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Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Tracleer

bosentan

Procedure no: EMEA/H/C/000401/P46/087

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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LIST OF ABBREVIATIONS

AE adverse event

AESI adverse event of special interest

ALT alanine aminotransferase

AST aspartate aminotransferase

bid twice daily

CL confidence limit

EOT end of treatment

ET Endothelin

EU European Union

EUTP exceptional use treatment period

FOIA Freedom of Information Act

HGR Human Genetic Resources

MedDRA Medical Dictionary for Regulatory Activities

PAH pulmonary arterial hypertension

PBRER Periodic Benefit-Risk Evaluation Report

PIP Paediatric Investigation Plan

PT preferred term

PY person-years

SAE serious adverse event

SMQ standardized MedDRA query

SOC system organ class

TEAE treatment-emergent adverse event

tid three times daily

ULN upper limit of the normal range

WHO World Health Organization

Introduction

Bosentan (TRACLEER) is an oral endothelin (ET) receptor antagonist that competes with the binding of ET-1 to both ETA and ETB receptors. In Europe, bosentan (TRACLEER) is approved for the following therapeutic indications:

"Treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with World Health Organization (WHO) functional class III. Efficacy has been shown in:

- *Primary (idiopathic and heritable) pulmonary arterial hypertension*
- *Pulmonary arterial hypertension secondary to scleroderma without significant interstitial pulmonary disease*
- *Pulmonary arterial hypertension associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology.*

Some improvements have also been shown in patients with pulmonary arterial hypertension WHO functional class II.

TRACLEER is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease."

A dispersible tablet formulation of TRACLEER with good acceptability by children with PAH was developed to allow age- and weight-appropriate dosing. This 32 mg quadrisectable tablet was approved in the European Union (EU) in 2009.

In 2015, the EU Summary of Product Characteristics was amended to include data generated in paediatric studies with bosentan conducted according to the agreed EU Paediatric Investigation Plan (PIP) and with posology recommendations for children above 1 year of age.

The FUTURE 3 paediatric study in PAH subjects was conducted as part of the PIP:

- AC-052-373: Open-label, randomized, multicenter, multiple dose trial to evaluate pharmacokinetics, tolerability, safety and efficacy of the paediatric formulation of bosentan two versus three times a day in children from 3 months to less than 12 years of age with PAH (FUTURE 3 core)

The 6-month core study was followed by a 12-month extension study, which was not part of the PIP:

- AC-052-374: A prospective, multicenter, open-label extension of FUTURE 3 to assess the safety, tolerability and efficacy of the pediatric formulation of bosentan two versus three times a day in children with pulmonary arterial hypertension (FUTURE 3 extension).

Cumulative safety data for 64 paediatric subjects from the start of bosentan treatment in the FUTURE 3 core study up to the end of the extension study, ie, for a period of up to 18 months was adopted by the Committee for Human Medicinal Products on 25 June 2015 under Article 46 of Regulation (EC) No. 1901/2006 (the 'Paediatric Regulation') (EMEA/H/C/000401 P46 081).

Beyond the 12-month treatment period in the FUTURE 3 extension study, in countries where bosentan was not commercially available and where "compassionate use" or similar programs could not be implemented due to local regulations, bosentan study treatment was offered through an "Exceptional Use Treatment Period" (EUTP), if continued treatment was deemed beneficial by the investigator. A total of 10 paediatric subjects (hereafter referred to as participants) in 4 countries (Belarus, China, Russia, and Ukraine) continued receiving bosentan during the EUTP.

The purpose of this addendum to the clinical overview (D-20.371, dated 11 November 2020), is to assess the cumulative safety data for these 10 paediatric participants (0.8 to 10.9 years at FUTURE 3 core study entry), from the start of bosentan treatment in the core FUTURE 3 study up to the end of the EUTP, ie, for a median (range) duration of 246.2 (100.1 to 397.1) weeks. The present submission complies with Article 46 of Regulation (EC) No. 1901/2006 (the 'Paediatric Regulation').

1. Scientific discussion

1.1. Information on the pharmaceutical formulation used in the study

A dispersible 32 mg tablet formulation of TRACLEER was developed to allow age- and weight-appropriate dosing in children. This strength was approved in the European Union (EU) in 2009.

1.2. Clinical aspects

1.2.1. Introduction

The MAH provided the cumulative safety data of the 10 paediatric patients included in the study FUTUR 3 Extension Exceptional Use Treatment Period.

1.2.2. Clinical study

Description

Title of Study: A prospective, Multicenter, Open-label Extension of FUTURE 3 to Assess the Safety, Tolerability and Efficacy of the Pediatric Formulation of Bosentan Two Versus Three Times a Day in Children With Pulmonary Arterial Hypertension

Study Name: FUTURE 3 Study Extension Exceptional Use Treatment Period

Methods

Objective(s)

The objectives of the FUTURE 3 extension EUTP were:

- To provide participants with bosentan beyond the initial 12-month treatment period of the FUTURE 3 extension*.
- To monitor the long-term safety and tolerability of the pediatric formulation of bosentan in participants who completed the FUTURE 3 extension.

FUTURE 3 extension was a prospective, multicenter, multinational, open-label, double-arm exploratory Phase 3 extension study, which enrolled children with idiopathic or heritable pulmonary arterial hypertension (PAH) or PAH persisting after complete repair of a congenital heart defect who had completed the FUTURE 3 core study. During the FUTURE 3 extension study, participants received 32 mg dispersible tablets of bosentan, adjusted to their body weight at each visit (if required), according to the same dosing regimen as in the FUTURE 3 core study, ie, 2 mg/kg twice daily (bid) or three times

a day (tid). Participants were treated for a period of 12 months or up to premature discontinuation of study treatment.

In countries where the 32 mg dispersible tablets of bosentan were not available either commercially or through "compassionate use" or similar programs, and if continued treatment was deemed beneficial by the investigator, an EUTP was included at the end of the FUTURE 3 extension 12-month treatment period. During the EUTP, all participants continued receiving bosentan until the latest of one of the following:

- Participant or the investigator decided to discontinue the study treatment permanently;
- Participant reached the age of 13 years (if the adult formulation of bosentan, if appropriate, was available commercially or via "compassionate use" or similar programs);
- An alternative treatment was made available;
- Sponsor decided to stop the development of the pediatric formulation of bosentan. A 60-day posttreatment follow-up was performed at the end of EUTP.

Study population /Sample size

The number of subjects included in the EUTP was not driven by any statistical consideration. All participants who entered the EUTP received bosentan during the period.

A total number of 10 participants* were included in the safety analysis.

During the study conduct, a potential compliance issue with China's Human Genetic Resources ("HGR") Regulations was identified in early 2020. To ensure compliance with the data exporting rules under the HGR Regulation, a subset of data from Chinese participants (from 19 November 2019) was excluded from the final analysis. Nonetheless, any and all significant safety information (Death, serious adverse event [SAE] and/or Pregnancy), are included in this report.

The applicable standards of Good Clinical Practices and ethical considerations were adhered to when not conflicting with China's Human Genetic Resources ("HGR") Regulations. Note that no significant safety events were reported for any participants from China in the FUTURE 3 study after data cut-off date, 19 November 2019.

*exclusion of 0 Chinese participants.

Eligibility Criteria

Participants were eligible for the EUTP if they had completed the 12-month treatment period of the FUTURE 3 extension study, continued treatment with bosentan was deemed beneficial by the investigator, and bosentan was not available either commercially or via "compassionate use" or similar programs.

Exclusion Criteria

Participants with known intolerance or hypersensitivity to bosentan or any of its excipients, any clinically significant laboratory abnormality that precluded the continuation of bosentan therapy, aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >3× the upper limit of the normal (ULN) range, moderate to severe hepatic impairment (ie, Child-Pugh Class B or C), or were pregnant, were not eligible for the EUTP.

Treatments

Bosentan dispersible tablets 32 mg, oral administration, bulk batch numbers CXFC, DTHD, rework of DKHC, GTXF, FP018, MMWY, TNPZ, FP023, JP019.

During the EUTP, the median (range) duration of exposure to bosentan (n=10) was 160.1 (26.3 to 324.7) weeks, corresponding to a total exposure of 33 subject-years.

Over the FUTURE 3 core and extension studies and the EUTP, the median (range) duration of exposure to bosentan (n=10) was 246.2 (100.1 to 397.1) weeks, corresponding to a total exposure of 47 subject-years.

Outcomes/endpoints

No efficacy data were collected during the EUTP.

Safety data:

Safety was evaluated based on adverse events (AEs), clinical laboratory tests (hematology and serum chemistry), vital signs measurements, physical examination, body weight, and height/length.

Statistical Methods

No sample size determination was done for the EUTP. Only those participants who completed the FUTURE 3 core (AC-052-373) and FUTURE 3 extension studies (AC-052-374) in specific countries could enter the EUTP.

