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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: EMEA/H/C/000715/P46/073.1

Note

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

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List of abbreviations used in the text

AE Adverse event
AMD Age related macular degeneration
APGAR Appearance, pulse, grimace, activity, respiration score
AP-ROP Aggressive posterior retinopathy of prematurity
CAT Cardiff acuity test
CEO Critical Expert Overview
CNV Choroidal neovascularization
CVFQ Children's Visual Function Questionnaire
DME Diabetic macular edema
eCRS electronic Case Retrieval Strategy
EEA European Economic Area
EMA European Medicines Agency
ETDRS Early Treatment Diabetic Retinopathy Study
EU European Union
IA2 Interim analysis 2
LogMAR logarithm of Minimum Angle of Resolution
LS Least squares
MAH Marketing Authorization Holder
nAMD Neovascular age-related macular degeneration
PDR Proliferative diabetic retinopathy
PIP Pediatric Investigation Plan
ROP Retinopathy of prematurity
RVO Retinal vein occlusion
SAE Serious adverse event
VA Visual acuity
VEGF Vascular endothelial growth factor

1. Introduction

On 27 September 2022, the MAH submitted a completed paediatric RAINBOW EXTENSION study (CRFB002H2301E) for Lucentis (ranibizumab), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measures.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The Lucentis (ranibizumab) clinical development program in ROP includes two paediatric clinical studies. H2301 was a 24-week randomized, controlled clinical trial comparing two doses of ranibizumab (0.2 mg and 0.1 mg) to laser therapy for the treatment of ROP in preterm infants. The primary objective of this study was to demonstrate that intravitreal ranibizumab 0.2 mg had superior efficacy to laser therapy in the treatment of ROP as measured by the absence of active ROP and absence of unfavourable structural outcomes in both eyes 24 weeks after starting study treatment, as assessed by the Investigator.

Based on the results from core Study CRFB002H2301, Lucentis® (ranibizumab) 0.2 mg was approved in the EU in 09/2019 for the treatment of retinopathy of prematurity (ROP) in preterm infants with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 3+) or AP-ROP (aggressive posterior ROP) disease. Study H 2301E1 was designed to evaluate the long-term efficacy and safety of intravitreal ranibizumab compared to laser ablation therapy in preterm neonates with ROP. All patients who successfully completed the core study were invited to participate in the extension study and were followed up to their 5th birthday.

Two interim analyses were performed previously as prespecified in the H2301E1 protocol. The first interim analysis was conducted to comply with the plan for specific follow-up as agreed with EMA's Paediatric Committee in the Paediatric Investigation Plan (PIP) and provided data on ocular structural abnormalities in patients 40 weeks after the start of intravitreal ranibizumab treatment in Study H2301.

The second interim analysis (IA2) evaluated long-term efficacy and safety data, including data on ocular structural abnormalities, ocular and visual function, VA, and additional cognitive and growth assessments at the patient’s 2 years corrected age. The results from this analysis were also reported in a publication (Marlow et al 2021).

This report presents cumulative study results of the final analysis, up to the end of Study H2301E1 when the last patient had completed their 5th birthday visit (data cut-off 21-Apr-2022).

At the time of the approval, the MAH agreed that the results of the final report for H2301E1 be subject to a Category 1 commitment (Annex II D condition) as a PAES, interventional, with a due date 30-Jun-2023 for submission of final study results.

2.2. Information on the pharmaceutical formulation used in the study

Ranibizumab is formulated as a sterile solution for intravitreal injection, aseptically filled in a sterile glass vial at a concentration of 10 mg/mL.

The formulation is presented as a single-use sterile, clear to slightly opalescent, colourless to pale yellow and preservative free aqueous solution for intravitreal injection supplied in glass vials. All primary packaging materials are standard quality, suitable for packaging sterile liquid products, and comply with relevant pharmacopeial requirements.

A syringe suitable to accurately deliver volumes of 10 µL and 20 µL of the solution into the eye was used. This syringe is a sterile, single-use disposable syringe intended for medical purposes. The syringe was individually packaged. A standard injection needle (e.g., 30 G, ½ inch stainless steel) as for the adults will be used for the injection in premature neonates.

2.3. Clinical aspects

2.3.1. Introduction

Ranibizumab is a recombinant humanized immunoglobulin G1 kappa (IgG1κ) isotype monoclonal antibody fragment that selectively binds 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. VEGF-A has been shown to cause neovascularization and leakage in models of ocular angiogenesis. The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation.

Lucentis is indicated in adults for:
- The treatment of neovascular (wet) age-related macular degeneration (AMD)
- The treatment of visual impairment due to diabetic macular oedema (DME)
- The treatment of proliferative diabetic retinopathy (PDR)
- The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)
- The treatment of visual impairment due to choroidal neovascularisation (CNV)

Lucentis is indicated in preterm infants for:
- The treatment of retinopathy of prematurity (ROP) with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 3+) or AP-ROP (aggressive posterior ROP) disease.

Background of prior clinical paediatric Core study CRFB002H2301
Ranibizumab was investigated as a potential treatment for ROP in Study H2301, a randomized, open-label, three-arm parallel-group trial comparing intravitreal ranibizumab at two dose levels (0.1 mg and 0.2 mg) to laser ablation therapy in the treatment of ROP in preterm infants with a birth weight of < 1500 g and bilateral ROP. To be eligible, patients had to have one of the following retinal findings in each eye:
- Zone I, stage 1+, 2+, 3 or 3+ disease, or
- Zone II, stage 3+ disease, or
- Aggressive posterior (AP)-ROP.

