



Clinical trial results:

A multicenter, Investigator-Masked, Parallel Group, Randomized, Study of the Efficacy and Safety of Indomethacin 0.1% Eyedrops Compared with Ketorolac 0.5% Eyedrops in the Ocular Inflammation After Cataract Surgery.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2007-004686-18 |
| Trial protocol | FR PT DE |
| Global end of trial date | 27 July 2009 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 27 August 2020 |
| First version publication date | 27 August 2020 |

Trial information

Trial identification

| | |
|-----------------------|-----|
| Sponsor protocol code | 539 |
|-----------------------|-----|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Bausch & Lomb Incorporated |
| Sponsor organisation address | 1400 North Goodman Street, Rochester, United States, |
| Public contact | Manager Clinical Science, Bausch&Lomb Dr Gerhard Mann chem.-Fabrik GmbH, Raphaele.SiouMermet@bausch.com |
| Scientific contact | Manager Clinical Science, Bausch&Lomb Dr Gerhard Mann chem.-Fabrik GmbH, Raphaele.SiouMermet@bausch.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 27 July 2009 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 27 July 2009 |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 July 2009 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To show that indomethacin 0.1% eye drops are at least as effective as ketorolac 0.5% eye drops in the prevention of ocular inflammation (aqueous flare) following cataract surgery measured by laser Flare Meter 24 hours and 1 week after surgery.

Protection of trial subjects:

This study was conducted in compliance with the protocol and in accordance with Good Clinical Practices (GCPs), ICH guidelines (CPMP/ICH/135/95), applicable local regulations, and the Declaration of Helsinki (2004).

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 10 July 2008 |
| 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 | Poland: 20 |
| Country: Number of subjects enrolled | Portugal: 9 |
| Country: Number of subjects enrolled | France: 27 |
| Country: Number of subjects enrolled | Germany: 67 |
| Worldwide total number of subjects | 123 |
| EEA total number of subjects | 123 |

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) | 28 |

| | |
|---------------------|----|
| From 65 to 84 years | 93 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Approximately 120 subjects (120 eyes), of either gender, 18 years of age or older, who planned to undergo cataract surgery by phacoemulsification were to be enrolled in this study. Potential subjects who met the eligibility requirements were to be scheduled for six study visits over a period of approximately 90 days.

Period 1

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

Blinding implementation details:

Subjects masked to treatment name

Arms

| | |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Indomethacin |

Arm description: -

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Indomethacin ophthalmic solution 0.1% |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Eye drops |
| Routes of administration | Ocular use |

Dosage and administration details:

Subjects were to be instructed to instill one drop QID for three weeks, starting 24 hours prior to surgery.

| | |
|------------------|-----------|
| Arm title | Ketorolac |
|------------------|-----------|

Arm description: -

| | |
|--|------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Ketorolac 0.5% ophthalmic solution |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Eye drops |
| Routes of administration | Ocular use |

Dosage and administration details:

Subjects were to be instructed to instill one drop QID for three weeks, starting 24 hours prior to surgery.

| Number of subjects in period 1 | Indomethacin | Ketorolac |
|---------------------------------------|--------------|-----------|
| Started | 59 | 64 |
| Completed | 55 | 57 |
| Not completed | 4 | 7 |
| Consent withdrawn by subject | 2 | - |
| Adverse event, non-fatal | - | 1 |
| Other | - | 2 |
| Peroperative complication | - | 1 |
| Lost to follow-up | 1 | 2 |
| Protocol deviation | 1 | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Treatment |
|-----------------------|-----------|

Reporting group description: -

| Reporting group values | Treatment | Total | |
|---|-----------|-------|--|
| Number of subjects | 123 | 123 | |
| 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) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 28 | 28 | |
| From 65-84 years | 93 | 93 | |
| 85 years and over | 2 | 2 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 69 | 69 | |
| Male | 54 | 54 | |

End points

End points reporting groups

| | |
|--------------------------------|--------------|
| Reporting group title | Indomethacin |
| Reporting group description: - | |
| Reporting group title | Ketorolac |
| Reporting group description: - | |

Primary: Aqueous Flare by LFM measurement at Day 1

| | |
|------------------------|---|
| End point title | Aqueous Flare by LFM measurement at Day 1 |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| Day 1 | |

| End point values | Indomethacin | Ketorolac | | |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 43 | 43 | | |
| Units: ph/ms | | | | |
| arithmetic mean (standard deviation) | 18.50 (\pm 9.67) | 16.25 (\pm 8.71) | | |

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | Non-inferiority at Day 1 |
| Comparison groups | Indomethacin v Ketorolac |
| Number of subjects included in analysis | 86 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[1] |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.56 |
| Confidence interval | |
| level | 95 % |
| sides | 1-sided |
| upper limit | 5.5 |

Notes:

[1] - Non-inferiority of Indomethacin treatment was demonstrated if the upper limit of the 95% CI for the mean difference was less than the upper limit of the non-inferiority margin (15).