All 10 participants who entered and received bosentan during the EUTP were included in the exceptional-use set.

No statistical hypothesis was specified for the EUTP (as such all analyses were conducted in an exploratory manner). No efficacy evaluation was scheduled during the EUTP. The statistical evaluation of the safety and tolerability endpoints variables was performed descriptively: for all continuous safety variables, descriptive statistics included the N, mean, standard deviation, median, minimum and maximum, Q1 and Q3. Categorical variables were summarized using frequency counts and percentages.

Assessor's comment

This study only included 10 paediatric patients from FUTURE 3 extension study. The main objective of the study was to provide bosentan to patients who completed FUTURE 3 extension study in countries where bosentan was not commercially available and where "compassionate use" or similar programs could not be implemented due to local regulations. Therefore, no efficacy evaluation was expected, and analysis of safety data was conducted in an exploratory manner only.

Results

STUDY POPULATION:

Of 64 participants randomized in the FUTURE 3 core study, 58 (90.6%) participants entered and received 2 mg/kg bosentan bid (n=31) or tid (n=27) in the FUTURE 3 extension study. Of the 58

participants in the FUTURE 3 extension study, a total of 10 participants entered the EUTP and continued receiving 2 mg/kg bosentan bid (n=7) or tid (n=3) up to Amendment B (participants in the tid arm switched to bid dosing). After implementation of Amendment B all participants received 2 mg/kg bosentan bid. Of the 10 participants in the EUTP, 3 prematurely discontinued the study (for administrative reasons, death, and withdrawal of consent) and 4 participants completed the study. As of 19 November 2019 (cut-off used for participants in China), all 3 participants in China were ongoing in the EUTP.

Of the 10 participants in the EUTP, 6 (60.0%) participants were female and 7 (70.0%) were white. The median age at FUTURE 3 core study entry was 3.5 years (range 0.8 to 10.9 years) and that at EUTP entry was 5.1 years (range 2.2 to 12.4 years). Of the 10 participants, 3 each were from Belarus, China, and Russia, and 1 participant from Ukraine. 4 participants each had associated PAH persisting after complete repair of a congenital heart defect and PAH associated with congenital heart disease with systemic-to-pulmonary shunts, and 2 participants had idiopathic PAH. At FUTURE 3 core study entry, the mean time from initial diagnosis was 0.7 years and most participants were in WHO functional class I or II (4 participants each).

During the EUTP, 6 participants received at least 1 concomitant PAH-specific medication (ie, phosphodiesterase type-5 inhibitors) along with the study treatment (bosentan).

No significant deviations from the protocol in terms of study design or conduct were reported during the EUTP.

Efficacy results

No efficacy data were collected during the EUTP.

Safety results

To prevent a violation of the HGR Regulation, from 19 November 2019 onwards safety data from participants in China have only been reported in the safety database. Note that no significant safety events were reported for any participants from China in the FUTURE 3 Extension study EUTP after this data cut-off date.

During the EUTP (n=10), 8 participants (80.0%) had at least 1 treatment-emergent AE (TEAE) up to end of treatment (EOT) +7 days, corresponding to an adjusted incidence rate of 24.5 events per 100 person-years (PY) (95% confidence limits [CLs]: 12.2, 48.9). Treatment-emergent AEs reported in at least 2 participants during the EUTP and their adjusted incidence rates per 100 PY were pyrexia (9.2 events) and pneumonia, pulmonary hypertensive crisis, viral respiratory tract infection, and upper respiratory tract infection (6.1 events each). The majority of TEAEs during the EUTP were of mild or moderate intensity. One participant died during the EUTP due to a pulmonary hypertensive crisis. The cause of death was considered by the investigator to be not related to study treatment. The participant received bosentan for a total of 1120 days, including 512 days over the combined FUTURE 3 core and extension studies. A total of 4 participants (40.0%) had at least 1 treatment-emergent SAE up to EOT +7 days, corresponding to an adjusted incidence rate of 12.2 events per 100 PY (95% CLs: 4.6, 32.6). An SAE of pulmonary hypertensive crisis was reported in 2 participants (including the death case described above). Most SAEs were reported in the system organ class of Respiratory, thoracic, and mediastinal disorders, with an adjusted incidence rate of 9.2 events per 100 PY. None of the SAEs were considered by the investigator to be related to study treatment. None of the 10 participants had AEs leading to premature discontinuation of study treatment during the EUTP. A total of 2 participants (20.0%) had at least 1 treatment-emergent adverse event of special interest (AESI) up to EOT +7

