



## Clinical trial results:

**A multicenter, open-label, single-arm study to evaluate the PK, safety, tolerability and efficacy of a new artemether-lumefantrine (2.5 mg: 30 mg) dispersible tablet in the treatment of infants and neonates <5 kg body weight with acute uncomplicated Plasmodium falciparum malaria**

### Summary

EudraCT number	2023-000804-21
Trial protocol	Outside EU/EEA
Global end of trial date	10 May 2024

### Results information

Result version number	v1 (current)
This version publication date	01 November 2024
First version publication date	01 November 2024

### Trial information

#### Trial identification

Sponsor protocol code	CCOA566B2307
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04300309
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland, CH-4056
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.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?	Yes

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 May 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 May 2024
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to assess the key pharmacokinetics (PK) parameter of artemether in infants and neonates < 5 kg body weight dosed with the new formulation of artemether-lumefantrine dispersible tablet.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 December 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Burkina Faso: 7
Country: Number of subjects enrolled	Congo, The Democratic Republic of the: 21
Worldwide total number of subjects	28
EEA total number of subjects	0

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	6
Infants and toddlers (28 days-23 months)	22
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0
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## Subject disposition

### Recruitment

Recruitment details:

Participants took part in 3 investigative sites in 2 countries.

### Pre-assignment

Screening details:

The Screening procedures began once the study informed consent had been obtained. Screening was performed within 12 hours before the first study drug administration.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Cohort 1

Arm description:

Infants >28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days

Arm type	Experimental
Investigational medicinal product name	artemether-lumefantrine
Investigational medicinal product code	COA566
Other name	
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

The investigational product was artemether-lumefantrine 2.5 mg:30 mg (COA566 2.5 mg:30 mg), supplied in the form of oral dispersible tablets.

The study treatment was 2 oral dispersible tablets (i.e. artemether-lumefantrine 5 mg:60 mg), twice daily, for 3 days.

<b>Arm title</b>	Cohort 2
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Arm description:

Term neonates 1-28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days

Arm type	Experimental
Investigational medicinal product name	artemether-lumefantrine
Investigational medicinal product code	COA566
Other name	
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

The investigational product was artemether-lumefantrine 2.5 mg:30 mg (COA566 2.5 mg:30 mg), supplied in the form of oral dispersible tablets.

The study treatment was 2 oral dispersible tablets (i.e. artemether-lumefantrine 5 mg:60 mg), twice daily, for 3 days.

<b>Number of subjects in period 1</b>	Cohort 1	Cohort 2
Started	22	6
Full Analysis Set (FAS)	22	6
Per-Protocol Set (PPS)	17 <sup>[1]</sup>	6
PK Set	22	6
Completed treatment phase	22	6
Completed Core follow-up (43 days)	22	6
Completed	21	6
Not completed	1	0
Lost to follow-up	1	-

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Notes:

[1] - 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: FAS, PPS and PK Set are analysis sets

## Baseline characteristics

### Reporting groups

Reporting group title	Cohort 1
Reporting group description:	
Infants >28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days	
Reporting group title	Cohort 2
Reporting group description:	
Term neonates 1-28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days	

Reporting group values	Cohort 1	Cohort 2	Total
Number of subjects	22	6	28
Age Categorical			
Units: participants			
1-7 days	0	1	1
8-14 days	0	0	0
15-28 days	0	5	5
>28 days	22	0	22
Age Continuous			
Units: days			
median	96.0	22.5	
full range (min-max)	53.0 to 157.0	1.0 to 26.0	-
Sex: Female, Male			
Units: participants			
Female	15	3	18
Male	7	3	10
Race/Ethnicity, Customized			
Units: Subjects			
Black or African American	22	6	28
Plasmodium species			
Parasitemia determinations were performed in peripheral blood. Microscopic species determination was confirmed with polymerase chain reaction (PCR)-based methods. The assessments were performed at a central reference laboratory.			
Units: Subjects			
P. falciparum asexual forms	21	6	27
P. vivax	0	0	0
P. ovale	0	0	0
P. malariae	1	0	1
P. knowlesi	0	0	0
Plasmodium falciparum density			
Parasitemia determinations were performed in peripheral blood. Giemsa stained thick fields were examined at a central reference laboratory. The parasite density was calculated according to the following formula: (number of Plasmodium falciparum parasites * actual leukocytes)/number of leucocytes counted (200 thick films fields examined)			
Units: parasites/μL			
median	8400	3660	
full range (min-max)	748 to 156400	384 to 52700	-
Weight			
Units: kilograms			

median	4.82	3.50	
full range (min-max)	3.89 to 4.98	2.80 to 4.24	-

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## End points

### End points reporting groups

Reporting group title	Cohort 1
Reporting group description: Infants >28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days	
Reporting group title	Cohort 2
Reporting group description: Term neonates 1-28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days	

### Primary: Artemether Cmax after first dose

End point title	Artemether Cmax after first dose <sup>[1]</sup>
End point description: Artemether Cmax represents the highest concentration between the concentrations at 1 hour and 2 hours after first dose. Pharmacokinetic (PK) parameters were calculated by non-compartmental analysis based on artemether plasma concentrations.	
End point type	Primary
End point timeframe: 1 and 2 hours after first dose (Day 1)	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No statistical analysis was planned for this endpoint.	

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	5		
Units: ng/mL				
geometric mean (confidence interval 90%)	68.0 (45.1 to 103)	62.2 (33.6 to 115)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Lumefantrine Day 8 concentration (C168h)

End point title	Lumefantrine Day 8 concentration (C168h)
End point description: Pharmacokinetic (PK) parameters were calculated by non-compartmental analysis based on lumefantrine plasma concentrations. Dosing times were 0, 8, 24, 36, 48 and 60 hours.	
End point type	Secondary
End point timeframe: 168 hours after first dose (corresponding to 108 hours after last dose)	

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	6		
Units: ng/mL				
geometric mean (confidence interval 90%)	353 (250 to 498)	480 (265 to 870)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Lumefantrine Cmax after last dose

End point title	Lumefantrine Cmax after last dose
End point description: Lumefantrine Cmax represents the highest concentration among four sampling time points after last dose. Pharmacokinetic (PK) parameters were calculated by non-compartmental analysis based on lumefantrine plasma concentrations. Dosing times were 0, 8, 24, 36, 48 and 60 hours.	
End point type	Secondary
End point timeframe: 62, 66, 68 and 84 hours after first dose (corresponding to 2, 6, 8 and 24 hours after last dose)	

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	6		
Units: ng/mL				
geometric mean (confidence interval 90%)	3180 (2530 to 4000)	3510 (1880 to 6540)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: DHA Cmax after first dose

End point title	DHA Cmax after first dose
End point description: Dihydroartemisinin (DHA) is an active metabolite of artemether. DHA Cmax represents the highest concentration between the concentrations at 1 hour and 2 hours after first dose. Pharmacokinetic (PK) parameters were calculated by non-compartmental analysis based on DHA plasma concentrations.	

End point type	Secondary
End point timeframe:	
1 and 2 hours after first dose (Day 1)	

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	5		
Units: ng/mL				
geometric mean (confidence interval 90%)	11.5 (7.58 to 17.4)	15.7 (8.53 to 28.9)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Parasite Clearance Time (PCT)

End point title	Parasite Clearance Time (PCT)
End point description:	
PCT is defined as time from the first dose until the first total and continued disappearance of asexual parasite forms which remained at least a further 48 hours. PCT is based on uncorrected parasite counts. Patients who received rescue medication before parasite clearance were censored at the first use of rescue medication.	
Patients without parasite clearance were censored at the time of last parasite assessment.	
PCT was calculated using the Kaplan-Meier method.	
End point type	Secondary
End point timeframe:	
Up to 48 hours after first dose	

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	6		
Units: hours				
median (inter-quartile range (Q1-Q3))	35.0 (24.0 to 35.8)	30.6 (23.8 to 47.6)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Fever clearance Times (FCT)

End point title	Fever clearance Times (FCT)
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End point description:

FCT is defined as time from the first dose until the first time the axillary body temperature decreased below and remained below 37.5°C axillary or 38.0°C oral/tympanic/rectal for at least a further 24 hours. Patients who received rescue medication before fever clearance were censored at the first use of rescue medication.

Patients without fever clearance were censored at the time of last parasite assessment.

FCT was calculated using the Kaplan-Meier method.

End point type	Secondary
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End point timeframe:

Up to 36 hours after first dose

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	1		
Units: hours				
median (inter-quartile range (Q1-Q3))	15.7 (3.9 to 29.7)	7.6 (7.6 to 7.6)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: PCR-corrected Adequate Clinical and Parasitological Response (ACPR) – PPS analysis

End point title	PCR-corrected Adequate Clinical and Parasitological Response (ACPR) – PPS analysis
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End point description:

PCR-corrected ACPR, defined as the absence of parasitemia, was evaluated on Days 15, 29 and 43. Microscopic species identification was confirmed and determined by polymerase chain reaction (PCR) genotyping methods to establish malaria recrudescence/reinfection.

A participant was considered as PCR-corrected ACPR if the participant did not meet any of the criteria of early treatment failure, late clinical failure or late parasitological failure and had absence of parasitemia on Days 15, 29 or 43 irrespective of axillary temperature unless the presence of parasitemia after 7 days was due to reinfection based on PCR. A presence of parasitemia after 7 days of treatment initiation was considered as a reinfection only if the parasitemia was clear before Day 8 and none of the parasite strain(s) detected on Day 8 or later matched with the parasite strain at baseline based on PCR.

End point type	Secondary
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End point timeframe:

Days 15, 29 and 43

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	6		
Units: percentage of participants				
number (confidence interval 95%)				
Day 15 (n=17, 6)	100 (80.49 to 100)	100 (54.07 to 100)		

Day 29 (n=17, 6)	100 (80.49 to 100)	100 (54.07 to 100)		
Day 43 (n=17, 6)	94.1 (71.31 to 99.85)	100 (54.07 to 100)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: PCR-corrected Adequate Clinical and Parasitological Response (ACPR) – FAS analysis

End point title	PCR-corrected Adequate Clinical and Parasitological Response (ACPR) – FAS analysis
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End point description:

PCR-corrected ACPR, defined as the absence of parasitemia, was evaluated on Days 15, 29 and 43. Microscopic species identification was confirmed and determined by polymerase chain reaction (PCR) genotyping methods to establish malaria recrudescence/reinfection. A participant was considered as PCR-corrected ACPR if the participant did not meet any of the criteria of early treatment failure, late clinical failure or late parasitological failure and had absence of parasitemia on Days 15, 29 or 43 irrespective of axillary temperature unless the presence of parasitemia after 7 days was due to reinfection based on PCR. A presence of parasitemia after 7 days of treatment initiation was considered as a reinfection only if the parasitemia was clear before Day 8 and none of the parasite strain(s) detected on Day 8 or later matched with the parasite strain at baseline based on PCR.

End point type	Secondary
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End point timeframe:

Days 15, 29 and 43

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	6		
Units: percentage of participants				
number (confidence interval 95%)				
Day 15 (n=22, 6)	100 (84.56 to 100)	100 (54.07 to 100)		
Day 29 (n=22, 6)	95.5 (77.16 to 99.88)	100 (54.07 to 100)		
Day 43 (n=22, 6)	90.9 (70.84 to 98.88)	100 (54.07 to 100)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: PCR-uncorrected Adequate Clinical and Parasitological Response (ACPR)

End point title	PCR-uncorrected Adequate Clinical and Parasitological Response (ACPR)
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End point description:

PCR-uncorrected ACPR, defined as the absence of parasitemia, was evaluated on Days 8, 15, 29 and 43.

A participant was considered as PCR-uncorrected ACPR if the participant did not meet any of the criteria of early treatment failure, late clinical failure or late parasitological failure and had absence of parasitemia on Days 8, 15, 29 or 43 irrespective of axillary temperature.

End point type	Secondary
End point timeframe:	
Days 8, 15, 29 and 43	

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	6		
Units: percentage of participants				
number (confidence interval 95%)				
Day 8 (n=22, 6)	100 (84.56 to 100)	100 (54.07 to 100)		
Day 15 (n=22, 6)	100 (84.56 to 100)	100 (54.07 to 100)		
Day 29 (n=22, 6)	77.3 (54.63 to 92.18)	100 (54.07 to 100)		
Day 43 (n=22, 6)	63.6 (40.66 to 82.80)	100 (54.07 to 100)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with recrudescence events

End point title	Number of participants with recrudescence events
End point description:	
Recrudescence is defined as appearance of asexual parasites after clearance of initial infection with a genotype identical to that of parasites present at baseline. Recrudescence had to be confirmed by PCR analysis.	
End point type	Secondary
End point timeframe:	
Days 15, 29 and 43	

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	6		
Units: participants				
Day 15 (n=22, 6)	0	0		
Day 29 (n=22, 6)	1	0		
Day 43 (n=22, 6)	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with new infections events

End point title	Number of participants with new infections events
End point description: New infection is defined as appearance of asexual parasites after clearance of initial infection with a genotype different from those parasites present at baseline. New infection had to be confirmed by PCR analysis.	
End point type	Secondary
End point timeframe: Days 15, 29 and 43	

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	6		
Units: participants				
Day 15 (n=22, 6)	0	0		
Day 29 (n=22, 6)	4	0		
Day 43 (n=22, 6)	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Adverse Events (AEs)

End point title	Number of participants with Adverse Events (AEs)
End point description: Number of participants with adverse events (any AEs regardless of seriousness), including changes in laboratory results qualifying and reported as adverse events.	
End point type	Secondary
End point timeframe: From first dose of study treatment until Day 43	

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	6		
Units: participants	17	4		

Statistical analyses

No statistical analyses for this end point

**Secondary: Number of participants with Serious Adverse Events (SAEs)**

End point title	Number of participants with Serious Adverse Events (SAEs)
End point description: Number of participants with serious adverse events (SAEs), including changes in laboratory results qualifying and reported as serious adverse events.	
End point type	Secondary
End point timeframe: From first dose of study treatment until 12 months of age (assessed up to maximum 1 year)	

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	6		
Units: participants	0	0		

**Statistical analyses**

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Non-serious adverse events were collected from first dose of study treatment until Day 43. Deaths and serious adverse events were collected from first dose of study treatment until 1 year of age (assessed up to maximum 1 year).

Adverse event reporting additional description:

Adverse events are assessed in the Safety Set, including all patients who received at least one dose of study treatment.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.1
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### Reporting groups

Reporting group title	Cohort 1
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Reporting group description:

Infants >28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days

Reporting group title	Pooled Cohort
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Reporting group description:

All infants and neonates who received at least one dose of artemether-lumefantrine

Reporting group title	Cohort 2
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Reporting group description:

Term neonates 1-28 days of age treated with artemether-lumefantrine (5 mg:60 mg) twice daily for 3 days

Serious adverse events	Cohort 1	Pooled Cohort	Cohort 2
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Cohort 1	Pooled Cohort	Cohort 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 22 (77.27%)	21 / 28 (75.00%)	4 / 6 (66.67%)
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 22 (31.82%)	8 / 28 (28.57%)	1 / 6 (16.67%)
occurrences (all)	7	8	1
General disorders and administration			

site conditions			
Pyrexia			
subjects affected / exposed	8 / 22 (36.36%)	10 / 28 (35.71%)	2 / 6 (33.33%)
occurrences (all)	13	15	2
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Vomiting			
subjects affected / exposed	6 / 22 (27.27%)	7 / 28 (25.00%)	1 / 6 (16.67%)
occurrences (all)	7	8	1
Infections and infestations			
Bacterial rhinitis			
subjects affected / exposed	2 / 22 (9.09%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	2	2	0
Ear infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Gastrointestinal fungal infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Malaria			
subjects affected / exposed	9 / 22 (40.91%)	9 / 28 (32.14%)	0 / 6 (0.00%)
occurrences (all)	9	9	0
Rhinitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	1 / 6 (16.67%)
occurrences (all)	0	1	1

**More information**

**Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 June 2023	To enable additional optional pharmacokinetics (PK) checks for artemether and lumefantrine and additional interim assessments by the data monitoring committee (DMC). In addition, text related to public health emergencies and safety reporting was updated.

Notes:

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**Interruptions (globally)**

Were there any global interruptions to the trial? No

**Limitations and caveats**

None reported