



Clinical trial results:

A Phase 2b, Multicenter, Open-Label Study in Rheumatoid Arthritis Subjects who Completed Preceding Study M13-390 with Adalimumab Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2012-003881-42 |
| Trial protocol | BE DE RO SK |
| Global end of trial date | 22 October 2013 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 18 May 2016 |
| First version publication date | 14 June 2015 |
| Version creation reason | • Correction of full data set potential category issues |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | M13-692 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01752855 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | AbbVie Deutschland GmbH & Co. KG |
| Sponsor organisation address | Abbott House, Vanwall Business Park Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL64XE |
| Public contact | Global Medical Information, AbbVie, 001 800-633-9110, |
| Scientific contact | Andy Payne, AbbVie , andy.payne@abbvie.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 | 22 October 2013 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 22 October 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

A Phase 2b, open-label extension (OLE) study in rheumatoid arthritis (RA) patients designed to collect long-term safety, tolerability, efficacy, and immunogenicity data of the proposed new adalimumab formulation.

Protection of trial subjects:

- Only participants that met all the study inclusion and none of the exclusion criteria were allowed entry into the study.
- Participants read and understood information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 03 December 2012 |
| 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 | Slovakia: 17 |
| Country: Number of subjects enrolled | United States: 32 |
| Country: Number of subjects enrolled | Romania: 10 |
| Country: Number of subjects enrolled | Belgium: 3 |
| Country: Number of subjects enrolled | Czech Republic: 25 |
| Country: Number of subjects enrolled | Germany: 1 |
| Worldwide total number of subjects | 88 |
| EEA total number of subjects | 56 |

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) | 71 |
| From 65 to 84 years | 17 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of the 96 subjects who completed Study M13-390, 88 subjects (92%, 88/96) enrolled in the OLE Study M13-692 at 20 study sites located in North America and Europe.

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 |
| Arm title | New Formulation for 48 weeks |

Arm description:

New formulation of adalimumab 40 mg every other week for 24 weeks in Study NCT01712178, followed by 24 weeks of treatment with the new formulation of adalimumab 40 mg every other week

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | New formulation adalimumab |
| Investigational medicinal product code | |
| Other name | Humira |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subcutaneous injection of the new formulation of adalimumab 40 mg every other week for 24 weeks

| | |
|------------------|--|
| Arm title | Current Formulation for 24 Weeks, New Formulation for 24 Weeks |
|------------------|--|

Arm description:

Current formulation of adalimumab 40 mg every other week for 24 weeks in Study NCT01712178, followed by 24 weeks of treatment with the new formulation of adalimumab 40 mg every other week

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | New formulation adalimumab |
| Investigational medicinal product code | |
| Other name | Humira |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subcutaneous injection of the new formulation of adalimumab 40 mg every other week for 24 weeks

| Number of subjects in period 1 | New Formulation for 48 weeks | Current Formulation for 24 Weeks, New Formulation for 24 Weeks |
|--------------------------------|------------------------------|--|
| | | |
| Started | 44 | 44 |
| Completed | 43 | 40 |
| Not completed | 1 | 4 |
| Consent withdrawn by subject | - | 2 |
| Adverse event, non-fatal | 1 | - |
| Lack of efficacy | - | 2 |

Baseline characteristics

Reporting groups

| | |
|---|--|
| Reporting group title | New Formulation for 48 weeks |
| Reporting group description: New formulation of adalimumab 40 mg every other week for 24 weeks in Study NCT01712178, followed by 24 weeks of treatment with the new formulation of adalimumab 40 mg every other week | |
| Reporting group title | Current Formulation for 24 Weeks, New Formulation for 24 Weeks |
| Reporting group description: Current formulation of adalimumab 40 mg every other week for 24 weeks in Study NCT01712178, followed by 24 weeks of treatment with the new formulation of adalimumab 40 mg every other week | |

| Reporting group values | New Formulation for 48 weeks | Current Formulation for 24 Weeks, New Formulation for 24 Weeks | Total |
|--|------------------------------|--|-------|
| Number of subjects | 44 | 44 | 88 |
| Age categorical Units: Subjects | | | |
| In utero | | | 0 |
| Preterm newborn infants (gestational age < 37 wks) | | | 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) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 55.7 | 52 | |
| standard deviation | ± 10.8 | ± 12 | - |
| Gender categorical Units: Subjects | | | |
| Female | 37 | 37 | 74 |
| Male | 7 | 7 | 14 |

Subject analysis sets

| | |
|---|---------------|
| Subject analysis set title | Overall Study |
| Subject analysis set type | Full analysis |
| Subject analysis set description: The study population consisted of all randomized subjects who received at least one dose of adalimumab. All randomized subjects were included in the analyses. | |

| Reporting group values | Overall Study | | |
|------------------------|---------------|--|--|
| Number of subjects | 88 | | |

| | | | |
|--|--------|--|--|
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age continuous Units: years | | | |
| arithmetic mean | 53.9 | | |
| standard deviation | ± 11.5 | | |
| Gender categorical Units: Subjects | | | |
| Female | 74 | | |
| Male | 14 | | |

End points

End points reporting groups

| | |
|---|--|
| Reporting group title | New Formulation for 48 weeks |
| Reporting group description: New formulation of adalimumab 40 mg every other week for 24 weeks in Study NCT01712178, followed by 24 weeks of treatment with the new formulation of adalimumab 40 mg every other week | |
| Reporting group title | Current Formulation for 24 Weeks, New Formulation for 24 Weeks |
| Reporting group description: Current formulation of adalimumab 40 mg every other week for 24 weeks in Study NCT01712178, followed by 24 weeks of treatment with the new formulation of adalimumab 40 mg every other week | |
| Subject analysis set title | Overall Study |
| Subject analysis set type | Full analysis |
| Subject analysis set description: The study population consisted of all randomized subjects who received at least one dose of adalimumab. All randomized subjects were included in the analyses. | |

Primary: Mean Change From Baseline in Disease Activity Score 28 (DAS28) at Weeks 36 and 48

| | |
|--|--|
| End point title | Mean Change From Baseline in Disease Activity Score 28 (DAS28) at Weeks 36 and 48 ^[1] |
| End point description: The Disease Activity Score (DAS28) is a validated index of rheumatoid arthritis disease activity. Twenty-eight tender joint counts, 28 swollen joint counts, C-reactive protein, and general health are included in the DAS28 score. Scores on the DAS28 range from 0 to 10. A DAS28 score >5.1 indicates high disease activity, a DAS28 score <3.2 indicates low disease activity, and a DAS28 score <2.6 indicates clinical remission. | |
| End point type | Primary |
| End point timeframe: Baseline (Study NCT01712178 Week 0 Visit), Weeks 36 and 48 | |

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: Within-group analyses: (Mean change [2-sided 95%CI]) for New Formulation for 48 wks from baseline to Wk 36: -2.4 (-2.7, -2); (Mean change [2-sided 95%CI]) for New Formulation for 48 wks from baseline to Wk 48: -2.4 (-2.8, -2); (Mean change [2-sided 95%CI]) for Current Formulation for 24 wks, New Formulation for 24 wks from baseline to Wk 36: -2.2 (-2.5, -1.9); (Mean change [2-sided 95%CI]) for Current Formulation for 24 wks, New Formulation for 24 wks from baseline to Wk 48: -2.3 (-2.7, -1.9)

| End point values | New Formulation for 48 weeks | Current Formulation for 24 Weeks, New Formulation for 24 Weeks | | |
|--------------------------------------|------------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 44 ^[2] | 44 ^[3] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 36 | -2.4 (± 1.17) | -2.2 (± 1.05) | | |
| Week 48 | -2.4 (± 1.29) | -2.2 (± 1.28) | | |

Notes:

[2] - All available data were included. The last available values were used to replace any missing values.

[3] - All available data were included. The last available values were used to replace any missing values.

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With an American College of Rheumatology (ACR) 20 Response at Weeks 36 and 48

| | |
|-----------------|---|
| End point title | Percentage of Participants With an American College of Rheumatology (ACR) 20 Response at Weeks 36 and 48 ^[4] |
|-----------------|---|

End point description:

American College of Rheumatology 20% (ACR20) response. A participant is a responder if the following 3 criteria for improvement from baseline are met:

- ≥ 20% improvement in tender joint count;
- ≥ 20% improvement in swollen joint count; and
- ≥ 20% improvement in at least 3 of the 5 following parameters:
 - o Physician global assessment of disease activity
 - o Patient global assessment of disease activity
 - o Patient assessment of pain
 - o Disability Index of the Health Assessment
 - o CRP (Acute phase reactant (Erythrocyte sedimentation rate/C-reactive protein))

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

End point timeframe:

Baseline (Study NCT01712178 Week 0 Visit), Weeks 36 and 48

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: Within-group analyses: (Percentage [2-sided 95%CI]) for New Formulation for 48 wks at Week 36: (72.7 (57.2, 85)); (Percentage [2-sided 95%CI]) for New Formulation for 48 Wks at Week 48: 74.4 (58.8, 86.5); (Percentage [2-sided 95%CI]) for Current Formulation for 24 wks, New Formulation for 24 wks at Week 36: 76.7 (61.4, 88.2); (Percentage [2-sided 95%CI]) for Current Formulation for 24 wks, New Formulation for 24 wks at Week 48: 80 (64.4, 90.9)

| End point values | New Formulation for 48 weeks | Current Formulation for 24 Weeks, New Formulation for 24 Weeks | | |
|-----------------------------------|------------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 44 ^[5] | 44 ^[6] | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 36 | 72.7 | 76.7 | | |
| Week 48 | 74.4 | 80 | | |

Notes:

[5] - All participants who received at least one dose of study drug

[6] - All participants who received at least one dose of study drug

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With an American College of Rheumatology (ACR) 50 Response at Weeks 36 and 48

| | |
|-----------------|---|
| End point title | Percentage of Participants With an American College of Rheumatology (ACR) 50 Response at Weeks 36 and 48 ^[7] |
|-----------------|---|

End point description:

American College of Rheumatology 50% (ACR50) response. A participant is a responder if the following 3 criteria for improvement from baseline are met:

- ≥ 50% improvement in tender joint count;

- ≥ 50% improvement in swollen joint count; and
- ≥ 50% improvement in at least 3 of the 5 following parameters:
 - o Physician global assessment of disease activity
 - o Patient global assessment of disease activity
 - o Patient assessment of pain
 - o Disability Index of the Health Assessment
 - o CRP (Acute phase reactant (Erythrocyte sedimentation rate/C-reactive protein))

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

End point timeframe:

Baseline (Study NCT01712178 Week 0 Visit), Weeks 36 and 48

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: Within-group analyses: (Percentage [2-sided 95%CI]) for New Formulation for 48 wks at Week 36: (50 (34.6, 65.4); (Percentage [2-sided 95%CI]) for New Formulation for 48 Wks at Week 48: 53.5 (37.7, 68.8); (Percentage [2-sided 95%CI]) for Current Formulation for 24 wks, New Formulation for 24 wks at Week 36: 51.2 (35.5, 66.7); (Percentage [2-sided 95%CI]) for Current Formulation for 24 wks, New Formulation for 24 wks at Week 48: 57.5 (40.9, 73.0)

| End point values | New Formulation for 48 weeks | Current Formulation for 24 Weeks, New Formulation for 24 Weeks | | |
|-----------------------------------|------------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 44 ^[8] | 44 ^[9] | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 36 | 50 | 51.2 | | |
| Week 48 | 53.5 | 57.5 | | |

Notes:

[8] - All participants who received at least one dose of study drug

[9] - All participants who received at least one dose of study drug

Statistical analyses

No statistical analyses for this end point

Primary: Mean Change From Baseline in Health Assessment Questionnaire (HAQ-DI) at Weeks 36 and 48

| | |
|-----------------|--|
| End point title | Mean Change From Baseline in Health Assessment Questionnaire (HAQ-DI) at Weeks 36 and 48 ^[10] |
|-----------------|--|

End point description:

The Health Assessment Questionnaire - Disability Index (HAQ-DI) is a patient-reported questionnaire specific for rheumatoid arthritis. It consists of 20 questions referring to eight domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and daily activities. Participants assessed their ability to do each task over the past week using the following response categories: without any difficulty (0); with some difficulty (1); with much difficulty (2); and unable to do (3). Scores on each task were summed and averaged to provide an overall score ranging from 0 to 3, where zero represents no disability and three very severe, high-dependency disability. The minimal clinically important difference (MCID) defined for the HAQ-DI is 0.22. HAQ remission indicating normal physical function is defined by HAQ-DI < 0.5.

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

End point timeframe:

Baseline (Study NCT01712178 Week 0 Visit), Weeks 36 and 48

Notes:

[10] - 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: Within-group analyses: (Mean change [2-sided 95%CI]) for New Formulation for 48 wks from baseline to Wk 36: -0.5 (-0.7, -0.3); (Mean change [2-sided 95%CI]) for New Formulation for 48 wks-from baseline to Wk 48: -0.5 (-0.7, -0.4); (Mean change [2-sided 95%CI]) for Current Formulation for 24 wks, New Formulation for 24 wks-from baseline to Wk 36: -0.5 (-0.7, -0.3); (Mean change [2-sided 95%CI]) for Current Formulation for 24 wks, New Formulation for 24 wks-from baseline to Wk 48: -0.5 (-0.7, -0.3)

| End point values | New Formulation for 48 weeks | Current Formulation for 24 Weeks, New Formulation for 24 Weeks | | |
|--------------------------------------|------------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 44 ^[11] | 43 ^[12] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 36 | -0.5 (± 0.6) | -0.5 (± 0.69) | | |
| Week 48 | -0.5 (± 0.57) | -0.5 (± 0.58) | | |

Notes:

[11] - Data were analyzed for 44 and 43 participants, respectively, at weeks 36 and 48.

[12] - Data were analyzed for 43 participants at week 36 and 40 participants at week 48.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Positive for Anti-adalimumab Antibody

| | |
|--|--|
| End point title | Percentage of Participants Positive for Anti-adalimumab Antibody |
| End point description: Percentage of participants with anti-adalimumab antibody | |
| End point type | Secondary |
| End point timeframe: Week 24 through Week 48 | |

| End point values | New Formulation for 48 weeks | Current Formulation for 24 Weeks, New Formulation for 24 Weeks | | |
|-----------------------------------|------------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 44 ^[13] | 44 ^[14] | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 13.6 | 18.2 | | |

Notes:

[13] - All participants who received at least one dose of study drug

[14] - All participants who received at least one dose of study drug

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the time of study drug administration until 70 days following the last dose, approximately 58 weeks. Serious adverse events were collected from the time the participant signed the informed consent.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 15.1 |

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Current Formulation for 24 Weeks, New Formulation for 24 Weeks |
|-----------------------|--|

Reporting group description:

Current formulation of adalimumab 40 mg every other week for 24 weeks in Study NCT01712178, followed by 24 weeks of treatment with the new formulation of adalimumab 40 mg every other week

| | |
|-----------------------|------------------------------|
| Reporting group title | New Formulation for 48 weeks |
|-----------------------|------------------------------|

Reporting group description:

New formulation of adalimumab 40 mg every other week for 24 weeks in Study NCT01712178, followed by 24 weeks of treatment with the new formulation of adalimumab 40 mg every other week

| Serious adverse events | Current Formulation for 24 Weeks, New Formulation for 24 Weeks | New Formulation for 48 weeks | |
|---|--|------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 2 / 44 (4.55%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 44 (2.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 44 (2.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Osteoarthritis | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 44 (2.27%) | 1 / 44 (2.27%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Current Formulation for 24 Weeks, New Formulation for 24 Weeks | New Formulation for 48 weeks | |
|---|--|------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 19 / 44 (43.18%) | 18 / 44 (40.91%) | |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 3 / 44 (6.82%) | 2 / 44 (4.55%) | |
| occurrences (all) | 3 | 2 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 3 / 44 (6.82%) | 3 / 44 (6.82%) | |
| occurrences (all) | 3 | 3 | |
| Gastrointestinal disorders | | | |
| Dyspepsia | | | |
| subjects affected / exposed | 3 / 44 (6.82%) | 3 / 44 (6.82%) | |
| occurrences (all) | 3 | 3 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 3 / 44 (6.82%) | 0 / 44 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 4 / 44 (9.09%) | 3 / 44 (6.82%) | |
| occurrences (all) | 5 | 3 | |
| Infections and infestations | | | |
| Cystitis | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 4 / 44 (9.09%) | |
| occurrences (all) | 3 | 7 | |
| Nasopharyngitis | | | |

| | | | |
|-----------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 7 / 44 (15.91%) | 6 / 44 (13.64%) | |
| occurrences (all) | 12 | 10 | |
| Oral herpes | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 3 / 44 (6.82%) | |
| occurrences (all) | 2 | 3 | |
| Upper respiratory tract Infection | | | |
| subjects affected / exposed | 4 / 44 (9.09%) | 4 / 44 (9.09%) | |
| occurrences (all) | 4 | 5 | |

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