days, corresponding to an adjusted incidence rate of 6.1 events per 100 PY (95% CLs: 1.5, 24.5). These were increased blood bilirubin in 1 participant and abnormal hepatic function and anemia in 1 participant. The AESI of increased blood bilirubin and anemia were considered by the investigator to be unrelated to study treatment, while abnormal hepatic function (ALT/AST increase <3× ULN) was considered to be study treatment related. Study treatment was interrupted due to the AESI of increased blood bilirubin, while no action was taken with study treatment due to the AESI of anemia and abnormal hepatic function. All 3 AESI resolved without sequelae. Two participants had a transient decrease in hemoglobin to ≤10 g/dL. Overall, the nature and type of AEs reported during the EUTP were consistent with those reported in the core and extension studies and are in line with the known safety profile of bosentan in adults and children.

Over the FUTURE 3 core and extension studies and the EUTP (n=10), 9 participants (90.0%) had at least 1 TEAE up to EOT +7 days, corresponding to an adjusted incidence rate of 18.98 events per 100 PY (95% CLs: 9.9, 36.5). Frequently reported TEAEs and their adjusted incidence rates per 100 PY were upper respiratory tract infection (8.4 events) and nasopharyngitis, pneumonia, worsening of PAH, and pyrexia (6.3 events each). The majority of TEAEs were of mild or moderate intensity. A total of 4 participants (40.0%) had at least 1 treatment-emergent SAE up to EOT +7 days, corresponding to an adjusted incidence rate of 8.4 events per 100 PY (95% CLs; 3.2, 22.5). The SAEs reported over the combined period were the same as those reported during the EUTP (described above), except an SAE of epistaxis (reported during the extension study and considered unrelated to study treatment) in the participant who died due to a pulmonary hypertensive crisis. A total of 2 participants (20.0%) had at least 1 treatment-emergent AESI up to EOT +7 days, corresponding to an adjusted incidence rate of 4.2 events per 100 PY (95% CLs: 1.1, 16.9). The AESI reported over the combined period were the same as those reported during the EUTP (discussed above). Over the combined period, 2 participants (20.0%) had hemoglobin values ≤10 g/dL, both reported during the EUTP. None of the 10 participants who entered EUTP had treatment-emergent marked abnormalities in liver function (ie, ALT / AST ≥3× ULN) from bosentan treatment start in the FUTURE 3 core study up to EOT +7 days in the EUTP. Overall, the nature of AEs reported during the FUTURE 3 core and extension studies and the EUTP was consistent with the known safety profile of bosentan in adults and children.

STUDY LIMITATIONS: The main objective of the EUTP of the FUTURE 3 extension (AC-052-374) study was to provide participants with bosentan beyond the 12-month treatment period of the FUTURE 3 extension study, ie, to avoid unintended discontinuation of a PAH-specific treatment. Providing bosentan as a study treatment required monitoring safety on an individual participant-level. No formal hypothesis was formulated, and the sample size was small, therefore these results are exploratory in nature.

CONCLUSION(S):

Overall, the nature and type of AEs reported during the EUTP were consistent with those reported previously in the FUTURE 3 core and extension studies and are in line with the known safety profile of bosentan in adults and children and no new concerns were identified. Following a detailed assessment of the totality of the data available from the trial, the sponsor has concluded that the exclusion of data from sites in China from 19 November 2019 until the database lock date (1 September 2020) has no clinically relevant impact on the conclusions regarding the safety of bosentan in this study, given the extensive long- term safety information already available.

Assessor's comment

As mentioned above no efficacy evaluation was available, and analysis of safety data was conducted in an exploratory manner only. Regarding the nature of the event reported during the study, the TEAEs reported in the 10 patients during the EUTP were largely in line with the known safety profile of bosentan and the PAH underlying condition. No significant new safety concern emerged from this study.

1.2.3. Discussion on clinical aspects

The main objective of the study was to provide bosentan to patients previously included in the study FUTURE 3 extension in countries where bosentan was not available. The nature and type of AEs reported during the EUTP were consistent with the known safety profile of bosentan in adults and children. No new safety concern was identified from EUTP safety data.

2. CHMP's overall conclusion and recommendation

The main objective of the study was to provide bosentan to patients from FUTURE 3 extension study in countries where bosentan was not commercially available and where "compassionate use" or similar programs could not be implemented due to local regulations.

Exploratory safety analysis limited on the 10 patients included in this EUTP study did not raised any new safety concern in paediatric patients. No further action is required.

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**

3. Additional clarification requested

N/A