The results demonstrated that ranibizumab 0.2 mg was an efficacious and safe treatment for preterm neonates with ROP up to 24 weeks of treatment. Patients treated with ranibizumab 0.2 mg were 2 times more likely to achieve treatment success (defined as absence of active ROP and absence of unfavorable structural outcomes in both eyes 24 weeks after the first study treatment) compared with laser therapy. This was not statistically significant as the one-sided p-value was above the significance level of 0.025 but it was nevertheless considered clinically relevant. Treatment with ranibizumab was safe and well tolerated in patients with ROP.

The MAH submitted a final report for:

- CRFB002H2301E1, RAINBOW extension study: an extension study to evaluate the long-term efficacy and safety of ranibizumab compared with laser therapy for the treatment of infants born prematurely with retinopathy of prematurity.

2.3.2. Clinical study

Study CRFB002H2301E1

RAINBOW extension study: an extension study to evaluate the long-term efficacy and safety of ranibizumab compared with laser therapy for the treatment of infants born prematurely with retinopathy of prematurity.

Description

Methods

Objectives

The purpose of this study was to evaluate the long-term efficacy and safety of intravitreal ranibizumab compared with laser ablation therapy in patients who were treated for retinopathy of prematurity (ROP) in the core study CRFB002H2301

Study design

This was a multicentre, open-label extension study where the VA assessment at the child's 5th birthday visit was performed by an assessor who was masked to study treatment. The study had 2 distinct periods (Epochs). Treatment with study ranibizumab (either as re-treatment after ranibizumab had already been injected in the same eye or as switch ranibizumab treatment from study laser therapy administered in the core study) was permitted for eligible eyes with recurrence/worsening of ROP up to and including Week 40 from the baseline visit in the core study (Epoch 1). The remainder of the extension study up to the 5th birthday visit (Epoch 2) was observational, with no study treatment planned to be administered.

Study population/ Sample size

The study population consisted of male and female preterm infants/children who had successfully completed the 24-week core study H2301 and met eligibility for this study [Study H2301E1-Section 9.3].

Key inclusion criteria:
- Signed informed consent from parent(s) or legal guardian(s), in compliance with local requirements
- The patient successfully completed the core study H2301, as defined by providing assessments at the Visit 112 (the last scheduled visit in the core study) or, if appropriate, at the last of the additional assessment visits as per protocol in H2301, whichever was latest
- The patient received study treatment in both eyes at baseline of study H2301

Key exclusion criteria:
- Patient had a medical condition or personal circumstance which precluded study participation or

compliance with study procedures, as assessed by the Investigator
• Patient had been discontinued from the core study H2301 at any time

Treatments

Ranibizumab solution for injection was supplied (open label) in vials. Each vial contained ranibizumab in the concentration of 10 mg/mL (labeled as 'RFB002 0.5 mg/0.05 mL').

Treatment received at the baseline visit in core study (H2301): Ranibizumab 0.1 mg, Ranibizumab 0.2 mg, Laser

Ranibizumab dose in extension study (H2301E1) could be given during Epoch 1, the duration of which was up to and including 40 weeks after the first study treatment in the core study H2301 [Study H2301E1-Section 9.4].: Ranibizumab 0.1 mg, Ranibizumab 0.2 mg, Ranibizumab 0.2 mg

Outcomes/endpoints

Primary endpoint
Visual acuity assessed by ETDRS with Lea symbols optotypes in the better-seeing eye at the patient's 5th birthday visit as recorded by the masked accessor.

Secondary endpoints

● For ocular and non-ocular adverse events, the number and percentage of patients having any AE, e.g. number of hospitalization/ prolongation of hospitalization due to SAE from the 1st study treatment in the core study up to 40 weeks post baseline visit in the core study, the patient's 2 years corrected age, and the patient's 5th birthday
● Visual acuity in the worse-seeing eye at the patient's 5th birthday using ETDRS and visual acuity score (Lea symbols optotypes).
● The number and percentage of patients with absence of active ROP at 40 weeks and 52 weeks post baseline visit in the core study.
● The number and percentage of patients with the absence of all ocular structural abnormalities in both eyes at or before 40 weeks post baseline visit in the core study, at or before the patient's 2 years corrected age, at or before the patient's 5thbirthday. The number and percentage of patients with the absence of each ocular structural abnormality considered individually at or before 40 weeks post baseline visit in the core study, at or before the patient's 2 years corrected age, at or before the patient's 5th birthday.
● The number and percentage of patients with recurrence of ROP defined as ROP receiving any intervention after the 1st study treatment in the core study up to 40 weeks and 52 weeks post baseline visit in the core study
● The number of ranibizumab injections up to and including 40 weeks post baseline in the core study
● The refraction in each eye as measured in diopters at the patient's 2 years corrected age, and at the patient's 5th birthday
● Measurement of standing/sitting height and leg length in centimeters and weight in grams at the patient's 2 years corrected age, at the patient's 5th birthday.
Head circumference measured in centimeters at the patient's 2 years corrected age and 5th birthday.
● Respiratory function as measured by the number and percentage of patients with oxygen supplementation and with presence of wheezing symptoms
Hearing function as measured by the number and percentage of patients with the presence of hearing impairment
The duration of hospitalization after first hospital discharge home, weight at first hospital discharge

home as measured in days/months at the patient's 2 years corrected age, at the patient's 5th birthday.

Randomisation and blinding (masking)

In the core study, patients were randomized to 1 of the 3 treatment arms (ranibizumab 0.2 mg, ranibizumab 0.1 mg, and laser). Treatment arm assignment and patient identifier in the extension study remained the same as in the core study.

This is an open-label study where the VA assessment at the child's 5th birthday visit was performed by an assessor who was masked to study treatment. The investigators, patients/parents/legal guardians and the Clinical Trial Team (CTT) were unmasked to the treatments administered during the core and extension studies.

Statistical Methods

All analyses were carried out on the Extension Safety Set, which was a subset of the Safety Set from the core study.

For the purposes of classifying an eye by ROP disease status, the worst disease present in any clock hour of the eye, ranked in descending order from worst to best, was used to classify the eye at core baseline and during the study. The better-seeing eye and the worse-seeing eye at the 5th birthday visit were defined as the eye with a higher and lower ETDRS letter score, respectively. If both eyes had the same ETDRS letter score, then the left eye was assigned as the worse-seeing eye.

The primary efficacy endpoint was the VA score in the better-seeing eye at the patients' 5th birthday visit, as recorded by the investigator.

As the primary hypothesis testing in the core study did not show statistical significance, no hypothesis testing was carried out for the primary endpoint in the extension study and only descriptive statistics (i.e., point estimate, and the 95% confidence interval) are provided for the comparison between ranibizumab 0.2 mg and laser. Summary statistics were calculated based on a stratified analysis of variance (ANOVA) model with VA as the continuous response variable, ROP zone (I and II) at core baseline and treatment arm as factors.

Two-sided 95% confidence intervals, assuming normality, were produced for the VA within each treatment arm and the difference in VA between a pair of treatment arms was calculated from least squares means. No p-values are displayed for this analysis.

The planned analysis for the secondary endpoint of 'recurrence of ROP up to 52 weeks post-baseline visit in the core study' was not carried out. Patients were able to receive study treatment up to Week 40 only, after which the study was purely observational. Results from this analysis would have been identical to those for the 'recurrence of ROP up to 40 weeks post-baseline visit in the core study' since recurrence (defined as ROP receiving any post-baseline intervention after the 1st study treatment in the core study) remained unchanged at Week 52. Therefore, this analysis at Week 52 was not considered meaningful by the MAH and thus not performed.

Apart from the analysis of systemic safety risks based on the search criteria defined in the program-level electronic Case Retrieval Strategy (eCRS), an analysis based on a broader medical review of all relevant AEs that could be considered related to overall developmental impairment associated with CNS disorders was also performed.

Results

Baseline data

Baseline demographics and ROP disease characteristics of the Extension Safety Set were generally comparable across treatment arms and representative of the Enrolled Set from the core study. More than half of all patients were Caucasian (61.1%) and approximately half were female (52.2%). The mean gestational age at birth was 26.1 weeks (with a slightly higher proportion of patients in the

gestational age category ≤ 24 weeks for ranibizumab 0.2 mg than for ranibizumab 0.1 mg and laser), and the mean corrected age at extension baseline was 25.05 weeks. The mean birth weight was lower in the ranibizumab 0.2 mg arm (793.2 g) than in the ranibizumab 0.1 mg arm (862.4 g) and the laser arm (859.4 g). Overall, ROP was present in Zone I in 38.3% of patients and in Zone II in 61.7% of patients.

Number analysed

Of the 201 infants who had completed the core study, 180 (90%) were enrolled in this extension study and 156 (86.7%) completed the 5-year evaluation. Of the patients who had completed their 5th birthday visit, 79.5% had their vision assessed by ETDRS (83.3%, 78.2% and 76.6% for ranibizumab 0.2 mg, ranibizumab 0.1 mg, and laser, respectively).

The majority of patients (76.7%) had stage 3+ disease.

Protocol deviations:
Overall, 19 patients (10.6%) had at least one protocol deviation, with the proportion of patients with protocol deviations balanced across treatment arms. The most common protocol deviation was missing a visit due to Coronavirus disease 2019 (COVID-19) (5.0%), followed by delaying a visit due to COVID-19 (2.2%). One patient in the laser arm had a protocol deviation with impact on the primary efficacy endpoint of VA - the VA assessment at the 5th birthday visit was performed by an unmasked assessor who knew which study treatment the patient had received at core study baseline

Exposure:
In both ranibizumab arms, the majority of patients (77.0% for ranibizumab 0.2 mg and 76.9% for ranibizumab 0.1 mg) received only the initial ranibizumab treatment in the core study. The mean number of injections per patient was the same for both ranibizumab arms (2.5 injections). In the laser arm, 11 patients (20.4%) switched to ranibizumab treatment during the core study, with a mean of 2.4 injections per patient. Apart from one patient in the ranibizumab 0.1 mg arm who received ranibizumab retreatment in both eyes at the extension baseline visit, no further study treatments were given during the extension study.

Efficacy results

Overall, 180 of the 201 patients who completed the core study (89.6%) entered the extension study and 156/180 (86.7%) completed the 5th birthday visit. The number/proportion of completers was comparable across the three treatment arms [Study H2301E-Section 10.1].

Two patients discontinued the post-treatment follow-up 1 (from Extension baseline to Week 40): one (1.9%) in the laser arm died and one (1.6%) in the ranibizumab 0.2 mg arm withdrew consent. In post-treatment follow-up 2 (from Week 40 to the patient's 5th birthday visit), discontinuations were reported for 6 patients (9.8%) in the ranibizumab 0.2 mg arm, 10 patients (15.4%) in the ranibizumab 0.1 mg arm, and 6 patients (11.1%) in the laser arm. The most common reasons for discontinuation from post-treatment follow-up 2 were withdrawal of informed consent and loss to follow-up, with no meaningful differences between the treatment groups [Study H2301E1-Section 10.1].

Primary efficacy results
The primary objective was to evaluate the visual function of patients by assessing the visual acuity (ETDRS with Lea symbols optotypes) in the better-seeing eye at the patient's 5th birthday.
The better-seeing eye was defined as the eye with the higher ETDRS score at the 5th birthday visit. Visual acuity using ETDRS could not be assessed for all patients due to cognitive impairment or other reasons.

Overall, 79.5% (124/156) of the patients who completed the 5th birthday visit had an ETDRS score recorded. Of the 5th birthday visit completers, similar proportions across the treatment arms had an ETDRS score record: 83.3% (45/54) in the ranibizumab 0.2 mg arm, 78.2% (43/55) in the ranibizumab 0.1 mg arm, and 76.6% (36/47) in the laser arm.

The LS means of the ETDRS score in the better-seeing eye was numerically higher in the ranibizumab 0.2 mg arm compared to the laser arm. The difference in LS means between the ranibizumab 0.2 mg and laser arms was 4.7 letters (95% CI: -1.1, 10.5). The difference in LS mean ETDRS score between the ranibizumab 0.1 mg and laser arms was 2.5 (95%CI: -3.4, 8.3). [Study H2301E1-Section 11.1].

Secondary efficacy results

Visual Acuity
Visual acuity of the worse-seeing eye
The LS mean ETDRS letter score in the worse-seeing eye at the 5th birthday visit was numerically higher for ranibizumab 0.2 mg than for ranibizumab 0.1 mg and laser. The difference in LS means between the ranibizumab 0.2 mg and laser arms in the worse-seeing eye was 8.0 letters (95% CI: -0.8, 16.7). The difference in LS means between the ranibizumab 0.1 mg and laser arms was 1.6 letters (95%CI: -7.3, 10.5) [Study H2301E1-Section 11.2.1].

Low visual acuity
Low Visual Acuity Testing was only performed in patients who had a score of either '0' or 'missing' on the ETDRS assessment and is presented by best and worst eye separately (as defined by ROP disease status at core study baseline). Results of an ETDRS assessment would be considered 'missing' if the ETDRS assessment could not be performed due to cognitive impairment or other reasons [Study H2301E1-Section 11.2.1].

The number of best eyes with an ETDRS score of '0' or 'missing' in the ranibizumab 0.2 mg, ranibizumab 0.1 mg, and laser arms, was 10, 12 and 13, respectively. Of those, 2, 2 and 3 best eyes in the ranibizumab 0.2 mg, ranibizumab 0.1 mg, and laser arms, respectively, had a Low Visual Acuity Testing record.

The number of worst eyes with an ETDRS score of '0' or 'missing' in the ranibizumab 0.2 mg, ranibizumab 0.1 mg, and laser arms, was 9, 16, and 12, respectively. Of those, 1, 5 and 2 worst eyes in the ranibizumab 0.2 mg, ranibizumab 0.1 mg, and laser arms, respectively, had a Low Visual Acuity Testing record.

The vision of an eye assessed with Low Visual Acuity Testing was scored based on a 'Yes' answer in the order of 'Count fingers' > 'Hand movement' > 'Light perception'. If all assessments had answers 'No', the best vision was 'None of the above'. All best eyes with a Low Visual Acuity Testing record had an answer 'Yes' to at least one of the assessments. Of all the worst eyes with a Low Visual Acuity Testing record, 2 in the ranibizumab 0.1 mg arm and 1 in the laser arm had answers 'No' to all assessments, resulting in a score of 'None of the above.' [Study H2301E1-Section 11.2.1].

Absence of ocular structural abnormalities
Overall, the absence of all ocular structural abnormalities was observed in a higher proportion of patients in the ranibizumab 0.2 mg arm (98.3%) and the ranibizumab 0.1 mg arm (93.8%) than in the laser arm (88.7%). The odds of an absence of all ocular structural abnormalities were 7.77 times higher in the ranibizumab 0.2 mg arm than in the laser arm (95% CI: 0.8838, 68.2337; p = 0.0172). No child developed new structural ocular abnormalities after Week 40 post-core baseline - the absence of all ocular structural abnormalities was observed in the same proportion at the patient's 5th birthday visit as at the patient's 2 years corrected age and at Week 40 [Study H2301E1-Section 11.2.2].

Absence of active ROP
All patients with available results at the Week 40 visit had an absence of active ROP. At Week 52, all patients had an absence of active ROP except for 1 patient in the laser arm. For this patient, ROP was reported in three clock hours of the left eye (Zone II Stage 3, without presence of vascular changes),

which was subsequently reported as resolved at the 2 years corrected age visit [Study H2301E1-Section 11.2.3].

Recurrence of ROP
Recurrence of ROP was defined as ROP receiving any post-baseline intervention after the 1st study treatment in the core study. In the ranibizumab arms, post-baseline interventions were ranibizumab retreatment or switch to laser. In the laser arm, post-baseline interventions were supplementary laser treatments after 11 days post-baseline, or switch to ranibizumab; supplementary laser treatment within 11 days post-baseline was not counted as recurrence. In the Extension Safety Set, the proportion of patients receiving post-baseline intervention up to Week 40 was comparable across the two ranibizumab arms (19 patients, 31.1% for ranibizumab 0.2 mg and 22 patients, 33.8% for ranibizumab 0.1 mg). In the laser arm, 11 patients (20.4%) received post-baseline intervention. This number excluded the additional 7 patients (13.0%) who received supplementary laser within 11 days post-baseline. No recurrence of ROP requiring retreatment occurred in the ranibizumab 0.2 mg arm during the extension study. One patient in the ranibizumab 0.1 mg arm received retreatment in both eyes at the extension baseline visit, which was the latest ROP recurrence requiring retreatment [Study H2301E1-Section 11.2.4].

Occurrence of myopia and high myopia
Refractive error was categorized into myopia (-0.25 diopters or worse) and high myopia (-5.00 diopters or worse). At the 5th birthday visit, the occurrence of myopia was lower for both eyes in the ranibizumab 0.2 mg arm compared to the laser arm (Best eye: 36.5 % vs. 50 %, Worst Eye: 48.1% vs. 56.5%) Similarly, high myopia was less frequently observed in both eyes for ranibizumab 0.2 mg compared to laser (Best eye: 5.8% vs. 19.6%, Worst eye: 5.8% vs. 17.4%). While the occurrence of myopia was similar in the ranibizumab 0.1 mg and laser arms, high myopia was less frequent in the ranibizumab 0.1 mg arm than in the laser arm. [Study H2301E1-Table 11-5].

Exploratory results

Nystagmus, abnormal fixation behavior, strabismus, and abnormal pupillary light reaction

Ocular findings of nystagmus, abnormal fixation behavior, strabismus, and abnormal pupillary light reaction were reported with similar frequencies in both eyes and across the 3 treatment arms at the 5th birthday visit. The total number of patients with at least one ocular finding in the best eye was 14 (26.9%) for ranibizumab 0.2 mg, 13 (23.6%) for ranibizumab 0.1 mg and 14 (29.8%) for laser, and the total number of patients with at least one ocular finding in the worst eye was 12 (23.1%) for ranibizumab 0.2 mg, 13 (24.1%) for ranibizumab 0.1 mg and 14 (29.8%) for laser. Similar frequencies of ocular findings were reported at the 3 years corrected age visit. At the 2 years corrected age visit, numerically fewer patients overall had ocular findings in both eyes in the ranibizumab 0.2 mg arm than in the ranibizumab 0.1 mg and laser arms [Study H2301E1-Section 11.3.1].

Children visual function questionnaire
Overall, the composite and subscale scores of the CVFQ were comparable across treatment arms at the patient's 5th birthday visit. The mean (SD) composite scores were 79.07 (13.191) in the ranibizumab 0.2 mg arm, 78.08 (11.743) in the ranibizumab 0.1 mg arm, and 78.13 (11.991) in the laser arm. Numerically similar scores were observed at the 2 years corrected age visit and the 3 years corrected age visit, with no significant differences between treatment arms at either of the visits [StudyH2301E1-Section 11.3.2].

Cardiff acuity test
CAT was added at the patient's 2 and 3 year visit in protocol amendment v01. Consequently, at the Year 2 visit CAT was conducted only in patients who attended the study visit following approval and implementation of the amendment (67/180 patients) [Study H2301E1-IA2 Report-Section 6.5.1].
At 2 years corrected age, LogMAR VA scores (larger LogMAR scores indicating poorer VA) for the binocular assessment were reported for 22 patients in the ranibizumab 0.2 mg arm, 26 patients in the ranibizumab 0.1 mg arm, and 19 patients in the laser arm. A numerical difference favoring ranibizumab 0.2 mg compared to ranibizumab 0.1 mg and laser was observed, with mean (SD) values of 0.38 (0.30), 0.43 (0.32) and 0.47 (0.28), respectively.

At the patient's 3 years corrected age visit, VA scores for the binocular assessment were reported for 48 patients in the ranibizumab 0.2 mg group, 45 patients in the ranibizumab 0.1 mg group, and 42 patients in the laser group. A numerical difference favoring ranibizumab 0.2 mg compared to ranibizumab 0.1 mg and laser was observed, with mean (SD) values of 0.23 (0.21), 0.30 (0.25) and 0.31 (0.25), respectively. LogMAR scores for the binocular and monocular assessment across all 3 treatment arms were numerically lower overall at 3 years corrected age than at 2 years corrected age, indicating an improvement in visual acuity over time [Study H2301E1-Section 11.3.3].

Visual function assessment
Peripheral vision was assessed by the Investigator at the patient's 5th birthday visit. Overall, the results for peripheral vision were comparable across treatment arms. For the majority of patients in all 3 treatment arms, the binocular assessments of peripheral vision were reported as normal or minor impairment, with only 1 patient (2.5%) in the laser arm having a reported major impairment [Study H2301E1-Section 11.3.4].

Full peripheral retinal vascularization
More patients had full peripheral retinal vascularization in the ranibizumab 0.2 mg arm than in the ranibizumab 0.1 mg or laser arms, at both the patient's 2 years corrected age and the 5th birthday visit. At 2 years corrected age, full peripheral retinal vascularization was reported in 33 patients (56.9%) in the ranibizumab 0.2 mg arm and in 26 patients (44.8%) in the ranibizumab 0.1 mg arm. Full peripheral retinal vascularization was not anticipated to occur in patients in the laser arm due to the nature of laser ablation therapy, where the resulting scar tissue prevents vascularization to progress past this boundary towards the periphery. However, occurrence of full peripheral retinal vascularization was reported in 9 patients (18.0%) from the laser arm. At the 5th birthday visit, full peripheral retinal vascularization was reported in 30 patients (56.6%) in the ranibizumab 0.2 mg arm, 23 patients (41.1%) in the ranibizumab 0.1 mg arm and 13 patients (27.7%) in the laser arm [Study H2301E1-Section 11.3.5].

Safety results
All analyses were carried out on the Extension Safety Set, which was a subset of the Safety Set from the core study and included all patients who had entered the extension study.

The ocular safety events were collected as study endpoints only as specified per the protocol, and were not recorded as AEs. Safety assessments consisted of ocular examinations and collection of ocular and non-ocular AEs and SAEs. They also included monitoring of haematology, serum chemistry and urine as part of routine clinical practice, as well as assessment of vital signs, hearing function and respiratory function [Study H2301E1-Section 9.5.2].

The majority of patients (77.0% for ranibizumab 0.2 mg and 76.9% for ranibizumab 0.1 mg) received only the initial ranibizumab treatment administered in the core study with a mean number of injection of 2.5 per patient. In the laser arm, 11 patients (20.4%) switched to ranibizumab treatment during the core study, with a mean of 2.4 injections per patient. Apart from one patient in the ranibizumab 0.1 mg arm who received ranibizumab retreatment in both eyes at the extension baseline visit, no further study treatments were given during the extension study. [Study H2301E1-Section 10.6.1].

Ocular adverse events
- Overall, 67 patients (37.2%) experienced ocular AEs, with a numerically lower incidence of AEs in the ranibizumab 0.2 mg arm (31.1%) than in the ranibizumab 0.1 mg (40.0%) and laser (40.7%) arms. The most frequent ocular AEs overall were strabismus (18.9%), myopia (7.8%), and conjunctivitis (5.6%). A higher incidence of strabismus and conjunctivitis was reported in the laser arm than in the ranibizumab 0.2 mg arm. Apart from a lower rate of myopia and a higher rate of nystagmus, ranibizumab 0.1 mg had a similar AE profile as laser [Study H2301E1 -Table 12-1].
- The majority of ocular AEs were mild or moderate in severity. Severe ocular AEs were reported for 3.9% of patients overall, with no clinically relevant differences between the ranibizumab 0.2 mg, ranibizumab 0.1 mg and laser arms (3.3%, 4.6%, and 3.7%, respectively). The only ocular AE that was suspected to be related to the study treatment was an event of strabismus of moderate severity in the laser arm [Study H2301E1-Section 12.1.2.2].
- Ocular SAEs were reported for 8 patients (4.4%) overall, with no ocular SAEs reported in the ranibizumab 0.2 mg arm. The most frequent ocular SAEs overall were retinal detachment and ROP,

each reported in 2 patients (1.1%). None of the ocular SAEs were suspected by the Investigator to be related to study procedure/treatment [Study H2301E1-Section 12.2.2].
• There were no ocular AEs leading to permanent study discontinuation; one patient each in the ranibizumab 0.1 mg and laser arms had progression/worsening of ROP leading to study treatment discontinuation [Study H2301E1-Section 12.2.3].

Non-ocular adverse events
• Overall, 145 patients (80.6%) experienced non-ocular AEs, with the lowest incidence in the ranibizumab 0.2 mg arm (75.4%), followed by the ranibizumab 0.1 mg arm (81.5%) and the laser arm (85.2%). The most frequently reported non-ocular AEs overall were nasopharyngitis (17.2%), pyrexia (17.2%), and bronchitis (12.2%). Developmental delay, otitis media, bronchiolitis, ear infection and laryngospasm were reported more frequently for ranibizumab 0.2 mg than for laser. Apart from a higher rate of bronchiolitis ranibizumab 0.1 mg had a comparable non-ocular AE profile as the laser arm [Study H2301E1-Section 12.1.1].
• The majority of non-ocular AEs were mild or moderate in severity. Severe non-ocular AEs were reported for 18.3% of patients overall, with no clinically relevant differences between the ranibizumab 0.2 mg, ranibizumab 0.1 mg and laser arms (21.3%, 15.4%, and 18.5%, respectively) [Study H2301E1-Section 12.1.2.2].
• Non-ocular SAEs were reported in 69 patients (38.3%) overall, with a higher proportion of patients with non-ocular SAEs in the laser arm (46.3%) than in the ranibizumab 0.2 mg and 0.1 mg arms (34.4% and 35.4%, respectively). The most frequent non-ocular SAEs overall were bronchitis (6.1%), pneumonia (5.6%,) and bronchiolitis (3.9%). The incidence of bronchiolitis and febrile convulsion was higher for ranibizumab 0.2 mg than for laser. SAEs of developmental delay were reported in the ranibizumab 0.2 mg arm only. Apart from one SAE of pharyngitis in the laser treatment arm and one SAE of pulmonary hypertension in the ranibizumab 0.2 mg treatment arm, all other non-ocular SAEs were not suspected by the Investigator to be related to study procedure/study treatment [Study H2301E1-Section 12.2.2].
• Two deaths were reported during the extension study, both in the laser arm. Neither death was suspected by the Investigator of being related to study treatment or procedure [Study H2301E1-Section 12.2.1].
• There were no non-ocular AEs leading to permanent study discontinuation [Study H2301E1-Section 12.2.3].
• The overall incidence of neurodevelopmental impairment-related terms based on the eCRS search strategy was balanced between the ranibizumab 0.2 mg and laser treatment arms. Based on a medical review of all AEs of neuro-/developmental impairment, it was confirmed that these events were predominantly reported in patients born extremely premature, i.e. with an extremely low birth weight ≤1000g, and a history of CNS lesions prior to first treatment at core study baseline. None of the neuro-/developmental impairment AEs were assessed as related to ranibizumab treatment by the investigator. Within the AEs of neuro-/developmental impairment related terms, a higher number of events of developmental delay and motor developmental delay was reported in the ranibizumab 0.2 mg arm as compared to laser. It should be noted that the mean gestational age at birth as well as birth weight for the pre-term infants randomized to ranibizumab 0.2 mg (25.8 weeks; 793.2 g) was lower as compared to that for the laser arm (26.4 weeks; 859.4 g) [Study H2301E1-Section 12.7].

Additional safety assessments
Mullen Scales of Early Learning and Gross Motor function were used to assess the long-term effects of ranibizumab treatment on the neurodevelopmental outcomes of cognitive and motor development.
• The cognitive status of patients as assessed by Mullen Scales of Early Learning was comparable across treatment arms both at the patient's 2 years corrected age and at the 5thbirthday visit. At both time points, the majority of patients in each treatment arm showed low impairment (Level 1) or no impairment (Level 0) of their gross motor ability. The proportion of patients with no impairment in the ranibizumab 0.2 mg, ranibizumab 0.1 mg, and laser arms respectively was 39.3%, 41.5% and 20.4% at 2 years corrected age and 45.9%, 41.5% and 37.0% at the 5th birthday visit. The proportion of patients with low impairment was 36.1%, 33.8% and 44.4% at 2 years corrected age and 31.1%, 35.4% and 33.3% at the 5th birthday visit. [Study H2301E1-Section 12.6.3].
• Laboratory data, vital signs, growth parameters, hearing and respiratory function, and duration of hospitalization all demonstrated comparable results between treatment arms [Study H2301E1-Section-

12.6.4].

MAH Overall conclusions
• Preterm infants with ROP treated with ranibizumab 0.2 mg showed better visual acuity, higher rate of absence of ocular structural abnormalities, and reduced rates of myopia and high myopia compared with laser therapy at the patient's 5th birthday visit.
• Based on the results of the assessments in Study H2301E1, Ranibizumab 0.2 mg is safe and well-tolerated in patients with ROP up to the patient's 5th birthday. The long-term safety profile of ranibizumab 0.2 mg was in line with safety data from the core study, with no new safety signals observed. Results from extension Study H2301E1 demonstrated the long-term efficacy and safety of ranibizumab 0.2 mg for the treatment of pre-term infants with retinopathy of prematurity and the results are consistent with the favorable benefit/risk profile that was established in the core study.

2.3.3. Discussion on clinical aspects

The purpose of this study was to evaluate the long-term efficacy and safety of intravitreal ranibizumab compared with laser ablation therapy in patients who were treated for retinopathy of prematurity (ROP) in the core study CRFB002H2301.

Of the 201 infants who had completed the core study, 180 (90%) were enrolled in this extension study and 156 (86.7%) completed the 5-year evaluation, the proportion of completers was comparable across the three treatment arms. Apart from one patient in the ranibizumab 0.1 mg arm who received ranibizumab retreatment in both eyes at the extension baseline visit, no further study treatments were given during the extension study.

The primary endpoint was set as Visual acuity assessed by ETDRS with Lea symbols optotypes in the better-seeing eye at the patient's 5thbirthday visit as recorded by the masked accessor (79.5% of patients could be assessed by ETDRS) and was numerically higher in the ranibizumab 0.2 mg arm compared to the laser arm with 4.7 letters (95% CI: -1.1, 10.5) and in the ranibizumab 0.1 mg compared to laser arm with 2.5 letters (95%CI: -3.4, 8.3).

Regarding the secondary endpoints, the LS mean ETDRS letter score in the worse-seeing eye at the 5th birthday visit was numerically higher for ranibizumab 0.2 mg than for ranibizumab 0.1 mg and laser.

Low Visual Acuity Testing was only performed in patients who had a score of either '0' or 'missing' on the ETDRS assessment and is presented by best and worst eye separately. Overall, patients in the ranibizumab 0.2 arm score best in comparison with the other arms.

Absence of all ocular structural abnormalities was observed in a higher proportion of patients in the ranibizumab 0.2 mg arm (98.3%) and the ranibizumab 0.1 mg arm (93.8%) than in the laser arm (88.7%). The odds of an absence of all ocular structural abnormalities were 7.77 times higher in the ranibizumab 0.2 mg arm than in the laser arm. No child developed new structural ocular abnormalities after Week 40 post-core baseline - the absence of all ocular structural abnormalities was observed in the same proportion at the patients' 5th birthday visit as at the patients' 2 year's corrected age and at Week 40.

All patients with available results at the Week 40 visit had an absence of active ROP. At Week 52, all patients had an absence of active ROP except for 1 patient in the laser arm. which was subsequently reported as resolved at the 2 years corrected age visit.

The proportion of patients receiving post-baseline intervention up to Week 40 was comparable across the two ranibizumab arms (19 patients, 31.1% for ranibizumab 0.2 mg and 22 patients, 33.8% for ranibizumab 0.1 mg). In the laser arm, 11 patients (20.4%) received post-baseline intervention. No

recurrence of ROP requiring retreatment occurred in the ranibizumab 0.2 mg arm during the extension study. This confirms long-term effect of the ranibizumab treatment. One patient in the ranibizumab 0.1 mg arm received retreatment in both eyes at the extension baseline visit, which was the latest ROP recurrence requiring retreatment.

At the 5th birthday visit, the occurrence of myopia was lower for both eyes in the ranibizumab 0.2 mg arm compared to the laser arm (Best eye: 36.5 % vs. 50 %, Worst Eye: 48.1% vs. 56.5%) Similarly, high myopia was less frequently observed in both eyes for ranibizumab 0.2 mg compared to laser (Best eye: 5.8% vs. 19.6%, Worst eye: 5.8% vs. 17.4%). While the occurrence of myopia was similar in the ranibizumab 0.1 mg and laser arms, high myopia was less frequent in the ranibizumab 0.1 mg arm than in the laser arm.

Regarding Exploratory results, 'Nystagmus, abnormal fixation behavior, strabismus, and abnormal pupillary light reaction' and '*Children visual function questionnaire'* showed overall comparable results across treatment arms at the patient's 5th birthday visit.

CAT (Cardiff acuity test) was added at the patient's 2 and 3 year visit. LogMAR scores for the binocular and monocular assessment across all 3 treatment arms were numerically lower overall at 3 years corrected age than at 2 years corrected age, indicating an improvement in visual acuity over time.

Peripheral vision results at the patient's 5th birthday visit were comparable across treatment arms. More patients had full peripheral retinal vascularization in the ranibizumab 0.2 mg arm than in the ranibizumab 0.1 mg or laser arms, at both the patient's 2 years corrected age and the 5th birthday visit. At the 5th birthday visit, full peripheral retinal vascularization was reported in 30 patients (56.6%) in the ranibizumab 0.2 mg arm, 23 patients (41.1%) in the ranibizumab 0.1 mg arm and 13 patients (27.7%) in the laser arm.

With regards to safety, the incidence of ocular AEs was lower in the ranibizumab 0.2 mg group (31.1%) compared to the ranibizumab 0.1 mg (40.0%) and laser group (40.7%). Severe ocular AEs showed no clinically relevant differences between the ranibizumab 0.2 mg, ranibizumab 0.1 mg and laser arms (3.3%, 4.6%, and 3.7%).

The incidence of non-ocular AEs was lowest in the ranibizumab 0.2 mg arm (75.4%), followed by the ranibizumab 0.1 mg arm (81.5%) and the laser arm (85.2%).

The most frequently reported non-ocular AEs overall were nasopharyngitis (17.2%), pyrexia (17.2%), and bronchitis (12.2%), with no non-ocular AEs leading to permanent study discontinuations.

There was a higher proportion of patients with non-ocular SAEs in the laser arm (46.3%) than in the ranibizumab 0.2 mg and 0.1 mg arms (34.4% and 35.4%, respectively). The most frequent non-ocular SAEs overall were bronchitis (6.1%), pneumonia (5.6%,) and bronchiolitis (3.9%) with no non-ocular AEs leading to permanent study discontinuation Two deaths occurred during H2301E1, with both patients from the laser group never having received any ranibizumab treatment.

The overall incidence of neurodevelopmental impairment-related terms was similar between the ranibizumab 0.2 mg (16.4%) and laser treatment arms (16.7%). According to the MAH, a medical review confirmed that these events were predominantly reported in patients born extremely premature. None of the neuro-/developmental impairment AEs were assessed as related to ranibizumab treatment. Within the AEs of neuro-/developmental impairment related terms, a higher number of events of developmental delay and motor developmental delay was reported in the ranibizumab 0.2 mg arm (11.5%, 3.3%) as compared to laser (5.6%, 0%). Nevertheless, overall, rates of non-ocular AEs were as expected for a preterm population with comorbidities.

Regarding Additional safety assessments, cognitive status of patients as assessed by Mullen Scales of Early Learning was comparable across treatment arms both at the patient's 2 years corrected age and

at the 5th birthday visit and Laboratory data, vital signs, growth parameters, hearing and respiratory function, and duration of hospitalization all demonstrated comparable results between treatment arms

3. CHMP overall conclusion and recommendation

Overall, it is agreed with the MAH that efficacy of intravitreal Lucentis (ranibizumab) 0.2 mg has been maintained and is numerically better than 0.1 mg ranibizumab and laser.

The presented data did not reveal any new safety concern in ROP patients who showed a consistent long-term safety profile with no new safety signals observed.

The benefit-risk balance of Lucentis 0.2 mg in the treatment of ROP in preterm infants remains positive.

X Fulfilled:

In view of the available data, Novartis identified amendments to be introduced to the product information due to the results of the paediatric study and this is agreed on. As agreed, the CSR was submitted via this stand-alone Article 46 procedure but it should be followed by a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 to be submitted no later than 25 Nov 2022.

Annex: Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies

N/A

Clinical studies

Product Name: Lucentis Active substance: Ranibizumab

Study title	Study number	Date of completion	Date of submission of final study report
RAINBOW extension study: an extension study to evaluate the long-term efficacy and safety of ranibizumab compared with laser therapy for the treatment of infants born prematurely with retinopathy of prematurity.	CRFB002H2301E1	data cut-off 21-Apr-2022	27 September 2022