Primary: Aqueous Flare by LFM measurement at Day 7

| | |
|------------------------|---|
| End point title | Aqueous Flare by LFM measurement at Day 7 |
| End point description: | |

| | |
|----------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| 7 days | |

| End point values | Indomethacin | Ketorolac | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 42 | 41 | | |
| Units: ph/ms | | | | |
| arithmetic mean (standard deviation) | 11.88 (± 7.23) | 15.01 (± 9.58) | | |

Statistical analyses

| Statistical analysis title | Non-inferiority at 7 days |
|---|--------------------------------|
| Comparison groups | Indomethacin v Ketorolac |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[2] |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -4.38 |
| Confidence interval | |
| level | 95 % |
| sides | 1-sided |
| upper limit | -0.94 |

Notes:

[2] - Non-inferiority of Indomethacin treatment was demonstrated if the upper limit of the 95% CI for the mean difference was less than the upper limit of the non-inferiority margin (8).

Secondary: Aqueous Flare by LFM measurement at Day 30

| | |
|------------------------|--|
| End point title | Aqueous Flare by LFM measurement at Day 30 |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 30 days | |

| End point values | Indomethacin | Ketorolac | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 55 | 59 | | |
| Units: ph/ms | | | | |
| arithmetic mean (standard deviation) | 9.20 (± 7.60) | 8.94 (± 8.27) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Aqueous Flare by LFM measurement at Day 90

End point title Aqueous Flare by LFM measurement at Day 90

End point description:

End point type Secondary

End point timeframe:

90 days

| End point values | Indomethacin | Ketorolac | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59 | 61 | | |
| Units: ph/ms | | | | |
| arithmetic mean (standard deviation) | 7.70 (\pm 6.85) | 8.12 (\pm 7.61) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Central retinal thickness at Day 30

End point title Central retinal thickness at Day 30

End point description:

End point type Secondary

End point timeframe:

30 days

| End point values | Indomethacin | Ketorolac | | |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59 | 61 | | |
| Units: um | | | | |
| arithmetic mean (standard deviation) | 221.6 (\pm 34.1) | 232.1 (\pm 55.6) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Central retinal thickness at Day 90

| | |
|-----------------|-------------------------------------|
| End point title | Central retinal thickness at Day 90 |
|-----------------|-------------------------------------|

End point description:

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

End point timeframe:

90 days

| End point values | Indomethacin | Ketorolac | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 55 | 57 | | |
| Units: um | | | | |
| arithmetic mean (standard deviation) | 227.9 (± 39.5) | 227.5 (± 37.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Slit Lamp Examination: Anterior Chamber Cells, > 50 cells

| | |
|-----------------|---|
| End point title | Slit Lamp Examination: Anterior Chamber Cells, > 50 cells |
|-----------------|---|

End point description:

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

End point timeframe:

90 days

| End point values | Indomethacin | Ketorolac | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59 | 61 | | |
| Units: Subjects | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Slit Lamp Examination: Anterior Chamber Flare, Intense

| | |
|-----------------|--|
| End point title | Slit Lamp Examination: Anterior Chamber Flare, Intense |
|-----------------|--|

End point description:

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

End point timeframe:

90 days

| End point values | Indomethacin | Ketorolac | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59 | 61 | | |
| Units: Subjects | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Slit Lamp Examination: Conjunctival hyperaemia, Severe

End point title Slit Lamp Examination: Conjunctival hyperaemia, Severe

End point description:

End point type Secondary

End point timeframe:

90 days

| End point values | Indomethacin | Ketorolac | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59 | 61 | | |
| Units: Subjects | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Slit Lamp Examination: Perikeratic Circle, Severe

End point title Slit Lamp Examination: Perikeratic Circle, Severe

End point description:

End point type Secondary

End point timeframe:

90 days

| End point values | Indomethacin | Ketorolac | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59 | 61 | | |
| Units: Subjects | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Post Surgical Pain at Day 0

| | |
|-----------------|-----------------------------|
| End point title | Post Surgical Pain at Day 0 |
|-----------------|-----------------------------|

End point description:

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

End point timeframe:

Day 0

| End point values | Indomethacin | Ketorolac | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59 | 61 | | |
| Units: Subjects | | | | |
| Absent | 40 | 34 | | |
| Mild | 16 | 25 | | |
| Moderate | 3 | 2 | | |
| Severe | 0 | 0 | | |
| Unbearable | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Post Surgical Pain at Day 1

| | |
|-----------------|-----------------------------|
| End point title | Post Surgical Pain at Day 1 |
|-----------------|-----------------------------|

End point description:

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

End point timeframe:

