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Human Medicines Evaluation 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

Note

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

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1. Introduction

On 24 May 2018, 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 was also provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the RAINBOW study CRFB002H2301 is part of a clinical development program. It is also part of a European Medicines Agency Paediatric Investigation Plan (PIP) for Lucentis.

The variation application consisting of the full relevant data package (i.e. containing the RAINBOW CSR and the results from an interim analysis of the RAINBOW extension study) is expected to be submitted by Q4/2018. – A line listing of all the concerned studies is annexed.

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 currently marketed formulation in the EU was used.

The formulation contains:
- α,α-trehalose dehydrate,
- histidine hydrochloride,
- histidine,
- polysorbate 20,
- water for injections.

During review of PIP [EMEA-000527-PIP03-13], the PDCO Formulation Working Group concluded that as the formulation is already optimised there is no concern for its intravitreal injection to the paediatric population.

2.3. Clinical aspects

2.3.1. Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative pathologic process that occurs in the incompletely vascularised, developing retina of low birth-weight preterm neonates.

The pathogenesis involves 2 discrete phases: Phase 1 occurs from roughly 22 to 30 weeks postmenstrual age, and Phase 2 from roughly 31 to 44 weeks postmenstrual age. Phase 1 involves relative hyperoxia and decreased VEGF levels, whereas Phase 2 involves relative hypoxia and increased vascular endothelial growth factor (VEGF) levels (Mintz-Hittner et al. 2011).

Incidence and severity of ROP were found to rise with degree of prematurity at birth, low gestational age and low birth-weight being the main risk factors (Hartnett and Penn 2012, Fierson et al. 2013). The vascular changes of ROP may be mild and regress completely with time without major long-term sequelae, or may increase in severity and lead to macular dragging, total retinal detachment, severe visual impairment, and lifelong blindness (Hardy et al. 2004).

ROP is a significant cause of blindness in children in both developed and developing countries, with approximately 50 000 children blind from ROP worldwide every year (Gilbert 2008, Mintz-Hittner et al. 2011).

Ablation of the peripheral avascular retina with cryotherapy was the first standard treatment for ROP, with efficacy demonstrated in the CRYO-ROP study (Cryotherapy for Retinopathy of Prematurity Cooperative Group 1988). At 15 years after cryotherapy, treated eyes had 40 % less unfavourable structural outcomes and 30 % less unfavourable visual acuity outcomes, compared with the control eyes (Palmer et al. 2005).

In the 1990s, the use of laser photocoagulation to ablate the peripheral avascular retina gained widespread acceptance, and this modality has now almost completely replaced cryotherapy. Laser ablation therapy (hereafter referred to as laser therapy) is associated with better long-term structural, visual, and refractive outcomes than cryotherapy (Connolly et al. 2002, Ng et al. 2002, Houston et al. 2013).

In 2003, the Early Treatment for Retinopathy of Prematurity (ETROP) study demonstrated that early ablation therapy was associated with better visual and structural outcomes at 9 months, compared with therapy initiated at later stages of ROP (Good 2004). The authors developed a clinical algorithm to identify for early treatment those eyes with ROP characteristics that had the highest risk for retinal detachment and blindness (Type I ROP), while minimising treatment of those eyes with ROP characteristics likely to show spontaneous regression (Type II ROP).

The results suggested that, in most circumstances, peripheral retinal ablation should be considered for any eye with Type I ROP:
• Zone I, any stage ROP with plus disease
• Zone I, stage 3 ROP with or without plus disease
• Zone II, stage 2 or 3 ROP with plus disease

Conversely, continued serial examinations should be considered for any eye with Type II ROP:
• Zone I, stage 1 or 2 ROP without plus disease
• Zone II, stage 3 ROP without plus disease

Treatment should be considered for any eye with Type II ROP if it progresses to Type I status (Good 2004).

The findings from the ETROP study, incorporating revisions to the ROP classification system, provided the basis for current clinical guidelines recommending that the following types of ROP should be treated (International Committee for the Classification of Retinopathy of Prematurity 2005, Royal College of Paediatrics and Child Health 2008, Fierson et al. 2013):
• Zone I, any ROP with plus disease
• Zone I, stage 3 ROP without plus disease
• Zone II, stage 3 ROP with plus disease
• Aggressive posterior ROP (AP-ROP)

With respect to Zone II stage 2+ ROP, there are conflicting opinions on whether the available clinical data support the benefits of early treatment (Royal College of Paediatrics and Child Health 2008). Hence, the treatment guidelines for this ROP category differ on whether treatment should be initiated (Fierson et al. 2013) or allow the decision to treat or monitor closely to be made by an experienced ophthalmologist (Royal College of Paediatrics and Child Health 2008).

Despite improvement in the technology and timing of ROP treatment, it remains a leading cause of childhood blindness worldwide. The ETROP study reported 14 % unfavourable visual acuity outcome

and 9 % unfavourable structural outcome at 9 months despite ablation therapy (Good 2004). In addition, laser therapy may not be possible for certain patients. The conduct of laser therapy usually requires general anaesthesia and adequate visualisation of the retina, which may be problematic in preterm neonates with associated comorbidities. Thus, there is a high unmet medical need for new treatment options for patients with ROP.

