# EU Clinical Trials Register

## Clinical trial results:
## A Double-Blind, Randomised, Placebo-Controlled, Parallel-Group, 12-Week Study of Pitavastatin in High-Risk Hyperlipidaemia in Childhood P/0230/2012, P/0231/2012, P/0232/2012 and P/0233/2012.

### Summary

| EudraCT number | 2011-004964-32 |
|---|---|
| Trial protocol | NL GR FR ES NO IT |
| Global end of trial date | 20 March 2013 |

### Results information

| Result version number | v1 (current) |
|---|---|
| This version publication date | 01 February 2016 |
| First version publication date | 31 July 2015 |

### Trial information

### Trial identification

| Sponsor protocol code | NK-104-4.01EU |
|---|---|

### Additional study identifiers

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

Notes:

### Sponsors

| Sponsor organisation name | Kowa Research Europe, Ltd |
|---|---|
| Sponsor organisation address | 105 Wharfedale Road, Winnersh Triangle, Wokingham, United Kingdom, RG41 5RB |
| Public contact | Regulatory Affairs, Kowa Research Europe Co, Ltd., +44 (0)118 922 9000, |
| Scientific contact | Regulatory Affairs, Kowa Research Europe Co, Ltd., +44 (0)118 922 9000, |

Notes:

### Paediatric regulatory details

| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
|---|---|
| EMA paediatric investigation plan number(s) | EMEA-000300-PIP01-08, EMEA-000054-PIP01-07, EMEA-000302-PIP01-08, EMEA-000301-PIP01-08 |
| 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 | 20 May 2013 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 20 March 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 20 March 2013 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to compare the efficacy of pitavastatin 1 mg QD, 2 mg QD, and 4 mg QD to placebo in terms of the percentage reduction in LDL-C in children or adolescent patients with high-risk hyperlipidaemia at steady state (Week 12).

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. Each patient was assured of his/her right to withdraw from the study at any time. Close monitoring of all subjects was adhered to throughout the trial conduct.
Patients were discouraged from starting any new medication without first consulting the Investigator, unless the new medication was required for emergency use. In general, any medication not excluded by the protocol was permitted.

| | |
|---|---|
| Background therapy: - | |
| Evidence for comparator: - | |
| Actual start date of recruitment | 20 April 2012 |
| 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 | Netherlands: 40 |
| Country: Number of subjects enrolled | Norway: 15 |
| Country: Number of subjects enrolled | Spain: 9 |
| Country: Number of subjects enrolled | France: 5 |
| Country: Number of subjects enrolled | Greece: 22 |
| Country: Number of subjects enrolled | Italy: 15 |
| Worldwide total number of subjects | 106 |
| EEA total number of subjects | 106 |

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) | 67 |
| Adolescents (12-17 years) | 39 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

# Subject disposition

## Recruitment

Recruitment details: -

## Pre-assignment

Screening details:

The study consisted of an up to 5-week screening/wash out period, and all participants were screened at specialist lipid clinics.

## 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 | Subject, Investigator, Monitor, Data analyst |

### Arms

| Are arms mutually exclusive? | Yes |
|---|---|
| **Arm title** | Pitavastatin 1 mg |

Arm description: -

| Arm type | Experimental |
|---|---|
| Investigational medicinal product name | Pitavastatin |
| Investigational medicinal product code | NK-104 |
| Other name | PITAVASTATIN CALCIUM |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Pitavastatin 1 mg was to be taken orally, once daily in the morning. Duration of treatment is 12 weeks.

| **Arm title** | Pitavastatin 2 mg |
|---|---|

Arm description: -

| Arm type | Experimental |
|---|---|
| Investigational medicinal product name | Pitavastatin |
| Investigational medicinal product code | NK-104 |
| Other name | PITAVASTATIN CALCIUM |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Pitavastatin 2 mg was to be taken orally, once daily in the morning. Duration of treatment is 12 weeks.

| **Arm title** | Pitavastatin 4 mg |
|---|---|

Arm description: -

| Arm type | Experimental |
|---|---|
| Investigational medicinal product name | Pitavastatin |
| Investigational medicinal product code | NK-104 |
| Other name | PITAVASTATIN CALCIUM |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Pitavastatin was to be taken orally, once daily in the morning. Pitavastatin 2 mg was received for the first 4 weeks and then pitavastatin 4 mg for the remaining 8 weeks of the treatment period.

| **Arm title** | Placebo group |
|---|---|

| Arm description: - | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo was to be taken orally, once daily in the morning. Duration of treatment is 12 weeks.

| Number of subjects in period 1 | Pitavastatin 1 mg | Pitavastatin 2 mg | Pitavastatin 4 mg |
|---|---|---|---|
| Started | 26 | 27 | 26 |
| Completed | 26 | 26 | 24 |
| Not completed | 0 | 1 | 2 |
| Consent withdrawn by subject | - | - | 1 |
| Adverse event, non-fatal | - | 1 | 1 |

| Number of subjects in period 1 | Placebo group |
|---|---|
| Started | 27 |
| Completed | 27 |
| Not completed | 0 |
| Consent withdrawn by subject | - |
| Adverse event, non-fatal | - |

## Baseline characteristics

### Reporting groups

| | |
|---|---|
| Reporting group title | Pitavastatin 1 mg |
| Reporting group description: - | |
| Reporting group title | Pitavastatin 2 mg |
| Reporting group description: - | |
| Reporting group title | Pitavastatin 4 mg |
| Reporting group description: - | |
| Reporting group title | Placebo group |

Reporting group description: -

| Reporting group values | Pitavastatin 1 mg | Pitavastatin 2 mg | Pitavastatin 4 mg |
|---|---|---|---|
| Number of subjects | 26 | 27 | 26 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 15 | 15 | 17 |
| Adolescents (12-17 years) | 11 | 12 | 9 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 10.5 | 11.1 | 10.3 |
| standard deviation | ± 2.75 | ± 2.87 | ± 2.66 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 14 | 17 | 12 |
| Male | 12 | 10 | 14 |

| Reporting group values | Placebo group | Total | |
|---|---|---|---|
| Number of subjects | 27 | 106 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 20 | 67 | |
| Adolescents (12-17 years) | 7 | 39 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |

| | | | |
|---|---|---|---|
| 85 years and over | 0 | 0 | |

| | | | |
|---|---|---|---|
| Age continuous<br>Units: years | | | |
|     arithmetic mean | 10.4 | | |
|     standard deviation | ± 3.26 | - | |
| Gender categorical<br>Units: Subjects | | | |
|     Female | 15 | 58 | |
|     Male | 12 | 48 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Pitavastatin 1 mg |
| Reporting group description: - | |
| Reporting group title | Pitavastatin 2 mg |
| Reporting group description: - | |
| Reporting group title | Pitavastatin 4 mg |
| Reporting group description: - | |
| Reporting group title | Placebo group |
| Reporting group description: - | |
| Subject analysis set title | Pitavastatin 1 mg vs. Placebo |
| Subject analysis set type | Full analysis |

Subject analysis set description:

The Full Analysis Set was defined as all randomized patients who received at least 1 dose of study drug and had a valid baseline lipid measurement and at least 1 valid post-baseline lipid measurement.

| | |
|---|---|
| Subject analysis set title | Pitavastatin 2 mg vs. Placebo |
| Subject analysis set type | Full analysis |

Subject analysis set description:

The Full Analysis Set was defined as all randomized patients who received at least 1 dose of study drug and had a valid baseline lipid measurement and at least 1 valid post-baseline lipid measurement.

| | |
|---|---|
| Subject analysis set title | Pitavastatin 4 mg vs. Placebo |
| Subject analysis set type | Full analysis |

Subject analysis set description:

The Full Analysis Set was defined as all randomized patients who received at least 1 dose of study drug and had a valid baseline lipid measurement and at least 1 valid post-baseline lipid measurement.

### Primary: The primary efficacy endpoint of this study was the percent change in LDL-C from baseline to Week 12 with LOCF

| | |
|---|---|
| End point title | The primary efficacy endpoint of this study was the percent change in LDL-C from baseline to Week 12 with LOCF |

End point description:

| | |
|---|---|
| End point type | Primary |

End point timeframe:

From baseline to Week 12

| End point values | Pitavastatin 1 mg | Pitavastatin 2 mg | Pitavastatin 4 mg | Placebo group |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 26 | 26 | 24 | 27 |
| Units: percent change in LDL-C | | | | |
| least squares mean (standard error) | -23.5 (± 2.09) | -30.1 (± 2.11) | -39.3 (± 2.18) | 1 (± 2.06) |

### Statistical analyses

| Statistical analysis title | Pitavastatin 1 mg vs. Placebo |
| --- | --- |
| Comparison groups | Pitavastatin 1 mg v Placebo group |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -24.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -30.3 |
| upper limit | -18.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.94 |


| Statistical analysis title | Pitavastatin 2 mg vs. Placebo |
| --- | --- |
| Comparison groups | Pitavastatin 2 mg v Placebo group |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -31.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -37 |
| upper limit | -25.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.96 |


| Statistical analysis title | Pitavastatin 4 mg vs. Placebo |
| --- | --- |
| Comparison groups | Pitavastatin 4 mg v Placebo group |
| Number of subjects included in analysis | 51 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -40.3 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -46.2 |
| upper limit | -34.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.99 |

## Secondary: Percent change in LDL-C from baseline over 12 weeks of treatment

| | |
|---|---|
| End point title | Percent change in LDL-C from baseline over 12 weeks of treatment |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| From baseline over 12 weeks of treatment (Week 4, Week 8, and Week 12) | |

| End point values | Pitavastatin 1 mg | Pitavastatin 2 mg | Pitavastatin 4 mg | Placebo group |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 26 | 26 | 24 | 27 |
| Units: Percent change in LDL-C | | | | |
| number (not applicable) | | | | |
| Percent change in week 4 | -24.1 | -31.1 | -28.7 | 0.5 |
| Percent change in week 8 | -24.2 | -20.7 | -39.5 | -1.5 |
| Percent change in week 12 | -23.3 | -29.7 | -40.3 | 1.3 |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentages of patients who achieved American Heart Association minimal (130 mg/dL [3.4 mmol/L]) and ideal (110 mg/dL [2.8 mmol/L]) LDL-C targets

| | |
|---|---|
| End point title | Percentages of patients who achieved American Heart Association minimal (130 mg/dL [3.4 mmol/L]) and ideal (110 mg/dL [2.8 mmol/L]) LDL-C targets |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| From baseline to week 12 with LOCF | |

| End point values | Pitavastatin 1 mg | Pitavastatin 2 mg | Pitavastatin 4 mg | Placebo group |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 26 | 26 | 24 | 27 |
| Units: Percentages of patients | | | | |
| number (not applicable) | | | | |
| LDL-C <130 mg/dL | 3.8 | 30.8 | 37.5 | 0 |
| LDL-C <110 mg/dL | 0 | 7.7 | 16.7 | 0 |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent changes in HDL-C, non–high-density lipoprotein cholesterol (non–HDL-C), total cholesterol (TC), TG, apolipoprotein A1 (Apo A1), and apolipoprotein B (Apo B)

| End point title | Percent changes in HDL-C, non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), TG, apolipoprotein A1 (Apo A1), and apolipoprotein B (Apo B) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

From baseline to week 12 with LOCF

| End point values | Pitavastatin 1 mg | Pitavastatin 2 mg | Pitavastatin 4 mg | Placebo group |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 26 | 26 | 24 | 27 |
| Units: Percent change | | | | |
| least squares mean (standard error) | | | | |
| HDL-C | 6.1 (± 2.5) | -2.4 (± 2.52) | -3.1 (± 2.61) | 1.1 (± 2.46) |
| non-HDL | -22.9 (± 2.14) | -28.5 (± 2.15) | -37.2 (± 2.23) | 1.1 (± 2.1) |
| TC | -17.8 (± 1.78) | -24.2 (± 1.79) | -31.3 (± 1.86) | 0.9 (± 1.75) |
| TG | -7.6 (± 6.26) | -5.9 (± 6.43) | 0.3 (± 6.6) | 2 (± 6.15) |
| Apo A1 | 1.1 (± 2.16) | -3.6 (± 2.16) | -2.2 (± 2.24) | -0.8 (± 2.12) |
| Apo B | -21.6 (± 2.24) | -25 (± 2.25) | -28.8 (± 2.33) | 0.4 (± 2.2) |

## Statistical analyses

No statistical analyses for this end point

**Secondary: Changes in TC:HDL-C ratio, non-HDL-C:HDL-C ratio, and Apo B:Apo A1 ratio**

| End point title | Changes in TC:HDL-C ratio, non-HDL-C:HDL-C ratio, and Apo B:Apo A1 ratio |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

From baseline to week 12 with LOCF

| End point values | Pitavastatin 1 mg | Pitavastatin 2 mg | Pitavastatin 4 mg | Placebo group |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 26 | 26 | 24 | 27 |
| Units: Ratio | | | | |
| least squares mean (standard error) | | | | |
| TC:HDL-C ratio | -1.36 (± 0.151) | -1.32 (± 0.152) | -1.73 (± 0.157) | -0.04 (± 0.148) |
| non-HDL-C:HDL-C ratio | -1.36 (± 0.151) | -1.32 (± 0.152) | -1.73 (± 0.157) | -0.04 (± 0.148) |
| Apo B:Apo A1 ratio | -0.25 (± 0.032) | -0.24 (± 0.032) | -0.3 (± 0.033) | 0 (± 0.031) |

**Statistical analyses**

No statistical analyses for this end point

# Adverse events

## Adverse events information

Timeframe for reporting adverse events:

The evaluation of safety during the double-blind period was based primarily on the frequency of adverse events, SAEs, discontinuations due to adverse events, clinical laboratory assessments etc.

| Assessment type | Systematic |
|---|---|

## Dictionary used

| Dictionary name | MedDRA |
|---|---|
| Dictionary version | 15.0 |

### Reporting groups

| Reporting group title | Pitavastatin 1 mg |
|---|---|
| Reporting group description: - | |
| Reporting group title | Pitavastatin  2 mg |
| Reporting group description: - | |
| Reporting group title | Pitavastatin 4 mg |
| Reporting group description: - | |
| Reporting group title | Placebo |

Reporting group description: -

| Serious adverse events | Pitavastatin 1 mg | Pitavastatin  2 mg | Pitavastatin 4 mg |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 1 / 27 (3.70%) | 0 / 26 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Facial bones fracture | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 1 / 27 (3.70%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Placebo | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Facial bones fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 27 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events | Pitavastatin 1 mg | Pitavastatin 2 mg | Pitavastatin 4 mg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 18 / 26 (69.23%) | 16 / 27 (59.26%) | 11 / 26 (42.31%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 6 / 26 (23.08%) | 5 / 27 (18.52%) | 1 / 26 (3.85%) |
| occurrences (all) | 7 | 7 | 1 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 26 (11.54%) | 2 / 27 (7.41%) | 0 / 26 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Abdominal discomfort | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 1 | 0 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 0 | 1 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 4 / 26 (15.38%) | 6 / 27 (22.22%) | 2 / 26 (7.69%) |
| occurrences (all) | 4 | 6 | 2 |
| Influenza | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 0 / 27 (0.00%) | 2 / 26 (7.69%) |
| occurrences (all) | 0 | 0 | 2 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 26 (7.69%) | 0 / 27 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |

| Non-serious adverse events | Placebo | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 15 / 27 (55.56%) | | |

| | | | |
|---|---|---|---|
| **Nervous system disorders** | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | | |
| occurrences (all) | 2 | | |
| **Gastrointestinal disorders** | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | | |
| occurrences (all) | 3 | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 3 / 27 (11.11%) | | |
| occurrences (all) | 3 | | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 27 (11.11%) | | |
| occurrences (all) | 3 | | |
| **Infections and infestations** | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 6 / 27 (22.22%) | | |
| occurrences (all) | 6 | | |
| Influenza | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | | |
| occurrences (all) | 3 | | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | | |
| occurrences (all) | 0 | | |

## 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