Day 1

| End point values | Indomethacin | Ketorolac | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59 | 61 | | |
| Units: Subjects | | | | |
| Absent | 42 | 46 | | |
| Mild | 14 | 14 | | |
| Moderate | 2 | 1 | | |
| Severe | 1 | 0 | | |
| Unbearable | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Fundoscopy, Macula: Number of subjects with deterioration at Day 30

| | |
|------------------------|---|
| End point title | Fundoscopy, Macula: Number of subjects with deterioration at Day 30 |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 30 days | |

| End point values | Indomethacin | Ketorolac | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59 | 61 | | |
| Units: Subjects | 2 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Fundoscopy, Retina: Number of subjects with deterioration at Day 30

| | |
|------------------------|---|
| End point title | Fundoscopy, Retina: Number of subjects with deterioration at Day 30 |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 30 days | |

| End point values | Indomethacin | Ketorolac | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59 | 61 | | |
| Units: Subjects | 1 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Fundoscopy, Macula: Number of subjects with deterioration at Day 90

| | |
|-----------------|---|
| End point title | Fundoscopy, Macula: Number of subjects with deterioration at Day 90 |
|-----------------|---|

End point description:

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

End point timeframe:

90 days

| End point values | Indomethacin | Ketorolac | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59 | 61 | | |
| Units: Subjects | 2 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Fundoscopy, Retina: Number of subjects with deterioration at Day 90

| | |
|-----------------|---|
| End point title | Fundoscopy, Retina: Number of subjects with deterioration at Day 90 |
|-----------------|---|

End point description:

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

End point timeframe:

90 days

| End point values | Indomethacin | Ketorolac | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59 | 61 | | |
| Units: Subjects | 1 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects using concomitant medications to treat inflammation related to cataract surgery

| | |
|-----------------|--|
| End point title | Proportion of subjects using concomitant medications to treat inflammation related to cataract surgery |
|-----------------|--|

End point description:

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

End point timeframe:

90 days

| End point values | Indomethacin | Ketorolac | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59 | 61 | | |
| Units: Subjects | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

3 weeks

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | NA |
|--------------------|----|

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Indomethacin |
|-----------------------|--------------|

Reporting group description: -

| | |
|-----------------------|-----------|
| Reporting group title | Ketorolac |
|-----------------------|-----------|

Reporting group description: -

| Serious adverse events | Indomethacin | Ketorolac | |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 2 / 62 (3.23%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| IOL Subluxation | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 62 (1.61%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 62 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cauda equina syndrome | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 0 / 62 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 59 (0.00%) | 1 / 62 (1.61%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Indomethacin | Ketorolac | |
|---|----------------|----------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 59 (5.08%) | 3 / 62 (4.84%) | |
| Eye disorders | | | |
| Corneal oedema | | | |
| subjects affected / exposed | 3 / 59 (5.08%) | 3 / 62 (4.84%) | |
| occurrences (all) | 3 | 3 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 12 November 2007 | For the purpose of subject safety, an exclusion criterion was added to ensure that women met pregnancy prevention criteria immediately prior to and during the study. |
| 15 July 2008 | <ul style="list-style-type: none">• To meet enrollment within specified timelines, the number of sites was increased from initially six to 11, the expectation that each site was to enroll an estimated 20 subjects was removed and the requirement that no more than 30% of the subjects could enroll at a single site was removed. As Germany is the country in the European Union that has the highest number of centres using the LFM this country was added to increase the number of sites, by addition of 5 sites.• Identified that the study was considered Phase III in Germany and Phase IV in France, Poland, and Portugal. Updated the protocol to note that the test article was commercially available in most of the countries where the study took place.• Tobramycin was added as a permitted therapy because gentamicin (an allowed therapy according to the original protocol) was not routinely used at some investigational sites. Gentamicin and tobramycin belong to the same class of antibiotics (aminoglycosides) and have similar characteristics.• Added that the Kowa FM 500, Kowa FC 1000, and Kowa FM 600 could be used for the flare measurements, because there is a high correlation of flare counts between the Kowa C 500 and Kowa C 1000 and the technical characteristics of the Kowa FM 500 and Kowa FM 600 are similar. |
| 06 November 2008 | <ul style="list-style-type: none">• Changed the contact for reporting SAEs to be the Clinical Study Manager, who would then forward the information to Global Safety & Vigilance.• The Investigators were originally instructed to exclude subjects that had participated in a clinical study within 30 days before inclusion, but this was later added into the protocol as an exclusion criterion for further clarification.• As general anesthesia does not modify aqueous flare values, the inclusion criteria were changed to allow it as part of the cataract surgery.• Revised the exclusion criterion to exclude subjects who had diabetic retinopathy, as diabetes without retinopathy does not always increase blood-aqueous barrier permeability, and this was already covered in the inclusion criterion where preoperative flare values were to be ≤ 15 ph/ms.• Added Acetazolamide, Pilocarpin, and Intracameral anaesthesia to the disallowed medications list, as these modify flare values after their administration.• Removed the method of measuring bottle weights to assess treatment compliance since the amount of missing drops is not directly correlated to the number of drops used and would not offer a reliable representation of treatment compliance.• The Kowa FM 2000 was added to list of devices that could be used to gather flare measurements after the supplier confirmed the technical characteristics were similar to the Kowa FM 500, Kowa FC 1000, and Kowa FM 600. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported