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Human Medicines Division

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

## Lucentis

Ranibizumab

Procedure no: EMA/PAM/0000245278

## Note

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

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# 1. Introduction

On 8 January 2025, the MAH submitted a completed paediatric study for Lucentis, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

# 2. Scientific discussion

## *2.1. Information on the development program*

The MAH stated that study CRFB002H2403 is a stand alone study.

## *2.2. Information on the pharmaceutical formulation used in the study*

Ranibizumab is a recombinant humanized immunoglobulin G1-κ isotype monoclonal antibody fragment that selectively binds vascular endothelial growth factor (VEGF)-A. It binds with high affinity to the receptor binding site of active forms of VEGF-A, including the biologically active, cleaved form of this molecule, VEGF110.

Ranibizumab is formulated as a sterile solution for intravitreal injection, aseptically filled in a sterile glass vial at a concentration of 10 mg/mL. Ranibizumab is also available as a 10 mg/mL solution for injection in a pre-filled syringe; this formulation is approved for use in adult indications only.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

The MAH submitted a final report for:

- Study CRFB002H2403 (hereafter referred to as H2403).

### 2.3.2. Clinical study

### Study CRFB002H2403 (hereafter referred to as H2403)

### Description

This was a multicenter, single-arm, open-label study evaluating the effectiveness and safety of ranibizumab 0.2 mg when administered in a real-world clinical setting in ROP patients in China. Ranibizumab was approved in China for treatment of ROP in August 2021, based on the results of the core Study CRFB002H2301. Data on the real-world effectiveness of ranibizumab specifically targeting Chinese ROP patients were sparse. Therefore, H2403 study aimed to collect effectiveness and safety data of ranibizumab from the routine medical practice in ROP participants in China.

## Methods

### *Study participants*

The study population consisted of 62 preterm infants with ROP from six sites in China [Study H2403-Table 14.1-3.1]. Of these, 9 participants (14.5%) discontinued from the study before the Week 24 visit: 7 participants (11.3%) due to parent(s) or legal guardian(s) decision, 1 participant (1.6%) due to AE, and 1 participant (1.6%) due to loss to follow-up [Study H2403-Table 10-1].

Of the 62 enrolled participants, 61 (98.4%) received at least 1 intravitreal injection of ranibizumab and were included in the FAS and the Safety Set. One (1.6%) participant discontinued the study before receiving initial ranibizumab treatment due to parent(s) or legal guardian(s) decision [Study H2403-Listing 16.2.1-1.1].

Of the 61 participants included in the full analysis set, 57.4% were male and 42.6% were female, and all were of Chinese ethnicity. The median gestational age at birth was 27.0 weeks and ranged from 23 weeks to 33 weeks [Study H2403-Table 10-2].

All treated participants had bilateral ROP at baseline, and the same zone and stage of ROP in both eyes. ROP was present in Zone I in 9 participants (14.8%) and in Zone II in 52 participants (85.2%). A-ROP was reported in 4 participants (6.6%), and the most common ROP disease reported was stage 3+ in Zone II (50 participants; 82.0%). Additionally, 51 participants (83.6%) had extra-retinal vessels, judged to be a sign of active ROP disease [Study H2403-Table 10-3].

A total of 51 participants received at least 1 prior medication before baseline, with no participant receiving a prior medication to treat ROP. Seven participants had at least 1 prior surgical procedure [Study H2403-Table 14.1-6.6]; all were non-ocular procedures to treat conditions that were part of the patient's medical history [Study H2403-Table 14.1-6.4].

### *Treatments*

Ranibizumab was administered in the clinical practice setting in accordance with the local package insert.

### *Objectives, outcomes and endpoints*

<table>
<tr><th colspan="2">Primary objective and endpoints</th></tr>
<tr><td>Objective<br><br>• To evaluate the real-world effectiveness of ranibizumab 0.2 mg in the treatment of ROP in Chinese premature infants over a 24-week observation period.</td><td>Endpoints<br><br>The absence of active ROP and absent unfavorable structural outcomes in both eyes during the observational period of 24 weeks after starting study treatment. To achieve a successful outcome, participants could not have:<br><br>• Required intervention for ROP in either eye at or before the 24-week assessment visit with a treatment modality other than ranibizumab<br><br>• Had active ROP in either eye at the 24-week assessment visit as defined by the presence of any of the following features:<br><br>• Vessel dilatation of plus disease in at least 2 quadrants (some persisting tortuosity is allowed)</td></tr>
</table>

| | |
|---|---|
| | • Extra-retinal vessels extending from the retina into the vitreous and judged to be a sign of active ROP disease<br>• Had unfavorable structural outcomes in either eye at or before 24-week assessment visit as defined by the presence of any of the following features:<br>  • Retrolental membrane obscuring the view of the posterior pole<br>  • Substantial temporal retinal vessel dragging causing abnormal structural features/macular ectopia<br>  • Posterior retinal fold involving the macula<br>  • Retinal detachment involving the macula |
| **Secondary objectives and endpoints** | |
| **Objective**<br>• To evaluate the ocular and systemic safety for up to 24 weeks in premature infants diagnosed with ROP and treated with intravitreal ranibizumab 0.2 mg | **Endpoint**<br>• Assessed by ocular examinations, monitoring of AEs throughout the study, and by the assessment of length, weight, and head circumference and lower leg length at Baseline, Week 12, and Week 24 |
| **Objective**<br>• To evaluate the real-world clinical outcomes of ranibizumab 0.2 mg in the treatment of ROP | **Endpoints**<br>• The time to intervention with a second modality for ROP or development of unfavorable structural outcome<br>• Proportion of participants with re-treatment of ROP receiving any post-baseline intervention at or before 24 weeks<br>• The number of ranibizumab administrations needed in the treatment of participants with ROP |
| **Objective**<br>• To evaluate fundus features of ranibizumab 0.2 mg in the treatment of ROP | **Endpoint**<br>• Full retinal vascularization in 12 clock hours at the 24-week assessment |

***Sample size***

N/A

***Randomisation and blinding (masking)***

N/A

***Statistical Methods***

In this study, only data collected using case report forms based on the study site's routine medical records were used for statistical analyses.

Safety analyses were conducted on the safety set, defined as participants who received at least one dose of study treatment.

The Full Analysis Set (FAS) was used for the analyses of the demographic analysis, baseline characteristic analysis, primary analysis and other effectiveness evaluations. Participants who provided data for at least one of the analyses were considered evaluable for FAS [Study H2403-Appendix 16.1.1-Section 7.7.1].

Refer to [Study H2403-Section 9.9] for more details on the data analysis methods.

## Results

***Baseline data***

**Table 10-2 Participant demographics (FAS)**

| Characteristic Categories/Statistics | Full Analysis Set N=61 |
|---|---|
| Gender, n (%) | |
| Male | 35 (57.4) |
| Female | 26 (42.6) |
| Missing | 0 |
| Gestational Age (completed weeks) | |
| n | 61 |
| Mean (SD) | 27.4 (2.18) |
| Median | 27.0 |
| Min, Max | 23, 33 |
| Missing | 0 |
| Gestational Age category, n (%) | |
| ≤ 24 weeks | 4 (6.6) |
| > 24 - < 27 weeks | 18 (29.5) |
| ≥ 27 weeks | 39 (63.9) |
| Age (months) | |
| n | 61 |
| Mean (SD) | 2.34 (0.778) |
| Median | 2.30 |
| Min, Max | 1.0, 4.0 |
| Missing | 0 |
| Race, n (%) | |
| Asian | 61 (100) |
| Non - Asian | 0 (0.0) |
| Missing | 0 |
| Ethnicity, n (%) | |
| Chinese | 61 (100) |
| Non - Chinese | 0 (0.0) |
| Missing | 0 |

n: Number of participants meeting the criterion (for categorical variables); number of participants with non-missing assessment (for continuous variables).

Source: Table 14.1-4.1

***Efficacy results***

Treatment success was defined as the absence of requiring intervention other than ranibizumab for ROP, the absence of active ROP, and the absence of unfavorable structural outcomes in both eyes during the observational period of 24 weeks after starting study treatment [Study H2403-Section 9.9.2.6].

Of total enrolled 62 participants, 53 (85.5%) had a Week 24 visit and therefore completed the study [Study H2403-Table 10-1]. Of these 53 evaluable participants, treatment success was observed for 48 participants (90.6%; 95% CI: 79.3%, 96.9%), and treatment failure occurred in 5 participants (9.4%). Among the participants with an unsuccessful outcome, the reasons for treatment failure were: requirement for other intervention for ROP at or before the 24-week assessment (5 participants; 9.4%), and unfavorable structural outcomes in either eye at or before the 24-week assessment (1 participant; 1.9%). No participants had active ROP in either eye at the 24-week assessment (Table 3-2).

Other interventions required for ROP included retinal laser coagulation in 3 participants, vitrectomy in 3 participants, and epiretinal membrane peel in 1 participant [Study H2403-Listing 16.2.5-2.4]. The unfavorable structural outcome observed was reported as "substantial temporal retinal vessel dragging causing abnormal structural features/macular ectopia" [Study H2403-Listing 16.2.6-1.2]. Refer to [Study H2403-Section 10.3.1.1] for further information.

***Safety results***

The safety risks defined in the currently effective ranibizumab RMP are ocular safety risks including infectious endophthalmitis, intraocular inflammation, retinal detachment and retinal tear, intraocular pressure increase and a systemic safety risk neurodevelopmental impairment - ROP indication. Ocular risks are important identified risks and non-ocular risks important potential risk.

One participant (1.6%) experienced increased intraocular pressure [Study H2403-Table 14.3.1-5.1] which was mild in severity and was assessed as not related to ranibizumab treatment or study procedure by the investigator. No action was taken with ranibizumab treatment, and the outcome of this AE was complete recovery after carteolol hydrochloride eye drops treatment [Study H2403-Listing 16.2.7-1.4].

None of the participants experienced infectious endophthalmitis, intraocular inflammation, retinal detachment and retinal tear, or AEs related to neurodevelopmental impairment as assessed by the investigator [Study H2403-Section 10.5.4].

*Ocular AEs/SAEs*

Ocular AEs were reported in 11 participants (18.0%). The most frequently reported ocular AEs were retinal hemorrhage (5 participants; 8.2%) and vitreous hemorrhage (4 participants; 6.6%). The other ocular AEs reported were conjunctival hemorrhage and intraocular pressure increased, each reported in 1 participant (1.6%) [Study H2403-Table 10-8]. None of these ocular AEs led to participant's discontinuation from the study.

Of these ocular AEs, 1 event of conjunctival hemorrhage was assessed by the investigator as related to both ranibizumab treatment and study procedure. Two events of vitreous hemorrhage that were reported in the same participant were assessed by the investigator as related to ranibizumab

treatment but not related to study procedure. One event of retinal hemorrhage was assessed by the investigator as related to study procedure, but not related to ranibizumab [Study H2403-Listing 16.2.7-1.1]. The outcome of these ocular AEs was complete recovery.

One ocular SAE was reported in one participant (1.6%). The SAE reported was vitreous hemorrhage, which required a fluorescence assisted vitrectomy procedure [Study H2403-Section 10.5.2.1]. This SAE was assessed by the investigator as related to ranibizumab treatment but not related to study procedure. No action was taken with ranibizumab treatment, and the outcome of this event was complete recovery [Study H2403-Listing 16.2.7-1.2].

Two (3.3%) participants had an overdose of ranibizumab. Both participants received a dose of 0.25 mg [Study H2403-Listing 16.2.5-1.1]; one was an initial treatment while the other was a retreatment, and both were administered according to the investigator's judgement [Study H2403-Section 10.3.2.2.3]. The overdose in each case did not lead to the participant's discontinuation from the study. No AEs were associated to the overdose in either of these cases.

*Non-ocular AEs/SAEs*

Non-ocular AEs were reported in 36 participants (59.0%). The most frequently reported non-ocular AE was pneumonia (11 participants; 18.0%), followed by anemia (9 participants; 14.8%) and hypoproteinemia (7 participants; 11.5%) [Study H2403-Table 10-9]. None of the non-ocular AEs were assessed by the investigator as related to ranibizumab treatment or study procedure [Study H2403-Listing 16.2.7-1.1].

Non-ocular SAEs were reported in 19 participants (31.1%). The most frequently non-ocular SAE was pneumonia (9 participants; 14.8%), followed by bronchopulmonary dysplasia (3 participants; 4.9%) [Study H2403-Table 10-11]. None of the non-ocular SAEs were assessed by the investigator as related to ranibizumab treatment or study procedure [Study H2403-Listing 16.2.7-1.2].

One participant (1.6%) experienced a SAE of bronchopulmonary dysplasia, which led to permanent discontinuation of ranibizumab treatment due to fatal outcome [Study H2403-Table 14.3.1-3.1]. This participant was hospitalized on 31 Dec 2023, 65 days after ranibizumab administration, due to shortness of breath and cyanosis for half a day. The participant was diagnosed with bronchopulmonary dysplasia and pulmonary hypertension and was treated with non-invasive ventilator assisted ventilation. The participant was discharged on 10 Jan 2024. On 22 Feb 2024, the participant returned to hospital for follow-up and received further non-invasive ventilator assisted ventilation. On 29 Feb 2024, the participant had cyanosis, shortness of breath and pale face and died the same day. The cause of death stated in the death certificate was bronchopulmonary dysplasia. The study investigator did not suspect a relationship between the event of bronchopulmonary dysplasia and ranibizumab treatment or study procedure [Study H2403-Section 10.5.2].

There were no other non-ocular AEs reported that led to participant's discontinuation from the study [Study H2403-Listing 16.2.7-1.3].

## 2.3.3. Discussion on clinical aspects

This was a multicenter, single-arm, open-label study evaluating the effectiveness and safety of ranibizumab 0.2 mg when administered in a real-world clinical setting in ROP patients in China. Of enrolled 62 participants, 61 received treatment with ranibizumab and 53 completed the study. The study results on effectiveness are in line with expected efficacy and no new safety concern is identified.

The adverse events reported are in line with the established safety profile or prevalent morbidity in this vulnerable population. The study results have been reported as required by the legislation, but they do not warrant any regulatory action.

# 3. CHMP's overall conclusion and recommendation

☒ **Fulfilled**:

No regulatory action required.