Both cryotherapy and laser therapy ablate the avascular peripheral retina and destroy the majority of the retinal cells that produce VEGF, which plays an important role in the pathogenesis of ROP (Smith 2008). Because of the role of VEGF in ROP, there is a growing body of evidence supporting the use of targeted pharmacologic inhibition of VEGF in the management of ROP (Sonmez et al 2008, Sato et al. 2009). There are a number of reports of favourable experience with the off-label use of intravitreal bevacizumab or ranibizumab in the management of ROP (Chung et al 2007, Travassos et al 2007, Honda et al 2008, Kusaka et al 2008, Lalwani et al 2008, Mintz-Hittner and Kuffel Jr 2008, Quiroz-Mercado et al 2008, Ahmed et al 2010, Altinsoy et al 2010, Dorta and Kychenthal 2010, Law et al. 2010, Lee et al. 2010, Nazari et al. 2010, Zepeda-Romero et al. 2010, Harder et al. 2011, Mintz-Hittner et al. 2011, Wu et al. 2011, Lin et al. 2012, Mota et al. 2012, Castellanos et al. 2013, Kim et al. 2014). Most reports used approximately 50 % of the adult intravitreal dose per eye, although efficacy has also been reported with lower doses (Harder et al. 2011, Kim et al. 2014).

Ranibizumab is a recombinant humanised immunoglobulin G1 K isotype monoclonal antibody fragment targeted against human 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 neovascularisation and leakage in ocular angiogenesis models. 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.

The purpose of the submitted study was to determine if intravitreal ranibizumab is superior to laser therapy in the treatment of ROP. The study assessed the ability of these treatments to lead to regression of active ROP and prevent the development of ocular complications that are associated with poor visual outcome.

2.3.2. Clinical study

The MAH submitted the final report for clinical study CRFB002H2301, RAINBOW: a randomized, controlled study evaluating the efficacy and safety of ranibizumab compared with laser therapy for the treatment of infants born prematurely with retinopathy of prematurity.

Description

The study was a randomised, multicenter, open-label, 3-arm, parallel-group, superiority study evaluating the efficacy and safety of intravitreal ranibizumab 0.1 mg and 0.2 mg compared with laser therapy for the treatment of retinopathy of prematurity (ROP) in preterm infants with a birth weight of < 1500 g and bilateral ROP.

Methods

Objectives

The primary objective of the study was to demonstrate that intravitreal ranibizumab 0.2 mg has superior efficacy to laser therapy in the treatment of ROP as measured by treatment success, defined as 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.

The study defined active ROP as the presence of vessel dilation of plus disease in at least 2 quadrants (with some persisting tortuosity being allowed) or extra-retinal vessels extending from the retina into the vitreous and judged to be a sign of active ROP disease. Unfavourable structural outcomes were defined by the presence of any of the following features: retrolental membrane obscuring the view of the posterior pole, substantial temporal retinal vessel dragging causing abnormal structural features/ macular ectopia, posterior retinal fold involving the macula, or retinal detachment involving the macula.

Treatment success was achieved if patients did not experience any of the following conditions:

- death,
- requirement of intervention for ROP in either eye with a treatment modality other than the modality of the first investigational treatment,
- active ROP in either eye,
- unfavourable structural outcomes in either eye.

Key secondary objectives of the study were:

- to demonstrate that intravitreal ranibizumab 0.1 mg has 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 investigational treatment, as assessed by the Investigator,
- to demonstrate that intravitreal ranibizumab 0.2 mg had superior efficacy to intravitreal ranibizumab 0.1 mg 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 investigational treatment, as assessed by the Investigator.

Other secondary objectives were:

- to evaluate the time to intervention with a second modality for ROP or development of unfavourable structural outcome or death,
- to evaluate the recurrence of ROP receiving any post-baseline intervention at 24 weeks or before,
- to evaluate the ocular and systemic safety of intravitreal ranibizumab 0.1 mg and 0.2 mg in the treatment of ROP as assessed by ocular examination, monitoring of adverse events (AEs) throughout the study, and by the assessment of length, weight, head circumference and lower leg length at Baseline, Day 85, and Day 169,
- to evaluate the systemic pharmacokinetics (PK) of intravitreal ranibizumab in patients with ROP, as evaluated by sparse-sampling population PK methods,
- to evaluate the effects of investigational treatment on systemic VEGF levels in patients with ROP, as evaluated by sparse-sampling population concentration-response methods,
- to assess the number of ranibizumab administrations needed in the treatment of patients with ROP.

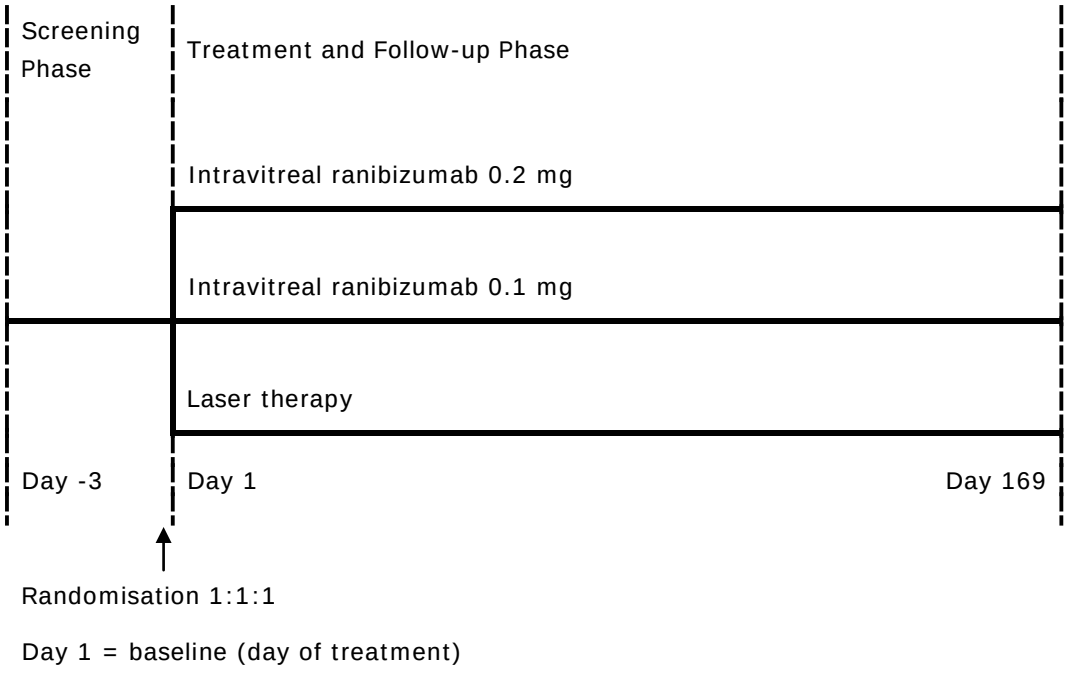
Study design

Patients were randomized in 1:1:1 ratio to receive 0.1 or 0.2 mg intravitreal ranibizumab or laser therapy at Baseline.

Re-treatment with ranibizumab at the same dose at least 28 days after the previous ranibizumab treatment in either eye was allowed if there were signs of ROP worsening. During the study, a patient could receive rescue treatment (a study treatment modality different from the initially assigned treatment received at Baseline) in the event of unsatisfactory response to the initial randomized treatment, i.e., a patient randomised to ranibizumab 0.1 mg or 0.2 mg could receive laser therapy in either eye, and a patient randomised to laser therapy could receive ranibizumab 0.2 mg in either eye. In patients randomised to laser who received rescue ranibizumab, re-treatment with ranibizumab 0.2 mg was allowed.

Only the eye with worsening of ROP was re-treated. If both eyes had these signs, then both eyes were re-treated.

Figure 1. Study design.



Day 1 = baseline (day of treatment)

Study population / Sample size

The study population consisted of male and female preterm infants with bilateral ROP who required treatment. Approximately 180 patients were planned to be randomised, to provide at least 48 evaluable patients in each of the 3 treatment arms, i.e. at least 144 evaluable patients in total.

Inclusion criteria

Patients eligible for inclusion had to fulfil all of the following criteria prior to receiving the first investigational treatment:

1. signed informed consent from parent(s) or legal guardian(s), in compliance with local requirements,
2. male or female preterm infants with a birth weight of less than 1500 g, and
3. bilateral ROP with 1 of the following retinal findings in each eye:

- Zone I, stage 1+, 2+, 3 or 3+ disease, or
- Zone II, stage 3+ disease, or
- AP-ROP.

Exclusion criteria

Patients fulfilling any of the following criteria prior to receiving the first investigational treatment were not eligible for inclusion in this study. No additional exclusions were allowed to be applied by the Investigator, in order to ensure that the study population was representative of all eligible patients.

Investigational treatment not clinically appropriate for the patients who had:

1. ROP disease characteristic in either eye other than that listed in Section 9.3.1 at the time of the first investigational treatment, or
2. a history of hypersensitivity (either the patient or the mother) to any of the investigational treatments or to drugs of similar chemical classes.

Risk of confounding efficacy and/or safety assessments in patients who:

3. received any previous surgical or nonsurgical treatment for ROP (e.g., ablative laser therapy or cryotherapy, vitrectomy),
4. been previously exposed to any intravitreal or systemic anti-VEGF agent (either the patient or the mother during this child's pregnancy),
5. used (either the patient or the mother) other investigational drugs as part of another clinical study (other than vitamins and minerals) within 30 days or within 5 half-lives of the other investigational drug, whichever was longer,
6. ocular structural abnormalities that were assessed by the Investigator to have had a clinically significant impact on study assessments,
7. active ocular infection within 5 days before or on the day of first investigational treatment
8. a history of hydrocephalus requiring treatment,
9. a history of any other neurological conditions that are assessed by the Investigator to have a significant risk of severe impact on visual function, or
10. any other medical conditions or clinically significant comorbidities or personal circumstances that were assessed by the Investigator to have a clinically relevant impact on study participation, any of the study procedures, or on efficacy assessments (e.g. poor life expectancy, pupil not able to be adequately dilated, unable to comply with the visit schedule).

Treatments

Test product, dose and mode of administration: intravitreal injections of ranibizumab 0.1 mg and ranibizumab 0.2 mg. Patients received their randomised treatment on Day 1. Re-treatment with ranibizumab for either eye occurred for worsening of ROP at least 28 days after the previous ranibizumab treatment in that eye. Up to 2 re-treatments with ranibizumab per eye to treat ROP recurrence were allowed. The dose used was the same as the dose to which the patient was randomised. Only the eye with worsening of ROP was re-treated. If both eyes had these signs, then both eyes were re-treated.

Reference therapy, dose and mode of administration: laser ablation therapy (hereafter laser therapy). For patients who received initial laser therapy, the Investigator decided at the Day 2, Day 4 and Day 8 assessments if supplementary laser treatment was necessary for any eye. Supplementary laser treatment had to be performed within the next 3 days of the Investigator's decision. If at the Day 8 assessment the Investigator decided that supplementary laser treatment was not necessary for either eye, no further laser treatment was allowed for the patient from this time point onwards.

Outcomes / Endpoints

The primary efficacy variable was 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.
To achieve this outcome, patients could not fulfil any of the following criteria:

- death at or before the 24-week assessment visit,
- required intervention for ROP at or before the 24-week assessment visit with a treatment modality other than the modality of the first investigational treatment,
- had active ROP in either eye at the 24-week assessment visit as defined by the presence of any of the following features:
  - vessel dilatation of plus disease in at least 2 quadrants (some persisting tortuosity was allowed),
  - extra-retinal vessels extending from the retina into the vitreous and judged to be a sign of active ROP disease,
- had unfavourable structural outcomes in either eye at or before 24-week assessment visit as defined by the presence of any of the following features:
  - retrolental membrane obscuring the view of the posterior pole,
  - substantial temporal retinal vessel dragging causing abnormal structural features/ macular ectopia,
  - posterior retinal fold involving the macula,
  - retinal detachment involving the macula.

A patient could be defined as a ‘success’ (favourable outcome) or ‘failure’ (unfavourable outcome) for each of the criteria above. Patients were defined as a ‘success’ for the primary efficacy variable only if they were a ‘success’ for each component. Consequently, a patient was defined as a ‘failure’ for the primary efficacy variable if they were defined as a ‘failure’ for at least one of the criteria above.

Secondary efficacy variables included:

- the criteria that a patient could not fulfil to be a treatment success:
  - death from any cause at or before the 24-week assessment visit,
  - requirement of intervention for ROP in either eye at or before the 24-week assessment visit with a treatment modality other than the modality of the first investigational treatment,
  - active ROP in either eye at the 24-week assessment visit,
  - unfavourable structural outcomes in either eye at or before 24-week assessment visit,
- the time after the first investigational treatment to the first occurrence of one of the following:
  - death,
  - intervention for ROP with a treatment modality other than the modality of the first investigational treatment,
  - an unfavourable structural outcome in either eye,
- requirement of none, 1, 2 or 3 ranibizumab treatments in each eye by patient,
- recurrence of ROP receiving any post-baseline intervention at 24 weeks or before.

The presence of fundus features was assessed in both eyes by the Investigator at all study visits, using images taken by RetCam digital photography and/or as assessed by indirect ophthalmoscopy, according to protocol.

Safety was assessed based on AEs, vital signs, physical findings, hospitalisation, and requirement for respiratory support.

Statistical methods

A 3-step sequential testing procedure was used for primary (ranibizumab 0.2 mg against laser) and the 2 key secondary comparisons (ranibizumab 0.1 mg against laser and ranibizumab 0.2 mg against 0.1 mg). Under this testing procedure, the primary comparison was conducted at the first step followed by the key secondary comparisons if the primary comparison was statistically significant. If the efficacy comparison at any step was not statistically significant, the remaining efficacy comparisons were assessed descriptively. Otherwise the comparison continued to the next step.

All hypotheses were tested at a pre-specified level of significance (two-sided α=0.05). This testing procedure controlled familywise type I error rate at a pre-specified level of significance because, for each hypothesis, testing was conditional upon rejecting all hypotheses earlier in the sequence.

The comparisons were performed using the stratified Cochran–Mantel–Haenszel test for binomial proportions. Stratification was based on ROP zone, derived at randomisation from the Case Report Form (CRF) page. Mantel–Haenszel odds ratios, adjusted one-sided p-values and their 2-sided 95 % CIs were also presented. A sensitivity analysis was performed by repeating the primary efficacy analysis with the stratification by ROP zone information obtained from the Interactive Response Technology (IRT).

At each step, if superiority was claimed, Mantel–Haenszel odds ratio, adjusted one-sided p-value and the two-sided 95 % CI of the comparison were presented. The adjusted one-sided p-value was calculated as follows for the primary objective; the same approach was taken for the key secondary objectives:

- 0.5*(two-sided p-value) if the Mantel–Haenszel odds ratio of ranibizumab 0.2 mg to laser was in favour of ranibizumab 0.2 mg
- 1-0.5*(two-sided p-value) if the Mantel–Haenszel odds ratio of ranibizumab 0.2 mg to laser was in favour of laser.

Missing data to be used for the statistical inference of the primary variable was imputed by eye. Imputation of missing data was only undertaken if the value of the primary variable was missing.

The primary analysis of the hypotheses was undertaken after imputing missing values related to the occurrence of active ROP and unfavourable structural outcomes at Week 24, assuming the following:

- If the last non-missing value of a criterion was ‘success’, then the missing value of the criterion at Week 24 remained missing.
- If the last non-missing value of a criterion was ‘failure’, then the missing value of the component at Week 24 was imputed as ‘failure’.

The imputed value of the primary variable was then derived from the imputed values of the individual components. The primary analysis was undertaken after imputing missing values of the primary variable at 24 weeks.

The primary efficacy variable was also assessed by a binary logistic regression model by using treatment group and ROP zone at randomisation from the CRF as factors. The odds ratio (OR) of the primary variable was displayed (with values > 1 in favour of ranibizumab) with its two-sided 95 % CI and one-sided p-value. If the number of events of some cells was very small (< 5 for at least one cell), then exact logistic regression was used to assess the primary efficacy variable.

All secondary efficacy analyses were performed based on observed data unless otherwise specified. No imputation of missing data was undertaken on secondary efficacy variables. – No interim analysis was performed.

Results

Recruitment / Number analysed

A total of 225 patients from 87 sites in 26 countries were enrolled and randomised. The majority of patients completed the treatment phase (218 patients, 96.9 %), i.e. they received initial (baseline) investigational treatment; study treatment in the follow-up phase was completed by 89.3 % of patients overall, with a slightly higher proportion of patients in the ranibizumab 0.1 mg group (71 patients, 92.2 %) and ranibizumab 0.2 mg (66 patients, 89.2 %) groups than in the laser group (64 patients, 86.5 %). – All patients of the Randomised Set were included in the Full Analysis Set (FAS), and 80.4 % of all randomised patients were included in the Per-Protocol Set (181 patients overall), with a higher proportion of patients in both ranibizumab groups (86.5 % for ranibizumab 0.2 mg, 81.8 % for ranibizumab 0.1 mg) than in the laser group (73.0 %). The Safety Set contained 218 patients.

Baseline data

59.1 % of the patients were Caucasian and 52.4 % of the patients were female. The mean gestational age at birth was 26.1 weeks, with a similar mean gestational age in all 3 treatment groups (range 25.8–26.5 weeks). Treatment groups were generally well balanced with respect to baseline demographics.

38.2% of patients were classified ROP Zone I and 61.3 % were classified ROP Zone II. AP-ROP was reported for 30 patients (13.3 %). The most frequent baseline ROP disease classification was Zone II Stage 3+ (60.0 %), followed by Zone I Stage 3+ (16.4 %) and Zone I AP-ROP (12.9 %).

Mean birth weight was slightly lower in the ranibizumab 0.2 mg group (790.6 g) than in the ranibizumab 0.1 mg (885.6 g) and laser (830.6 g) groups. 48.4 % of the patients had a birth weight of ≤ 750 g (52.7 % for ranibizumab 0.2 mg vs. 42.9 % for ranibizumab 0.1 mg and 50.0 % for laser).

Efficacy results

Results of the primary objective – treatment success

The highest treatment success with 80.0 % was observed in the ranibizumab 0.2 mg group, compared with 75.0 % in the ranibizumab 0.1 mg group and 66.2 % in the laser group. The difference between ranibizumab 0.2 mg and laser was clinically relevant with an odds ratio (OR) of 2.19 (95 % confidence interval (CI) [0.9932, 4.8235]), indicating that patients treated with ranibizumab 0.2 mg were 2 times more likely to achieve treatment success compared with laser therapy, even though for the primary endpoint the one-sided p-value 0.0254 was marginally above the significance level of 0.025.

A pre-specified sensitivity analysis was conducted to repeat the primary analysis with an alternative imputation rule, whereby the imputed value of the missing ocular criterion at Week 24 was derived from the value at the Week 20 visit. This alternative imputation rule was based on the results of prior studies,[1] which concluded that recurrence with unfavourable structural endpoints occurred at 6.2 ± 5.7 weeks after laser treatment or fewer than 100 days after ranibizumab treatment, indicating that active ROP and unfavourable structural outcomes are stable between Week 20 and Week 24. With this rule, if assessment of either active ROP or unfavourable structural outcomes at Week 24 was missing but available at Week 20, the result of Week 20 was imputed for Week 24. Overall, this affected the imputed ocular outcomes at Week 24 of 3 patients, including 2 patients in the ranibizumab 0.2 mg group (1 patient who was imputed from missing to success and 1 patient who remained failure due to

[1] Mintz-Hittner et al 2011, Stahl et al 2018

death) and 1 patient in the laser group (who remained failure due to switch). In this sensitivity analysis, treatment success was higher in the ranibizumab 0.2 mg group compared to the laser group (80.3 % vs. 66.2 %; OR 2.22, 95 % CI [1.0088, 4.8890]), and the difference was statistically significant (p=0.0230).

Other sensitivity analyses (with missing data not imputed, missing data imputed as 'success', missing data imputed as 'failure', and using sensitivity logistic regression) confirmed the results of the primary analysis, with the highest treatment success observed in the ranibizumab 0.2 mg group, followed by the ranibizumab 0.1 mg and laser groups.

Results of secondary objectives

Key secondary efficacy endpoints were not tested, as a 3-step sequential testing procedure was used for the primary (ranibizumab 0.2 mg against laser) and the 2 key secondary comparisons (ranibizumab 0.1 mg against laser and ranibizumab 0.2 mg against ranibizumab 0.1 mg), and the one-sided p-value 0.0254 in the primary efficacy analysis was marginally above the significance level of 0.025.

Results of the other secondary efficacy endpoints are summarised in the following subsections.

Individual components of the primary variable indicating treatment failure

Death at or before 24-week assessment visit

12 patients died at or before the 24-week assessment, with a similar proportion of patients in all treatment groups (4 patients (5.4 %) in the ranibizumab 0.2 mg group, 4 patients (5.2 %) in the ranibizumab 0.1 mg group, and 4 patients (5.4 %) in the laser group).

Intervention for ROP in either eye at or before the 24-week visit with a treatment modality other than the modality of the first study treatment

A lower proportion of patients in both ranibizumab groups compared with the laser group required intervention for ROP in either eye at or before the 24-week assessment visit with a treatment modality other than the modality of the study treatment received at Baseline (i.e. patients who switched treatment (switch to laser in the ranibizumab groups, switch to ranibizumab treatment in the laser group, or switch to standard of care in all groups); 11 patients (14.9 %) for ranibizumab 0.2 mg and 13 patients (16.9 %) for ranibizumab 0.1 mg vs. 18 patients (24.3 %) for laser).

Active ROP in either eye at the 24-week visit

Active ROP was defined by the presence of any of the following features: vessel dilation of plus disease in at least 2 quadrants of the eye (some persisting tortuosity was allowed) and extra-retinal vessels extending from the retina into the vitreous and judged to be a sign of active ROP disease.

- Vessel dilation of plus disease in at least 2 quadrants of the eye was reported for 3 patients overall, all in the ranibizumab 0.1 mg group (4.3 %). Of those 3 patients, 2 patients were reported with ROP Zone I, and 1 patient was reported with ROP Zone II at Baseline.
- Extra-retinal vessels extending from the retina into the vitreous and judged to be a sign of active ROP disease was not reported for any patient at 24 weeks after the first study treatment.

Unfavourable structural outcomes in either eye at or before the 24-week visit

Unfavourable structural outcomes (as defined below) in either eye at or before the 24-week assessment visit were less common in the ranibizumab 0.2 mg group (1 patient, 1.4 %) than in the ranibizumab 0.1 mg (5 patients, 6.7 %) and laser (7 patients, 10.1%) groups:

- Retrolental membrane obscuring the view of the posterior pole was not reported for any patient in any treatment group.
- The proportion of patients with substantial temporal retinal vessel dragging causing abnormal structural features/macular ectopia was numerically lower in the ranibizumab 0.2 mg group (1 patient, 1.4 %) than in the ranibizumab 0.1 mg group (3 patients, 4.0 %) and the laser group (4 patients, 5.8 %).
- Posterior retinal fold involving the macula occurred only in the ranibizumab 0.2 mg (1 patient, 1.4 %) and laser (2 patients, 2.9 %) groups
- Retinal detachment involving the macula occurred only in the ranibizumab 0.1 mg (3 patients, 4.0 %) and laser (3 patients, 4.3 %) groups.

Recurrence of ROP receiving any post-baseline intervention at 24 weeks or before

The proportion of patients with recurrence of ROP receiving any post-baseline intervention at or before 24 weeks (i.e. ranibizumab re-treatment or switch to laser in the ranibizumab groups, switch to ranibizumab treatment in the laser group) was comparable in both ranibizumab groups (23/74 patients (31.1 %) for ranibizumab 0.2 mg and 24/77 patients (31.2 %) for ranibizumab 0.1 mg). In the laser group, 14/74 patients (18.9 %) received post-baseline study treatment.

Number of ranibizumab administrations needed in the treatment of patients with ROP

In the ranibizumab groups, approximately 3/4 of patients (78.1 % in the ranibizumab 0.2 mg group and 77.6 % in the ranibizumab 0.1 mg group) received only an initial ranibizumab treatment, whereas slightly less than 1/4 of patients required re-treatment. The mean number of injections/patient was similar in the 2 ranibizumab groups (2.4 injections in the ranibizumab 0.2 mg group vs. 2.5 injections in the ranibizumab 0.1 mg group). In the laser group 13/69 patients (18.8 %) switched to ranibizumab treatment and received a mean of 2.2 ranibizumab injections/patient).

Pharmacokinetic/pharmacodynamic and immunogenicity results

After intravitreal administration, ranibizumab was detected in serum, with highest mean concentrations generally achieved on Day 1, within 24 hours after injection. Mean ranibizumab serum concentrations on Day 1 were approximately twice as high in the ranibizumab 0.2 mg group compared to the ranibizumab 0.1 mg group. Day 29 mean concentrations were about 14-fold and 17-fold lower than Day 1 levels, respectively, while corresponding median concentrations were 7-fold and 8-fold lower in the ranibizumab 0.2 mg group and ranibizumab 0.1 mg group, respectively. Serum concentrations overall (across dose groups and time) demonstrated a high individual variation.

Across treatment groups, there was a trend for a reduction in systemic VEGF concentrations between Day 1 and Day 15, with return toward Baseline by Day 29. Similar VEGF profiles were observed for ranibizumab- and laser-treated patients, despite a high variability in the VEGF data.

Anti-ranibizumab antibodies after treatment with ranibizumab 0.2 mg were detected in 7.0 % (3/43), 2.4 % (1/42) and 9.7 % (3/31) of patients on Days 1, 15, and 29, respectively. The corresponding percentages after ranibizumab 0.1 mg treatment were 4.5 % (2/44), 5.3 % (2/38) and 8.3 % (2/24), indicating a low incidence of anti-ranibizumab antibodies.

Safety results

Ocular and systemic safety of intravitreal ranibizumab 0.1 mg and 0.2 mg in the treatment of ROP

Generally, the incidence of ocular and non-ocular AEs as well as ocular and non-ocular serious adverse events (SAEs) was balanced across treatment groups.

Non-ocular AEs and SAEs were generally typical comorbidities in preterm infants, and no clinically relevant differences were seen between treatment groups.

Ocular AEs

Overall, 76 patients (34.9 %) experienced ocular AEs, with no clinically relevant differences between treatment groups. The most frequent ocular AE overall was retinal haemorrhage (23 patients, 10.6 %), followed by conjunctival haemorrhage (14 patients, 6.4 %), conjunctivitis (10 patients, 4.6 %), and ROP (8 patients, 3.7 %).

The majority of ocular AEs were mild or moderate in severity; severe ocular AEs were reported for 2 patients (2.7 %) in the ranibizumab 0.2 mg group, 1 patient (1.3 %) in the ranibizumab 0.1 mg group, and 2 patients (2.9 %) in the laser group. Of those 5 patients with severe ocular AEs, 4 patients had severe events of ROP (1 patient in the ranibizumab 0.2 mg group, 1 patient in the ranibizumab 0.1 mg group, and 2 patients in the laser group). Other severe ocular AEs included atrophy of globe, exophthalmos, endophthalmitis, eye disorder, orbital infection (all experienced by the same 1 patient in the ranibizumab 0.1 mg group) and nystagmus (1 patient in the ranibizumab 0.2 mg group).

The most common related ocular AE, conjunctival haemorrhage, occurred more frequently with ranibizumab compared to laser (6 patients (8.2 %) in the ranibizumab 0.2 mg group and 6 patients (7.9 %) in the ranibizumab 0.1 mg group vs. 2 patients (2.9 %) in the laser group). All other related ocular AEs occurred with low incidences (< 3 % overall) and in comparable proportions of patients across treatment groups.

Overall, 9 patients (4.1%) experienced at least one ocular SAE. There were no clinically relevant differences between treatment groups. The most frequent ocular SAE was ROP (6 patients, 2.8 % overall).

There were no ocular AEs leading to permanent study discontinuation.

Non-ocular AEs

Overall, 177 patients (81.2 %) experienced non-ocular AEs, with no clinically relevant differences between treatment groups; the most frequent non-ocular AEs by preferred term were pyrexia (19 patients, 8.7 %), dermatitis diaper (18 patients, 8.3 %), anemia (18 patients, 8.3%), and nasopharyngitis (18 patients, 8.3 %).

Severe non-ocular AEs were reported for 44 patients (20.2 %) overall (17 patients (23.3 %) for ranibizumab 0.2 mg, 15 patients (19.7 %) for ranibizumab 0.1 mg, 12 patients (17.4 %) for laser), with no relevant differences between treatment groups. The majority of these severe AEs occurred in 1 or 2 patients only.

The incidence of non-ocular SAEs was similar across treatment groups (70 patients, 32.1 % overall; 24 patients (32.9 %) in the ranibizumab 0.2 mg group; 24 patients (31.6 %) in the ranibizumab 0.1 mg group; 22 patients (31.9 %) in the laser group); the most common non-ocular SAEs by preferred term were pneumonia, bronchiolitis, and bronchopulmonary dysplasia (all 6 patients (2.8 %) overall), followed by apnoea and respiratory failure (both 4 patients (1.8 %) overall).

The only non-ocular AE suspected to be related to study treatment was an SAE of respiratory failure (with fatal outcome) in the ranibizumab 0.1 mg group.

Overall, 12 patients (5.5 %) died during the study, with similar proportions across treatment groups (4 patients in each group). The most commonly affected primary SOC was respiratory, thoracic and mediastinal disorders (5 patients (2.3 %) overall; 2 patients (2.7 %) in the ranibizumab 0.2 mg group, 1 patient (1.3 %) in the ranibizumab 0.1 mg group and 2 patients (2.9 %) in the laser group), followed by infections and infestations (3 patients (1.4 %) overall; 2 patients (2.7 %) in the ranibizumab 0.2 mg group, 1 patient (1.3 %) in the ranibizumab 0.1 mg group and 0 patients (0 %) in the laser group).

Except for 1 event of respiratory failure, none of the events leading to death was suspected by the Investigator to be related to study treatment.

In addition, there was 1 patient (in the ranibizumab 0.2 mg group; 1.4%) who experienced a non-ocular AE leading to permanent study discontinuation (AE of gastroenteritis).

Other safety assessments

No safety concerns arose from laboratory safety parameters and vital sign/physical examination assessments.

2.3.3. Discussion on clinical aspects

Efficacy

Ranibizumab was efficacious in the treatment of ROP. 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 unfavourable structural outcomes in both eyes 24 weeks after the first study treatment) compared with laser therapy, which can be considered clinically relevant even though the primary endpoint did not demonstrate statistical significance as the one-sided p-value 0.0254 was marginally above the significance level of 0.025. As a consequence of the sequential testing strategy, the key secondary objectives were not analysed.

In a sensitivity analysis where missing outcomes of active ROP and unfavourable structural outcomes at Week 24 were imputed from the results observed at the Week 20 visit, treatment success was statistically significantly higher for ranibizumab 0.2 mg when compared with laser (OR 2.22, 95 % CI [1.0088, 4.8890], p=0.0230). This sensitivity analysis resulted in the inclusion of 3 additional patients in the analysis (2 patients from the ranibizumab 0.2 mg group and 1 patient from the laser group), of which 1 patient (from the ranibizumab 0.2 mg group) was imputed from missing to success, whereas the other 2 patients remained failures.

Other secondary efficacy endpoints were also in favour of ranibizumab treatment. Among the patients receiving ranibizumab 0.2 mg at Baseline, 14.9 % needed additional intervention with another treatment modality and only 1 patient had unfavourable structural outcomes at Week 24; these unfavourable structural outcomes are associated with poor vision in the long term and thus important predictors of the vision.[2] In contrast, among the patients receiving laser treatment at Baseline, 24.3 % required intervention with another treatment modality, and 10.1 % had unfavourable structural outcomes at Week 24.

The proportion of patients with recurrence of ROP, as defined as any post-baseline study intervention up to 24 weeks after initial treatment (i.e. ranibizumab re-treatment or switch to laser in the

[2] McLoone et al. 2006

ranibizumab groups, switch to ranibizumab treatment in the laser group), was higher in both ranibizumab groups than in the laser group (31.1 % and 31.2 % vs. 18.9 %). This may be explained as laser photocoagulation therapy is known to destruct peripheral tissue responsible for continuous elevation of VEGF. Hence it is hypothesised that laser photocoagulation, albeit unable to inhibit existing excessive VEGF and therefore having a slower onset, may minimise the risk of ROP recurrence at the cost of an increased risk for less favourable structural and visual outcome.

Safety

In the laser group 13/69 patients (18.8 %) switched to ranibizumab treatment (with a mean of 2.2 injections/patient) compared with 11/73 patients (15.1 %) and 10/76 patients (13.2 %) in the ranibizumab groups who switched treatment modality. The mean number of injections/patient was similar in the 2 ranibizumab groups (2.4 injections in the ranibizumab 0.2 mg group vs. 2.5 injections in the ranibizumab 0.1 mg group).

The incidence of ocular and non-ocular AEs and SAEs was generally balanced across treatment groups. The only PT consistently reported at a higher incidence in the ranibizumab groups than in the laser group was conjunctival haemorrhage. None of the events of conjunctival haemorrhage was severe in intensity or considered an SAE.

Apart from conjunctival haemorrhage (6.4 % overall), very few AEs were suspected by the Investigator to be related to study treatment or procedure (13.3 % overall for ocular AEs, 0.5 % for non-ocular AEs).

Non-ocular AEs and SAEs were generally typical comorbidities in preterm infants, and no clinically relevant differences were seen between treatment groups.

No safety concerns arose from laboratory safety and vital sign/physical examination assessments.

Conclusions

• Ranibizumab 0.2 mg was an efficacious treatment for preterm neonates with ROP; patients treated with ranibizumab 0.2 mg were 2 times more likely to achieve treatment success compared with laser therapy, which is considered clinically relevant.

• Ranibizumab treatment is safe and well tolerated in patients with ROP. The observed safety profile was as expected in a preterm population, and ocular AEs/SAEs were generally consistent with the established profile for ranibizumab in adults.

• The benefit–risk profile of ranibizumab remains positive also for the ROP indication.

Considering the results of the study and the high unmet medical need for new treatment options for ROP patients, Novartis intends to submit a Type II variation to reflect the study results in the EU SmPC.

3. Rapporteur's overall conclusion and recommendation

The submitted study is part of clinical development programme and was carried out according to the Paediatric Investigation Plan of Lucentis. Ranibizumab was found efficacious in treatment of retinopathy of prematurity.

An 80.0 % treatment success was observed in the ranibizumab 0.2 mg group, compared with 75.0 % in the ranibizumab 0.1 mg group and 66.2 % in the laser group. However, the one-sided p-value 0.0254 for the primary endpoint was above the significance level of 0.025. The finding may be argued

to be clinically relevant as, compared with laser therapy, the patients treated with ranibizumab 0.2 mg were 2 times more likely to achieve treatment success. The findings of higher treatment success were further supported by sensitivity analyses.

First, the imputed value of the missing ocular criterion at Week 24 was derived from the value at Week 20. This affected 3 patients, 2 patients in the ranibizumab 0.2 mg group (1 patient who was imputed from missing to success and 1 patient who remained failure due to death) and 1 patient in the laser group (who remained failure due to switch). In this sensitivity analysis, treatment success was higher in the ranibizumab 0.2 mg group compared with the laser group (80.3 % vs. 66.2 %; OR 2.22, 95 % CI [1.0088, 4.8890]), and the difference was statistically significant (p=0.0230).

Second, also other sensitivity analyses (with missing data not imputed, missing data imputed as 'success', missing data imputed as 'failure', and using sensitivity logistic regression) confirmed the results of the primary analysis, with the highest treatment success observed in the ranibizumab 0.2 mg group, followed by the ranibizumab 0.1 mg and laser groups.

Among patients receiving ranibizumab 0.2 mg, 14.9 % needed additional intervention with another treatment modality and only 1 patient (1.4%) had unfavourable structural outcomes at or before Week 24. Among the patients receiving laser treatment at Baseline 24.3 % required intervention with another treatment modality and 7 patients (10.1 %) had unfavourable structural outcomes.

On the other hand, the proportion of patients with recurrence of ROP, as defined as any post-baseline study intervention up to 24 weeks after initial treatment (i.e. ranibizumab re-treatment or switch to laser in the ranibizumab groups, switch to ranibizumab treatment in the laser group), was higher in both ranibizumab groups than in the laser group (31.1 % and 31.2 % vs. 18.9 %).

The incidence of ocular and non-ocular AEs and SAEs was balanced across treatment groups, and the safety profile was as expected in a preterm population. The ocular AEs/SAEs were consistent with the established profile for ranibizumab in adults.

Although the result for the primary endpoint did not reach statistical significance, the overall findings indicate clinical benefit in the treatment of retinopathy of prematurity. Considering the role of VEGF in the pathogenesis of ROP, the findings are biologically, pharmacologically and medically plausible and ranibizumab could thus be an alternative to laser treatment. However, before any conclusions on the benefit can be made it will be necessary to evaluate follow-up data. In particular, the recurrence of ROP and the need for re-treatments in the ranibizumab groups are important concerns. Although the unfavourable structural changes in ROP are key predictors of the vision, and ranibizumab has demonstrated treatment success, only long term follow-up will confirm the final outcome of the study treatments regarding visual acuity.

☒ Fulfilled:

No further action required, however, further data are expected in the context of a variation prior any conclusion on product information amendments is made. The MAH should commit to submit this variation application by 31 December 2018.

The variation should reflect the results of the submitted study and, in particular, the follow-up results from the predefined interim analysis of the long-term safety study as described in the paediatric investigational plan (EMEA-000527-PIP04-13-M01).

Annex. Line listing of the studies included in the development program

The studies listed by chronological date of completion:

Clinical studies

Product Name: Lucentis Active substance: ranibizumab

Study title	Study number	Date of completion	Date of submission of final study report
A randomized, open-label, controlled, multicenter study evaluating the efficacy and safety of ranibizumab compared with laser therapy for the treatments of infants born prematurely with retinopathy of prematurity (ROP)	CRFB002H2301	14 December 2017 (LPLV)	May 2018
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 (ROP)	CRFB002H2301E1	Ongoing	The planned completion date of the study is Q4/2022. An interim analysis report is expected to be submitted by Q4/2018 with the variation application.