Clinical trial results:
A Phase III, Open-Label, Single-Arm, Multicenter Study to Evaluate the Safety and Immunogenicity of a Trivalent, Surface Antigen Inactivated Subunit Influenza Virus Vaccine Produced in Mammalian Cell Culture (Optaflu®) in Healthy Adults.

Summary

EudraCT number	2013-000621-30
Trial protocol	DE
Global end of trial date	08 September 2013

Results information

Result version number	v2 (current)
This version publication date	29 July 2016
First version publication date	22 October 2014
Version creation reason	• Correction of full data set Required for the re-QC because of EudraCT system glitch as possible updates to results are required. Moreover, the study is now transferred to another primary user.

Trial information

Trial identification

Sponsor protocol code	V58_33S

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01880697
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Vaccines and Diagnostics
Sponsor organisation address	Via Fiorentina 1, Siena, Italy,
Public contact	Head of Central and Northern Europe, Novartis Vaccines and Diagnostics GmbH, +49 080246465401, dietrich.bosse@novartis.com
Scientific contact	Head of Central and Northern Europe, Novartis Vaccines and Diagnostics GmbH, +49 080246465401, dietrich.bosse@novartis.com
Sponsor organisation name	Novartis Vaccines and Diagnostics
Sponsor organisation address	Via Fiorentina 1, Siena, Italy,
Public contact	Novartis Vaccines , Posting Director, RegistryContactVaccinesUS@novartis.com
Scientific contact	Novartis Vaccines , Posting Director, RegistryContactVaccinesUS@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric	No

investigation plan (PIP)	
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 September 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Immunogenicity Objective
To evaluate the antibody response to each influenza vaccine antigen after vaccination with the TIVc vaccine, as measured by single radial hemolysis (SRH) or hemagglutination inhibition (HI) assay in accordance with Guidance CPMP/BWP/214/96

Safety Objective
To evaluate the safety of TIVc in adult subjects in compliance with the requirements of the current European Union recommendations for clinical trials related to yearly licensing of influenza vaccines (CPMP/BWP/214/96)

Protection of trial subjects:

This clinical study was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations, including the European Directive 2001/20/EC, the US CFR Title 21, and the Japanese Ministry of Health, Labor, and Welfare, Novartis codes on the protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 August 2013
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	Germany: 126
Worldwide total number of subjects	126
EEA total number of subjects	126

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)	82
From 65 to 84 years	44
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled from 1 study centre in Germany

Pre-assignment

Screening details:

All enrolled subjects were included in the study

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	TIVc (≥18 to ≤ 60 Years)

Arm description:

Adult subjects received one dose of the cell-derived trivalent, surface antigen inactivated subunit influenza virus vaccine (TIVc) formulation 2013/2014 Northern Hemisphere

Arm type	Experimental
Investigational medicinal product name	Trivalent influenza virus vaccine (surface antigen, inactivated, cell-based)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Single 0.5-mL dose intramuscularly on day 1

Arm title	TIVc (≥ 61 Years)

Arm description:

Elderly subjects received one dose of the cell-derived trivalent, surface antigen inactivated subunit influenza virus vaccine (TIVc) formulation 2013/2014 Northern Hemisphere

Arm type	Experimental
Investigational medicinal product name	Trivalent influenza virus vaccine (surface antigen, inactivated, cell-based)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Single 0.5-mL dose intramuscularly on day 1

Number of subjects in period 1	TIVc (≥18 to ≤ 60 Years)	TIVc (≥ 61 Years)
Started	63	63
Completed	63	63

Baseline characteristics

Reporting groups	
Reporting group title	TIVc (≥18 to ≤ 60 Years)
Reporting group description:	
Adult subjects received one dose of the cell-derived trivalent, surface antigen inactivated subunit influenza virus vaccine (TIVc) formulation 2013/2014 Northern Hemisphere	
Reporting group title	TIVc (≥ 61 Years)
Reporting group description:	
Elderly subjects received one dose of the cell-derived trivalent, surface antigen inactivated subunit influenza virus vaccine (TIVc) formulation 2013/2014 Northern Hemisphere	

Reporting group values	TIVc (≥18 to ≤ 60 Years)	TIVc (≥ 61 Years)	Total
Number of subjects	63	63	126
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	39.3	68.3	
standard deviation	± 10.7	± 4.8	-
Gender categorical			
Units: Subjects			
Female	38	33	71
Male	25	30	55

Subject analysis sets	
Subject analysis set title	Enrolled Set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All screened subjects who provided informed consent, provided demographic and/or baseline screening assessments and received a Subject ID.	
Subject analysis set title	Per Protocol Set
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects who had received study vaccination and provided immunogenicity data both at baseline and after vaccination, and were not excluded due to reasons defined prior to unblinding or analysis, e.g. did not withdraw informed consent and did not have RT-PCR confirmed influenza during the study.	
Subject analysis set title	Safety Set (solicited AEs and other solicited events)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects in the Exposed Set who provided post-vaccination reactogenicity data	
Subject analysis set title	Safety Set (unsolicited AEs)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects in the Exposed Set who had post-vaccination unsolicited AE records	

Reporting group values	Enrolled Set	Per Protocol Set	Safety Set (solicited AEs and other solicited events)
Number of subjects	126	123	126
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	53.8	53.5	53.8
standard deviation	± 16.7	± 16.8	± 16.7
Gender categorical Units: Subjects			
Female	71	70	71
Male	55	53	55

Reporting group values	Safety Set (unsolicited AEs)		
Number of subjects	126		
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	53.8		
standard deviation	± 16.7		
Gender categorical Units: Subjects			
Female	71		
Male	55		

End points

End points reporting groups

Reporting group title	TIVc (≥18 to ≤ 60 Years)
Reporting group description:	
Adult subjects received one dose of the cell-derived trivalent, surface antigen inactivated subunit influenza virus vaccine (TIVc) formulation 2013/2014 Northern Hemisphere	
Reporting group title	TIVc (≥ 61 Years)
Reporting group description:	
Elderly subjects received one dose of the cell-derived trivalent, surface antigen inactivated subunit influenza virus vaccine (TIVc) formulation 2013/2014 Northern Hemisphere	
Subject analysis set title	Enrolled Set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All screened subjects who provided informed consent, provided demographic and/or baseline screening assessments and received a Subject ID.	
Subject analysis set title	Per Protocol Set
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects who had received study vaccination and provided immunogenicity data both at baseline and after vaccination, and were not excluded due to reasons defined prior to unblinding or analysis, e.g. did not withdraw informed consent and did not have RT-PCR confirmed influenza during the study.	
Subject analysis set title	Safety Set (solicited AEs and other solicited events)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects in the Exposed Set who provided post-vaccination reactogenicity data	
Subject analysis set title	Safety Set (unsolicited AEs)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects in the Exposed Set who had post-vaccination unsolicited AE records	

Primary: Number of subjects reporting unsolicited adverse events after receiving one dose of TIVc.

End point title	Number of subjects reporting unsolicited adverse events after receiving one dose of TIVc.[1]
End point description:	
The number of subjects in both age groups reporting any unsolicited AEs (between Day 1 to 4), serious adverse events (SAEs), medically attended AEs, AEs leading to premature withdrawal (throughout the study period), after receiving one dose of TIVc is reported. The analysis was performed on the Solicited Safety Set.	
End point type	Primary
End point timeframe:	
Day 1 through Day 22 post-vaccination	

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: All safety analyses were run in the safety population.

End point values	TIVc (≥18 to ≤ 60 Years)	TIVc (≥ 61 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	63		
Units: Subjects				
Any AE (Day 1 to 4)	6	4		
At least Possibly related AE	2	0		
Any SAE	1	0		
At least Possibly related SAE	0	0		
Medically attended AE	4	3		
AE leading to discontinuation	0	0		
Death	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of subjects with Single Radial Hemolysis (SRH) areas ≥25mm2, against each of three vaccine strains after receiving one dose of TIVc

End point title	Percentage of subjects with Single Radial Hemolysis (SRH) areas ≥25mm2, against each of three vaccine strains after receiving one dose of TIVc[2]

End point description:

Immunogenicity was assessed in terms of percentages of subjects in both age groups with SRH areas ≥25mm2 against each of the three vaccine strains, three weeks after receiving one dose of TIVc. The related European (CHMP) criterion for the assessment of immunogenicity is met if the percentage of subjects achieving post-vaccination SRH areas ≥ 25mm2 is >70% for adults aged 18 to ≤60 years and >60% for subjects aged ≥61 years. The analysis was performed on the Per Protocol Set.

End point type	Primary

End point timeframe:

Day 22 post-vaccination

Notes:

[2] - 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: There was no statistical null hypothesis associated with the immunogenicity objective.

End point values	TIVc (≥18 to ≤ 60 Years)	TIVc (≥ 61 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	61		
Units: Percentage of subjects				
number (confidence interval 95%)				
Day 1 (H1N1 strain)	66 (53 to 78)	41 (29 to 54)		
Day 22 (H1N1 strain)	98 (91 to 100)	84 (72 to 92)		
Day 1 (H3N2 strain)	44 (31 to 57)	39 (27 to 53)		
Day 22 (H3N2 strain)	92 (82 to 97)	77 (65 to 87)		
Day 1 (B strain)	68 (55 to 79)	77 (65 to 87)		
Day 22 (B strain)	98 (91 to 100)	98 (91 to 100)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of subjects achieving seroconversion or significant increase by SRH area, against each of three vaccine strains after receiving one dose of TIVc

End point title	Percentage of subjects achieving seroconversion or significant increase by SRH area, against each of three vaccine strains after receiving one dose of TIVc[3]

End point description:

Immunogenicity was assessed in terms of percentages of subjects in both age groups achieving seroconversion or significant increase by SRH area against each of the three vaccine strains, three weeks after receiving one dose of TIVc. Seroconversion is defined as percentage of subjects with a pre-vaccination SRH area ≤4mm2 achieving a post-vaccination SRH area ≥25 mm2. Significant increase is defined as percentage of subjects with a pre-vaccination SRH area >4mm2 achieving at least 50% increase in post-vaccination SRH area. The related European (CHMP) criterion for the assessment of immunogenicity is met if the percentage of subjects achieving post-vaccination SRH areas ≥ 25mm2 is >40% for adults aged 18 to ≤60 years and >30% for subjects aged ≥61 years. The analysis was performed on the Per Protocol Set.

End point type	Primary

End point timeframe:

Day 22 post-vaccination

Notes:

[3] - 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: There was no statistical null hypothesis associated with the immunogenicity objective.

End point values	TIVc (≥18 to ≤ 60 Years)	TIVc (≥ 61 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	61		
Units: Percentage of subjects				
number (confidence interval 95%)				
H1N1 strain	68 (55 to 79)	56 (42 to 68)		
H3N2 strain	65 (51 to 76)	46 (33 to 59)		
B strain	58 (45 to 70)	39 (27 to 53)		

Statistical analyses

No statistical analyses for this end point

Primary: Geometric mean ratio (GMR) of post-vaccination versus pre-vaccination Geometric Mean Areas (GMAs), against each of three vaccine strains after receiving one dose of TIVc

End point title	Geometric mean ratio (GMR) of post-vaccination versus pre-vaccination Geometric Mean Areas (GMAs), against each of three vaccine strains after receiving one dose of TIVc[4]

End point description:

The antibody responses were evaluated in terms of GMRs of post-vaccination GMAs to pre-vaccination GMAs against each of the three vaccine strains, three weeks after receiving one dose of TIVc. The related European (CHMP) criterion for the assessment of immunogenicity is met if the GMR day 22/day 1 is >2.5 for adults aged 18 to ≤60 years and > 2.0 in for subjects aged ≥61 years. The analysis was performed on the Per Protocol Set.

End point type	Primary

End point timeframe:

Day 22/Day 1

Notes:

[4] - 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: There was no statistical null hypothesis associated with the immunogenicity objective.

End point values	TIVc (≥18 to ≤ 60 Years)	TIVc (≥ 61 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	61		
Units: Ratio				
geometric mean (confidence interval 95%)				
H1N1 strain	2.89 (2.16 to 3.86)	3.14 (2.29 to 4.31)		
H3N2 strain	2.52 (2.03 to 3.12)	2.05 (1.67 to 2.53)		
B strain	1.82 (1.54 to 2.16)	1.5 (1.28 to 1.76)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of subjects with hemagglutination inhibition (HI) titer ≥ 1:40, against each of three vaccine strains after receiving one dose of TIVc

End point title	Percentage of subjects with hemagglutination inhibition (HI) titer ≥ 1:40, against each of three vaccine strains after receiving one dose of TIVc[5]

End point description:

Immunogenicity was assessed in terms of percentages of subjects in both age groups with HI titers ≥40, against each of the three vaccine strains, three weeks after receiving one dose of TIVc. The related European (CHMP) criterion for the assessment of immunogenicity is met if the percentage of subjects achieving HI titers ≥ 40 is >70% for adults aged 18 to ≤60 years and >60% for subjects aged ≥61 years. The analysis was performed on the Per Protocol Set.

End point type	Primary

End point timeframe:

Day 22 post-vaccination

Notes:

[5] - 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: There was no statistical null hypothesis associated with the immunogenicity objective.

End point values	TIVc (≥18 to ≤ 60 Years)	TIVc (≥ 61 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	61		
Units: Percentage of subjects				
number (confidence interval 95%)				
Day 1 (H1N1 strain)	68 (55 to 79)	66 (52 to 77)		
Day 22 (H1N1 strain)	100 (94 to 100)	97 (89 to 100)		
Day 1 (H3N2 strain)	89 (78 to 95)	87 (76 to 94)		

Day 22 (H3N2 strain)	97 (89 to 100)	95 (86 to 99)		
Day 1 (B strain)	58 (45 to 70)	46 (33 to 59)		
Day 22 (B strain)	94 (84 to 98)	80 (68 to 89)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentages of subjects with Seroconversion or Significant Increase in HI antibody titers after receiving one dose of TIVc

End point title	Percentages of subjects with Seroconversion or Significant Increase in HI antibody titers after receiving one dose of TIVc[6]

End point description:

Immunogenicity was assessed in terms of percentages of subjects in both age groups achieving seroconversion or significant increase in HI antibody titers after receiving one dose of TIVc.
Seroconversion is defined as percentage of subjects with a pre-vaccination HI titer <10 to a post-vaccination titer ≥40. Significant increase is defined as percentage of subjects with a pre-vaccination HI titer >10 to at least a 4-fold increase in post-vaccination HI antibody titers.
The related European (CHMP) criterion for the assessment of immunogenicity is met if>40 % for adults aged 18 to ≤60 years and>30% for subjects aged ≥61 years achieve seroconversion or significant increase in post-vaccination HI titers.
The analysis was performed on the Per Protocol Set.

End point type	Primary

End point timeframe:

Day 22 post-vaccination

Notes:

[6] - 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: There was no statistical null hypothesis associated with the immunogenicity objective.

End point values	TIVc (≥18 to ≤ 60 Years)	TIVc (≥ 61 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	61		
Units: Percentage of subjects				
number (confidence interval 95%)				
H1N1 strain	63 (50 to 75)	43 (30 to 56)		
H3N2 strain	47 (34 to 60)	26 (16 to 39)		
B strain	48 (35 to 61)	28 (17 to 41)		

Statistical analyses

No statistical analyses for this end point

Primary: Geometric mean ratio (GMR) of post-vaccination versus pre-vaccination HI antibody titers, against each of three vaccine strains after receiving one dose of TIVc

End point title	Geometric mean ratio (GMR) of post-vaccination versus pre-vaccination HI antibody titers, against each of three vaccine strains after receiving one dose of TIVc[7]

End point description:

The antibody responses following one dose of TIVc were evaluated in terms of GMRs of post-vaccination against pre-vaccination geometric mean HI titers against each of the three vaccine strains, three weeks after receiving one dose of TIVc. The related European (CHMP) criterion for the assessment of immunogenicity is met if the GMR day 22/day 1 is >2.5 for adults aged 18 to ≤60 years and >2.0 for subjects aged ≥61 years. The analysis was performed on the Per Protocol Set.

End point type	Primary

End point timeframe:

Day 22/Day1

Notes:

[7] - 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: There was no statistical null hypothesis associated with the immunogenicity objective.

End point values	TIVc (≥18 to ≤ 60 Years)	TIVc (≥ 61 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	61		
Units: Ratio				
number (confidence interval 95%)				
H1N1 strain	8.8 (5.66 to 14)	3.61 (2.61 to 5.01)		
H3N2 strain	3.52 (2.4 to 5.15)	2.22 (1.63 to 3.01)		
B strain	3.31 (2.45 to 4.47)	2.4 (1.81 to 3.17)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects reporting solicited adverse events after receiving one dose of TIVc.

End point title	Number of subjects reporting solicited adverse events after receiving one dose of TIVc.[8]

End point description:

The number of adult and elderly subjects reporting solicited local and systemic adverse events and other solicited adverse events after receiving one dose of TIVc.

End point type	Primary

End point timeframe:

Day 1 to Day 4 post-vaccination. Analysis was done on the solicited safety set population.

Notes:

[8] - 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: All safety analyses were run in the safety population.

End point values	TIVc (≥18 to ≤ 60 Years)	TIVc (≥ 61 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	63		
Units: Subjects				
Any Local	32	18		
Injection site induration	9	2		

Injection site erythema	5	4		
Injection site ecchymosis	1	1		
Injection site pain	31	18		
Any Systemic	17	8		
Shivering/Chills	1	1		
Myalgia	1	1		
Arthralgia	3	3		
Fatigue	10	2		
Headache	11	6		
Malaise	3	2		
Fever (≥ 38°C)	1	0		
Prophylactic use of analgesics/antipyretics	2	0		
Therapeutic use of analgesics/antipyretics	2	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All solicited AEs and unsolicited AEs were collected from Day 1 to Day 4; serious adverse events (SAEs), medically attended AEs, AEs leading to premature withdrawal were collected from Day 1 to Day 22.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	TIVc (≥18 to ≤ 60 Years)

Reporting group description:

Adult subjects received one dose of the cell-derived trivalent, surface antigen inactivated subunit influenza virus vaccine (TIVc) formulation 2013/2014 Northern Hemisphere

Reporting group title	TIVc (≥ 61 Years)

Reporting group description:

Elderly subjects received one dose of the cell-derived trivalent, surface antigen inactivated subunit influenza virus vaccine (TIVc) formulation 2013/2014 Northern Hemisphere

Serious adverse events	TIVc (≥18 to ≤ 60 Years)	TIVc (≥ 61 Years)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 63 (1.59%)	0 / 63 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Tooth infection			
subjects affected / exposed	1 / 63 (1.59%)	0 / 63 (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	TIVc (≥18 to ≤ 60 Years)	TIVc (≥ 61 Years)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 63 (57.14%)	22 / 63 (34.92%)	
Nervous system disorders			
Headache			

subjects affected / exposed	11 / 63 (17.46%)	6 / 63 (9.52%)	
occurrences (all)	13	6	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	10 / 63 (15.87%)	2 / 63 (3.17%)	
occurrences (all)	10	2	
Injection site induration			
subjects affected / exposed	4 / 63 (6.35%)	1 / 63 (1.59%)	
occurrences (all)	9	2	
Injection site pain			
subjects affected / exposed	32 / 63 (50.79%)	18 / 63 (28.57%)	
occurrences (all)	33	18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported