



Clinical trial results:

Long term, single-arm, open-label extension study of protocol AC-055-305 to assess the safety, tolerability and efficacy of macitentan in subjects with Eisenmenger Syndrome

Summary

| | |
|--------------------------|-------------------------------------|
| EudraCT number | 2012-004411-31 |
| Trial protocol | IT BG GB DE AT PT ES HU CZ RO PL GR |
| Global end of trial date | 12 January 2018 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 27 July 2018 |
| First version publication date | 27 July 2018 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | AC-055-308 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01739400 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Actelion Pharmaceuticals Ltd. |
| Sponsor organisation address | Gewerbestrasse 16, Allschwil, Switzerland, 4123 |
| Public contact | Clinical Trial Disclosure Desk, Actelion Pharmaceuticals Ltd., clinical-trials-disclosure@its.jnj.com |
| Scientific contact | Clinical Trial Disclosure Desk, Actelion Pharmaceuticals Ltd., clinical-trials-disclosure@its.jnj.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 | 22 January 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 12 January 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 January 2018 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To assess the long-term safety and tolerability of macitentan in subjects with Eisenmenger Syndrome (ES) beyond the treatment of the AC-055-305/MAESTRO double-blind (DB) study (EudraCT number 2012-003335-33), and to assess the long-term efficacy of macitentan in this subject population.

Protection of trial subjects:

Prior to the start of the study, each study site consulted an Independent Ethics Committee (IEC) or Institutional Review Board (IRB), i.e., a review panel that was responsible for ensuring the protection of the rights, safety and well-being of human subjects involved in a clinical investigation. The study was conducted in compliance with the principles of the 'Declaration of Helsinki', the International Council for Harmonisation (ICH)-Good Clinical Practice (GCP) guidelines, and with the laws and regulations of the country in which the clinical research was conducted.

Both Actelion and the investigator had the right to terminate the study at any time, and in such a case, were responsible for protecting the subjects' interests. Prior to any study procedure and after adequate explanation of the aims, methods, objectives, and potential hazards of the study, written informed consent was obtained from each participating adult subject (including Down Syndrome subjects who were able to consent), as well as from the parent(s) or legal representative(s) of each participating minor, and from the parent(s)/legal representative(s) or caregiver(s) of each participating subject with Down Syndrome, who was not able to personally read and sign the informed consent. Additionally, written assent was obtained from each minor and each Down Syndrome subject who was unable to give written consent. All subjects who participated in the hemodynamic sub-study were required to sign a separate informed consent form (ICF). Informed consent/assent was obtained in accordance with the national laws or regulations.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 10 September 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Austria: 3 |
| Country: Number of subjects enrolled | Bulgaria: 5 |
| Country: Number of subjects enrolled | Chile: 7 |
| Country: Number of subjects enrolled | China: 68 |
| Country: Number of subjects enrolled | France: 17 |
| Country: Number of subjects enrolled | Germany: 3 |
| Country: Number of subjects enrolled | Greece: 3 |
| Country: Number of subjects enrolled | Malaysia: 3 |
| Country: Number of subjects enrolled | Mexico: 29 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Philippines: 2 |
| Country: Number of subjects enrolled | Poland: 9 |
| Country: Number of subjects enrolled | Portugal: 7 |
| Country: Number of subjects enrolled | Romania: 8 |
| Country: Number of subjects enrolled | Russian Federation: 19 |
| Country: Number of subjects enrolled | Serbia: 9 |
| Country: Number of subjects enrolled | Spain: 3 |
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Country: Number of subjects enrolled | United States: 5 |
| Country: Number of subjects enrolled | Vietnam: 16 |
| Worldwide total number of subjects | 217 |
| EEA total number of subjects | 59 |

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) | 14 |
| Adults (18-64 years) | 200 |
| From 65 to 84 years | 3 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 51 sites in 19 countries (geographical regions: Asia-Pacific, Eastern Europe, Latin America, North America and Western Europe).

Pre-assignment

Screening details:

217 subjects from the AC-055-305/DB study (EudraCT 2012-003335-33) were enrolled in this open-label (OL) study without knowledge of their study treatment allocation (macitentan or placebo) in the DB study. As the DB study did not meet its primary endpoint, the sponsor decided to prematurely terminate this OL study.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|-----------|------------|
| Arm title | Macitentan |
|-----------|------------|

Arm description:

Macitentan 10 mg, film-coated tablet, oral use, once daily

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Macitentan |
| Investigational medicinal product code | ACT-064992 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Macitentan 10 mg, taken orally once daily

| Number of subjects in period 1 | Macitentan |
|--------------------------------|------------|
| Started | 217 |
| Completed | 191 |
| Not completed | 26 |
| Adverse event, serious fatal | 7 |
| Consent withdrawn by subject | 14 |
| Physician decision | 3 |
| Lost to follow-up | 2 |

Baseline characteristics

Reporting groups

| | |
|------------------------------|---------------|
| Reporting group title | Overall study |
| Reporting group description: | |
| Overall study | |

| Reporting group values | Overall study | Total | |
|--|---------------|-------|--|
| Number of subjects | 217 | 217 | |
| Age categorical | | | |
| Units: Subjects | | | |
| 12 - 17 years | 14 | 14 | |
| 18 - 64 years | 200 | 200 | |
| 65 - 84 years | 3 | 3 | |
| ≥ 85 years | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| median | 32.0 | | |
| full range (min-max) | 12 to 82 | - | |
| Gender categorical | | | |
| Units: | | | |
| Female | 143 | 143 | |
| Male | 74 | 74 | |
| Race | | | |
| Units: Subjects | | | |
| White | 103 | 103 | |
| Chinese | 70 | 70 | |
| Other Asian | 22 | 22 | |
| Other | 22 | 22 | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Not Hispanic or Latino | 177 | 177 | |
| Hispanic or Latino | 40 | 40 | |
| Enrollment by geographical region | | | |
| Units: Subjects | | | |
| Asia-Pacific | 89 | 89 | |
| Eastern Europe | 50 | 50 | |
| Latin America | 36 | 36 | |
| North America | 5 | 5 | |
| Western Europe-Israel | 37 | 37 | |
| WHO functional class | | | |
| WHO functional class of subjects Class I: no symptoms with exercise or at rest. No limitation of activity. Class II: No symptoms at rest but slight limitation with ordinary activities causing symptoms (e.g. short of breath with climbing a flight of stairs, grocery shopping, or making the bed). Class III: may not have symptoms at rest but activities greatly limited by shortness of breath, fatigue, or near fainting. Class IV: symptoms at rest (e.g. dyspnea and/or fatigue) and inability to carry out any physical activity without symptoms. Patients in class IV manifest signs of right heart failure | | | |
| Units: Subjects | | | |
| class I | 0 | 0 | |
| class II | 131 | 131 | |

| | | | |
|-----------------------|--------------|-----|--|
| class III | 86 | 86 | |
| class IV | 0 | 0 | |
| Down syndrome status | | | |
| Units: Subjects | | | |
| Yes | 20 | 20 | |
| No | 197 | 197 | |
| Body Mass Index (BMI) | | | |
| Units: kg/m2 | | | |
| median | 21.2 | | |
| full range (min-max) | 11.9 to 42.2 | - | |

Subject analysis sets

| | |
|----------------------------|---------------------------|
| Subject analysis set title | All-enrolled analysis set |
| Subject analysis set type | Full analysis |

Subject analysis set description:

The all-enrolled analysis set includes all subjects enrolled in AC-055-308 / OL, whether or not they took at least one dose of macitentan during the OL study.

| | |
|----------------------------|--------------------|
| Subject analysis set title | DB-macitentan |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

All enrolled subjects treated with macitentan in the AC-055-308 / OL study who received macitentan in the DB study (AC-055-305, EudraCT 2012-003335-33).

| | |
|----------------------------|--------------------|
| Subject analysis set title | DB-placebo |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

All enrolled subjects treated with macitentan in the AC-055-308 / OL study who received placebo in the DB study (AC-055-305, EudraCT 2012-003335-33).

| Reporting group values | All-enrolled analysis set | DB-macitentan | DB-placebo |
|------------------------|---------------------------|---------------|------------|
| Number of subjects | 217 | 109 | 108 |
| Age categorical | | | |
| Units: Subjects | | | |
| 12 - 17 years | 14 | 12 | 2 |
| 18 - 64 years | 200 | 94 | 106 |
| 65 - 84 years | 3 | 3 | 0 |
| ≥ 85 years | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| median | 32.0 | 33.0 | 31.5 |
| full range (min-max) | 12 to 82 | 12 to 82 | 14 to 62 |
| Gender categorical | | | |
| Units: | | | |
| Female | 143 | 77 | 66 |
| Male | 74 | 32 | 42 |
| Race | | | |
| Units: Subjects | | | |
| White | 103 | 52 | 51 |
| Chinese | 70 | 35 | 35 |
| Other Asian | 22 | 11 | 11 |
| Other | 22 | 11 | 11 |
| Ethnicity | | | |

| | | | |
|--|--------------|--------------|--------------|
| Units: Subjects | | | |
| Not Hispanic or Latino | 177 | 89 | 88 |
| Hispanic or Latino | 40 | 20 | 20 |
| Enrollment by geographical region | | | |
| Units: Subjects | | | |
| Asia-Pacific | 89 | 45 | 44 |
| Eastern Europe | 50 | 24 | 26 |
| Latin America | 36 | 18 | 18 |
| North America | 5 | 1 | 4 |
| Western Europe-Israel | 37 | 21 | 16 |
| WHO functional class | | | |
| WHO functional class of subjects Class I: no symptoms with exercise or at rest. No limitation of activity. Class II: No symptoms at rest but slight limitation with ordinary activities causing symptoms (e.g. short of breath with climbing a flight of stairs, grocery shopping, or making the bed). Class III: may not have symptoms at rest but activities greatly limited by shortness of breath, fatigue, or near fainting. Class IV: symptoms at rest (e.g. dyspnea and/or fatigue) and inability to carry out any physical activity without symptoms. Patients in class IV manifest signs of right heart failure | | | |
| Units: Subjects | | | |
| class I | 0 | 0 | 0 |
| class II | 131 | 66 | 65 |
| class III | 86 | 43 | 43 |
| class IV | 0 | 0 | 0 |
| Down syndrome status | | | |
| Units: Subjects | | | |
| Yes | 20 | 10 | 10 |
| No | 197 | 99 | 98 |
| Body Mass Index (BMI) | | | |
| Units: kg/m2 | | | |
| median | 21.2 | 20.9 | 21.4 |
| full range (min-max) | 11.9 to 42.2 | 11.9 to 38.9 | 14.5 to 42.2 |

End points

End points reporting groups

| | |
|---|---------------------------|
| Reporting group title | Macitentan |
| Reporting group description: Macitentan 10 mg, film-coated tablet, oral use, once daily | |
| Subject analysis set title | All-enrolled analysis set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: The all-enrolled analysis set includes all subjects enrolled in AC-055-308 / OL, whether or not they took at least one dose of macitentan during the OL study. | |
| Subject analysis set title | DB-macitentan |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All enrolled subjects treated with macitentan in the AC-055-308 / OL study who received macitentan in the DB study (AC-055-305, EudraCT 2012-003335-33). | |
| Subject analysis set title | DB-placebo |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All enrolled subjects treated with macitentan in the AC-055-308 / OL study who received placebo in the DB study (AC-055-305, EudraCT 2012-003335-33). | |

Primary: Change in exercise capacity as measured by 6-minute walking distance (6MWD) Month 6 and 12

| | |
|---|--|
| End point title | Change in exercise capacity as measured by 6-minute walking distance (6MWD) Month 6 and 12 |
| End point description: NOTE: The MAESTRO-OL study was exploratory in nature and no primary efficacy and safety endpoint were defined in the clinical protocol. This exploratory efficacy outcome measure was selected to be reported as a primary safety endpoint here. All efficacy analyses were considered exploratory. The analyses of the exploratory efficacy endpoints focused on the absolute values and on the change from DB baseline to Week 16 in the DB study and to Month 6 and Month 12 in the OL study. For missing 6MWD values in the OL study, the following imputation rules were applied: If the reason for missing data was death, a distance of zero (0) meters was imputed for all 6MWD visits from the date of death. For any other reasons, the last available value was carried forward. | |
| End point type | Primary |
| End point timeframe: From baseline in DB study (AC-055-305) up to month 12 in this OL study. | |

| End point values | DB-macitentan | DB-placebo | | |
|--|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 109 | 108 | | |
| Units: meter (m) | | | | |
| arithmetic mean (standard deviation) | | | | |
| 6MWD at DB study baseline | 370.6 (± 74.1) | 381.6 (± 76.7) | | |
| 6MWD at Week 16 in DB study | 395.1 (± 88.4) | 399.9 (± 80.6) | | |
| Change in 6MWD from DB study baseline to Week 16 | 24.4 (± 71.0) | 18.2 (± 53.0) | | |
| 6MWD at Month 6 in OL study | 396.8 (± 96.5) | 425.0 (± 72.1) | | |
| Change in 6MWD from DB study baseline to Month 6 | 26.2 (± 77.9) | 43.4 (± 51.5) | | |

| | | | | |
|---|----------------------|---------------------|--|--|
| 6MWD at Month 12 in OL study | 397.1 (\pm 103.9) | 421.5 (\pm 76.5) | | |
| Change in 6MWD from DB study baseline to Month 12 | 26.5 (\pm 79.8) | 39.9 (\pm 55.1) | | |

Statistical analyses

| Statistical analysis title | Analysis of exercise capacity |
|----------------------------|-------------------------------|
|----------------------------|-------------------------------|

Statistical analysis description:

The MAESTRO-OL study was exploratory in nature and no primary efficacy and safety endpoint were defined in the clinical protocol. All efficacy analyses are considered exploratory. No hypothesis testing were defined, hence no p-values will be presented.

| | |
|---|------------------------------------|
| Comparison groups | DB-macitentan v DB-placebo |
| Number of subjects included in analysis | 217 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| P-value | = 0 |
| Method | no p-value as exploratory analysis |

Notes:

[1] - The analyses of the exploratory efficacy endpoints focused on the absolute values and on the change from DB baseline to Week 16 in the DB study and to Month 6 and Month 12 in this OL study.

Primary: Change in WHO functional class (FC) at Month 6 and 12

| | |
|-----------------|---|
| End point title | Change in WHO functional class (FC) at Month 6 and 12 |
|-----------------|---|

End point description:

NOTE: The MAESTRO-OL study was exploratory in nature and no primary efficacy and safety endpoint were defined in the clinical protocol. This exploratory efficacy outcome measure was selected to be reported as a primary efficacy endpoint here. For missing WHO FC values in the OL study, the following imputation rules were applied: If the reason for missing data was death, class IV was imputed for all WHO visits from the date of death. For any other reasons, the last available value was carried forward. Class I: no symptoms with exercise or at rest. No limitation of activity. Class II: No symptoms at rest but slight limitation with ordinary activities causing symptoms (e.g. short of breath with climbing stairs). Class III: may not have symptoms at rest but activities greatly limited by shortness of breath, fatigue, or near fainting. Class IV: symptoms at rest and inability to carry out any physical activity without symptoms. Patients in class IV manifest signs of right heart failure.

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

End point timeframe:

From baseline in DB study (AC-055-305) up to month 12 in this OL study.

| End point values | DB-macitentan | DB-placebo | | |
|---|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 109 | 108 | | |
| Units: subjects | | | | |
| WHO functional class I at DB study baseline | 0 | 0 | | |
| WHO functional class II at DB study baseline | 66 | 65 | | |
| WHO functional class III at DB study baseline | 43 | 43 | | |
| WHO functional class IV at DB study baseline | 0 | 0 | | |

| | | | | |
|--|----|----|--|--|
| WHO functional class I at Week 16 in DB study | 3 | 1 | | |
| WHO functional class II at Week 16 in DB study | 70 | 77 | | |
| WHO functional class III at Week 16 in DB study | 36 | 30 | | |
| WHO functional class IV at Week 16 in DB study | 0 | 0 | | |
| Improvement from DB study baseline to Week 16 | 10 | 15 | | |
| Worsening from DB study baseline to Week 16 | 0 | 1 | | |
| WHO functional class I at Month 6 in OL study | 5 | 7 | | |
| WHO functional class II at Month 6 in OL study | 74 | 79 | | |
| WHO functional class III at Month 6 in OL study | 28 | 22 | | |
| WHO functional class IV at Month 6 in OL study | 2 | 0 | | |
| Improvement from DB study baseline to Month 6 | 19 | 27 | | |
| Worsening from DB study baseline to Month 6 | 3 | 1 | | |
| WHO functional class I at Month 12 in OL study | 5 | 7 | | |
| WHO functional class II at Month 12 in OL study | 74 | 79 | | |
| WHO functional class III at Month 12 in OL study | 28 | 22 | | |
| WHO functional class IV at Month 12 in OL study | 2 | 0 | | |
| Improvement from DB study baseline to Month 12 | 20 | 31 | | |
| Worsening from DB study baseline to Month 12 | 4 | 3 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis of change in WHO functional class |
| Statistical analysis description: The MAESTRO-OL study was exploratory in nature and no primary efficacy and safety endpoint were defined in the clinical protocol. All efficacy analyses are considered exploratory. No hypothesis testing were defined, hence no p-values will be presented. | |
| Comparison groups | DB-macitentan v DB-placebo |
| Number of subjects included in analysis | 217 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[2] |
| P-value | = 0 |
| Method | no p-value as exploratory analysis |

Notes:

[2] - The analyses of the exploratory efficacy endpoints focused on the absolute values and on the change from DB baseline to Week 16 in the DB study and to Month 6 and Month 12 in this OL study.

Primary: Change in Borg dyspnea score at Month 6 and 12

| | |
|-----------------|--|
| End point title | Change in Borg dyspnea score at Month 6 and 12 |
|-----------------|--|

End point description:

The Borg dyspnea score rates the severity of dyspnea (difficult or labored breathing) on a scale from 0 ('Nothing at all') to 10 ('Very, very severe – maximal'). NOTE: The MAESTRO-OL study was exploratory in nature and no primary efficacy and safety endpoint were defined in the clinical protocol. This exploratory efficacy outcome measure was selected to be reported as a primary safety endpoint here. For missing Borg dyspnea index values in the OL study, the following imputation rules were applied: If the reason for missing data was death, a value of 10 was imputed for all Borg visits from the date of death. For any other reasons, the last available value was carried forward.

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

End point timeframe:

From baseline in DB study (AC-055-305) up to month 12 in this OL study.

| End point values | DB-macitentan | DB-placebo | | |
|--|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 109 | 108 | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Borg dyspnea score at DB study baseline | 3.0 (± 1.9) | 2.9 (± 1.8) | | |
| Borg dyspnea score at Week 16 in DB study | 2.7 (± 1.9) | 1.9 (± 1.6) | | |
| Change from DB study baseline to Week 16 | -0.3 (± 1.4) | -0.2 (± 1.5) | | |
| Borg dyspnea score at Month 6 in OL study | 2.8 (± 2.0) | 2.5 (± 1.8) | | |
| Change from DB study baseline to Month 6 | -0.1 (± 2.0) | -0.4 (± 1.5) | | |
| Borg dyspnea score at Month 12 in OL study | 2.9 (± 2.0) | 2.6 (± 1.9) | | |
| Change from DB study baseline to Month 12 | -0.1 (± 2.1) | -0.3 (± 1.6) | | |

Statistical analyses

| | |
|----------------------------|--------------------------------|
| Statistical analysis title | Analysis of Borg dyspnea score |
|----------------------------|--------------------------------|

Statistical analysis description:

The MAESTRO-OL study was exploratory in nature and no primary efficacy and safety endpoint were defined in the clinical protocol. All efficacy analyses are considered exploratory. No hypothesis testing were defined, hence no p-values will be presented.

| | |
|---|------------------------------------|
| Comparison groups | DB-macitentan v DB-placebo |
| Number of subjects included in analysis | 217 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[3] |
| P-value | = 0 |
| Method | no p-value as exploratory analysis |

Notes:

[3] - The analyses of the exploratory efficacy endpoints focused on the absolute values and on the change from DB baseline to Week 16 in the DB study and to Month 6 and Month 12 in this OL study.

Primary: Change in peripheral oxygen saturation (SpO2) at rest at Month 6 and 12

| | |
|-----------------|--|
| End point title | Change in peripheral oxygen saturation (SpO2) at rest at |
|-----------------|--|

End point description:

NOTE: The MAESTRO-OL study was exploratory in nature and no primary efficacy and safety endpoint were defined in the clinical protocol. This exploratory efficacy outcome measure was selected to be reported as a primary efficacy endpoint here. No imputation of missing data for SpO2 was applied. Oxygen saturation assessed by pulse oximetry: peripheral oxygen saturation (SpO2) at rest before the 6-minute walk test (6MWT)

End point type

Primary

End point timeframe:

From baseline in DB study (AC-055-305) up to month 12 in this OL study.

| End point values | DB-macitentan | DB-placebo | | |
|---|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 109 ^[4] | 108 ^[5] | | |
| Units: percent (%) | | | | |
| arithmetic mean (standard deviation) | | | | |
| SpO2 at DB study baseline | 84.2 (± 5.6) | 85.4 (± 5.0) | | |
| SpO2 at Week 16 in DB study | 85.3 (± 5.8) | 85.6 (± 5.4) | | |
| Change in SpO2 from DB study baseline to Week 16 | 1.1 (± 4.0) | 0.2 (± 4.5) | | |
| SpO2 at Month 6 in OL study | 85.9 (± 5.9) | 87.4 (± 5.4) | | |
| Change in SpO2 from DB study baseline to Month 6 | 1.5 (± 4.9) | 2.0 (± 4.3) | | |
| SpO2 at Month 12 in OL study | 86.4 (± 6.3) | 87.1 (± 5.0) | | |
| Change in SpO2 from DB study baseline to Month 12 | 2.0 (± 4.4) | 1.6 (± 4.9) | | |

Notes:

[4] - Out of 109 subjects 104 subjects were analyzed at month 6 and 92 subjects at month 12.

[5] - Out of 109 subjects 103 subjects were analyzed at month 6 and 84 subjects at month 12.

Statistical analyses

| Statistical analysis title | Analysis of peripheral oxygen saturation (SpO2) |
|--|---|
| Statistical analysis description: | |
| The MAESTRO-OL study was exploratory in nature and no primary efficacy and safety endpoint were defined in the clinical protocol. All efficacy analyses are considered exploratory. No hypothesis testing were defined, hence no p-values will be presented. | |
| Comparison groups | DB-macitentan v DB-placebo |
| Number of subjects included in analysis | 217 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[6] |
| P-value | = 0 |
| Method | no p-value as exploratory analysis |

Notes:

[6] - The analyses of the exploratory efficacy endpoints focused on the absolute values and on the change from DB baseline to Week 16 in the DB study and to Month 6 and Month 12 in this OL study.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From OL study treatment initiation up to 30 days after study treatment discontinuation

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

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 20 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Macitentan |
|-----------------------|------------|

Reporting group description:

Macitentan 10 mg to be taken daily, film-coated tablet, oral use

| Serious adverse events | Macitentan | | |
|---|-------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 62 / 217 (28.57%) | | |
| number of deaths (all causes) | 7 | | |
| number of deaths resulting from adverse events | 1 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Endometrial adenocarcinoma | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Glioblastoma | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Vascular disorders | | | |
| Arterial perforation | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|-----------------|--|--|
| Surgical and medical procedures | | | |
| Drug therapy | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgery | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Pregnancy | | | |
| subjects affected / exposed | 3 / 217 (1.38%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Chest discomfort | | | |
| subjects affected / exposed | 2 / 217 (0.92%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest pain | | | |
| subjects affected / exposed | 3 / 217 (1.38%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Allergy to arthropod sting | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |

| | | | |
|---|-----------------|--|--|
| Ovarian cyst ruptured | | | |
| subjects affected / exposed | 2 / 217 (0.92%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchiectasis | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemoptysis | | | |
| subjects affected / exposed | 9 / 217 (4.15%) | | |
| occurrences causally related to treatment / all | 0 / 11 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary alveolar haemorrhage | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary arterial hypertension | | | |
| subjects affected / exposed | 4 / 217 (1.84%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 3 / 217 (1.38%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |

| | | | |
|---|-----------------|--|--|
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary infarction | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Depression | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Antineutrophil cytoplasmic antibody positive | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Arrhythmia | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 217 (0.46%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrial fibrillation | | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac arrest | | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Cardiac failure | | | | |
| subjects affected / exposed | 3 / 217 (1.38%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiogenic shock | | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Right ventricular failure | | | | |
| subjects affected / exposed | 6 / 217 (2.76%) | | | |
| occurrences causally related to treatment / all | 3 / 7 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Supraventricular tachycardia | | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ventricular arrhythmia | | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Ventricular extrasystoles | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhagic transformation stroke | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 2 / 217 (0.92%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 2 / 217 (0.92%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytopenia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Retinal artery embolism | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyschezia | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Urinary retention | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal disorder | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Appendicitis perforated | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Brain abscess | | | |
| subjects affected / exposed | 2 / 217 (0.92%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis viral | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Peritonitis | | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 5 / 217 (2.30%) | | | |
| occurrences causally related to treatment / all | 0 / 5 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Postoperative wound infection | | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pyelonephritis acute | | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory tract infection | | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sepsis | | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tuberculous pleurisy | | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Upper respiratory tract infection | | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Viral pharyngitis | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wound infection | | | |
| subjects affected / exposed | 1 / 217 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Macitentan | | |
|---|--------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 152 / 217 (70.05%) | | |
| Investigations | | | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 20 / 217 (9.22%) | | |
| occurrences (all) | 29 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 18 / 217 (8.29%) | | |
| occurrences (all) | 20 | | |
| Headache | | | |
| subjects affected / exposed | 29 / 217 (13.36%) | | |
| occurrences (all) | 34 | | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 13 / 217 (5.99%) | | |
| occurrences (all) | 13 | | |
| Fatigue | | | |
| subjects affected / exposed | 11 / 217 (5.07%) | | |
| occurrences (all) | 11 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 14 / 217 (6.45%) | | |
| occurrences (all) | 15 | | |
| Gastrointestinal disorders | | | |

| | | | |
|---|--|--|--|
| Diarrhoea subjects affected / exposed occurrences (all) | 18 / 217 (8.29%) 20 | | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Haemoptysis subjects affected / exposed occurrences (all) | 23 / 217 (10.60%) 28 24 / 217 (11.06%) 42 | | |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 20 / 217 (9.22%) 27 61 / 217 (28.11%) 119 21 / 217 (9.68%) 35 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 03 April 2013 | <p>Amendment 1 resulting in Global Protocol Version 2.</p> <p>Changes included:</p> <ul style="list-style-type: none">- A summary of the potential risks associated with macitentan and the methodology for risk management were added.- Sections related to study assessments (for e.g., review of the documents, order of assessments, 6MWT and Borg dyspnea index, etc.) were slightly modified in order to clarify the instructions relevant to the investigators.- The "risks" section of the ICF was revised to account for the possibility of interruption or permanent discontinuation of study medication based on specific decreases in hemoglobin levels.-The ICF was revised to include additional information about the potential risk of macitentan to align with updates to the Macitentan IB for non-oncology indications. The ICF was also updated to clarify the duties of the trial subjects following a change in the sponsor's insurance company. |
| 19 September 2013 | <p>Amendment 2 resulting in Global Protocol Version 3.</p> <p>Changes included:</p> <ul style="list-style-type: none">- The number of study sites was increased to improve the rate of recruitment.- Results of all protocol-mandated laboratory assessments to be collected in the database. A Central Laboratory was to be used for the analysis of all laboratory variables requested in the protocol.- Monthly laboratory and safety monitoring at a site visit was added in order to improve sponsor oversight.- The reason for permanent discontinuation was now documented in the eCRF.- Throughout the protocol, upper limits for liver abnormality were updated to reflect the FDA guidance on DILI.- For hemoglobin monitoring, clarification on re-tests for assessing hemoglobin change was provided.- Collection of information on concomitant medication was extended to all visits.- Instructions for collection and handling of local laboratory samples and, where applicable, reporting of results within the eCRF of local analyses of local laboratory samples were added.- Instructions on performing and recording unscheduled visits were added.- Updated definitions of alert flags for abnormal laboratory values were included in the appropriate appendix.- The ICF was updated to reflect the increased number of planned study sites.- The ICF was updated to reflect the expanded instructions for unscheduled visits.- The risk section of the ICF was updated to account for the latest results of controlled studies. |

| | |
|-------------|--|
| 16 May 2014 | <p>Amendment 3 resulting in Global Protocol Version 4.</p> <p>Changes included:</p> <ul style="list-style-type: none"> - The recruitment period was made consistent with the updated study planned duration of the AC-055-305 / MAESTRO study. - The number of study centers selected for the AC-055-305 / MAESTRO study was increased to improve recruitment speed. The same change was implemented in the MAESTRO-OL protocol. - Eligibility criteria was opened up to females of childbearing potential truly abstinent and to subjects with Down Syndrome (if they had support from a caregiver or family member). - To address anticipated difficulties in Down Syndrome subjects, adaptations were made to the 6MWT to accommodate these subjects and to safeguard study outcome. - Clarification regarding which prohibited concomitant treatments must lead to study treatment discontinuation was added. - Clarifications were added on when to perform the requested laboratory re-tests for hemoglobin monitoring. - The timeline to review the laboratory report was shortened in order to identify any potential clinically significant abnormality as early as possible. - Clarifications on medication errors and pre-existing medical conditions were added. - The ICF was updated to reflect the protocol changes. |
|-------------|--|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported