	89	
Adolescents (12-17 years)	134	35	
Adults (18-64 years)	0	0	
Gender categorical Units: Subjects			
Female	164	48	
Male	208	76	

End points

End points reporting groups

Reporting group title	AR101
Reporting group description: A peanut-derived oral immunotherapy drug	
Reporting group title	Placebo
Reporting group description: Matching placebo	
Subject analysis set title	AR101 ITT Population Ages 4-17
Subject analysis set type	Intention-to-treat
Subject analysis set description: The pre-specified primary efficacy population includes subjects Ages 4-17 in the ITT Population	

Subject analysis set title	Placebo ITT Population Ages 4-17
Subject analysis set type	Intention-to-treat
Subject analysis set description: The pre-specified primary efficacy population includes subjects Ages 4-17 in the ITT Population	

Primary: Primary Efficacy End point: Percentage of subjects ages 4-17 who tolerated a single highest dose of at least 1000 mg in the Exit Oral Food Challenge

End point title	Primary Efficacy End point: Percentage of subjects ages 4-17 who tolerated a single highest dose of at least 1000 mg in the Exit Oral Food Challenge
End point description:	
End point type	Primary
End point timeframe: Exit oral food challenge (after approximately 1 year of blinded therapy)	

End point values	AR101 ITT Population Ages 4-17	Placebo ITT Population Ages 4-17		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	372	124		
Units: Percentage of Patients				
number (confidence interval 95%)				
"Responder "	50.3 (45.2 to 55.3)	2.4 (0.8 to 6.9)		

Statistical analyses

Statistical analysis title	Treatment difference at 1000 mg
Statistical analysis description: Farrington-Manning test for the difference (AR101 - Placebo) in percentage of subjects ages 4-17 who tolerated a single highest dose of at least 1000 mg	
Comparison groups	AR101 ITT Population Ages 4-17 v Placebo ITT Population Ages

	4-17
Number of subjects included in analysis	496
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Farrington-Manning test
Parameter estimate	Risk difference (RD)
Point estimate	47.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	38
upper limit	57.7

Secondary: Secondary Efficacy End point: Percentage of subjects ages 4-17 who tolerated a single highest dose of at least 600 mg in the Exit Oral Food Challenge

End point title	Secondary Efficacy End point: Percentage of subjects ages 4-17 who tolerated a single highest dose of at least 600 mg in the Exit Oral Food Challenge

End point description:

End point type	Secondary

End point timeframe:

Exit oral food challenge (after approximately 1 year of blinded therapy)

End point values	AR101 ITT Population Ages 4-17	Placebo ITT Population Ages 4-17		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	372	124		
Units: Percentage of Patients				
number (confidence interval 95%)				
Responder	67.2 (62.3 to 71.8)	4 (1.7 to 9.1)		

Statistical analyses

Statistical analysis title	Treatment difference at 600 mg

Statistical analysis description:

Farrington-Manning test for the difference (AR101 - Placebo) in percentage of subjects ages 4-17 who tolerated a single highest dose of at least 600 mg

Comparison groups	AR101 ITT Population Ages 4-17 v Placebo ITT Population Ages 4-17

Number of subjects included in analysis	496
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Farrington-Manning test
Parameter estimate	Risk difference (RD)
Point estimate	63.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	53
upper limit	73.3

Secondary: Secondary Efficacy End point: Percentage of subjects ages 4-17 who tolerated a single highest dose of at least 300 mg in the Exit Oral Food Challenge

End point title	Secondary Efficacy End point: Percentage of subjects ages 4-17 who tolerated a single highest dose of at least 300 mg in the Exit Oral Food Challenge

End point description:

End point type	Secondary

End point timeframe:

Exit oral food challenge (after approximately 1 year of blinded therapy)

End point values	AR101 ITT Population Ages 4-17	Placebo ITT Population Ages 4-17		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	372	124		
Units: Percentage of Patients				
number (confidence interval 95%)				
Responder	76.6 (72.1 to 80.6)	8.1 (4.4 to 14.2)		

Statistical analyses

Statistical analysis title	Treatment difference at 300 mg

Statistical analysis description:

Farrington-Manning test for the difference (AR101 - Placebo) in percentage of subjects ages 4-17 who tolerated a single highest dose of at least 300 mg

Comparison groups	AR101 ITT Population Ages 4-17 v Placebo ITT Population Ages 4-17

Number of subjects included in analysis	496
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Farrington-Manning test
Parameter estimate	Risk difference (RD)
Point estimate	68.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	58.6
upper limit	78.5

Secondary: Secondary Efficacy End point: The maximum severity of symptoms in subjects ages 4-17 occurring at any challenge dose of peanut protein during the Exit Oral Food Challenge

End point title	Secondary Efficacy End point: The maximum severity of symptoms in subjects ages 4-17 occurring at any challenge dose of peanut protein during the Exit Oral Food Challenge

End point description:

End point type	Secondary

End point timeframe:

Exit oral food challenge (after approximately 1 year of blinded therapy)

End point values	AR101 ITT Population Ages 4-17	Placebo ITT Population Ages 4-17		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	372	124		
Units: Percentage of Patients				
number (not applicable)				
None	37.6	2.4		
Mild	32.0	28.2		
Moderate	25.3	58.9		
Severe or worse	5.1	10.5		

Statistical analyses

Statistical analysis title	Treatment difference in maximum severity

Statistical analysis description:

Cochran-Mantel-Haenszel test (using equally spaced scores), stratified by region (North America, Europe) for the difference between AR101 and Placebo in maximum severity of symptoms in subjects ages 4-17 occurring at any challenge dose of peanut protein during the Exit Oral Food Challenge

Comparison groups	AR101 ITT Population Ages 4-17 v Placebo ITT Population Ages 4-17

Number of subjects included in analysis	496
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel

Notes:

[1] - Subjects without an Exit Food Challenge were assigned the maximum severity during the Screening Food Challenge, which equates to no change from screening

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Through study completion (approximately 1 year)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	AR101 Safety Population (Age 4-17)
Reporting group description: -	
Reporting group title	Placebo Safety Population (Age 4-17)
Reporting group description: -	

Serious adverse events	AR101 Safety Population (Age 4-17)	Placebo Safety Population (Age 4-17)	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 372 (2.15%)	1 / 124 (0.81%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 372 (0.27%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 372 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	3 / 372 (0.81%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	2 / 372 (0.54%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 372 (0.27%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 372 (0.27%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis streptococcal			
subjects affected / exposed	1 / 372 (0.27%)	0 / 124 (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: 5 %

Non-serious adverse events	AR101 Safety Population (Age 4-17)	Placebo Safety Population (Age 4-17)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	367 / 372 (98.66%)	118 / 124 (95.16%)	
Vascular disorders			
Flushing			
subjects affected / exposed	49 / 372 (13.17%)	11 / 124 (8.87%)	
occurrences (all)	194	13	
Nervous system disorders			
Headache			
subjects affected / exposed	72 / 372 (19.35%)	28 / 124 (22.58%)	
occurrences (all)	208	94	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	88 / 372 (23.66%)	27 / 124 (21.77%)	
occurrences (all)	189	47	
Chest discomfort			

subjects affected / exposed	24 / 372 (6.45%)	1 / 124 (0.81%)	
occurrences (all)	42	1	
Ear and labyrinth disorders			
Ear pruritus			
subjects affected / exposed	25 / 372 (6.72%)	0 / 124 (0.00%)	
occurrences (all)	110	0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	51 / 372 (13.71%)	4 / 124 (3.23%)	
occurrences (all)	70	4	
Seasonal allergy			
subjects affected / exposed	6 / 372 (1.61%)	7 / 124 (5.65%)	
occurrences (all)	7	17	
Eye disorders			
Ocular hyperaemia			
subjects affected / exposed	34 / 372 (9.14%)	10 / 124 (8.06%)	
occurrences (all)	64	11	
Eye pruritus			
subjects affected / exposed	32 / 372 (8.60%)	16 / 124 (12.90%)	
occurrences (all)	39	21	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	194 / 372 (52.15%)	30 / 124 (24.19%)	
occurrences (all)	1055	93	
Vomiting			
subjects affected / exposed	154 / 372 (41.40%)	30 / 124 (24.19%)	
occurrences (all)	467	55	
Abdominal pain upper			
subjects affected / exposed	152 / 372 (40.86%)	26 / 124 (20.97%)	
occurrences (all)	1201	85	
Oral pruritus			
subjects affected / exposed	151 / 372 (40.59%)	20 / 124 (16.13%)	
occurrences (all)	1629	21	
Nausea			
subjects affected / exposed	146 / 372 (39.25%)	29 / 124 (23.39%)	
occurrences (all)	808	38	
Paraesthesia oral			

subjects affected / exposed	65 / 372 (17.47%)	8 / 124 (6.45%)	
occurrences (all)	762	15	
Diarrhoea			
subjects affected / exposed	61 / 372 (16.40%)	24 / 124 (19.35%)	
occurrences (all)	202	45	
Abdominal discomfort			
subjects affected / exposed	60 / 372 (16.13%)	17 / 124 (13.71%)	
occurrences (all)	367	27	
Lip swelling			
subjects affected / exposed	38 / 372 (10.22%)	5 / 124 (4.03%)	
occurrences (all)	78	4	
Tongue pruritus			
subjects affected / exposed	38 / 372 (10.22%)	7 / 124 (5.65%)	
occurrences (all)	115	10	
Lip pruritus			
subjects affected / exposed	36 / 372 (9.68%)	7 / 124 (5.65%)	
occurrences (all)	106	6	
Dysphagia			
subjects affected / exposed	20 / 372 (5.38%)	3 / 124 (2.42%)	
occurrences (all)	34	6	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	152 / 372 (40.86%)	42 / 124 (33.87%)	
occurrences (all)	366	117	
Throat irritation			
subjects affected / exposed	152 / 372 (40.86%)	34 / 124 (27.42%)	
occurrences (all)	1775	53	
Rhinorrhoea			
subjects affected / exposed	113 / 372 (30.38%)	28 / 124 (22.58%)	
occurrences (all)	337	53	
Sneezing			
subjects affected / exposed	98 / 372 (26.34%)	18 / 124 (14.52%)	
occurrences (all)	259	47	
Throat tightness			

subjects affected / exposed	86 / 372 (23.12%)	8 / 124 (6.45%)	
occurrences (all)	350	4	
Nasal congestion			
subjects affected / exposed	80 / 372 (21.51%)	28 / 124 (22.58%)	
occurrences (all)	180	61	
Oropharyngeal pain			
subjects affected / exposed	70 / 372 (18.82%)	19 / 124 (15.32%)	
occurrences (all)	199	29	
Wheezing			
subjects affected / exposed	58 / 372 (15.59%)	15 / 124 (12.10%)	
occurrences (all)	123	37	
Dyspnoea			
subjects affected / exposed	44 / 372 (11.83%)	5 / 124 (4.03%)	
occurrences (all)	77	4	
Asthma			
subjects affected / exposed	42 / 372 (11.29%)	10 / 124 (8.06%)	
occurrences (all)	58	14	
Rhinitis allergic			
subjects affected / exposed	32 / 372 (8.60%)	11 / 124 (8.87%)	
occurrences (all)	60	36	
Dysphonia			
subjects affected / exposed	25 / 372 (6.72%)	2 / 124 (1.61%)	
occurrences (all)	35	4	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	153 / 372 (41.13%)	34 / 124 (27.42%)	
occurrences (all)	438	119	
Urticaria			
subjects affected / exposed	143 / 372 (38.44%)	30 / 124 (24.19%)	
occurrences (all)	468	84	
Rash			
subjects affected / exposed	81 / 372 (21.77%)	18 / 124 (14.52%)	
occurrences (all)	146	42	
Swelling face			
subjects affected / exposed	39 / 372 (10.48%)	7 / 124 (5.65%)	
occurrences (all)	84	8	

Eczema			
subjects affected / exposed	32 / 372 (8.60%)	12 / 124 (9.68%)	
occurrences (all)	68	21	
Erythema			
subjects affected / exposed	27 / 372 (7.26%)	5 / 124 (4.03%)	
occurrences (all)	33	11	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	110 / 372 (29.57%)	39 / 124 (31.45%)	
occurrences (all)	187	57	
Nasopharyngitis			
subjects affected / exposed	57 / 372 (15.32%)	20 / 124 (16.13%)	
occurrences (all)	79	35	
Viral infection			
subjects affected / exposed	50 / 372 (13.44%)	13 / 124 (10.48%)	
occurrences (all)	76	14	
Pharyngitis streptococcal			
subjects affected / exposed	28 / 372 (7.53%)	5 / 124 (4.03%)	
occurrences (all)	35	8	
Gastroenteritis			
subjects affected / exposed	24 / 372 (6.45%)	5 / 124 (4.03%)	
occurrences (all)	30	6	
Gastroenteritis viral			
subjects affected / exposed	24 / 372 (6.45%)	7 / 124 (5.65%)	
occurrences (all)	34	9	
Influenza			
subjects affected / exposed	20 / 372 (5.38%)	8 / 124 (6.45%)	
occurrences (all)	24	9	
Otitis media			
subjects affected / exposed	20 / 372 (5.38%)	5 / 124 (4.03%)	
occurrences (all)	23	6	
Rhinitis			
subjects affected / exposed	20 / 372 (5.38%)	11 / 124 (8.87%)	
occurrences (all)	33	15	
Sinusitis			

subjects affected / exposed	16 / 372 (4.30%)	7 / 124 (5.65%)	
occurrences (all)	19	9	
Viral upper respiratory tract infection			
subjects affected / exposed	15 / 372 (4.03%)	7 / 124 (5.65%)	
occurrences (all)	20	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2015	Amendment 1 Changes: • Additional secondary endpoints added • Additional exclusion criteria added
25 April 2016	Amendment 2 Changes: • Additional exploratory endpoints added • Additional exclusion criteria added
29 August 2016	Amendment 3 Changes: • Exclusion criteria revised • Optional substudy added as an exploratory endpoint (for North America)
31 July 2017	Amendment 4 Changes: • To incorporate regulatory feedback from participating countries: - Subject continuation provisions prior to enrolling into follow-on study added - Primary and secondary objectives updated - European primary endpoint added • End of trial definition added • Clarified sites for substudy • Clarified adverse event reporting requirements

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported