25 July 2019
EMA/CHMP/406682/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lucentis

International non-proprietary name: ranibizumab

Procedure No. EMEA/H/C/000715/II/0074/G

Note

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

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Table of contents

List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
AMD	Age-related macular degeneration
AP-ROP	Aggressive posterior retinopathy of prematurity
AUC	Area under the curve
BEAT-ROP	Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity trial
CARE-ROP	Comparing Alternative Ranibizumab Dosages for Safety and Efficacy in Retinopathy of Prematurity trial
CE	Conformité Européene (European Conformity)
CI	Confidence interval
CNV	Choroidal neovascularization
DME	Diabetic macular edema
EMA	European Medicines Agency
ETROP	Early Treatment for Retinopathy of Prematurity trial
EU	European Union
IA1	First interim analysis for the RAINBOW Extension Study (H2301E1)
ISO	International Organization for Standardization
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MPA	Medical Products Agency (Sweden)
OR	Odds ratio
PDCO	Paediatric Committee
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
RMP	Risk Management Plan
ROP	Retinopathy of prematurity
RVO	Retinal vein occlusion
SAE	Serious adverse event
SBP	Summary of Biopharmaceutics
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
US	United States
VEGF	Vascular endothelial growth factor

The information between these lines is considered commercially confidential and may not be disclosed to third parties in accordance with the 'Principles to be applied for the deletion of commercially confidential information for the disclosure of European Medicines Agency documents'.

1. Background information on the procedure

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Limited submitted to the European Medicines Agency on 15 October 2018 an application for a group of variations.

The following changes were proposed:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB
B.IV.1.a.1	Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	Type IB	I

Extension of Indication to include new indication for Lucentis vial presentation: treatment of retinopathy of prematurity (ROP) in preterm infants; as a consequence, sections 2, 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance.
In addition, RMP version 18.0 is also submitted.

B.IV.1.a.1 – To introduce a low volume high accuracy syringe, as a stand-alone medical device for the administration of the Lucentis 0.2 mg paediatric dose (corresponding to 0.02 ml of the Lucentis 10 mg/ml solution for injection in vial presentations).

The requested group of variations proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0010/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0010/2017 was completed and the PDCO issued an opinion on compliance for the PIP P/0010/2017.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products, because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek scientific advice from the CHMP but did ask national scientific advice from the Rapporteur's Agency MPA (SE) in June and August 2018.

2. Recommendations

Based on the review of the submitted data, this application regarding the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB
B.IV.1.a.1	Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	Type IB	I

Extension of Indication to include: A new indication for Lucentis vial presentation: treatment of retinopathy of prematurity (ROP) in preterm infants; as a consequence, sections 2, 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance.
In addition, RMP version 18.0 is also submitted.

Introduction of a low volume high accuracy syringe, as a stand-alone medical device for the administration of the Lucentis 0.2 mg paediatric dose (corresponding to 0.02 ml of the Lucentis 10 mg/ml solution for injection in vial presentations)

☒ is recommended for approval.

The information after this line is considered commercially confidential and may not be disclosed to third parties in accordance with the 'Principles to be applied for the deletion of commercially confidential information for the disclosure of European Medicines Agency documents'.

3. Scientific discussion

3.1. Introduction

Ranibizumab is a recombinant humanised IgG1 κ isotype monoclonal antibody fragment (Fab) that selectively binds and neutralises vascular endothelial growth factor (VEGF)-A. Binding of VEGF-A to its receptors triggers angiogenesis and neovascularisation by promoting vascular endothelial cell proliferation/ migration and an increased vascular permeability resulting in leakage. The neutralisation of VEGF results in a reduced vascular leakage.

Lucentis (ranibizumab) is registered via Centralised Procedure (EMEA/H/C/000715) and is indicated in adults for:

- the treatment of neovascular (wet) age-related macular degeneration (AMD),
- the treatment of visual impairment due to choroidal neovascularisation (CNV),
- the treatment of visual impairment due to diabetic macular oedema (DME), and
- the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO).

Problem statement

The pathophysiology of ROP is characterised by abnormal neovascularisation. The disruption of angiogenesis in preterm infants with ROP typically occurs in 2 postnatal phases (Hellström et al 2013). In Phase 1 (~22 to 30 weeks postmenstrual age), high oxygen saturation in the immature retina (relative hyperoxia), coupled with low concentrations of growth factors and nutrients normally present *in utero* during the third trimester of pregnancy, lead to suppression of new vessel growth. As a result, the metabolically active but poorly vascularised retina becomes hypoxic. In Phase 2 (~31 to 44 weeks postmenstrual age), the hypoxic environment in the retina stimulates release of various angiogenic factors, such as vascular endothelial growth factor (VEGF), that lead to proliferation of new blood vessels. In preterm infants with disrupted angiogenesis, the abnormal neovascularisation and the leaky new blood vessels formed in this environment result in intraocular fibrosis, leading to retinal distortion, detachment, and visual disability.

A regulator of angiogenesis, VEGF, plays a key role in the progression of ROP and is involved in both phases of ROP pathophysiology. The levels of VEGF differ in the two phases of abnormal neovascularisation and are associated with different outcomes. Suppression of VEGF by non-physiologically high tissue oxygenation in Phase 1 of ROP inhibits normal vessel growth, whereas upregulation of VEGF induced by relative hypoxia in Phase 2 of ROP leads to pathological neovascularisation (Chen and Smith 2007). Excessive levels of VEGF lead to abnormal vascular proliferation and ultimately, if left untreated, to retinal detachment, which may result in blindness.

Treatment modalities targeted toward reducing VEGF levels have the potential to halt and reverse the hypoxic neovascular response (Smith 2008). Intravitreal injection of neutralising anti-VEGF antibodies had demonstrated a significant reduction in the neovascular response in animal studies (Aiello 1995). Higher ocular VEGF levels have been detected in the vitreous of ROP patients and are associated with more severe disease (Lashkari 2000, Sonmez et al 2008). Several publications have reported the successful treatment of infants with ROP with anti-VEGF agents (e.g. Mintz-Hittner et al 2011, Stahl et al 2018).

There is no approved medicinal treatment for ROP and the current standard of care is laser ablation therapy, which is effective, but ablation of the retina results in restricted visual fields.

The development programme and Compliance with CHMP Guidance/Scientific Advice

Development program

- No new preclinical studies have been submitted.
- Biopharmaceutical development.

For the proposed new indication, a low-volume, high-accuracy syringe for administration of a fixed volume of 20 µl of Lucentis® solution for injection, corresponding to a dose of 0.2 mg, for the treatment of the paediatric population via intravitreal injection, was developed. Development of a low-volume, high-accuracy syringe is part of the European Medicines Agency (EMA) Paediatric Investigation Plan (PIP) for ranibizumab (Lucentis).

- Clinical development programme (see Section 5.4).

Study H2301 (RAINBOW, Core study) A randomized, open-label, three-arm parallel-group study to determine if intravitreal ranibizumab is superior to laser ablation therapy in the treatment of ROP. In addition, two doses of ranibizumab are investigated (0.1 mg and 0.2 mg).

Study H2301E1 (RAINBOW extension) is a currently ongoing Extension Study evaluating the long-term efficacy and safety of ranibizumab 0.2 mg and 0.1 mg compared with laser therapy in treatment of ROP, 40 weeks post baseline visit in core study. Patients were eligible to participate in the Extension Study H2301E1 if they had successfully completed the 24-week Core Study H2301.

The remainder of the Extension Study is observational.

Both studies are part of the European Medicines Agency (EMA) Paediatric Investigation Plan (PIP) for ranibizumab (Lucentis) (PIP EMEA-000527-PIP04-13-M01). The positive opinion and report on the final PIP compliance check was received on 29 October 2018.

Compliance with CHMP guidance/Scientific Advice

A national advice was provided by the Swedish MPA on 08 June 2018 with a follow-up advice on 29 August 2018.

It was emphasised that it should be demonstrated that ranibizumab has no detrimental effects on visual function and that ranibizumab has a favourable outcome on visual function in the long-term compared with laser treatment. Subsequently, the clinical study protocol was amended to address these issues including the collection of additional visual function data (CRFB002H2301E1 v01, 31-Jul-2018).

3.2. Quality aspects

3.2.1. Pharmaceutical Development (3.2.P.2)

Novartis has recently developed a low-volume, high-accuracy syringe for administration of a fixed volume of 20 µl of Lucentis solution for injection, corresponding to a dose of 0.2 mg, for the treatment of the paediatric population via intravitreal injection. The low-volume high-accuracy syringe will be provided as a standalone device to be used in combination with Lucentis 10 mg/ml solution for injection in vial. The low-volume syringe will be provided together with an injection needle in the VISISURE device box.

The low-volume, high-accuracy syringe is sterile and intended to be used in combination with the registered presentations of Lucentis solution for injection in vials and the recommended devices: an 18-G × 1½-inch filter needle and a 30-G × ½ inch injection needle.

The syringe development consisted of a series of device prototypes leading to the final validated device design that meets the requirements of the device suitable to be placed on the market. This syringe was designed for accurate administration of a defined volume of 20 µl.

To minimise user variability and improve consistency between injections, the syringe includes a small-diameter barrel and a dose control feature, which ensures a fixed, pre-defined travel distance of the plunger. Based on the syringe design features, technical criteria and usability studies, this syringe is considered to be appropriate for the intravitreal delivery of the drug product to neonates.

The functionalities of the low-volume, high-accuracy syringe and 1-ml Plastipak™ syringe from Becton Dickinson, a syringe that has been used with Lucentis in clinical investigations involving paediatric population, are substantially equivalent for the intended use. Therefore, it is expected that the safety and efficacy profiles for both devices would be equivalent in the intended paediatric population; however, only the low-volume, high-accuracy syringe is intended for commercialisation as a standalone device for use with the paediatric population in the European Union.

Dose accuracy data obtained for the two syringes using the same gravimetric test and a target volume of 20 µl are provided below. In addition, information on compatibility of the drug product with the low-volume, high-accuracy syringe is provided. Information on compatibility of the drug product with 1-ml Plastipak syringe, a syringe that has been used for administration of Lucentis solution for injection to the adult population, is already filed in current section 3.2.P.2 and is not provided in this section dedicated to information on paediatric device development.

Dose accuracy

Dose accuracy testing was conducted on the CE-marked low-volume, high-accuracy syringe. The testing was carried out on three syringe lots that were filled by the test operator with two batches of Lucentis solution for injection. The analytical procedure used for testing was based on a gravimetric determination of the amount of liquid expelled from a syringe. The testing was conducted in a manner and under the conditions that are representative of proposed use, such as following proposed instructions for use and using an 18-G × 1½-inch filter needle and a 30-G × ½-inch injection needle. The target volume was set at manufacture to 20 µl.

The results show that the expelled volume for all samples tested was within the requirements set and consistent among the syringe lots and Lucentis batches tested. The expelled volumes observed as part of this testing are within the range of volumes observed for syringes used in paediatric clinical investigations with Lucentis with a target volume of 20 µl

The dose accuracy results for - syringe lots used in paediatric clinical investigations show that expelled volumes for two target volumes for individual syringe lots remain well differentiated with a low incidence of overlapping volumes.

Dosing errors/human factor study

Information on human factor studies is provided in section 3.2.P.2, accompanied by a summary included in subsection 5 (‘Human factor studies conducted for low-volume, high-accuracy syringe’) of section 3.2.P.2.

In brief, based on the human factors engineering evaluation studies, a comprehensive use-related risk analysis, a risk-benefit analysis and planned risk mitigation measures as presented in section 3.2.P.2,

Novartis considers that the low-volume high-accuracy syringe provided in the VISISURE device kit is reasonably safe and effective for the intended users, uses and use environments.

Following completion of human factors engineering evaluation studies, the instructions for use (unbranded) and a reminder card for the low-volume, high-accuracy syringe were submitted for information only.

Summary of human factor studies conducted for low-volume, high-accuracy syringe

The human factors engineering (HFE)/usability engineering activities undertaken during the development of the low-volume, high-accuracy syringe for delivery of 0.02 mL as part of VISISURE device kit were carried out in accordance with the IEC 62366-1:2015-part 1. The VISISURE device kit consists of the low-volume, high-accuracy syringe, a 30G (½ inch) injection needle, instructions for use (IFU) and a reminder card (a supportive labelling that outlines key use steps for the syringe).

Several HFE formative evaluation studies have been performed during the development of the VISISURE device kit to guide the device design and device kit labelling (that includes IFU and reminder card) and to gain confidence that the design has been optimized for safe and effective use. Details on the last two HFE formative evaluation studies, which have been performed with the devices, labelling and training materials similar to those of the final VISISURE device kit were submitted by the MAH.

In parallel to optimizing the design and conducting HFE activities during the development, use-related risks associated with the VISISURE device kit were iteratively analysed, updated and mitigated according to Novartis risk management procedures following ISO 14971 standard.

Finally, an HFE summative evaluation study was performed in four countries (UK, Spain, Germany and Italy) to collect evidence that the intended users are able to safely and effectively use the VISISURE device kit after receiving representative device training and following a representative time decay period.

A total of fifteen ophthalmologists/retinal surgeons and fifteen ophthalmic assistants participated in the HFE summative evaluation study. The ophthalmologists/retinal surgeons were trained on the use of the VISISURE device kit one to seven weeks prior to the evaluation session with the training material corresponding to device labelling.

The study was a non-interventional, simulated human factors evaluation requiring bilateral injection (two injections: one injection in each eye) in a simulated environment. The VISISURE device kit was made available to the participants during the evaluation session. According to the MHRA guidelines (Guidance for Medical Devices Including Drug-Device Combination Products, version 1.0, September 2017), the participants were not prompted to read the device labelling just prior to the evaluation.

The ophthalmologists/retinal surgeon participants' ability to use the VISISURE device kit with the specimen of Lucentis "vial + filter needle pack" presentation (anonymized and including the representative double-sided leaflet for adults and preterm infants) to simulate the preparation and injection into a "mock-up neonate" was assessed.

Overall, based on the evaluation, twenty-five out of thirty participants (ophthalmologists/retinal surgeons and ophthalmic assistants) successfully performed their respective steps without any use errors on the first evaluation and twenty-four out of thirty participants successfully performed the second evaluation without any use errors. The majority of the participants accurately delivered the dose of 0.02 mL within the tolerance limit.

Specifically focusing on the dose delivery, twelve out of fifteen ophthalmologists withdrew enough drug and also performed the air-liquid separation and removal of air bubbles correctly to give the intended dose (within the intended dose tolerance limit). Three out of fifteen (20%) withdrew enough drug but

performed the air-liquid separation step incorrectly (held the syringe not according to the IFU, i.e. incorrect orientation of the syringe) on both injections resulting in potential delivery of no dose to the patient. Later, during the root cause analysis or while looking at the instructions for use, two out of these three realised their use error for this step.

All the findings of the summative study were incorporated into the comprehensive medical device risk assessment. The outcome of this risk assessment resulted in:

- Modifications of the risk control measures outlined in the IFU, reminder card and corresponding education support for air-liquid separation step:

– by emphasising (pictorially and in text) the orientation of the syringe when performing the air-liquid separation technique

– by including caution statement in the IFU that non-compliance to the instructed air-liquid separation step in the IFU could result in an inaccurate dose and therefore strongly convey this message.

- Elaboration of an institutional educational plan to provide an educational support to institutions explaining how to use the low-volume, high-accuracy syringe for Lucentis administration to the paediatric population. This also reinforces that the specific low-volume, high-accuracy syringe as part of the VISISURE device kit has to be used for the paediatric indication, as instructed in the Lucentis vial patient leaflet.

Based on the updated risk assessment, a risk-benefit analysis was performed for the residual risks of using the VISISURE device kit. The benefits of using the VISISURE device kit, when used as intended, include high accuracy and high precision in delivering the prescribed 0.02 mL dose. The increase in the precision is by reducing the user's variability by design and the repeatability compared to the state-of-the-art syringes. Of the residual risk, in case the treatment effect is not satisfying (including use errors, which could result in administration of an incorrect dose among other reasons of unsatisfactory treatment), the ophthalmologist identifies disease progression during the frequent check-ups, and if required will apply the current standard of care – laser ablation.

However, besides the undesirability of undue treatment delays due to inappropriate dosing of ranibizumab which are not mentioned by the company, it should also be considered that inappropriate syringe preparation before intravitreal treatment could result in intravitreal air bubbles. It has been reported that this may be associated with potential serious complications in premature infants with ROP (e.g. Sukgen et al. Int Ophtalmol. 2017. 37;1:215-9). According to the authors, when considered the vitreous volume of the eye of the premature baby, the presence of air bubbles would easily cause elevated intraocular pressure (IOP) and subsequent compromised ocular perfusion; alternatively, air bubbles may cause sterile inflammatory reactions.

Accordingly, the MAH was asked to repeat an evaluation of the current instructions for use, to evaluate whether the changes that have been made have improved the correct use of the device. This additional evaluation assessed the impact of the changes made to the instructions for use (IFU), the reminder card and corresponding training materials for the VISISURE device kit, containing the low-volume, high-accuracy syringe, on the use of the syringe. A particular emphasis was made on the air-liquid separation step.

The evaluation was a non-interventional, simulated human factors evaluation requiring bilateral injection. The design of this evaluation was similar to the one used for the summative evaluation, including training and evaluation sessions that were separated by a decay period of 3 to 5 weeks. However, only ophthalmologists/retinal surgeons were evaluated as part of the HFE evaluation as changes made to the IFU, the reminder card and training materials affected only this user group. A

total of 15 ophthalmologists/retinal surgeons participated in this HFE evaluation. Similarly to the initial HFE summative evaluation, this HFE formative evaluation was a non-interventional, simulated human factors evaluation requiring bilateral injection (two injections: one injection in each eye) in a simulated environment. Overall, 15 out of 15 (100%) participants performed the air-liquid separation step successfully. All the participants held the syringe in the correct orientation. Additionally, no new use errors associated with the modified IFU, RC and corresponding training material were observed although one new use error was observed related to the 'assemble the injection needle onto the syringe step'. However, this error was likely not related to the changes made in the training materials.

The HFE evaluation results confirm that the risk mitigation measures to update the IFU for the VISISURE device kit are effective and significantly improved usability of the CE-marked syringe included in the VISISURE device kit. Based on the HFE evaluations and comprehensive use-related risk analysis, the VISISURE device kit used with Lucentis vial kit is safe and effective for the intended users, uses and use environments.

Compatibility

The low-volume, high-accuracy syringe has been shown to be physically and chemically compatible with the drug product. The evaluation of compatibility was based on a comparison of the results of analysis of Lucentis (batch S0043 885607) that was either subjected to contact with a syringe (incubation for 1 h) or not subjected to such contact.

The preparation of samples in syringes was conducted by following proposed instructions for use and using an 18-G × 1½-inch filter needle and a 30-G × ½-inch injection needle.

The compatibility data for the low-volume, high-accuracy syringe presented in the variation are consistent with those provided for 1 ml syringe in the registration package for ranibizumab submitted in year 2006. Section [3.2.P.2] of the dossier was updated to include relevant additional data on appearance (subsection 4 'Evaluation of compatibility of low-volume, high-accuracy syringe'). The data on appearance were obtained using the same batch of ranibizumab drug product as the one that was used to generate the compatibility data presented in section 3.2.P.2, which was provided as part of the variation.

Section [3.2.P.2] of the dossier was updated to include relevant information on the device

According to the variation guideline (2013/C 223/01), for a type I.B.IV.a.1 variation to add a CE-marked administration device, which is not an integrated part of the primary packaging, documentation on leachables is not required. Leachables study is part of the pre-requisite for CE-marking of the device and supports the general use of the device. Hence, the information was not provided as part of the initial submission for variation EMEA/H/C/000715/II/0074/G.

However, section [3.2.P.2] of the dossier was updated to include information on leachables (subsection 4 'Evaluation of compatibility of low-volume, high-accuracy syringe'). Observed leachables can be regarded as of no concern from a toxicological point of view, confirming that the syringe is suitable for use with the drug product to the same degree as 1 ml Plastipak™ syringe from Becton Dickinson, which was used in Study H2301 and is already available on the market and used for administration of the treatment with ranibizumab to the adult population.

Novartis confirms that the filter needle (or '18-G × 1½-inch filter needle' as mentioned in section 3.2.P.2) co-packed in the registered ranibizumab presentation (EU/1/06/374/004) has been used in compatibility testing of the low-volume, high-accuracy syringe as stated in section [3.2.P.2]. Thus, this filter needle (Becton Dickinson blunt filter needle, reference number 305211) is considered to be compatible with the syringe.

The compatibility data presented are representative of and support the intended use of the VISISURE device kit, including the low-volume, high-accuracy syringe and the injection needle, which is fully compatible with all currently registered ranibizumab vial presentations.

Labelling information and/or instructions for use (IFU) for a stand-alone device regulated under Directive 93/42/EEC amended by 2007/47/EC concerning medical devices were provided for the ease of assessment only. Therefore any subsequent revisions of these IFU are not considered regulatory relevant.

3.2.2. Regional (3.2.R)

The drug product vial may either be co-packed with medical devices (an individual filter needle or a filter needle with a 1 ml syringe and an injection needle) or medical devices may be provided separately (a filter needle, a syringe, an injection needle). Information on the device intended for administration with a low volume high accuracy syringe, which is CE-marked according to the Council Directive 93/42/EEC, is provided in Table R-1 below.

Table R-1 Medical device used with Lucentis solution for injection in a vial intended for administration with a low volume high accuracy syringe

Syringe §	Low-volume, high-accuracy syringe. The syringe consists of a syringe barrel, a plunger stopper, a plunger rod and a dose clip	Is	Novartis [Declaration of conformity]

§ This syringe is to be used for administration of the drug product only to a pediatric population (see [3.2.P.2])

Additional information on co-packed medical devices is provided in section 'Container Closure System' [3.2.P.7]. Information on the low-volume, high-accuracy syringe that is to be used for administration of the drug product only to a paediatric population is provided in section [3.2.P.2].

A reference to the CE certificate issued by the Notified Body for the low volume, high-accuracy syringe has been added to Table 1-1 of section [3.2.R]. In addition, a reference to the name/identity of the device (i.e. low-volume, high-accuracy syringe for delivery of 0.02 ml) that matches that stated on the EC certificate and Declaration of conformity has been added to Table 1-1 of section 3.2.R.

The original 52 certificate that was issued on October 3, 2018 by the Notified Body (BSI Assurance UK Limited) located in the UK. Due to Brexit, certification for the low-volume, high-accuracy syringe was transferred from BSI Assurance UK Limited, a Notified Body located in the UK, to BSI Group The Netherlands B.V., a Notified Body located in the Netherlands. Thus, an updated EC certificate was issued on February 22, 2019 by the Notified Body located in the Netherlands. In addition, a new Declaration of conformity issued by Novartis on February 28, 2019 and replacing previously submitted declaration (dated October 5, 2018) is provided in section 3.2.R.

Novartis considers that the low-volume high-accuracy syringe provided in a standalone device kit to be used in combination with Lucentis 10 mg/ml solution for injection in vial complies with the applicable regulatory requirement and is in line with regulatory guidance and feedback received throughout the development of the syringe.

The MAH discussed the option to develop a pre-filled syringe in the context of providing an improved drug delivery solution for a safer and more suitable administration, to minimize medication errors in preterm infants.

The agreed Paediatric Investigation Plan (PIP) mandated the development of an age-appropriate low-volume syringe to ensure accuracy of small volume delivery (quality measure). The binding element of the PIP did not mandate the development of a pre-filled syringe (PFS), as confirmed by the opinion

adopted by the PDCO, on 19-Oct-2018, confirming the compliance with all measures in the agreed PIP, including the quality measure based on submission of an EC certificate/Declaration of Conformity pertaining to the registration of the low-volume, high-accuracy syringe.

Novartis considers the current proposal to administer Lucentis to preterm infants with retinopathy of prematurity (ROP) with the proposed low-volume, high-accuracy syringe adequate and justified on the following basis:

- The entire volume of Lucentis solution has to be withdrawn from the vial for proper preparation and accurate delivery of the dose to both adults and pre-term infants. The lost volumes from the Lucentis vial presentation are small and similar for the adult and for the preterm infant treatment. Therefore, with the low number of candidates and the frequency of treatment for the preterm population, the foreseen losses are considered negligible and acceptable.
- A new layout of the product information has been designed providing separate and specific information for the treatment of preterm infants (double-sided leaflet), ensuring clarity and readability for both patients, parents/guardians and healthcare professionals.
- Results from a new (human factors engineering) HFE study for the low-volume, high-accuracy syringe demonstrated that the new IFU and reminder card are effective risk mitigation measures and have significantly improved usability.
- Multiple measures are being proposed to ensure correct administration and use of the low volume high accuracy syringe in the paediatric population, thereby minimizing medication errors.

The current PFS technologies would not meet the dose accuracy requirement mandated by the PIP and existing technologies would not be adaptable into a pre-filled low-volume syringe. A new PFS development program has a number of technical challenges and uncertainties and would not necessarily reduce usability risks.

Based on the above, Novartis considers administration of Lucentis using the low-volume, high-accuracy syringe a safe and the most suitable option in order to ensure accuracy of small volume delivery.

After discussions with the PDCO, the agreed PIP mandated the development of an age-appropriate low volume syringe, but not a PFS

An initial PIP for the condition Retinopathy of Prematurity (EMEA-000527-PIP04-13) was submitted to the Paediatric Committee (PDCO) on 27-May-2013 and approved on 06-Aug-2014 (EMA decision P/0186/2014). The PIP included two measures for completion by December 2018:

- A clinical study to evaluate the efficacy and ocular and systemic safety of ranibizumab 0.2 mg and 0.1 mg compared to laser for the treatment of ROP (clinical measure); and
- Development of an age-appropriate low-volume syringe to ensure accuracy of small volume delivery (quality measure).

The agreed PIP did not mandate development of a PFS and acknowledged that the current adult PFS presentation was not adapted to administer the proposed low volume to preterm infants.

To address the quality measure of the PIP, Novartis has undertaken the development of a sterile, low-volume, high-accuracy syringe for the administration of a fixed volume of 20 µL with high accuracy, corresponding to the proposed 0.2 mg dose for the treatment of preterm infants with ROP.

The proposed method of administration using the low volume high accuracy syringe, which is planned to be registered as a stand-alone device and fulfils the binding quality measure of the PIP, was

discussed during a pre-submission meeting with the Swedish Medicinal Products Agency (MPA). The MPA agreed with Novartis that the low volume high accuracy syringe developed by Novartis was appropriate for the treatment of this population. MPA also agreed to the proposal of a double-sided leaflet, with one side providing information for indications in the adult population and the other side addressing the paediatric indication exclusively, in order to reduce medication errors.

The PDCO adopted an opinion confirming the compliance of all measures in the agreed PIP, including the quality measure, on 19-Oct-2018 based on submission of an EC certificate/Declaration of Conformity pertaining to the registration of the low-volume, high-accuracy syringe for the administration of a fixed volume of 20 µL.

The use of the low volume high accuracy syringe requires to empty the entire Lucentis vial content for accurate administration of both the adult and pre-term infant dose.

The recommended dose of Lucentis 10 mg/mL solution for injection is 20 µL for pre-term infants and 50 µL for adults, corresponding to a 0.2 mg dose and a 0.5 mg dose respectively.

The preparation of the low volume high accuracy syringe for administration of a 20 µL dose of Lucentis in preterm infants requires a number of steps during which some drug product solution is left in the filter needle or used for priming. In addition, the drug product solution is also captured in the low-volume high-accuracy syringe assembly due to presence of dead volumes in the syringe and the injection needle (part of VISISURE kit). Finally, in order to allow high accuracy of the syringe, the dosing has to be made only on the cylindrical portion of the syringe barrel in order to remove the variability triggered by the stopper deformation when reaching the end of the barrel. Therefore a higher dead volume is calculated in the low volume high accuracy syringe compared to conventional syringes. This would also apply to a new high accuracy PFS technology. As a consequence, to accommodate the preparation and injection of Lucentis with the low volume high accuracy syringe, a minimum volume of 0.21 mL of drug product solution in the vial is required to deliver an accurate 20 µL dose. Thus, the entire fill volume of a vial (0.23 mL) will have to be used for preparation of a dose of Lucentis to be administered to preterm infants, as prompted in the VISISURE device kit IFU.

This minimum fill volume (0.21 mL) for the low volume high accuracy syringe is very similar to the minimum fill volume required to prepare an adult dose with a 1 mL syringe (0.22 mL) for a 50 µL dose and very close to the entire fill volume of a vial (0.23 mL). Therefore, the actual discarded volumes from the Lucentis vial presentation are small and similar for the adult and for the preterm infant treatment.

With the low number of candidates and the frequency of treatment for the preterm population, the foreseen losses are considered negligible and acceptable.

The proposed product information has been designed to provide separate and specific information for the treatment of preterm infants

In order to ensure clarity and readability for both patients and healthcare professionals, Novartis has proposed a double-sided patient leaflet for the Lucentis vial presentations, with one side of the leaflet providing information for all adult indications and the other side providing paediatric specific information exclusively. This approach has been agreed during a pre-submission meeting with the Swedish MPA.

The double-sided leaflet underwent a successful focused readability test. For this test key points of information were selected from the adults and premature babies sides of the leaflet. The test demonstrated that all participants were able to find the correct side of the leaflet. The results also demonstrated that for both sides of the leaflet, at least 90% of the participants were able to find each

point of key information and at least 90% of those were able to understand it. The Lucentis leaflet therefore fulfils the EU requirements for User Testing.

Developing a new pre-filled low-volume syringe for use in preterm infants

Novartis has evaluated the feasibility to adapt existing technologies, including the Lucentis adult PFS technology, current PFS technologies available on the market and the low volume high accuracy syringe, for the development of a high accuracy PFS for low volume to treat preterm infants.

The current Lucentis PFS technology used to deliver a dose of 50 µL in indications for the adult population does not meet the dose accuracy requirement of the PIP for ROP in preterm infants. With the current adult PFS, the dose accuracy would be much wider for the preterm infant dose (at least +/- 50% for 20 µL). This is much wider than the proposed low volume high accuracy syringe dose accuracy for the administration of 20 µL, which complies with the PIP requirements.

More generally, current PFS technologies available on the market are considered less capable than the low volume high accuracy syringe to deliver accurately a 20 µL volume and would not meet the dose accuracy requirements of the PIP. Therefore, a complete new paediatric PFS development using new technologies and new materials would be necessary and is expected to be lengthy. As a reference, the adult Lucentis PFS development for the 50 µL dose lasted several years and it remains to this date the only PFS marketed for delivering anti-VEGFs for ocular use.

The low volume high accuracy syringe was initially developed as a class I, single use, sterile syringe, not intended for use as a PFS. The materials and design are not adapted for use as a PFS, considering, for example, the specific long-term compatibility and stability constraints of a PFS technology and uncertainty regarding manufacturing feasibility. To reach high accuracy, the dose control feature and the thin barrel design could potentially be integrated into a new PFS technology however would lead to similar usability risks. For instance, the same air-liquid separation step (hammer swing) would be required to remove air bubbles. Therefore, the reduction of use related risks for a new pre-filled low-volume syringe as compared to the proposed syringe would have to be demonstrated in addition.

In conclusion, the current PFS technologies would not meet the dose accuracy requirement mandated by the PIP and existing technologies would not be adaptable into a pre-filled low-volume syringe. A new PFS development program has a number of technical challenges and uncertainties and would not necessarily reduce usability risks.

Measures to ensure correct administration and use of the low volume syringe in the paediatric population

Novartis proposes a number of measures to ensure correct administration and use of the low volume high accuracy syringe in the paediatric population and thereby to minimize medication errors. These measures include

- a double- sided leaflet, referring to the low volume syringe in the VISISURE kit on the side for guardians of babies born prematurely,
- the deregistration of the 'vial + injection kit' presentation (EU/1/06/374/001) at time of EC decision and
- the introduction of an institutional educational plan.

Based on recent HFE study using VISISURE, it was demonstrated that the proposed risk mitigations to improve the VISISURE labelling and training video have been effective. These changes have significantly improved the correct use of the low volume high accuracy syringe compared to the previously provided usability data.

Based on the above provided justification, Novartis considers administration of 20 µL Lucentis to preterm infants with ROP using the low volume high accuracy syringe a safe and the most suitable option in order to ensure accuracy of small volume delivery. While it may be assumed that a PFS has the potential for reducing risk over the use of a vial and a syringe, such a risk reduction has not been demonstrated to date.

3.3. Non-clinical aspects

No Environmental Risk Assessment (ERA) has been submitted. This is justified with the protein nature of ranibizumab and after injection to the patient's eye ranibizumab is completely metabolised and adsorbed in the body. Any medicinal product that reaches water streams via eventual spills during application or after disposal of unused drug is expected to be very rapidly degraded and mineralised to CO_2. Reference is made to Directive 2001/83/EC and Guideline CHMP/SWP/4447/00 corr 2.

It is agreed that Ranibizumab is not likely to pose a risk to the environment and the justification for not submitting an ERA is accepted.

3.4 Clinical Pharmacology

3.4.1. Introduction

The clinical trials were performed in accordance with GCP and the requirements set out for the clinical trials on medicinal products conducted in paediatric populations, as claimed by the applicant.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1. Phase 3 controlled studies (completed and ongoing).

Study	Objective, population	No. of treated patients	Treatment frequency, dose and duration
H2301 (RAINBOW Core) Completed Study no: CRFB002H2301	A randomized, controlled study of the efficacy and safety of ranibizumab IVT compared with laser therapy for the treatment of infants born prematurely with retinopathy of prematurity.	Randomised treatment arms: Ranibizumab 0.2 mg (N=74) Ranibizumab 0.1 mg (N=77) Laser (N=74)	**Forms**: ranibizumab solution for injection supplied in vials. Each vial contains ranibizumab in the concentration of 10 mg/ml (RFB002 0.5/0.05 ml). Laser therapy **Duration**: 169 days. **Doses**: ranibizumab 0.2 mg Day 1 ranibizumab 0.1 mg Day 1 Laser ablation Day 1 or an additional laser ablation until 3 days after the Day 8 assessment.
H2301E1 (RAINBOW Extension) Ongoing	An Extension Study to evaluate the long-term efficacy and safety of ranibizumab IVT compared with laser therapy for the treatment	Treatment arms based on initial randomised treatment in Core Study:	**Forms**: as in the Core Study Laser therapy **Duration**: 280 days **Doses**: as in the Core Study

Study	Objective, population	No. of treated patients	Treatment frequency, dose and duration
(planned completion date of the study is Q4/2022) Study no: CRFB002H2301E1	of infants born prematurely with retinopathy of prematurity. The study is ongoing.	Ranibizumab 0.2 mg (N=61) Ranibizumab 0.1 mg (N=65) Laser (N=54) (Ns represents the numbers of patients who completed the Core Study and entered the Extension Study as of 31-Aug-2018)	

IVT = intravitreal

3.4.2. Pharmacokinetics

Descriptive statistics of systemic ranibizumab concentrations are summarised in Table 5. The sampling windows were large: Day 1, within 24 hours after the first ranibizumab administration; Day 15, window 7 to 21 days after the first administration; and Day 29, window 22 to 28 days after the first administration (on Day 1). This limits the interpretability of the descriptive statistics.

Table 2. Descriptive statistics of systemic ranibizumab concentrations (ng/ml).

Visit	Statistic	Ranibizumab 0.2 mg N=49	Ranibizumab 0.1 mg N=46
Day 1	n	43	43
	Mean (CV%)	24.7 (212%)	12.1 (210%)
	Median	7.82	4.35
	Min, Max	0.0412, 294	BLQ, 158
Day 15	n	45	36
	Mean (CV%)	5.83 (81.5%)	27.7 (519%)
	Median	4.44	3.40
	Min, Max	BLQ, 22.7	BLQ, 868*
Day 29	n	31	24
	Mean (CV%)	1.81 (165%)	0.732 (73.1%)
	Median	1.07	0.566
	Min, Max	BLQ, 16.0	BLQ, 2.22

BLQ= below limit of quantification (< 0.015 ng/mL), with imputation as 0.0 for descriptive statistics; CV= coefficient of variation.
n= number of patients who had at least one valid PK concentration value.
Treatment arms were based on actual treatment received at Day 1.
PK serum sample concentration levels of ranibizumab are assessed in patients who received initial ranibizumab treatment and with an odd patient identification number.
Day 1: Within 24 hours after the first administration of ranibizumab.
* Excluding 868 ng/mL, Max is 8.88 ng/mL.
Source: [Study H2301-Table 11-11]

Population PK

Data

The popPK and the PK/PD analyses used the CRFB002H2301 (RAINBOW) study data. The RAINBOW study is a randomised, open-label, 3-arm, parallel-group, superiority study evaluating the efficacy and safety of intravitreal ranibizumab 0.1 mg, intravitreal ranibizumab 0.2 mg, and laser therapy for the treatment of ROP. Patients were randomised 1:1:1 to one of the 3 treatment arms.

Missing data in the PK dataset were treated as missing. Concentrations below the lower limit of quantification (LLOQ) were also treated as missing for the population PK analysis. Data from one subject who was administered 1 mg ranibizumab was not included in this analysis. Additionally, measurable ranibizumab PK observations after the patients were rescued by laser treatment excluded. All other ranibizumab PK time-points were included.

Objectives

The goal of this analysis was to characterise systemic exposure in patients using population PK model and to assess the relationship between systemic VEGF levels and PK.

Methods

The analysis was performed using the NONMEM software system, NONMEM 7.3.0. A previously developed ranibizumab population PK model for adults (Joshi et al, Genentec, Inc Report 05-1181,

2005) after allometric scaling of relevant PK parameters was used to simulate PK data, which then were compared with observed PK data from the ROP population. If a difference was identified, then the model was to be re-estimated using RAINBOW study data with patient´s weight included as a covariate for the model parameters.

The handling of outliers/missing data appears adequate. PK samples were available from 49 patients in the 0.2 mg arm and 46 patients in the 0.1 mg arm.

Results/conclusion
Since using the adult model parameters, re-sampling the preterm baby's weight as a fixed allometric covariate and adjusting for their creatinine clearance did not fit the data well, re-estimation of the model parameters for the paediatric population was performed. The same structural model was applied when re-estimating the preterm baby's PK parameters. The final model parameters are shown in Table 6 below.

The effect of the reduced patient creatinine clearance was included in the model however the median value (rather than individual ones) was used for all patients because the Serum Creatinine was measured at each site instead of at a central lab. Additionally ~23.3 % of the observed values were suspiciously low (<0.01 mg/dl).

The applicant states that for the final model the 50th percentile VPC went through the middle of the observed data and the range between 2.5th and 97.5th percentiles included most of the patient PK (Figure 2, Figure 3). The popPK model was used to calculate and then to summarise individual PK parameters, which are shown in the table below (Table 7). Epsilon shrinkage was reported to be 23 % and eta shrinkages were reported to be 23, 15 and 30 % for Cl/F V/F and Ka/F respectively.

Conclusions
The applicant concludes that the Visual predictive checks (VPC) indicated good model fit to the data. Ranibizumab PK is different in preterm babies compared to adults and required re-estimation of PK parameters. The apparent half-life of ranibizumab in serum after ITV administration is equivalent to the vitreous elimination from the eye is approximately 6 days in the studied population, in comparison to 9 days in adults. Systemic Cmax in patients receiving injections of 0.1 or 0.2 mg (per eye) is 7.6 or 16.2 fold higher than in adults receiving 0.5 mg (C_{max}) in one eye and AUC_{inf} is about 5 to 12 fold higher.

Table 3. Parameter Estimates of Final Model.

Parameter	Estimated Value (%RSE)	95% Confidence Interval	IIV as %CV (%RSE)
CL/F (L/day)	28.48 (3.96)	[26.26- 30.70]	34.92 (58.27)
Ka (1/day)	0.12 (2.56)	[0.12 - 0.13]	16.28 (53.05)
V/F (L)	27.58 (3.35)	[25.78 – 29.39]	290.56 (20.67)
Lognormal SD	0.60 (7.09)	[0.52 - 0.68]	

Derived from file at: /vob/CRFB002H/mas/mas_1/model/output_001/013-model.csv

Figure 1. Final Model VPC plot of 0.1 mg dose.

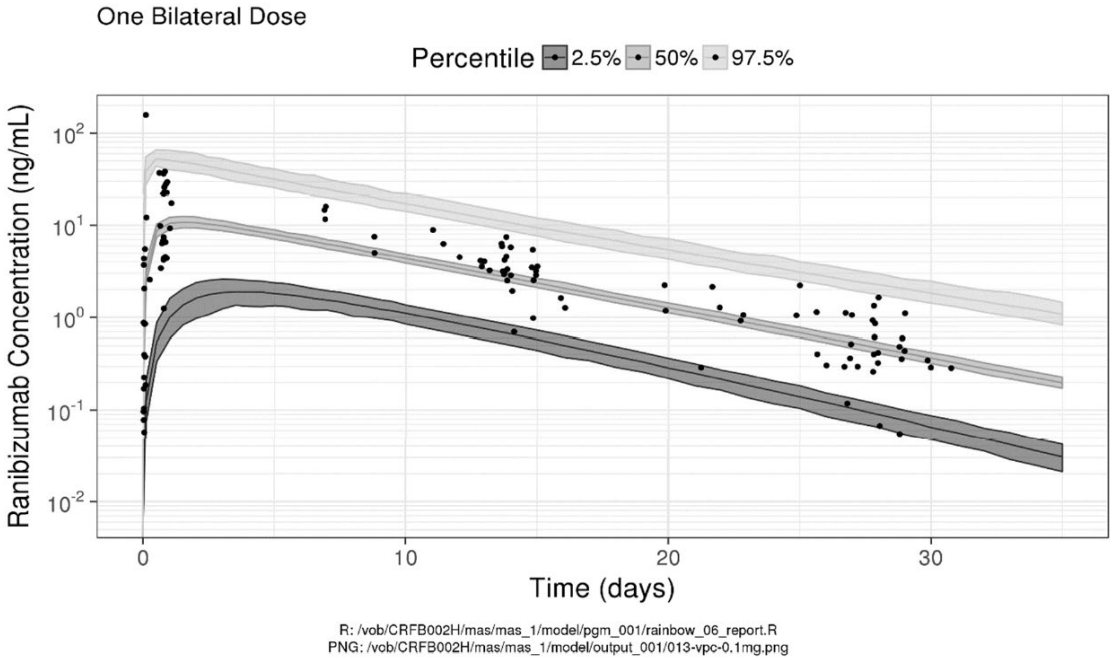


Figure 2. Final Model VPC plot of 0.2 mg dose.

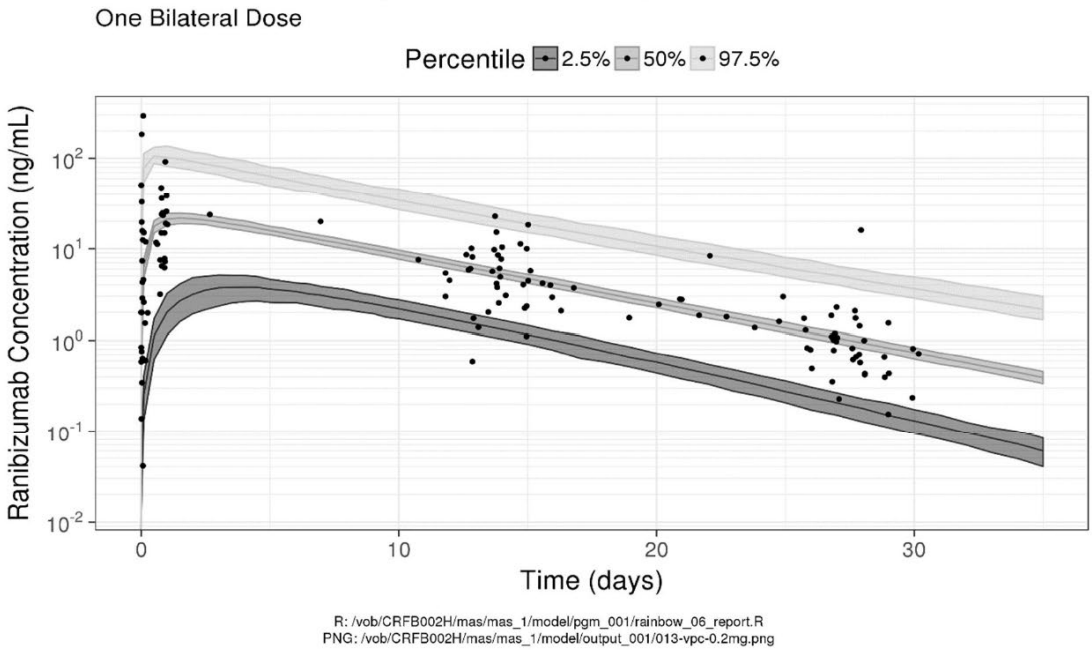
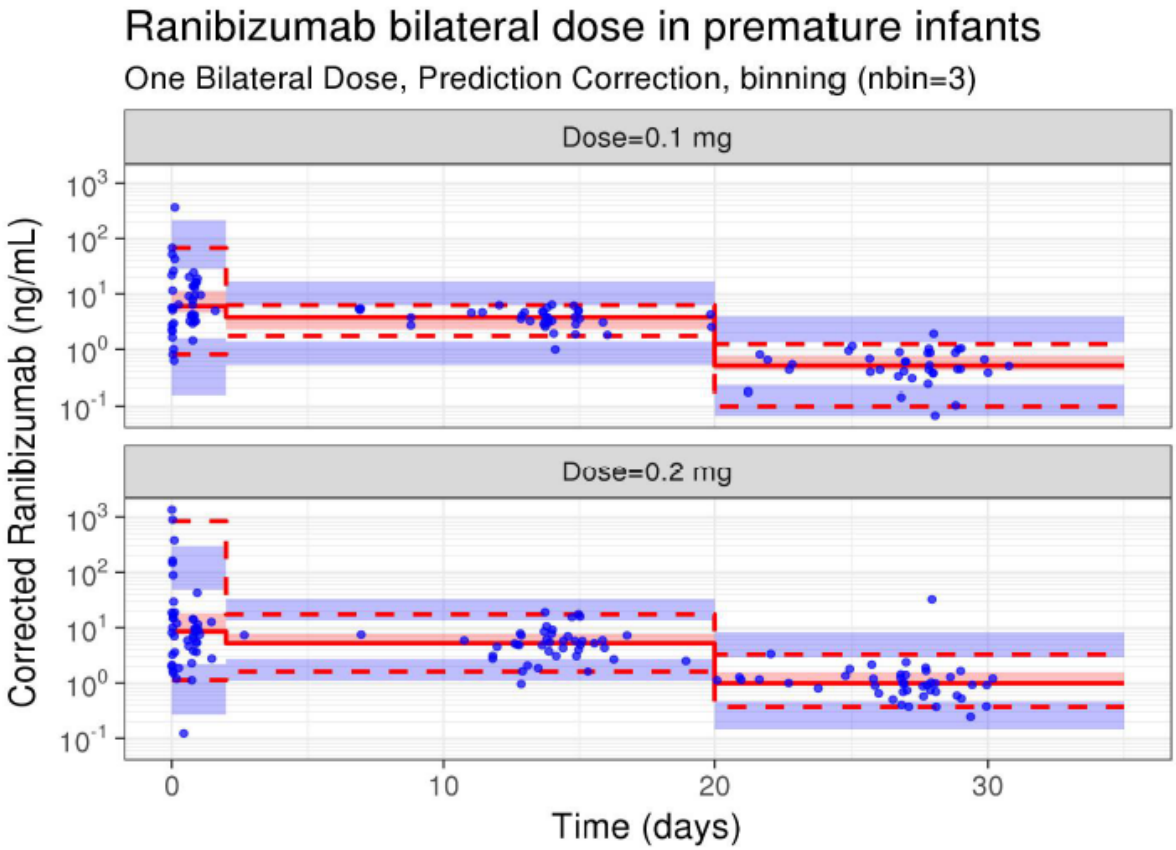


Figure 3. pcVPC



The red region represents the model-predicted 50th percentile and the blue regions represent the 2.5th and 97.5th percentiles of the model. The prediction-corrected observations are overlaid as well as its median (red line) and 2.5th and 97.5th percentiles of the data (red dashed line)

Table 4. Summary of *post hoc* predicted and calculated PK parameters for patients administered 0.1 mg or 0.2 mg ranibizumab bilaterally.

		0.1 mg N=75	0.2 mg N=86
Apparent V/F (L)	Mean (SD) Median [Range]	1.2 (1.6) 0.8 [0.0 - 9.5]	1.5 (3.0) 0.7 [0.0 - 25.7]
Apparent Cl/F (L/day)	Mean (SD) Median [Range]	1.9 (0.7) 1.8 [0.8 - 5.4]	1.9 (0.8) 1.7 [0.9 - 5.6]
Apparent Absorption Half Life $t_{1/2}$(Ka) (day)	Mean (SD) Median [Range]	5.7 (0.4) 5.6 [4.3 - 7.0]	5.6 (0.5) 5.6 [3.7 - 7.4]
Apparent Elimination Half Life $t_{1/2}$(Kel) (day)	Mean (SD) Median [Range]	0.4 (0.3) 0.3 [0.0 - 1.6]	0.4 (0.4) 0.3 [0.0 - 3.2]
T_{max} (day)	Mean (SD) Median [Range]	1.5 (0.8) 1.3 [0.2 - 4.4]	1.5 (0.9) 1.3 [0.1 - 5.8]
C_{max} (ng/mL)	Mean (SD) Median [Range]	12.6 (5.4) 11.5 [3.2 - 29.0]	26.2 (12.4) 24.3 [4.3 - 75.5]
AUC_{inf} (ng/mL * day)	Mean (SD) Median [Range]	119.2 (41.0) 113.6 [37.4 - 246.7]	240.9 (79.1) 232.0 [70.8 - 449.1]

The utility of the popPK model is mainly for descriptive purposes to provide adequate information in the SmPC (t1/2, Cmax, AUC).

The popPK model structure for ranibizumab in preterm babies with ROP was based on a previously developed popPK model for adults using body weight based allometric scaling on Cl/F and V/F with fixed exponents (0.75 and 1 for clearance and volume). Scaling of clearance using median creatinine clearance was also used with a fixed exponent taken from the adult model. Parameters ka, Cl/F, V/F and residual error were re-estimated. The scaling using median creatinine clearance and a fixed exponent from the adult model becomes a constant with a value of close to 1 (same for all children regardless of differences in age, weight or actual creatinine clearance) and can be removed from the model. From the visual predictive checks (VPC) provided it is difficult to interpret the adequacy of the model since percentiles of the observed data were not included.

The applicant was requested to provide updated VPCs for the 0.1 and 0.2 mg dose also showing lines for the percentiles of the observed data on linear and log scale, as well as a pcVPC (on linear and log scale) (see Bergstrand et al. The AAPS journal, 2011, 13.2: 143-151). Figures of the VPCs zoomed in at early time points were requested.

The applicant has provided updated plots (Figure 4 above). It would have been more useful if the updated VPCs had more than 3 bins. Overall, the previous VPC combined with the new VPC are deemed adequate.

Clearance appears to be estimated similarly as to the adult model while volume of distributions differs around 10 -fold.

For young children, ontogeny also needs to be considered. The model does not include ontogeny which may be a reason for difference in volume. Overall, based on the VPCs, the model is deemed adequate for descriptive purposes.

The PK data is sparsely sampled and there is shrinkage (between 20 and 30 %) which may lead to bias in post-hoc predicted estimates. Thus, there may be bias in the individual concentrations used in the linear PK/PD model.

3.4.3. PK/PD modelling

The aim of the PK/PD analysis was to evaluate the systemic free VEGF concentrations in relation to ranibizumab concentration.

The summary statistics of VEGF are described in Table 8. There are no clear trends in time for VEGF concentrations. A lower median value at day 15 in the Ranibizumab arms compared to laser therapy as well as lower median at day 29 for the 0.2 mg arm compared to the 0.1 arm and laser therapy can be seen but min, max and overall data are a largely overlapping (Figure 4).

Further, a linear model relating ranibizumab concentrations to VEGF concentrations was applied and calculated ranibizumab concentrations were plotted against the observed VEGF concentrations (Figure 5). The linear model indicated no significant correlation between VEGF concentrations and ranibizumab concentrations (p=0.600; Table 9).

Table 5: Summary of systemic VEGF concentration in plasma

Visit	Statistic	Ranibizumab 0.2 mg N=19	Ranibizumab 0.1 mg N=26	Laser N=51
Day 1	N	17	21	46
Pre-dose	Mean (CV%)	239 (94.6%)	230 (97.2%)	232 (104%)
Baseline	Median	136	130	136
	Min, Max	38.5, 716	39.3, 812	40.6, 959
Day 15	N	15	26	44
	Mean (CV%)	466* (323%)	118 (109%)	180 (119%)
	Median	71.8	67.0	86.1
	Min, Max	10.8, 5900*	BLQ, 539	30.1, 1020
Day 29	N	13	18	30
	Mean (CV%)	117 (71.8%)	176 (80.8%)	161 (82.1%)
	Median	89.0	140	123
	Min, Max	49.6, 341	24.9, 591	23.6, 481

Figure 4. VEGF concentrations vs time since first treatment, stratified by treatment arm.

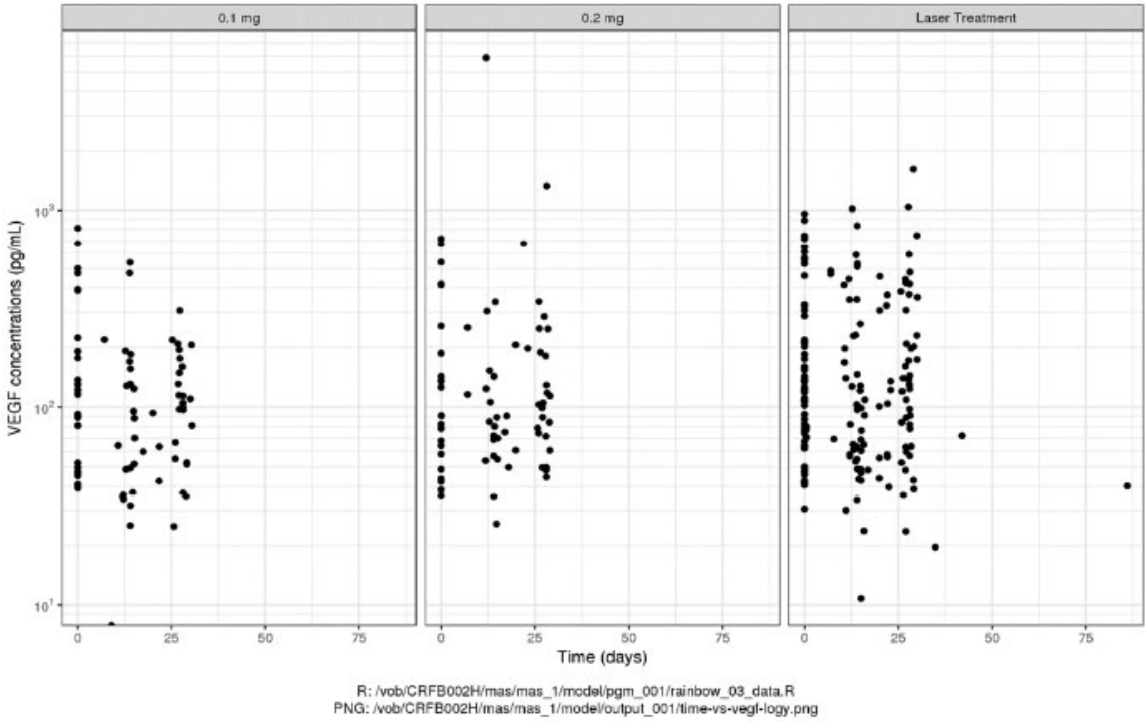


Figure 5. VEGF concentrations versus individual predicted Ranibizumab concentrations, including linear PK/PD model.

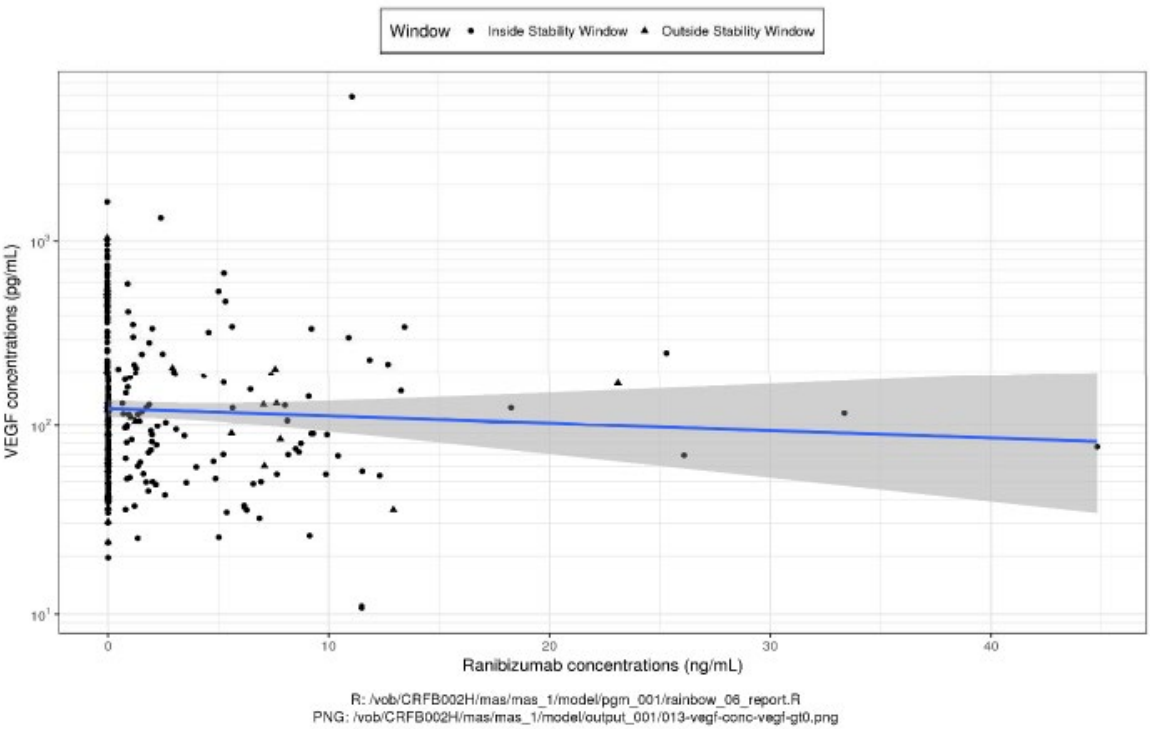


Table 6. Linear Model parameter estimates.

	Estimate	Std. Error	T value	Pr(>|t|)
Intercept	196.842	23.464	8.390	1.62×10^{-15}
Slope (ranibizumab concentrations (ng/mL)	2.510	4.374	0.525	0.566

R: /vob/CRFB002H/mas/mas_1/model/pgm_001/rainbow_06_report.R
TXT: /vob/CRFB002H/mas/mas_1/model/output_001/013-vegf-lm.txt (With outliers (VEGF != 0))

VEGF data from very few patients have been studied, especially in the ranibizumab arms. The median appears to be lower at day 15 in the Ranibizumab arms and the laser therapy arm compared to day 1. VEGF samples have been taken pre-dose, day 15 and day 29 (+/- 7 day window for 15 and 29 day dose). Most VEGF samples appear to be sampled at or close to the intended day 15 and day 29 thus, very sparse information regarding the VEGF concentrations between pre-dose and day 15 are available.

Individual plots of VEGF vs time have been provided.

It is noteworthy that the plasma concentrations of ranibizumab 0.2 mg in the pre-term infants are 16-fold higher (Cmax, from popPK analysis) than those observed in adults, however, the impact on the VEGF concentration is unclear, masked by the large interindividual variation. The MAH was requested to further discuss the rationale for selecting the 0.2 mg dose considering the apparent 16-fold higher systemic exposure in the paediatric population as compared to the adult population, as well as discuss local exposure.

In response to the RSI, the MAH has provided this rationale for selecting the 0.2 mg dose. The proportion of patients achieving treatment success was highest with ranibizumab 0.2 mg (80.0%), followed by ranibizumab 0.1 mg (75.0%) and laser (66.2%). The difference in treatment success was 14.7% for ranibizumab 0.2 mg compared to laser and 9.3% for ranibizumab 0.1 mg compared to laser. A higher numeric benefit for patients treated with ranibizumab 0.2 mg as compared with 0.1 mg was also observed for the secondary endpoints (e.g. switch, active ROP and unfavourable structural outcomes. No dose-related trends were observed for safety. However, the long-term safety would need to be further followed. Most of the patients received only one injection per eye, which provides some reassurance considering the higher systemic exposure observed as compared with the adult population.

The individual concentrations from the popPK model were used in the linear PK/PD model. Shrinkage was between 20 and 30 % in the popPK model which may lead to bias in the individual predicted ranibizumab concentrations. The linear VEGF model would indicate that systemic VEGF levels are not lowered despite the higher systemic ranibizumab concentrations. Since there is eta and epsilon shrinkage between 20-30 % in the popPK model the results from the PK/PD analysis may be biased. Furthermore, the sampling times points (pre-dose day 15 and day 29), the few numbers of subjects studied as well as some samples being analysed after 15 months (where stability of VEGF cannot be ensured), together raises uncertainties regarding systemic VEGF concentrations in these young children. In addition, PK model evaluation plots may indicate a model underestimation of high plasma concentrations. The possible effect on such bias in model predictions, and the relationship between VEFG and ranibizumab concentrations has not been discussed.

From the individual plots as well as for the previously provided linear PK/PD model however, there does not appear to be a trend for VEGF. Information regarding this can be provided in the SmPC. The

PK/PD analysis of VEGF can however not support safety regarding long-term neurodevelopmental outcome.

3.4.4. Immunogenicity

As an exploratory objective, the presence of anti-ranibizumab antibodies in patients with ROP initially treated with ranibizumab was assessed, provided there was sufficient volume remaining from serum PK samples. Due to sample volume limitations, if a sample screened positive and there was not adequate sample for a confirmatory assay, the sample was considered positive, as a conservative approach.

The incidence of antibodies against ranibizumab was low (< 10%). 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 (sampling within 24 hours post-dose), 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). As an immunogenic response is not expected within 24 hours after a single ranibizumab dose, Day 1 results suggest a low incidence of pre-existing anti-ranibizumab antibodies, and data across all days suggest a low incidence of treatment emergent antibodies.

It is not known whether clinically relevant differences in response/adverse events between patients with and without a positive antibody response could be identified.

Overall, as only few ADA positive results have been confirmed, no relationship can be established between positive ADA and efficacy outcomes.

3.4.5. Conclusions on clinical pharmacology

The popPK model is needed to provide adequate information to section 5.2 in the SmPC. A 12-fold higher AUC and a 16 fold higher Cmax in ROP patients compared to adults was seen. From the individual plots as well as for the previously provided linear PK/PD model, there does not appear to be a trend for VEGF. Information regarding the exposure of ranibizumab as well as the result form the PK/PD analysis can be provided in section 5.2 in the SmPC. The PK/PD analysis of VEGF can however not support safety regarding long-term neurodevelopmental outcome.

The proportion of patients achieving treatment success was highest with ranibizumab 0.2 mg (80.0%), followed by ranibizumab 0.1 mg (75.0%) and laser (66.2%). A higher numeric benefit for patients treated with ranibizumab 0.2 mg as compared with 0.1 mg was also observed for the secondary endpoints (e.g. switch, active ROP and unfavourable structural outcomes. No dose-related trends were observed for safety. However, the long-term safety would need to be further followed. Most of the patients received only one injection per eye, which provides some reassurance considering the higher systemic exposure observed as compared with the adult population.

3.5. Clinical efficacy

3.5.1. Main study

Results of the Core Study CRFB002H2301 presented in the Clinical Study Report were submitted earlier in 2018 as part of the Paediatric Investigation Plan (PIP) for Lucentis and assessed as an Article 46 process (EMA/H/C/715/P46).

There are three analyses planned in the RAINBOW Extension Study:

- Interim analysis 1 (IA1) will provide descriptive statistics for a subset of patients to evaluate ocular structural abnormalities.

- Interim analysis 2 (IA2) will be conducted on all patients at their 2 years' corrected age to report on the progress of the study to the scientific community.
- The final analysis will be conducted at the completion of the study.

The purpose of the IA1 is to provide long-term data on structural abnormalities at 9 months after start of treatment in the subset of patients for which this data is available, as outlined in the clinical measure of the Paediatric Investigation Plan (PIP EMEA- 000527-PIP04-13-M01). The PIP requires that the analysis should include at least half of the patients enrolled in the Core Study CRFB002H2301.

The IA1 was performed after the last patient had completed the last visit in the Core Study which was 14 December 2017. The cut-off date used for this first interim analysis was 31 December 2017. At the time of this cut-off, 144 patients had either completed (143 patients) the Week 40 visit in the Extension Study (corresponding to 40 weeks after the first study treatment in the Core Study) or had discontinued from the Extension Study prior to this time point (1 patient). Key results for this subset of 144 patients are reported in this first interim analysis (IA1) with the Extension Study currently ongoing.

The extension CRFB002H2301E1 was designed to evaluate the long-term efficacy and safety of intravitreal ranibizumab compared with laser ablation therapy in patients with ROP who successfully completed the Core Study.

Objectives

Core Study

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.

Extension Study

The absence of ocular structural abnormalities was evaluated as defined by the absence of all of the following fundus features in both eyes at or before the Week 40 visit (40 weeks after the first study treatment in the Core Study H2301):

- substantial temporal retinal vessel dragging causing abnormal structural features/ macular ectopia
- retrolental membrane obscuring the view of the posterior pole
- posterior retinal fold involving the macula
- retinal detachment involving the macula

Additional objectives of interim analysis 1 were:

- to explore the absence of active ROP in both eyes at Week 40, as defined by the absence of all of the following features:
    - vessel dilatation of plus disease in at least 2 quadrants (some persisting tortuosity is allowed)
    - extra-retinal vessels extending from the retina into the vitreous and judged to be a sign of active ROP disease
- to explore the recurrence of ROP at or before Week 40
- to explore the number of ranibizumab injections
- to explore the safety outcomes by analysing the type, frequency and severity of ocular and non-ocular adverse events.

Study design

Core Study

This was a randomised, multicenter, open-label, 3-arm, parallel-group, superiority study evaluating the efficacy and safety of intravitreal ranibizumab 0.1 mg, intravitreal ranibizumab 0.2 mg, and laser therapy for the treatment of ROP. The study consisted of a screening period (screening and randomization could occur up to 3 days before the administration of the first investigational treatment), followed by a treatment and follow-up period (Day 1 to Day 169). Randomization was stratified by ROP zone (in the worst eye) and by geographic region.

Patients were randomised 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 randomised 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.

The MAH was requested to clarify when unresponsive patients received retreatment with the same modality and when they were switched to another treatment modality and how standardization of this process was assured. In response to the RSI, the MAH explained that infants were retreated with the baseline treatment or switched over to a different treatment modality based on investigator's decision. No pre-defined criteria were established. Accordingly, no recommendations can be made in the SmPC in this respect. However, the MAH has updated the wording for section 4.2 of the SmPC in order to limit the administration of ranibizumab up to three injections, which is acceptable.

See also Treatments section below for further detail on the retreatment and rescue treatment protocol.

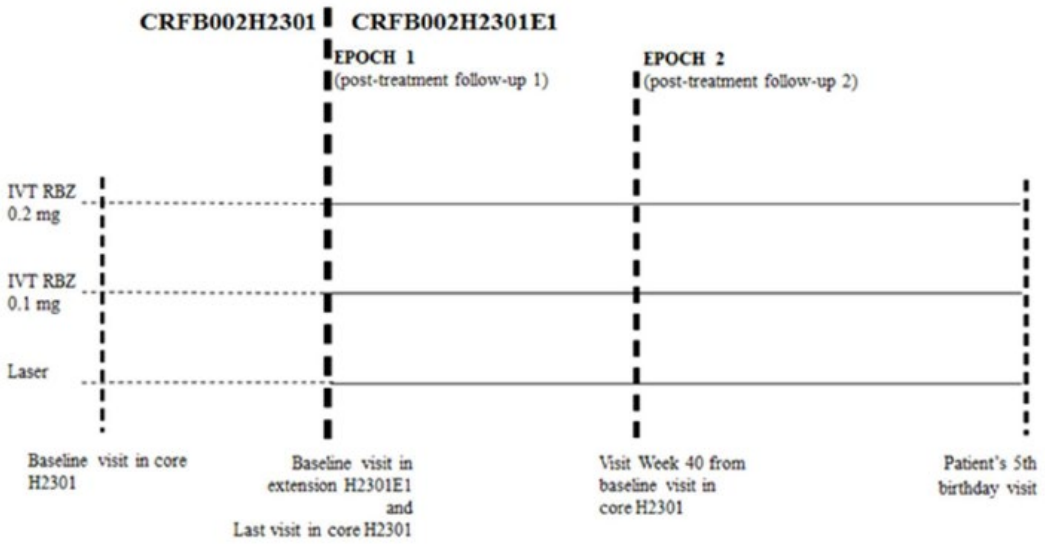
Extension Study

Ranibizumab as study treatment was permitted for eligible eyes up to and including the Week 40 visit (Epoch 1), corresponding to 40 weeks after a patient received the first study treatment in the Core Study CRFB002H2301. Treatment with ranibizumab was permitted either as re-treatment for patients who had received ranibizumab as the last treatment prior to joining the Extension Study or as switch treatment for patients who only received laser therapy in the Core Study CRFB002H2301 and required additional treatment in the Extension Study.

Patients who required switch treatment in the Extension Study were administered ranibizumab 0.2 mg. A maximum of 3 ranibizumab injections in each eye were allowed during the combined time period of the Core Study plus Epoch 1 of the Extension Study. The remainder of the Extension Study (Epoch 2) is observational.

The overall design of the study is summarised in Figure 8.

Figure 6. Study design.



Study population

Core Study

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).

The inclusion criteria aimed to capture preterm infants (regardless the gestational age) with a severity of ROP that would be amenable to treatment. According the International Classification for Retinopathy of Prematurity classification criteria includes localization (zone I, zone II, zone III), severity (stage 1, 2, 3, 4 or 5), extent criteria (dividing the retinal surface in 12 sections) and the presence or absence of plus disease. Patients were recruited on the basis that they had a Type 1 ROP (in need of treatment according to current guidelines applicable in Europe or similar) and placed in either Zone I with any stage with plus disease, Zone I with stage 3 without plus disease, and Zone II with stage 2 or 3 with plus disease.

Images taken both by RetCam digital photography and/or indirect ophthalmoscopy were used for the visualization of the fundus. It is expected that some patients were diagnosed and followed up by using indirect ophthalmoscopy and in some patients depending on the conditions of the study site and/or the investigator preference RetCam digital photographs were performed. It is not clear if differences in the method used for the selection may result in relevant differences in the final population recruited (according to severity, gestational age, or demographic characteristics).

Accordingly, the MAH was requested to provide the number and characteristics of the patients separately, in accordance with the method used and clarify to what degree patients were evaluated with one or both methods and whether there was a notable difference in outcome between the 2 methods for evaluation. However, in response, the MAH explained that most of the infants included were evaluated by either of the two methods (interchangeably) so that a separate analysis by method would not be informative.

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 on Day 1, 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.

The two investigated ranibizumab doses represent 20 % or 40 % of the ranibizumab dose administered per eye in adult ocular indications. With bilateral administration of the doses to be investigated, the total amount of ranibizumab administered to a ROP patient was lower than that administered unilaterally in adults.

The two doses were chosen to allow the evaluation of likely safe and efficacious doses in patients with ROP, based on modelling and simulation to assess the benefit–risk using predicted exposure levels and a PK model scaled for infants. The model assumes that:

- Potential efficacy increases when ocular exposure (as estimated by vitreous area under the curve AUC) increases
- Potential toxicity increases when systemic exposure (as estimated by serum AUC and maximum serum concentration C_{max}) increases

Ocular exposure in neonates after intravitreal ranibizumab 0.2 mg was expected to be similar to that seen in the treatment of age-related macular degeneration in adults (i.e., ranibizumab 0.5 mg) and similar to the ocular exposure estimated by the model following intravitreal bevacizumab 0.625 mg, as was administered in the BEAT-ROP study (Mintz-Hittner et al 2011).

Systemic exposure in neonates after bilateral intravitreal ranibizumab with doses as low as 0.1 mg was estimated to be greater than that in adult patients. However, bilateral intravitreal ranibizumab doses up to 0.3 mg were estimated to have less systemic exposure than that following bilateral bevacizumab 0.625 mg, as was administered in the BEAT-ROP study (Mintz-Hittner et al 2011). Although there is no clear association between systemic exposure and clinical adverse effects, it would be desirable to minimise systemic ranibizumab exposure in the vulnerable premature neonatal population.

Despite uncertainties of the modelling and simulation approach, it was estimated that bilateral intravitreal ranibizumab doses of 0.1 mg and 0.2 mg may have acceptable benefit–risk ratios based on clinical interpretation of the predicted ocular and systemic exposures. Published reports successfully treating ROP with ranibizumab monotherapy have used doses between 0.2 mg and 0.3 mg per eye (Castellanos et al 2013, Hoerster et al 2013, Lin et al 2012). There have also been reports of clinical efficacy in ROP with intravitreal bevacizumab doses as low as 20 % of the adult dose (0.25 mg, in combination with laser therapy) and 30 % of the adult dose (0.375 mg monotherapy) (Harder et al 2011, Kim et al 2014). It was estimated that anti-VEGF doses lower than the majority of published reports could be efficacious with fewer adverse effects.

As also discussed in the clinical pharmacology section, the MAH was requested to further discuss the rationale for selecting the 0.2 mg dose over the 0.1 mg dose both from a safety and efficacy standpoint including the apparent 16-fold higher systemic exposure in the paediatric population as compared to the adult population, as well as the local exposure. In response, the applicant has discussed that the 0.1 mg dose would give a lower vitreous exposure compared to adults while the 0,2 mg dose would provide exposures in the same range as in adults. Furthermore, the results in terms of treatment success rate seem to offer some support to the choice (see below).

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 variable*s 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.

Sample size

The sample size was initially calculated to 300 patients randomised 1:1:1 to ranibizumab 0.2 mg, ranibizumab 0.1 mg and laser. The planned sample size was later reduced to approximately 180 patients, following approval by the EMA to modify an agreed Paediatric Investigation Plan (PIP). The sample size of 180 was based on a power of 80 % to show superiority of ranibizumab 0.2 mg against laser therapy (92 % for 300 patients) and assuming a drop-out rate of 20 %. The sample size

calculations were based on a Cochran–Mantel–Haenszel test stratified by ROP zone. Event rates were based on published rates from the BEAT-ROP study for the recurrence of ROP at 54 weeks postmenstrual age using intravitreal bevacizumab (Mintz-Hittner et al 2011):

- Zone I
    - Laser – 42.4 %
    - Ranibizumab 0.2 mg – 6.5 %
- Zone II
    - Laser – 12.5 %
    - Ranibizumab 0.2 mg – 5.1 %

Changing the sample size during the conduct of a study may cause suspicion that the time of study termination is data driven. Because the RAINBOW study failed to show statistical significance in the primary endpoint, this is not considered an issue.

Randomisation

At Visit 1 (Screening Visit), all eligible patients were randomised 1:1:1 to one of the 3 treatment arms via Interactive Response Technology (IRT). Randomisation was stratified by ROP zone in the worst eye and geographic region based on neonatal mortality rate.

The randomisation procedure was appropriate.

Blinding (masking)

The investigators and patients/parents/legal guardians were unmasked to the treatments administered. However, to minimise the potential impact of treatment knowledge, randomisation data and aggregated statistical analysis by treatment was kept confidential from the Clinical Trial Team (CTT) until the database was locked for the primary analysis. Fundus images taken by RetCam digital photography were analysed at a reading that were blinded to the dose of ranibizumab administered.

The study was open-label, but there were measures to minimise bias related to treatment knowledge. Fundus image analysis is, however, always prone to subjective interpretation. It is noted that the readings were blinded to the dose of ranibizumab administered. It is not possible to blind images of the laser treatment group.

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.

The primary and secondary efficacy variables were analysed for the Full Analysis Set (FAS). The FAS consisted of all randomised patients to whom treatment regimen had been assigned and data was analysed using the intent-to-treat principle.

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.

Sensitivity analyses

For the primary efficacy analysis, missing data on the occurrence of active ROP and unfavourable structural outcomes at Week 24 were imputed as follows: if the last non-missing value of a criterion was 'success', then the missing value at Week 24 stayed missing (imputation rule 1).

The robustness of the primary analysis was assessed by the following sensitivity analyses:

- Repeating the primary analyses using the Per-Protocol Set
- Repeating the primary analyses without imputing data missing at Week 24
- Repeating the primary analyses imputing data missing at Week 24 by "success"
- Repeating the primary analyses imputing data missing at Week 24 by "failure"
- Repeating the primary analyses with imputation rule 2

A pre-specified sensitivity analysis with an alternative imputation rule (imputation rule 2) was performed in which missing outcomes of active ROP and unfavourable structural outcomes at Week 24

were imputed from the results at the Week 20 visit. This was based on the results of prior studies (Mintz-Hittner et al 2011, Stahl et al 2018), which concluded that recurrence with structural unfavourable endpoints occurred at 6.2±5.7 weeks after laser treatment, or before 100 days after ranibizumab treatment, respectively, indicating the stability of active ROP and unfavourable structural outcomes between Week 20 and Week 24.

- Sensitivity analysis using logistic regression
- Sensitivity analysis using ROP Zone information from the Interactive Response Technology.

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.

The statistical methods used were adequate.

Results

Recruitment/Numbers analysed

Core Study

A total of 225 patients from 87 sites in 26 countries were enrolled and randomised. The majority of patients (218 patients, 96.9 %) 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 also 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 %).

Seven patients were randomised but did not receive initial treatment and were discontinued from the study. These patients were not included in the Safety Set for safety analyses as they did not receive any study treatment but were included in the Full Analysis Set for efficacy analyses.

The FAS population included 225 patients and the Safety Population 118 patients since 7 patients did not receive treatment. In total, 17 patients discontinued after the initial treatment at baseline (17 in total, including 12 deaths). The distribution of discontinuations was comparable across the treatment groups.

Patient disposition is summarised in the table below.

Table 7. Patient disposition (Study H2301, Randomised set)

Disposition	Ranibizumab 0.2 mg N=74 n (%)	Ranibizumab 0.1 mg N=77 n (%)	Laser N=74 n (%)	Total N=225 n (%)
Number of patients who completed treatment phase	73 (98.6)	76 (98.7)	69 (93.2)	218 (96.9)
Number of patients who discontinued treatment phase	1 (1.4)	1 (1.3)	5 (6.8)	7 (3.1)
Primary reason for permanently discontinuing treatment phase				
Adverse event	0	0	1 (1.4)	1 (0.4)
Subject/Guardian decision	0	0	2 (2.7)	2 (0.9)
Physician decision	1 (1.4)	1 (1.3)	1 (1.4)	3 (1.3)
Lost to follow-up	0	0	1 (1.4)	1 (0.4)
Number of patients who completed study treatment in the follow-up phase	66 (89.2)	71 (92.2)	64 (86.5)	201 (89.3)
Number of patients who discontinued study treatment in the follow-up phase	7 (9.5)	5 (6.5)	5 (6.8)	17 (7.6)
Primary reason for permanently discontinuing study treatment in the follow-up phase				
Adverse event	1 (1.4)	0	0	1 (0.4)
Subject/Guardian decision	1 (1.4)	0	1 (1.4)	2 (0.9)
Death	4 (5.4)	4 (5.2)	4 (5.4)	12 (5.3)
Withdrawal of informed consent	1 (1.4)	1 (1.3)	0	2 (0.9)

Primary reason for permanently discontinuing study treatment as given by the Investigator on the dose record summary eCRF is summarised.

Extension Study

Of the 225 patients randomised into the Core Study CRFB002H2301, 218 patients were treated, and 201 patients (89.3%) completed the Core Study. – At the time of the data cut-off for the present interim analysis (31 December 2017), 144 patients had either completed Week 40 visit (143 patients) or had been discontinued in the Extension Study prior to Week 40 visit (1 patient discontinued due to death).

Conduct of the study

Baseline data

Core Study

Patient demographic data are summarised in the tables below. The demographic and disease characteristics of the study population were similar across the treatment group. The majority of patients were Caucasian (59.1 %), and there was a comparable proportion of males and females. Mean gestational age was 26.1 weeks and mean chronological age at baseline was 10.9 weeks. Mean birth weight was 836.4 g, with nearly half of patients weighing ≤ 750 g (48.4 %) at birth.

Treatment groups were generally well balanced with respect to baseline demographics.

Patients were stratified by Region (Region 1: Estonia, Japan, Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Italy, Croatia, Lithuania, Poland, United Kingdom, Hungary, Slovakia (Slovak Republic), United States, and Taiwan; Region 2: Malaysia, Russia, Romania, Mexico, Saudi Arabia, Turkey, Egypt, and India).

Table 8. Patient demographics (Study H2301, Randomised Set)

Characteristic	Ranibizumab 0.2 mg N=74	Ranibizumab 0.1 mg N=77	Laser N=74	Total N=225
Sex -n (%)				
Male	33 (44.6)	37 (48.1)	37 (50.0)	107 (47.6)
Female	41 (55.4)	40 (51.9)	37 (50.0)	118 (52.4)
Race -n (%)				
Caucasian	43 (58.1)	45 (58.4)	45 (60.8)	133 (59.1)
Black	0	4 (5.2)	3 (4.1)	7 (3.1)
Asian	27 (36.5)	22 (28.6)	23 (31.1)	72 (32.0)
Other	4 (5.4)	6 (7.8)	3 (4.1)	13 (5.8)
Ethnicity -n (%)				
Hispanic/Latino	3 (4.1)	5 (6.5)	2 (2.7)	10 (4.4)
East Asian	14 (18.9)	11 (14.3)	11 (14.9)	36 (16.0)
Southeast Asian	1 (1.4)	1 (1.3)	2 (2.7)	4 (1.8)
South Asian	11 (14.9)	10 (13.0)	9 (12.2)	30 (13.3)
West Asian	1 (1.4)	1 (1.3)	0	2 (0.9)
Russian	5 (6.8)	8 (10.4)	8 (10.8)	21 (9.3)
Mixed Ethnicity	0	2 (2.6)	2 (2.7)	4 (1.8)
Not reported	2 (2.7)	5 (6.5)	3 (4.1)	10 (4.4)
Unknown	2 (2.7)	3 (3.9)	0	5 (2.2)
Other	35 (47.3)	31 (40.3)	37 (50.0)	103 (45.8)
Gestational age at birth (weeks)				
n	74	77	74	225
Mean	25.8	26.5	26.2	26.1
SD	2.25	2.57	2.59	2.48
Median	25.0	26.0	26.0	26.0
Min, Max	23, 32	23, 32	23, 32	23, 32
Q1, Q3	24.0, 27.0	24.0, 28.0	24.0, 28.0	24.0, 28.0
Gestational age category -n (%)				
≤ 24 weeks	32 (43.2)	22 (28.6)	29 (39.2)	83 (36.9)
> 24-< 27 weeks	18 (24.3)	21 (27.3)	17 (23.0)	56 (24.9)
≥ 27 weeks	24 (32.4)	34 (44.2)	28 (37.8)	86 (38.2)
Geographical region –n (%)				
Region 1	45 (60.8)	45 (58.4)	44 (59.5)	134 (59.6)
Region 2	29 (39.2)	32 (41.6)	30 (40.5)	91 (40.4)
Chronological age at Baseline Visit (weeks)				
n	73	77	74	224
Mean	11.14	10.93	10.57	10.88
SD	3.955	4.062	4.483	4.160
Median	11.00	10.60	10.05	10.60
Min, Max	3.3, 27.9	3.6, 26.9	3.4, 30.3	3.3, 30.3
Q1, Q3	9.10, 13.00	8.30, 13.00	8.00, 12.70	8.30, 13.00
Postmenstrual age at Baseline Visit (weeks)				
n	73	77	74	224
Mean	36.92	37.44	36.74	37.04
SD	3.325	3.417	3.905	3.554
Median	36.70	36.90	36.30	36.60
Min, Max	30.3, 51.9	31.9, 54.9	30.6, 55.3	30.3, 55.3
Q1, Q3	34.70, 38.60	35.10, 39.00	34.70, 38.00	34.90, 38.70

n= number of patients meeting the criterion (for categorical variables); number of patients with non-missing assessment (for continuous variables).

Region classification is according to the status of neonatal care with neonatal mortality rate as the surrogate.
Region 1 is with lower mortality rates than Region 2.
Post menstrual age at Baseline = (Baseline Visit date - Start date of the mother's last normal menstrual period + 1)/7.
Chronological age at Baseline = [Baseline Visit date - (Start date of the mother's last normal menstrual period + gestational age at birth) + 1]/7

Table 9. Additional baseline characteristics (Study H2301, Randomised Set).

Characteristic	Ranibizumab 0.2 mg N=74	Ranibizumab 0.1 mg N=77	Laser N=74	Total N=225
Birth weight (g)				
n	70	73	66	209
Mean (SD)	790.6 (244.32)	885.6 (298.61)	830.6 (283.55)	836.4 (278.13)
Median	700.0	840.0	735.0	750.0
Min, Max	354, 1490	316, 1487	372, 1610	316, 1610
Q1, Q3	628.0, 915.0	652.0, 1125.0	610.0, 983.0	630.0, 1030.0
Birth weight category - n (%)				
≤ 750 g	39 (52.7)	33 (42.9)	37 (50.0)	109 (48.4)
> 750-≤ 1000 g	15 (20.3)	15 (19.5)	13 (17.6)	43 (19.1)
≥ 1000 g	16 (21.6)	25 (32.5)	16 (21.6)	57 (25.3)
Missing	4 (5.4)	4 (5.2)	8 (10.8)	16 (7.1)

Disease characteristics at baseline are summarised in Table 13. In total, 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 %).

The studied population included patients with bilateral ROP with Zone I, stage 1+, 2+, 3 or 3+ disease, or Zone II, stage 3+ disease, or AP-ROP (aggressive posterior retinopathy of prematurity). Of note, the sought indication in the MAH's proposed SmPC was initially considerably broader. However, in the response to the first RSI, the proposed indication has been updated to reflect the patient population included in the study. In addition, this indication is now more consistent with recommendations for treatment stated in recent literature.

Most of baseline demographics and disease characteristics were well balanced over treatment arms. Females represented 52.4% of the population. Gestational age at birth ranged from 23 to 32 weeks (mean 26.1 weeks), with a mean birth weight of 836.5 g (from 316 g to 1610 g). Infants were recruited at 10.8 weeks of chronological age (ranged from 3.3 to 30.3 weeks). The majority of subjects were Caucasian (59%) followed by Asian (32%) and African American subjects (3.1%). Overall, 60% of patients were recruited in Region 1 and 40% in Region 2. Patients from Region 1 and Region 2 exhibit a certain degree of heterogeneity, as they come from centers with wide differences in neonatal care, screening of the condition and the characteristics of the infants at risk.

The MAH was requested to describe the baseline characteristics of preterm infants from Region 1 and Region 2 separately and discuss the differences in response to treatment. According to the MAH, Region 1 is representative of the EU population. Of the 225 patients, 134 (60%) were recruited from Region 1, which included Estonia, Japan, Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Italy, Croatia, Lithuania, Poland, United Kingdom, Hungary, Slovakia, United States,

and Taiwan. Of the 134 patients in Region 1, 77 were from EU countries (34% of total population and 57% of Region 1), 21 from the United States, 29 from Japan, and 7 from Taiwan.

In the BEAT-ROP study (Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity), 67 % of the patients were Hispanic and for unknown reason ROP is reportedly more difficult to treat in these patients and may require more than one laser treatment (Stuart A, EyeNet Magazine, Feb 2014).

Accordingly, the MAH was requested to address any potential ethnic differences applicable to anti-VEGF treatment in ROP treatment and consider any implications for the risk management plan and product information. However, according to the MAH, only 10 patients of Hispanic ethnicity were enrolled in Study H2301. This sample size is too small for interpretation.

Table 10. ROP baseline characteristics by treatment group (Study H2301, Randomised Set).

Characteristic	Ranibizumab 0.2 mg N=74	Ranibizumab 0.1 mg N=77	Laser N=74	Total N=225
ROP Zone by patient from CRF - n (%)				
Zone I	28 (37.8)	30 (39.0)	28 (37.8)	86 (38.2)
Zone II	46 (62.2)	46 (59.7)	46 (62.2)	138 (61.3)
Missing	0	1 (1.3)	0	1 (0.4)
ROP Zone by patient from IRT - n (%)				
ZONE I	25 (33.8)	26 (33.8)	26 (35.1)	77 (34.2)
ZONE II	49 (66.2)	51 (66.2)	48 (64.9)	148 (65.8)
AP-ROP status by patient - n (%)				
AP-ROP	10 (13.5)	10 (13.0)	10 (13.5)	30 (13.3)
NON AP-ROP	64 (86.5)	66 (85.7)	64 (86.5)	194 (86.2)
Missing	0	1 (1.3)	0	1 (0.4)
ROP disease by patient - n(%)				
Zone I AP-ROP	10 (13.5)	10 (13.0)	9 (12.2)	29 (12.9)
Zone II AP-ROP	0	0	1 (1.4)	1 (0.4)
ZONE I/STAGE 3+	12 (16.2)	14 (18.2)	11 (14.9)	37 (16.4)
ZONE I/STAGE 3	3 (4.1)	4 (5.2)	1 (1.4)	8 (3.6)
ZONE I/STAGE 2+	3 (4.1)	1 (1.3)	5 (6.8)	9 (4.0)
ZONE I/STAGE 1+	0	1 (1.3)	2 (2.7)	3 (1.3)
ZONE II/STAGE 3+	46 (62.2)	45 (58.4)	44 (59.5)	135 (60.0)
ZONE II/STAGE 2+	0	0	1 (1.4)	1 (0.4)
ZONE II/STAGE 3	0	1 (1.3)	0	1 (0.4)
Missing	0	1 (1.3)	0	1 (0.4)
APGAR score at 1 minute				
n	62	61	61	184
Mean (SD)	4.3 (2.32)	5.2 (2.28)	4.2 (2.05)	4.6 (2.26)
Median	4.0	6.0	4.0	5.0
Min, Max	1, 9	1, 9	1, 8	1, 9
Q1, Q3	2.0, 6.0	4.0, 7.0	3.0, 6.0	3.0, 6.0
APGAR score at 5 minutes				
n	62	60	61	183
Mean (SD)	6.5 (1.96)	6.9 (2.18)	6.3 (2.02)	6.5 (2.06)
Median	7.0	7.0	7.0	7.0
Min, Max	1, 10	1, 10	1, 10	1, 10
Q1, Q3	6.0, 8.0	6.0, 8.0	5.0, 8.0	6.0, 8.0

Time from first diagnosis of ROP to Screening visit (weeks)				
n	74	76	74	224
Mean (SD)	2.6 (2.31)	2.4 (2.46)	2.1 (2.54)	2.4 (2.44)
Median	2.1	1.4	1.4	1.7
Min, Max	0, 11	0, 11	0, 15	0, 15
Q1, Q3	0.7, 4.0	0.3, 4.0	0.6, 2.6	0.4, 3.6
Time from ROP fulfilling treatment criteria to Screening Visit (weeks)				
n	74	76	74	224
Mean (SD)	0.2 (0.16)	0.4 (0.77)	0.3 (0.61)	0.3 (0.58)
Median	0.1	0.1	0.1	0.1
Min, Max	0, 1	0, 5	0, 5	0, 5
Q1, Q3	0.1, 0.3	0.1, 0.3	0.1, 0.4	0.1, 0.3

APGAR = appearance, pulse, grimace, activity, respiration, AP-ROP= aggressive posterior retinopathy of prematurity, ROP= retinopathy of prematurity, SD= standard deviation.
n = number of patients meeting the criterion (for categorical variables); number of patients with non-missing assessment (for continuous variables). Percentage (%) is calculated based on the patients in the Randomised Set within the treatment arm.

Extension Study

Baseline demographics of patients in the Extension Study were comparable across treatment groups.

Treatment groups were generally well balanced with respect to baseline demographics also in the Extension Study. Absence of active ROP and unfavourable structural outcomes at the last visit of Core Study = first visit of the Extension Study (i.e. 24 weeks after the first study treatment) was observed in 56/70 (80 %), 57/76 (75 %) and 45/68 (66.2 %) in ranibizumab 0.2 mg, 0.1 mg and laser groups, respectively.

Outcomes and estimation

Primary endpoint results

Treatment success, the primary efficacy variable, was defined as the absence of active ROP and absence of unfavourable structural outcomes before or at 24 weeks. If a patient died or switched investigational treatment before or at 24 weeks, the patient was considered as a treatment failure (i.e., having active ROP and unfavourable structural outcomes at 24 weeks).

The proportion of patients achieving treatment success was highest with ranibizumab 0.2 mg (80.0 %), followed by ranibizumab 0.1 mg (75.0 %) and laser (66.2 %) (see table below).

The odds of treatment success for ranibizumab 0.2 mg compared with laser were: OR=2.19 (95 % CI: 0.9932, 4.8235. The one-sided p-value (p=0.0254) was marginally above the significance level of 0.025.

The treatment difference calculated using CMH weights stratified by baseline ROP zone was 14.7 % for ranibizumab 0.2 mg compared to laser and 9.3 % for ranibizumab 0.1 mg compared to laser [SCE Appendix 1-Table 2-11].

As the primary comparison was marginally above the significance level of 0.025, the secondary comparisons (ranibizumab 0.1 mg vs. laser and ranibizumab 0.2 mg vs. 0.1 mg) were assessed descriptively. The odds ratios were numerically in favour of ranibizumab 0.1 mg compared with laser (OR=1.57; 95 % CI: 0.7604, 3.2587) and of ranibizumab 0.2 mg compared with ranibizumab 0.1 mg (OR=1.35; 0.95 % CI: 0.6101, 2.9810) [Study H2301-Table 14.2-1.9].

Table 11. Absence of active ROP and absence of unfavourable structural outcomes in both eyes 24 weeks after initial treatment: comparison between treatment arms (Study H2301, Full Analysis Set)

	Treatment success					
Treatment	**n/M (%)**	**95 % CI**	**Comparison**	**Odds ratio[a]**	**95 % CI**	**p-value[b]**
Ranibizumab 0.2 mg (N=74)	56/70 (80.0)	(0.6873, 0.8861)	Ranibizumab 0.2 mg vs Laser	2.19	(0.9932, 4.8235)	0.0254
Ranibizumab 0.1 mg (N=77)	57/76 (75.0)	(0.6374, 0.8423)				
Laser (N=74)	45/68 (66.2)	(0.5368, 0.7721)				

CI= confidence interval, M= total number of patients with non-missing value on primary efficacy outcome (including imputed values), n= number of patients with absence of active ROP and absence of unfavourable structural outcome in both eyes 24 weeks after the first study treatment (including imputed values),
If a patient died or switched study treatment before or at Week 24, then the patient was considered as having active ROP and unfavourable structural outcomes at Week 24.
[a] Odds ratio is calculated by using the Cochran-Mantel-Haenszel test with ROP Zone at baseline (Zone I and II; per CRF) as stratum factor. Multiplicity is controlled by sequential testing.
[b] one-sided p-value for pairwise comparison.
Source: [Study H2301-Table 11-5]

A pre-specified sensitivity analysis was performed with an alternative imputation rule, whereby results at the Week 20 visit were carried forward to fill in any missing outcomes of active ROP and unfavourable structural outcomes at Week 24 (imputation rule 2). This alternative imputation rule led to the outcome being changed for 1 patient in the ranibizumab 0.2 mg group (status changed from missing to success). Results of this sensitivity analysis were consistent with the primary analysis (see table below).

Table 12. Absence of active ROP and absence of unfavourable structural outcomes in both eyes 24 weeks after initial treatment: comparison between treatment arms – sensitivity analysis with alternative imputation rule (Study H2301, Full Analysis Set)

	Treatment success					
Treatment	**n/M (%)**	**95 % CI**	**Comparison**	**Odds ratio[a]**	**95 % CI**	**p-value[b]**
Ranibizumab 0.2 mg (N=74)	57/71 (80.3)	(0.6914, 0.8878)	Ranibizumab 0.2 mg vs Laser	2.22	(1.0088, 4.8890)	0.0230
Ranibizumab 0.1 mg (N=77)	57/76 (75.0)	(0.6374, 0.8423)				
Laser (N=74)	45/68 (66.2)	(0.5368, 0.7721)				

CI= confidence interval, M= total number of patients with non-missing value on the efficacy outcome (including imputed values), n= number of patients with absence of active ROP and absence of unfavourable structural outcome in both eyes 24 weeks after the first study treatment (including imputed values).
Imputation rule 2, differing from primary endpoint, considers missing outcomes of active ROP and unfavourable structural outcomes at Week 24 as absence of the 2 disease features, if absence of the 2 disease features is observed at Week 20.
[a] Odds ratio is calculated by using CMH test. Multiplicity is controlled by sequential testing.
[b] p-value for pairwise comparison is one-sided.
Source: [Study H2301-Table 11-7]

Other sensitivity analyses with missing data not imputed (Study H2301 - Table 14.2-1.6), missing data imputed as "success" (Table 14.2-1.7), missing data imputed as "failure" (Table 14.2-1.8), using sensitivity logistic regression (Table 14.2-1.10), and using treatment success using ROP Zone information obtained from the IRT (Table 14.2-3.1) were consistent with the primary analysis.

Additional *post hoc* analyses showed that the proportion of patients with treatment success was consistently higher for ranibizumab 0.2 mg vs. laser when deaths were not counted as treatment failures (83.6 % for ranibizumab 0.2 mg vs. 69.2 % for laser; OR=2.34; 95 % CI: 1.0068, 5.449; p=0.0234).

Table 13. Absence of active ROP and absence of unfavourable structural outcome in both eyes 24 weeks after first study treatment: comparison between arms - death not considered as treatment failure. Study H2301, Full Analysis Set SCE Appendix 1-Table 2-1

Table 2-1 (Page 1 of 1)
Absence of active ROP and absence of unfavorable structural outcome in both eyes 24 weeks after the first study treatment: comparison between treatment arms - death not considered as treatment failure
Full Analysis Set

Treatment	Absence of events n/M (%)	95% CI	Comparison	Odds Ratio [a]	95% Confidence Interval	p-value [b]
Ranibizumab 0.2 mg (N=74)	56/67(83.6)	(0.7252, 0.9151)	Ranibizumab 0.2 mg vs Laser	2.34	(1.0068, 5.4494)	0.0234
			Ranibizumab 0.1 mg vs Laser	1.64	(0.7564, 3.5413)	0.1063
Ranibizumab 0.1 mg (N=77)	57/73(78.1)	(0.6686, 0.8692)				
Laser Therapy (N=74)	45/65(69.2)	(0.5655, 0.8009)				

Secondary efficacy analysis results

Individual components of the primary efficacy variable indicating treatment failure

The individual components of the primary efficacy variable at or before 24 weeks after the first study treatment are summarised in the table below. Overall, ranibizumab 0.2 mg showed numerically lower rates of unfavourable structural outcomes and treatment switching at or before Week 24 compared with the laser group; both of these groups had no patients with active ROP (i.e., vessel dilatation of plus disease in at least 2 quadrants or extra-retinal vessels extending from retina into the vitreous) at Week 24.

Active ROP in either eye at or before Week 24 was reported only in the ranibizumab 0.1 mg group (3 patients, 4.3 %). In all 3 cases, active ROP was due to vessel dilatation of plus disease in at least 2 quadrants of the eye but not due to extra-retinal vessels extending from the retina into the vitreous [Study H2301-Table 14.2-5.1b].

Unfavourable structural outcomes (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, and retinal detachment involving the macula) in either eye at or before Week 24 were less frequently reported for ranibizumab 0.2 mg (1 patient, 1.4 %) compared with ranibizumab 0.1 mg (5 patients, 6.7 %) and laser (7 patients, 10.1 %).

An identical number of patients across the treatment groups (4 in each treatment group) died at or before the 24-week assessment. Deaths are further described in Section 5.2.2.1.

A lower proportion of patients in both ranibizumab groups than in the laser group required intervention for ROP in either eye at or before Week 24 with a treatment modality different from the initial treatment modality (i.e., the proportion of patients who switched treatment): 14.9 % for ranibizumab 0.2 mg and 16.9 % for ranibizumab 0.1 mg vs. 24.3 % for laser (see table below). Among the patients receiving ranibizumab 0.2 mg at baseline, fewer than 15 % required additional intervention with another treatment modality and only 1 patient had unfavourable structural outcomes at or before Week 24. In contrast, among the patients receiving laser treatment at baseline, nearly 1 in 4 patients

required intervention with another treatment modality, and over 10 % patients had unfavourable structural outcomes at or before Week 24.

Table 14: Summary of individual components of primary efficacy variable at or before 24 weeks after initial treatment (Study H2301, Full Analysis Set)

Individual component of primary efficacy variable	Ranibizumab 0.2 mg N=74		Ranibizumab 0.1 mg N=77		Laser N=74	
	n/M (%)	95% CI	n/M (%)	95% CI	n/M (%)	95% CI
Have active ROP in either eye at the 24-week assessment visit	0/65 (0.0)	(0.0000, 0.0552)	3/70 (4.3)	(0.0089, 0.1202)	0/62 (0.0)	(0.0000, 0.0578)
Have unfavorable structural outcomes in either eye at or before the 24-week assessment visit	1/73 (1.4)	(0.0003, 0.0740)	5/75 (6.7)	(0.0220, 0.1488)	7/69 (10.1)	(0.0418, 0.1979)
Death at or before 24-week assessment visit	4/74 (5.4)	(0.0149, 0.1327)	4/77 (5.2)	(0.0143, 0.1277)	4/74 (5.4)	(0.0149, 0.1327)
Requires 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 study treatment	11/74 (14.9)	(0.0766, 0.2504)	13/77 (16.9)	(0.0931, 0.2714)	18/74 (24.3)	(0.1510, 0.3569)

CI= confidence interval, M= total number of patients with non-missing outcomes for the specific category, n= number of patients met the specific category of the primary endpoint.
The 95% CI is using Clopper-Pearson exact method.
Source: [Study H2301-Table 11-8]

Individual components of the primary efficacy variable by ROP zone are summarised in Table 18.

Table 15. Summary of individual components of primary efficacy variable at or before 24 weeks after the first study treatment, by ROP Zone, secondary efficacy (Study H2301, Full Analysis Set)

	Ranibizumab 0.2 mg N=74		Ranibizumab 1.1 mg N=77		Laser N=74	
ROP Zone						
Individual component of primary efficacy variable	**n/M (%)**	**95% CI**	**n/M (%)**	**95% CI**	**n/M (%)**	**95% CI**
All patients						
Death at or before 24-week assessment visit	4/74 (5.4)	(0.0149, 0.1327)	4/77 (5.2)	(0.0143, 0.1277)	4/74 (5.4)	(0.0149, 0.1327)
Requires 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 study treatment	11/74 (14.9)	(0.0766, 0.2504)	13/77 (16.9)	(0.0931, 0.2714)	18/74 (24.3)	(0.1510, 0.3569)
Have active ROP in either eye at the 24-week assessment visit	0/65 (0.0)	(0.0000, 0.0552)	3/70 (4.3)	(0.0089, 0.1202)	0/62 (0.0)	(0.0000, 0.0578)
Have unfavorable structural outcomes in either eye at or before the 24-week assessment visit	1/73 (1.4)	(0.0003, 0.0740)	5/75 (6.7)	(0.0220, 0.1488)	7/69 (10.1)	(0.0418, 0.1979)
ROP Zone I						
Death at or before 24-week assessment visit	4/28 (14.3)	(0.0403, 0.3267)	2/30 (6.7)	(0.0082, 0.2207)	1/28 (3.6)	(0.0009, 0.1835)
Requires 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 study treatment	6/28 (21.4)	(0.0830, 0.4095)	6/30 (20.0)	(0.0771, 0.3857)	8/28 (28.6)	(0.1322, 0.4867)
Have active ROP in either eye at the 24-week assessment visit	0/24 (0.0)	(0.0000, 0.1425)	2/28 (7.1)	(0.0088, 0.2350)	0/21 (0.0)	(0.0000, 0.1611)
Have unfavorable structural outcomes in either eye at or before the 24-week assessment visit	0/28 (0.0)	(0.0000, 0.1234)	1/29 (3.4)	(0.0009, 0.1776)	2/23 (8.7)	(0.0107, 0.2804)
ROP Zone II						
Death at or before 24-week assessment visit	0/46 (0.0)	(0.0000, 0.0771)	2/46 (4.3)	(0.0053, 0.1484)	3/46 (6.5)	(0.0137, 0.1790)
Requires 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 study treatment	5/46 (10.9)	(0.0362, 0.2357)	7/46 (15.2)	(0.0634, 0.2887)	10/46 (21.7)	(0.1095, 0.3636)
Have active ROP in either eye at the 24-week assessment visit	0/41 (0.0)	(0.0000, 0.0860)	1/42 (2.4)	(0.0006, 0.1257)	0/41 (0.0)	(0.0000, 0.0860)
Have unfavorable structural outcomes in either eye at or before the 24-week assessment visit	1/45 (2.2)	(0.0006, 0.1177)	4/46 (8.7)	(0.0242, 0.2079)	5/46 (10.9)	(0.0362, 0.2357)

CI=confidence interval, M=total number of patients with non-missing outcomes for the specific category, n=number of patients met the specific category of the primary endpoint, RPO=retinopathy of prematurity.
The primary efficacy variable is absence of active ROP and absence of unfavorable structural outcomes in both eyes at Week 24.
The 95% CI is using Clopper-Pearson exact method.
ROP zone information is obtained from CRF.

Source: Table 14.2-4.1

In a Kaplan–Meier estimate of time to death or to treatment switch or to the first occurrence of unfavourable structural outcomes in either eye up to 24 weeks, the event probability estimate, i.e. the estimated probability that a patient experienced an event prior to Week 24, was lower with ranibizumab 0.2 mg (19.6%) and ranibizumab 0.1 mg (23.7%) than with laser (33.4%) in the overall study population.

Individual unfavourable structural outcomes in either eye at or before 24 weeks after the first study treatment are summarised in the table below. Overall, the number of patients with any unfavourable structural outcomes in either eye at or before 24 weeks after the first study treatment was low (< 5 patients for any unfavourable structural outcome for each treatment group):

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

Post-baseline interventions were allowed in cases of unsatisfactory response, as defined in [Study H2301-Section 9.4.6.4].

Post-baseline intervention in the ranibizumab groups included ranibizumab retreatment or switch to laser. A total of 23 (31.1 %) patients in ranibizumab 0.2 mg group and 24 (31.2 %) patients in ranibizumab 0.1 mg group received post-baseline intervention at or before 24 weeks [SCE-Section 3.2.3.2]. Of these patients receiving any post-baseline intervention, 16 (21.9 %) patients in the ranibizumab 0.2 mg group and 17 (22.4 %) patients in the ranibizumab 0.1 mg group received ranibizumab retreatment [SCS Appendix 1-Table 3-3].

In the laser group, switch to ranibizumab was considered as post-baseline intervention, whereas supplementary laser treatments (e.g., for skip lesions) were considered as part of the initial laser and not as post-baseline intervention if the supplemental laser was performed within 3 days after the Day 8 assessment. A total of 14 (18.9 %) patients in the laser group received post- baseline intervention [Study H2301-Table 11-10], including 13 patients who received ranibizumab and 1 patient who received supplemental laser after the allowed window of 3 days after the Day 8 assessment [Study H2301-Listing 16.2.5-1.2].

Table 16. Summary of unfavourable structural outcomes: at least one unfavourable structural outcome in either eye at or before 24 weeks after the first study treatment (Full Analysis Set)

ROP Zone	Ranibizumab 0.2 mg N=74		Ranibizumab 0.1 mg N=77		Laser N=74	
Unfavorable structural outcomes	**n/M (%)**	**95% CI**	**n/M (%)**	**95% CI**	**n/M (%)**	**95% CI**
All patients						
Retrolental membrane obscuring the view of the posterior pole	0/73 (0.0)	(0.0000, 0.0493)	0/75 (0.0)	(0.0000, 0.0480)	0/69 (0.0)	(0.0000, 0.0521)
Substantial temporal retinal vessel dragging causing abnormal structural features/macular ectopia	1/73 (1.4)	(0.0003, 0.0740)	3/75 (4.0)	(0.0083, 0.1125)	4/69 (5.8)	(0.0160, 0.1418)
Posterior retinal fold involving the macula	1/73 (1.4)	(0.0003, 0.0740)	0/75 (0.0)	(0.0000, 0.0480)	2/69 (2.9)	(0.0035, 0.1008)
Retinal detachment involving the macula	0/73 (0.0)	(0.0000, 0.0493)	3/75 (4.0)	(0.0083, 0.1125)	3/69 (4.3)	(0.0091, 0.1218)
ROP Zone I						
Retrolental membrane obscuring the view of the posterior pole	0/28 (0.0)	(0.0000, 0.1234)	0/29 (0.0)	(0.0000, 0.1194)	0/23 (0.0)	(0.0000, 0.1482)
Substantial temporal retinal vessel dragging causing abnormal structural features/macular ectopia	0/28 (0.0)	(0.0000, 0.1234)	0/29 (0.0)	(0.0000, 0.1194)	1/23 (4.3)	(0.0011, 0.2195)
Posterior retinal fold involving the macula	0/28 (0.0)	(0.0000, 0.1234)	0/29 (0.0)	(0.0000, 0.1194)	0/23 (0.0)	(0.0000, 0.1482)
Retinal detachment involving the macula	0/28 (0.0)	(0.0000, 0.1234)	1/29 (3.4)	(0.0009, 0.1776)	1/23 (4.3)	(0.0011, 0.2195)
ROP Zone II						
Retrolental membrane obscuring the view of the posterior pole	0/45 (0.0)	(0.0000, 0.0787)	0/46 (0.0)	(0.0000, 0.0771)	0/46 (0.0)	(0.0000, 0.0771)
Substantial temporal retinal vessel dragging causing abnormal structural features/macular ectopia	1/45 (2.2)	(0.0006, 0.1177)	3/46 (6.5)	(0.0137, 0.1790)	3/46 (6.5)	(0.0137, 0.1790)
Posterior retinal fold involving the macula	1/45 (2.2)	(0.0006, 0.1177)	0/46 (0.0)	(0.0000, 0.0771)	2/46 (4.3)	(0.0053, 0.1484)
Retinal detachment involving the macula	0/45 (0.0)	(0.0000, 0.0787)	2/46 (4.3)	(0.0053, 0.1484)	2/46 (4.3)	(0.0053, 0.1484)

CI= confidence interval, M= total number of patients with non-missing value for the specific category, n= number of patients having at least one unfavorable structural outcome in either eye at or before 24 weeks after the first study treatment, RPO= retinopathy of prematurity.
The 95% CI is using Clopper-Pearson exact method.
ROP zone information is obtained from CRF.
Source: Table 14.2-5.1a

Additional post hoc analyses

Other endpoints analysed *post hoc* included resolution of plus disease and resolution of proliferation (Stage 3 disease), as defined below:

- Resolution of plus disease (if either eye was assessed as mild plus, moderate plus or severe plus in ≥ 2 quadrants) was evaluated for patients with plus disease at baseline.

Resolution was defined as the first observation of absence of plus disease.

- Resolution of proliferation (Stage 3) was evaluated for patients with ROP Stage 3 at baseline. Resolution of proliferation is reflected by disappearance of Stage 3 and disease improvement, including regression into milder ROP stages e.g. Stage 2, Stage 1 or No ROP, with ROP stage defined as the most severe stage in both eyes.

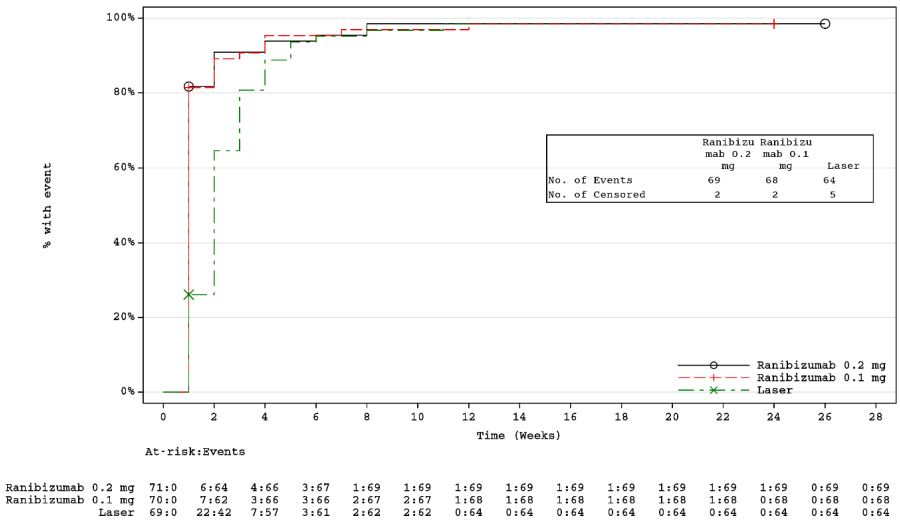
For both resolution of plus disease and resolution of proliferation, patients who died or dropped out/completed the study without resolution were included for censoring. Moreover, recurrences of plus disease or recurrences of proliferation after the resolution were disregarded.

Disease resolution – Resolution of plus disease

The presence of plus disease is an indication of ROP severity and for determining the adequate moment of treatment. Time to resolution of plus disease was defined as the first observation of absence of plus disease.

Resolution of plus disease in 25 % of patients occurred within 3 and 2 days with ranibizumab 0.2 mg and 0.1 mg, respectively (see Figure below), compared to 9 days with laser [SCE Appendix 1-Table 2-8]. The time to 75 % of patients experiencing resolution of plus disease was also considerably shorter in both ranibizumab groups (8 days) compared with the laser group (22.5 days) [SCE Appendix 1-Table 2-8].

Figure 7. Kaplan–Meier plot of time to resolution of plus disease for patients with plus disease at baseline (Study H2301, Full Analysis Set)



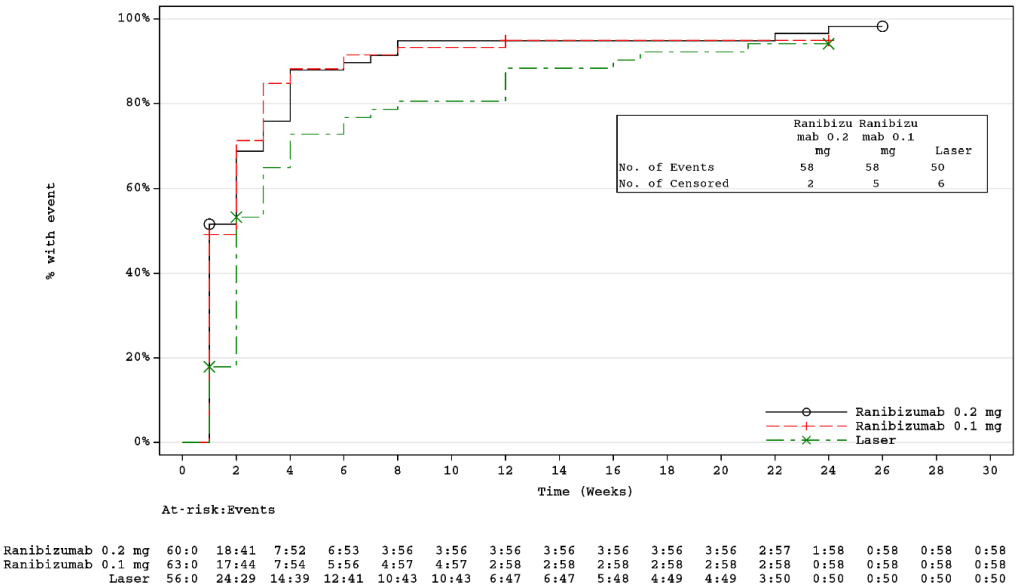
Censored patients are those who completed/dropped out of the study without experiencing resolution of plus disease.
Source: [SCE-Figure 3-2].

Time to resolution of proliferation

As ROP is a vasoproliferative disorder of the retina, proliferation (stage 3) of ROP is associated with unfavourable structural sequelae as well as unfavourable functional outcomes. Hence, proliferation is another indicator of treatment need. Resolution of proliferation is reflected by disappearance of Stage 3 and disease improvement, including regression into milder ROP stages e.g. Stage 2, Stage 1 or No ROP, with ROP stage defined as the most severe stage in both eyes.

The resolution of proliferation started earlier for the ranibizumab groups compared with the laser group, with a separation between ranibizumab 0.2 mg and laser apparent within the first week after initial treatment (see Figure below). Resolution of proliferation in 25 % of patients occurred within 5 days with either ranibizumab 0.2 mg or 0.1 mg compared to 15 days with laser [SCE Appendix 1-Table 2-9]. The time to 75 % of patients experiencing resolution of proliferation was also shorter in both ranibizumab groups (23 and 21 days for ranibizumab 0.2 mg and 0.1 mg, respectively) compared with the laser group (43 days) [SCE Appendix 1-Table 2-9].

Figure 8. Kaplan Meier plot of time to resolution of proliferation (Stage 3) in patients with ROP Stage 3 at baseline (Study H2301, Full Analysis Set)



Censored patients are those who completed/dropped out of the study without experiencing resolution of proliferation.
Source: [SCE-Figure 3-3].

Analyses indicate that both treatments were efficacious but there was a faster resolution of plus disease and resolution of proliferation for ranibizumab 0.2 mg than for laser therapy.

On the other hand, as noted previously, the proportion of patients with recurrence of ROP was higher in both ranibizumab groups than in the laser group (31.1 % and 31.2 % vs. 18.9 %).

A maximum of 3 ranibizumab injections in each eye were allowed in the studies, but 28 subjects appeared to have received 4–6 injections. In response to the RSI, this was appropriately explained by the MAH; in Study H2301, as per protocol, each eye could receive up to a maximum of three injections: the initial treatment plus up to two retreatments. Therefore, a patient could have received a maximum of six injections, i.e. three injections per eye. The patients receiving four-six injection for both eyes were allowed per protocol.

The vast majority of patients in the ranibizumab groups received two injections per patient, or one injection per eye), see table below.

Table 18-1 Treatment success in both eyes 24 weeks after the first study treatment: baseline treatment and retreatment subgroups (Study H2301)

	Treatment success n/M (%)	
	Ranibizumab 0.2 mg	Ranibizumab 0.1 mg
Patients requiring only baseline treatment	44/54 (81.5)	45/59 (76.3)
Patients requiring retreatment	12/16 (75.0)	12/17 (70.6)

n: Number of patients with absence of active ROP and absence of unfavorable structural outcomes in both eyes 24 weeks after the first study treatment (including imputed values).
M: The total number of patients with non-missing value on primary efficacy outcome (including imputed values). If a patient died or switched study treatment before or at Week 24, then the patient was considered as having active ROP and unfavorable structural outcomes at Week 24.
Source: [Appendix 5-Table AR-E4.1]

Subgroup analyses on the primary efficacy endpoint and AEs was performed for patients in the ranibizumab groups receiving only baseline ranibizumab treatment or ranibizumab retreatment. Overall, treatment success was consistent in the ranibizumab-treated patients, regardless whether patients received only baseline injection or were retreated (Table 18-1).

Ancillary analyses

The primary efficacy variable was analysed for the following subgroup variables:

- Gender (male, female)
- Gestational age (≤ 24 weeks, > 24 - < 27 weeks, ≥ 27 weeks)
- Birth weight (≤ 750 g, > 750 - < 1000 g, ≥ 1000 g)
- Geographical region (Region 1 and Region 2, as defined by the IRT)
- Baseline ROP zone (Zone I, Zone II; from CRF)
- AP-ROP status (AP-ROP, non AP-ROP)

Demographic and background factors

The patterns of treatment success in the different subgroups of demographic factors were broadly consistent with those observed for the overall population, although numerical variation was observed in some subgroups, particular those treated with laser.

- By gender, treatment success was achieved by 84.8 % of males and 75.7 % of females at Week 24 after initial treatment with ranibizumab 0.2 mg [Study H2301-Table 14.2-2.5]. The corresponding rates for the laser group were 54.3 % and 78.8 %, respectively.
- By gestational age, the proportion of patients with treatment success at Week 24 after the initial ranibizumab 0.2 mg treatment was 75.9 % for ≤ 24 weeks, 88.9 % for >24 weeks-≤ 27 weeks, and 78.3 % for ≥ 27 weeks [Study H2301-Table 14.2-2.4]. The corresponding rates for the laser group showed a wide variation: 44.4 %, 60.0 % and 92.3 %, respectively.
- By birth weight, the proportion of patients with treatment success at Week 24 after the initial ranibizumab 0.2 mg treatment was 80.6 % for ≤ 750 g, 73.3 % for >750-<1000 g, and 81.3 % for ≥1000 g [Study H2301-Table 14.2-2.2]. The corresponding rates for the laser group showed a wider variation: 51.4 %, 72.7 % and 86.7 %, respectively.
- By geographic region, treatment success was reported for 85.7 % of patients in Region 1 and 71.4 % of patients in Region 2 at Week 24 after initial ranibizumab 0.2 mg treatment [Study H2301-Table 14.2-2.7]. The corresponding rates for the laser group were 61.9 % and 73.1 %, respectively.

When the results of the study were analysed by birth weight and gestational age, ranibizumab treatments seemed to be more effective than laser therapy in the smallest infants groups (⩽750 g, ⩽ 24 weeks); laser therapy reported better response than ranibizumab in the oldest ones (⩾ 27 weeks) and in those weighing more than 1000 g. According to the MAH, differences observed between groups by gestational age and weight are likely due to chance rather than real differences. However, the possibility that more severely preterm infants may respond better to ranibizumab and that less severely preterm infants may respond better to laser cannot be totally excluded.

Disease factors

The patterns of treatment success in the different subgroups of baseline disease factors were broadly consistent with those observed for the overall population, although numerical variation was observed in some subgroups, particular those treated with laser.

- By baseline ROP status, the proportion of patients with treatment success at Week 24 after the initial ranibizumab 0.2 mg treatment was 67.9 % for ROP Zone I and 88.1 % for ROP Zone II [Study H2301-Table 14.2-2.9]. The corresponding rates for the laser group were 60.9 % and

68.9 %, respectively.

- By AP-ROP status, treatment success was reported in 86.7 % of patients with non AP-ROP at Week 24 after initial treatment with ranibizumab 0.2 mg. The corresponding rate for the laser-treated patients with non AP-ROP was 66.7 % [Study H2301-Table 14.2-2.12]. The number of AP-ROP patients was very small (8-10 per treatment group) and does not allow for a definitive subgroup analysis.

The study is part of the clinical development programme and was carried out according to the Paediatric Investigation Plan of Lucentis.

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 %).

When the response was analysed by Zones, patients with ROP Zone II (regardless if they were treated with ranibizumab or laser therapy) globally showed a higher effect than that observed in patients with ROP Zone I. Ranibizumab (both doses) showed a higher rate of success than laser therapy both in Zone I and Zone II, but differences between treatment in patients with posterior Zone I ROP can be considered marginal (ranibizumab 0.2 mg 67.9% vs ranibizumab 0.1 mg 70% vs laser therapy 60.9%). This is rather unexpected since it has been suggested in the literature (Zhang G et al. Retina 2017; 37:710–717; VanderVeen DK et al. Ophthalmology 2017;124:619-633) that ranibizumab (as anti-VEGF agent) is more effective in Zone I ROP while laser therapy would be a preferable option in Zone II ROP. The MAH was requested to further discuss this issue. Overall, it appears that more research is needed before any specific guidance can be established in this respect.

By regions, relevant differences in response were observed between Region 1 and Region 2. Ranibizumab (0.2 mg and 0.1 mg) achieved a high response (>80%), significantly superior to laser therapy (61.9%) in Region 1. In Region 2, 73.1% of infants treated with laser therapy (vs 71.4% on ranibizumab 0.2 mg and 64.5% on ranibizumab 0.1 mg) reached treatment success. It is uncertain

whether these differences between regions are related with baseline characteristics of the premature infants, ROP severity, level of standard care in neonatal intensive units or training in neonatal and ophthalmologic care for premature infants. The MAH was requested to justify the extrapolability of the global study results to the EU population.

In response to the RSI, the MAH performed additional analyses for treatment success of EU and non-EU patients (see Table 19-1 below). Treatment success in the EU was reported in 80.0% (24/30) of patients in the ranibizumab 0.2 mg group, 83.3% (25/30) in the ranibizumab 0.1 mg group and 63.3% (19/30) in the laser group, corresponding to an odds ratio of 2.33 (95% CI: 0.7295, 7.4661) in favour of ranibizumab 0.2 mg vs. laser. Therefore, the MAH considers the results of the Study H2301 population as being applicable and clinically meaningful to the European population.

Table 19-1 Treatment success in both eyes 24 weeks after the first study treatment: comparison between treatment arms – EU vs. non-EU (Study H2301)

	Treatment success				
Treatment	n/M (%)	95% CI	Comparison	Odds ratio[a]	95% CI
EU countries					
Ranibizumab 0.2 mg (N=31)	24/30 (80.0)	(0.6143, 0.9229)	Ranibizumab 0.2 mg vs Laser	2.33	(0.7295, 7.4661)
Ranibizumab 0.1 mg (N=30)	25/30 (83.3)	(0.6528, 0.9436)	Ranibizumab 0.1 mg vs Laser	2.97	(0.8758, 10.0568)
Laser therapy (N=32)	19/30 (63.3)	(0.4386, 0.8007)	-	-	-
Non-EU countries					
Ranibizumab 0.2 mg (N=43)	32/40 (80.0)	(0.6435, 0.9095)	Ranibizumab 0.2 mg vs Laser	2.10	(0.7111, 6.2118)
Ranibizumab 0.1 mg (N=47)	32/46 (69.6)	(0.5425, 0.8226)	Ranibizumab 0.1 mg vs Laser	1.08	(0.4227, 2.7368)
Laser therapy (N=42)	26/38 (68.4)	(0.5135, 0.8250)	-	-	-

CI= confidence interval, M= total number of patients with non-missing value on primary efficacy outcome (including imputed values), n= number of patients with absence of active ROP and absence of unfavourable structural outcome in both eyes 24 weeks after the first study treatment (including imputed values), ROP= retinopathy of prematurity. If a patient died or switched study treatment before or at Week 24, then the patient was considered as having active ROP and unfavourable structural outcomes at Week 24. CMH test was used with ROP Zone at Baseline (I and II) as stratum factor. a Odds ratio is calculated by using CMH test ROP zone information is obtained from CRF. Source: [Appendix 5-Table AR-E3.1]

Nevertheless, differences in response were observed between both Regions. Whereas ranibizumab showed significantly superior response (>80%) than laser therapy (61.9%) in Region 1, laser therapy showed higher treatment success than ranibizumab in Region 2 (73.1% vs 71.4% ranibizumab 0.2mg and 64.5% ranibizumab 0.1 mg).

It is uncertain whether the observed regional differences could be related to e.g. differences in baseline characteristics of the premature infants, ROP severity, level of standard care in neonatal intensive units or training in neonatal and ophthalmologic care for premature infants. Accordingly, the MAH was requested to provide an additional analysis of the primary endpoint components according the two pre-specified geographical regions. No relevant differences were observed in the response between regions except for the number of deaths: 4 in Region 1 (3.0%) and 8 in Region 2 (8.8%). While this could be related to patients' characteristics or the level of neonatal care in the corresponding countries it does not seem to be linked to ranibizumab treatment.

Overall, these findings may indicate clinical benefit for ranibizumab in the treatment of retinopathy of prematurity. 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 and structural changes such as retinal detachment.

In this regard, the results of the IA2 and the final report for H2301E1 could be considered as being important for the benefit-risk assessment of ranibizumab in this new indication.

RAINBOW Extension interim data

The RAINBOW Extension Study (H2301E1) is an ongoing open-label Extension Study of the long-term efficacy and safety of intravitreal ranibizumab compared with laser ablation therapy in patients with ROP who successfully completed the RAINBOW Core Study.

Ranibizumab treatment was permitted for eligible eyes up to and including the Week 40 visit (Epoch 1), corresponding to 40 weeks after a patient received the first study treatment in the Core Study. Treatment with ranibizumab was permitted either as re-treatment for patients, who had received ranibizumab as the last treatment prior to joining the Extension Study, or as switch treatment for patients, who only received laser therapy in the Core Study and required additional treatment in the Extension Study.

Patients who required switch treatment in the Extension Study were administered ranibizumab 0.2 mg. A maximum of 3 ranibizumab injections in each eye were allowed during the combined time period of the Core Study plus Epoch 1 of the Extension Study. The remainder of the Extension Study (Epoch 2) is observational.

All analyses were carried out on the Extension Safety Set. The Extension Safety Set is defined as the subset of the patients from the Safety Set of the Core Study who entered the Extension Study.

At the time of the data cut-off date of 31 December 2017 for the interim analysis IA1, data on structural abnormalities and AEs reported for the IA1 dataset were available in a total of 144 patients (50, 51 and 43 in the ranibizumab 0.2 mg, 0.1 mg and laser groups, respectively). Of these 144 patients, 143 had completed the Week 40 visit and 1 patient who had received laser treatment in Study H2301 died prior to Week 40.

The amended protocol of the Extension Study 2014-004048-36 (PIP number: 000527-PIP04-13) version v01 introduced measures to explore visual acuity at the child's 2 and 3 years' corrected age (Cardiff Acuity test), the refraction in each eye at the child's 3 years' corrected age (diopters) and visual function as per the responses collected on the vision function form (qualitative assessment) to capture visual function and peripheral vision at a supplemental visit at the patient's fifth birthday.

In the first RSI the Applicant was requested to present and discuss all available results on functional testing of vision. In response to this request, the MAH has included an additional, supplementary IA (supp-IA) that contains available results of vision function outcomes and safety from the ongoing H2301E1 study. This supp-IA has been conducted using a cut-off date of 06-Feb-2019 and it was explained that the next (predefined) interim analysis (IA2) is planned after the last patient has completed the visit at the corrected age of two years. The results are planned to be available in Q4 2019.

Data reported in the supp-IA contain the visual reception of Mullen scale of early learning (104 patients in total), CAT at two years of corrected age (26 patients), vision function rating (VA and peripheral vision) at the supplementary visit (21 and 29 patients, respectively) and safety data (including the growth parameters body weight, body height and head circumference at two years). The results are summarised further below (supp-IA data).

Results

Absence of ocular structural abnormalities

Table 20 below summarises the absence of all ocular structural abnormalities and individual components of ocular structural abnormalities at or before the Week 40 visit in the Extension Safety Set.

Overall, absence of ocular structural abnormalities observed at Week 40 was high in both ranibizumab groups: 49/50 patients (98.0 %) in the ranibizumab 0.2 mg group and 50/51 patients (98.0 %) in the ranibizumab 0.1 mg group; for both ranibizumab groups numerically higher compared with the laser group (38/43 patients [88.4 %]).

Substantial temporal retinal vessel dragging causing abnormal structural features or macular ectopia was reported in 1 patient in the ranibizumab 0.2 mg group and in 4 patients in the laser group. Posterior retinal fold was reported in 1 patient in the ranibizumab 0.2 mg group and in 1 patient in the laser group. Retinal detachment involving the macula was reported in 1 patient in the ranibizumab 0.1 mg group and in 1 patient in the laser group. Retrolental membrane obscuring the view of the posterior pole was not reported for any patient in any treatment group.

Absence of ROP

All patients in the IA1 analysis showed absence of active ROP at 40 weeks post baseline visit.

Recurrence of ROP

Recurrence of ROP, defined as patients receiving any post-baseline intervention up to the Week 40 visit in the IA1 Extension Safety Set, was reported in 13/50 (26.0 %) patients in the ranibizumab 0.2 mg group, in 18/51 (35.3 %) patients in the ranibizumab 0.1 mg group and in 8/43 (18.6 %) patients in the laser group (Table ia1-e1.3). Recurrence of ROP up to 24 weeks was reported for the Core Study in 23 patients (31.1 %) for ranibizumab 0.2 mg, 24 patients (31.2 %) for ranibizumab 0.1 mg and for 14 patients (18.9 %) in the laser group.

Extent of exposure

The number of ranibizumab injections received by eye and by patient up to the Week 40 visit for the Extension Safety Set is presented in the table below. On average, patients in the ranibizumab 0.2 mg and 0.1 mg groups received 2.3 and 2.6 ranibizumab injections, respectively. There were 8 patients who received ranibizumab injections in the laser group; on average, these patients received 2.4 ranibizumab injections. Overall, in the 3 treatment groups (including those who took at least one ranibizumab treatment in the laser group), the majority of patients received 2 ranibizumab injections.

During Epoch 1, of the 144 patients, only one patient received ranibizumab 0.1 mg re-treatment in both eyes at the Extension baseline visit. No other patient received study treatment in the Extension Study.

Overall, absence of ocular structural abnormalities in the IA1 patients up to the Week 40 visit was high in all treatment groups: 49/50 patients (98.0 %) in the ranibizumab 0.2 mg group, 50/51 patients (98.0 %) in the ranibizumab 0.1 mg group and 38/43 patients (88.4 %) in the laser group. – Active ROP was not reported in any patient at the Week 40 visit.

Recurrence of ROP up to the Week 40 visit was reported in 13/50 (26.0 %) patients in the ranibizumab 0.2 mg group, 18/51 (35.3 %) patients in the ranibizumab 0.1 mg group and in 8/43 (18.6 %) patients in the laser group. A similar trend was observed in the Core Study. The higher recurrence rate in the ranibizumab groups may be explained by the fact that laser photocoagulation therapy is known to destruct peripheral tissue responsible for continuous elevation of VEGF.

Table 17. Absence of all ocular structural abnormalities and individual components of ocular structural abnormalities at or before 40 weeks post baseline. Extension Safety Set

Absence of all ocular structural abnormalities, and individual components of ocular structural abnormalities at or before 40 weeks post baseline visit
Extension Safety Set

	Ranibizumab 0.2 mg N = 50		Ranibizumab 0.1 mg N = 51		Laser N = 43	
	n/M (%)	95% CI (1)	n/M (%)	95% CI (1)	n/M (%)	95% CI (1)
Absence of all ocular structural abnormalities at or before 40 weeks post core baseline visit	49/50 (98.0)	(0.8935, 0.9995)	50/51 (98.0)	(0.8955, 0.9995)	38/43 (88.4)	(0.7492, 0.9611)
Absence of individual ocular structural abnormality at or before 40 weeks post core baseline visit						
- Absence of substantial temporal retinal vessel dragging causing abnormal structural features/ macular ectopia	49/50 (98.0)	(0.8935, 0.9995)	51/51 (100)	(0.9302, 1.0000)	39/43 (90.7)	(0.7786, 0.9741)
- Absence of Retrolental membrane obscuring the view of the posterior pole	50/50 (100)	(0.9289, 1.0000)	51/51 (100)	(0.9302, 1.0000)	43/43 (100)	(0.9178, 1.0000)
- Absence of posterior retinal fold involving the macula	49/50 (98.0)	(0.8935, 0.9995)	51/51 (100)	(0.9302, 1.0000)	42/43 (97.7)	(0.8771, 0.9994)
- Absence of retinal detachment involving the macula	50/50 (100)	(0.9289, 1.0000)	50/51 (98.0)	(0.8955, 0.9995)	42/43 (97.7)	(0.8771, 0.9994)

n: Number of subjects not showing the ocular abnormality specified in the first column.
M: The total number of subjects with at least one non-missing value for the specific categorical variable.
- The 95% confidence interval for the proportion using Clopper-Pearson exact method.
- The absence of ocular structural abnormalities is defined by the absence of all of the following fundus features in both eyes at or before the given time point:

The absence of ocular structural abnormalities at Week 40 was high in both ranibizumab groups, and higher in both compared with the laser group. Active ROP was not reported in any patient at 40 weeks post baseline visit.

The proportion of IA1 patients who received post-baseline intervention was 26.0 % in the ranibizumab 0.2 mg group, 35.3 % in the ranibizumab 0.1 mg group and 18.6 % in the laser group, comparable to those reported at Week 24 in the Core Study (31.1 %, 31.2 % and 18.9 %, respectively. = 31/101 (30,7 %) vs. 8/43 (18.6 %), a difference of 165%.

As an explanation, the Applicant hypothesises 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 outcomes. The hypothesis could be considered plausible, but the claimed increased risk for less favourable structural and visual outcomes in laser therapy in comparison with ranibizumab needs to be substantiated, most likely by long-term follow up.

The Applicant was requested to further discuss the observed difference between ranibizumab and laser groups in post-baseline interventions. It was clarified that supplementary laser treatments were also allowed; as stated in the protocol (v02) and CSR, multiple supplementary laser treatments were allowed for both eyes until 3 days after the Day 8 assessment and such treatments were considered part of the complete laser treatment. Overall, 11 patients (14.9%) in the laser group received this supplementary laser treatment within the allotted time window. Accordingly, it can be agreed that the three treatment groups were similar within the referred to time period (up to Week 24).

Ranibizumab treatment was permitted for eligible eyes up to and including the Week 40 visit (Epoch 1), corresponding to 40 weeks after a patient received the first study treatment in the Core Study. A

maximum of 3 ranibizumab injections in each eye were allowed during the combined time period of the Core Study plus Epoch 1 of the Extension Study.

The data for this study is not yet complete; at the time of the data cut-off for the first interim analysis, 144 patients had either completed Week 40 visit (143 patients) or had been discontinued in the extension study H2301E1 prior to Week 40 visit. On the other hand, only 1 of these 144 patients received ranibizumab re-treatment Up to Week 40 of the extension study.

Overall, the completion of the extension study will provide a more complete picture.

Assessment of clinical impact of syringe variation in RAINBOW study

The MAH submitted a supplementary study report to the H2301 CSR: *Assessment of clinical impact of syringe variation in RAINBOW study* (07 May 2018).

This supplementary report presents the results of sensitivity analyses performed to investigate the potential impact of an observed syringe variation on the clinical outcomes in patients randomised to ranibizumab treatment in the RAINBOW study.

Prior to initiation of the RAINBOW study (first patient first visit: 30-Dec-2015), the MAH specified the use of the Becton Dickinson (BD) Plastipak 1 ml syringe for accurate delivery of intravitreal injection of target doses of 0.2 mg (20 µl) and 0.1 mg (10 µl) ranibizumab solutions.

As a consequence of this observed variation, and despite the absence of evidence at the time of investigation that any of the evaluated syringe lots were used in the RAINBOW study, the MAH notified all Health Authorities in countries where the RAINBOW study was being conducted (in October 2017) concerning the potential variance in the technical performance of the specified BD Plastipak 1 ml syringe and committed to further investigate the performance of the syringes used in the study and the potential impact on clinical outcomes.

For the RAINBOW study, Novartis Drug Supply Management (DSM) supplied 'BD Plastipak 1 ml syringe' (ref. 300013/303172) from two lots to the clinical sites where the specified syringe was not locally available. In countries where the specified BD Plastipak 1 ml syringe was available, the Novartis Country Pharma Organizations (CPO) or clinical sites sourced the syringes locally.

Of the 26 countries in which patients were enrolled, 9 countries (Egypt, Japan, Malaysia, Mexico, Romania, Russia, Saudi Arabia, Taiwan and the United States) exclusively received specified BD Plastipak 1 ml syringes provided by Novartis DSM (global supply), from 2 batches manufactured in 2013 and 2014 (lots 1309009 and 1407037). In one clinical site in the US, a non-specified 1 ml syringe was used for 1 patient in addition to the globally supplied syringes. In 15 countries (Austria, Belgium, Croatia, Czech Republic, Estonia, France, Germany, Greece, Hungary, India, Italy, Lithuania, Poland, Turkey and the United Kingdom), the majority of sites used locally sourced, off-the-shelf, specified BD Plastipak 1 ml syringes from different lots, while some sites also used non-specified 1 ml syringes to perform intravitreal injections of the study drug. In 2 countries (Denmark and Slovakia) no patients received any ranibizumab intravitreal injections.

The MAH conducted sensitivity analyses performed to investigate the potential impact of the observed syringe variation on the primary efficacy/pharmacokinetic (PK)/vascular endothelial growth factor (VEGF)/immunogenicity (anti-ranibizumab antibodies) variables, as well as on safety outcomes in the RAINBOW study. In general, patient baseline ROP characteristics were comparable across both ranibizumab treatment groups for both subgroup analyses: global vs. local supply (73 patients vs. 78 patients) and specified BD Plastipak 1 ml vs. non-specified syringes (127 patients vs. 24 patients)

Efficacy and PK variables were analyzed along with the systemic VEGF and anti-ranibizumab antibody levels for the global vs. local supply, and the specified BD Plastipak 1 ml vs. non-specified syringes subgroups. The primary efficacy, PK, VEGF and immunogenicity results observed in the 'global vs. local supply' and the 'specified BD Plastipak 1ml vs. non-specified syringes' subgroups were consistent with those of the overall population. Differences observed in the subgroups due to smaller sample size in certain subgroups need to be interpreted with caution.

The incidence of deaths, ocular and non-ocular AEs and SAEs were generally comparable across both the global vs. local supply and specified BD Plastipak 1 ml vs. non-specified syringes subgroups and consistent with the overall safety results reported in the study.

The MAH intends to provide the low-volume high-accuracy syringe and an injection needle in a standalone device kit (VISISURE), to be used in combination with Lucentis 10 mg/ml solution for injection in vial in the European Union.

No meaningful differences were observed. However, the respective subgroups were of modest size. Considering in vitro dose accuracy results for syringe lots used in paediatric clinical investigations provided by the MAH, it appears as if the doses administered using the 1-ml Plastipak™ syringe from Becton Dickinson in the RAINBOW study were higher than the target doses 10 and 20 microliter. The low-volume high-accuracy syringe intended for clinical use is likely to deliver a dose closer to the target dose.

Accordingly, the Applicant was asked to discuss whether this could have an impact on the efficacy of the treatment. It can be agreed with the Applicant that the impact on efficacy by the small volume difference from the low-volume high-accuracy syringe, if any, will be not be of clinical relevance.

Regarding the low-volume high-accuracy syringe in the standalone device kit proposed by the MAH, it should be noted that adults and preterm infants represent very different target populations with different needs (the number of candidates and the frequency of treatment is much higher in the adult than in the preterm population). In addition, the use of the commercially available vial for preterm infants implies discarding a relevant part of the total volume of the product. Finally, the product information for this indication/population will partially differ from the currently approved one. With this in mind, the development of a specific pre-filled low-volume syringe would have been the preferred option to minimise medication errors. This would allow providing the suitable dose/volume of 0.02 ml with its own product information (specific to the preterm infants). The current proposal is acceptable, however.

Long-term vision outcomes from supp-IA (cut-off 06-Feb-2019, submitted in Applicant's response to RSI)

The results of visual reception Mullen sub-scale, CAT and vision function assessment are summarized in the table below.

Table 18. Supplementary Interim Analysis data on vision function – Study H2301E1

	Ranibizumab 0.2 mg N=61	Ranibizumab 0.1 mg N=65	Laser N=54
n	37	38	29
Visual reception of the Mullen scale (T score, mean (SD)) at year 2	37.2 (12.70)	39.3 (14.04)	37.7 (12.40)
n	9	13	4
Cardiff Acuity Test (CAT, mean (SD)) [a]	0.37 (0.260)	0.40 (0.303)	0.63 (0.222)
Snellen equivalent of the mean CAT	20/40 – 20/50	20/50	20/80 – 20/100
n	5	8	8
Vision function rating – visual acuity [a]	4 normal 1 minor impairment	7 normal 1 minor impairment	7 normal 1 major impairment
n	6	14	9
Vision function rating – peripheral vision [a]	4 normal 1 minor impairment 1 Not available	8 normal 1 minor impairment 5 Not available	7 normal 1 major impairment 1 Not available

[a] binocular results presented, for VA from CAT at Year 2, summary statistics in LogMAR as well as mean in Snellen equivalent presented; for vision function rating, results from the supplementary visit are presented.
N represents the number of enrolled patients in the Study H2301E1.
n represents the number of patients with available data for specified assessments.
Source: [Appendix 5-Table ias-e1.1, Table ias–e 2.1, Table ias–e3.1 and Table ias–e 3.2].

Visual reception was assessed using the corresponding Mullen sub-scale at the corrected age of two years in Study H2301E1 and is presented as T score. The T score is an age-calibrated and standardized rating of the subscales of Mullen scale of early learning. Results of the visual reception subscale of the Mullen scale at two years corrected age have shown a mean T score of 37.2 to 39.3, which was well-distributed across the ranibizumab and laser treatment groups. The visual reception subscale scores were overall numerically similar across the treatment groups, indicating that there were no detrimental effects with ranibizumab treatment compared to laser therapy. The observed distribution of the T-score was towards the lower end of the cognitive scale and consistent to what is reported in a premature, low weight population (Grunau et al 2004, Harel-Gadassi et al 2018; Sommerfelt et al 1996; Vohr et al 1989).

Results of binocular CAT performed at Year 2 are presented in LogMar, the bigger the LogMAR score the poorer the visual acuity. The mean value in Snellen equivalent is also presented for comparison. The average LogMAR VA score (range) of 0.37 (0.1-0.7), 0.40 (0.0-1.1), 0.63 (0.4-0.9) in the ranibizumab 0.2 mg, 0.1 mg and laser treatment groups, respectively, suggest a numerically better vision in the ranibizumab groups than in the laser group. Therefore, despite the small sample size, there is no indication of deteriorating effects of ranibizumab on vision.

In addition, three patients have completed the Year 3 visit and CAT results at the Year 3 visit are available, one in each treatment group. The LogMAR score was 0.0, 0.1 and 0.1 for the patients in the ranibizumab 0.2 mg, 0.1 mg and laser groups, respectively.

Vision function outcome was assessed for VA and peripheral vision based on the routine assessments performed by the investigator in clinical practice, and results are summarized for the binocular vision function rating in the table above. Although it has been acknowledged that there is a lack of established vision function tests which are suitable for this age (when such assessments are performed in clinical practice, the assessments are reported in [Appendix 5-Listing ias–e1.2] for VA, and [Appendix 5-Listing ias-e1.1] for peripheral vision), results from vision function assessments which

were obtained for a few patients at the supplementary visit did not reveal any detrimental signal with ranibizumab treatment.

In summary, no detrimental effects in vision function with ranibizumab treatment were identified from the long-term data up to three years of age.

Summary of main study

The table below summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 19. Summary of efficacy for the RAINBOW study.

Title: RAINBOW study: 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				
Study identifier	CRFB002H2301			
Design	Randomized, open-label, 3-arm, parallel-group, superiority study evaluating the efficacy and safety of intravitreal ranibizumab 0.1 mg, intravitreal ranibizumab 0.2 mg, and laser ablation therapy for the treatment of ROP. Assessments to address the primary objective were performed at Day 169 (24 weeks after starting investigational treatment).			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks not applicable until 5 years of age of the subjects	
Hypothesis	Superiority			
Treatments groups	intravitreal ranibizumab 0.1 mg		77 subjects randomised	
	intravitreal ranibizumab 0.2 mg		74 subjects randomised	
	laser ablation therapy		74 subjects randomised	
Endpoints and definitions	Primary endpoint	ranibizumab 0.2 mg vs. laser therapy	treatment success: absence of active ROP and absence of unfavourable structural outcomes in both eyes 24 weeks after starting study treatment, as assessed by the Investigator	
	Secondary endpoint	ranibizumab 0.1 mg vs. laser therapy	treatment success: absence of active ROP and absence of unfavourable structural outcomes in both eyes 24 weeks after starting investigational treatment, as assessed by the Investigator	
	Secondary endpoint	ranibizumab 0.1 mg vs. 0.2 mg	treatment success: absence of active ROP and absence of unfavourable structural outcomes in both eyes 24 weeks after starting investigational treatment, as assessed by the Investigator	
Database lock	14 December 2017			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set, 24 weeks after the first study treatment			
Descriptive statistics and estimate variability	Treatment group	ranibizumab 0.1 mg	ranibizumab 0.2 mg	laser therapy
	Number of subjects	77	74	74
Effect estimate per comparison	Primary endpoint	Comparison groups		ranibizumab 0.2 mg vs. laser therapy
		Odds Ratio		2.19
		95 % Confidence Interval		0.9932, 4.8235
		P-value		0.0254
	Secondary endpoint	Comparison groups		ranibizumab 0.1 mg vs. laser therapy
		Odds Ratio		1.57
		95 % Confidence Interval		0.7604, 3.2587
		P-value		0.1118
	Secondary endpoint	Comparison groups		ranibizumab 0.1 mg vs. 0.2 mg
		Odds Ratio		1.35
		95 % Confidence Interval		0.6101, 2.9810
		P-value		0.2306

<table>
<tr><td>Notes</td><td colspan="3">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.</td></tr>
<tr><td>Analysis description</td><td colspan="3">Sensitivity analysis (Imputation rule 2 applied): if 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.</td></tr>
<tr><td rowspan="8">Effect estimate per comparison</td><td rowspan="4">Primary endpoint</td><td>Comparison groups</td><td>ranibizumab 0.2 mg vs. laser therapy</td></tr>
<tr><td>Odds Ratio</td><td>2.22</td></tr>
<tr><td>95 % Confidence Interval</td><td>1.0088, 4.8890</td></tr>
<tr><td>P-value</td><td>0.230</td></tr>
<tr><td rowspan="4">Secondary endpoint</td><td>Comparison groups</td><td>ranibizumab 0.1 mg vs. laser therapy</td></tr>
<tr><td>Odds Ratio</td><td>1.57</td></tr>
<tr><td>95 % Confidence Interval</td><td>0.7604, 3.2587</td></tr>
<tr><td>P-value</td><td>0.1118</td></tr>
<tr><td>Analysis description</td><td colspan="3">First interim analysis of the Extension Study: to provide long-term data on structural abnormalities 9 months after start of treatment in the subset of patients for which this data is available, as outlined in the clinical measure of the Paediatric Investigation Plan (the analysis should include at least half of the patients enrolled in the Core Study).</td></tr>
<tr><td>Descriptive statistics</td><td colspan="3">Absence of ocular structural abnormalities at the Week 40 visit:
– 49/50 patients (98.0 %) in the ranibizumab 0.2 mg group,
– 50/51 patients (98.0 %) in the ranibizumab 0.1 mg group and
– 38/43 patients (88.4 %) in the laser group.
Active ROP at Week 40 was not reported in any patient.
Recurrence of ROP up to the Week 40 visit reported in:
– 13/50 patients (26.0 %) in the ranibizumab 0.2 mg group,
– 18/51 patients (35.3 %) in the ranibizumab 0.1 mg group and
– 8/43 patients (18.6 %) in the laser group.
Post-baseline intervention necessary:
– 26.0 % in ranibizumab 0.2 mg group,
– 35.3 % in ranibizumab 0.1 mg group and
– 18.6 % in laser group
Mean number of injections
– 2.3 in ranibizumab 0.2 mg and
– 2.6 in ranibizumab 0.1 mg</td></tr>
</table>

3.5.2. Discussion on clinical efficacy

The MAH is seeking a new indication for Lucentis (ranibizumab) in preterm infants for the treatment of retinopathy of prematurity (ROP). The recommended dose is 0.2 mg given as a single intravitreal injection which can be given bilaterally on the same day. Further treatment may be administered if there are signs of disease activity.

The MAH submitted a randomised, multicenter, open-label, 3-arm, parallel-group, superiority study evaluating the efficacy and safety of intravitreal ranibizumab 0.1 mg, intravitreal ranibizumab 0.2 mg, and laser therapy for the treatment of ROP. A total of 225 preterm infants (mean gestational age 26.1 weeks) with ROP were randomised of which 218 received investigational treatment. Patients should have 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. Treatment success, the primary efficacy variable, was defined as the absence of active ROP and absence of unfavourable structural outcomes before or at 24 weeks. A 3-step sequential testing procedure was used for primary (ranibizumab 0.2 mg against laser) and 2 key secondary comparisons (ranibizumab 0.1 mg against laser and ranibizumab 0.2 mg against 0.1 mg).

The diagnosis and follow-up of the patients was made by using images taken by RetCam digital photography and/or indirect ophthalmoscopy. It was questioned whether differences in the method

used for the selection may have resulted in relevant differences in the final population recruited (according to severity, gestational age, or demographic characteristics) and/or a notable difference in outcome between the two methods. The MAH was requested to provide the number and characteristics of the patients separately, in accordance with the method used and clarify to what degree patients were evaluated with one or both methods and whether there was a notable difference in outcome between the 2 methods for evaluation. However, in response, the MAH explained that most of the infants included were evaluated by either of the two methods (interchangeably) so that a separate analysis by method would not be informative.

In the Core Study, 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. Statistical significance for superiority was not achieved for 0.2 mg ranibizumab compared with laser ablation therapy (OR: 2.19, CI: 0.9932, 4.8235). Since the efficacy comparison of the first step was not statistically significant (p=0.0254), the remaining efficacy comparisons were assessed descriptively. In the study, a non-inferiority test was not planned, and a non-inferiority margin was therefore not defined. Defining a non-inferiority margin post hoc is difficult as the choice may be suspected to depend on the outcome of the study (CPMP/EWP/482/99). However, with the achieved confidence interval (0.9932, 4.8235), it appears from the data that ranibizumab is at least as efficient as laser therapy with regard to the primary endpoint. The findings were further supported by the conducted sensitivity analyses.

During the follow-up period rescue therapy was permitted. In case of unsatisfactory response infants could be retreated with the assigned treatment or switched to another treatment (patients who received ranibizumab as initial treatment could switch to laser therapy and vice versa). The MAH was requested to clarify when unresponsive patients received retreatment with the same modality and when they were switched to another treatment modality and how standardization of this process was assured. In response to the RSI, the MAH explained that infants were retreated with the baseline treatment or switched over to a different treatment modality based on investigator's decision. No pre-defined criteria were established. Accordingly, no specific recommendations can be included in the SmPC. However, the MAH has updated the wording for section 4.2 of the SmPC in order to limit the administration of ranibizumab up to three injections, which is acceptable.

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. On the other hand, 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. Should these results translate to favourable findings for visual functioning, then they could be argued to be clinically relevant. However, this is currently not fully known.

The first interim analysis on the Extension Study provided additional data on the need for re-treatment, structural changes in the eye fundus and important safety data. Overall, the absence of ocular structural abnormalities observed at Week 40 was high in both ranibizumab groups, and higher than in the laser group. Importantly, all patients in the IA1 analysis showed absence of active ROP at 40 weeks post baseline visit.

Ranibizumab treatment was permitted for eligible eyes up to and including the Week 40 visit (Epoch 1), corresponding to 40 weeks after a patient received the first study treatment in the Core Study. A maximum of 3 ranibizumab injections in each eye were allowed during the combined time period of the Core Study plus Epoch 1 of the Extension Study. The data for this study is not yet complete; at the time of the data cut-off for the first interim analysis, 144 patients had either completed Week 40 visit (143 patients) or had been discontinued in the extension study H2301E1 prior to Week 40 visit. On the

other hand, only 1 of these 144 patients received ranibizumab re-treatment Up to Week 40 of the extension study.

The need for repeated injections in this population would be a potential concern from a safety perspective, in terms of repeated exposure to ranibizumab and the increased risk for ocular infections. However, 75% of patients in the ranibizumab 0.2 mg group received no more than 2 injections in total (one per eye) and none of the patients in this dose group required re-treatment beyond Week 24.

The majority of subjects were Caucasian (59%) followed by Asian (32%) and African American subjects (3.1%). Overall, 60% of patients were recruited in Region 1 and 40% in Region 2. The wide geographical distribution of patients determines the recruitment of patients with heterogeneous baseline characteristics (including birth weight, gestational age), and different standard of care (including screening of the condition, methods of diagnosis, management of the patients in the Neonatal Intensive Care Units).

Analysed by region, relevant differences in response were observed between Region 1 and Region 2. Ranibizumab (0.2 mg and 0.1 mg) achieved a high response (>80%), significantly superior to laser therapy (61.9%) in Region 1. In Region 2, 73.1% of infants treated with laser therapy (vs 71.4% on ranibizumab 0.2mg and 64.5% on ranibizumab 0.1 mg) reached treatment success. It was questioned whether these differences between regions could be explained by baseline characteristics of the premature infants, ROP severity, level of standard care in neonatal intensive units or training in neonatal and ophthalmologic care for premature infants. Accordingly, the MAH was requested to provide an additional analysis of the primary endpoint components according the two pre-specified geographical regions. No relevant differences were observed in the response between regions except for the number of deaths: 4 in Region 1 (3.0%) and 8 in Region 2 (8.8%). While this could be related to patients' characteristics or the level of neonatal care in the corresponding countries it does not seem to be linked to ranibizumab treatment.

When the response was analysed by Zones, patients with ROP Zone II (regardless they were treated with ranibizumab or laser therapy) globally showed a higher effect than that observed in patients with ROP Zone I. Ranibizumab (both doses) showed higher rate of success than laser therapy both in Zone I and Zone II, but differences between treatments in patients with Zone I ROP can be considered marginal (ranibizumab 0.2 mg 67.9% vs ranibizumab 0.1 mg 70% vs laser therapy 60.9%). This is rather unexpected since it has been suggested in the literature (Zhang G et al. Retina 2017; 37:710–717; VanderVeen DK et al. Ophthalmology 2017;124:619-633) that ranibizumab (as anti-VEGF agent) is more effective in Zone I ROP while laser therapy would be a preferable option in Zone II ROP. The MAH was requested to further discuss this issue. Overall, it appears that more research is needed before any specific guidance can be established in this respect.

Functional testing is described in the amended protocol submitted with the current application. However, no data on visual acuity or visual fields has yet been provided. The amended protocol introduces measures to explore visual acuity at the child's 2 and 3 years' corrected age (Cardiff Acuity test) and 5 years (ETDRS visual acuity test), refraction in each eye and visual function as per the responses collected on a vision function form (qualitative assessment) at a supplemental visit to capture visual function, and peripheral vision at the patient's fifth birthday.

In response to the initial RSI, the MAH has already included an additional, supplementary IA (supp-IA) that contains available results of vision function outcomes and safety from the ongoing H2301E1 study. This supp-IA has been conducted using a cut-off date of 06-Feb-2019.

Data reported in the supp-IA contain the visual reception of Mullen scale of early learning, an instrument to examine cognitive development (104 patients in total), CAT at two years of corrected age (26 patients), vision function rating (VA and peripheral vision) at the supplementary visit (21 and

29 patients, respectively) and safety data (including the growth parameters body weight, body height and head circumference at two years).

No detrimental effects in vision function with ranibizumab treatment were identified in these preliminary, partial data. No differences were apparent between patients treated with ranibizumab (either 0.1 mg or 0.2 mg) and laser therapy. This assessment of visual acuity is, however, based on very few patients and not considered sufficient to conclude on the long-term benefit of ranibizumab; however, they do not raise further concerns at this time.

The documentation of efficacy is compromised by a low number of subjects and the relatively short follow-up time. Lack of data on visual acuity and visual fields is considered a major weakness, as the eyes will still continue to develop for several years. Whatever data will become available from the Extension Study during the review period still involves significant uncertainties regarding the long-term outcome.

In line with this concern, a recent Cochrane review concluded that 'intravitreal bevacizumab/ranibizumab, when used as monotherapy, reduces the risk of refractive errors during childhood, but does not reduce the risk of retinal detachment or recurrence of ROP in infants with type 1 ROP. While the intervention might reduce the risk of recurrence of ROP in infants with zone I ROP, it can potentially result in higher risk of recurrence requiring retreatment in those with zone II ROP.

However, in the current study, late recurrence beyond 40 weeks after initial treatment was not observed, and the majority of patients received only one injection per eye.

Overall, the current data available are still insufficient to conclude on long-term visual outcome. In addition, it has been noted that the study protocol does not require the visual function assessor to be blinded to the assigned treatment allocation. To reduce bias, a protocol amendment should be implemented to require this to be the case, at the 5th year of age visual acuity assessment. In response to the second RSI, the MAH has agreed to implement a new protocol amendment that contains the requirement of a masked VA assessor for the visual acuity assessment at 5 years of age, which is the primary endpoint of the Study H2301E1.

The initially proposed indication (treatment of ROP in premature infants) was broader compared with the study population, which included patients with bilateral ROP with 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 AP-ROP (aggressive posterior retinopathy of prematurity). The indication has now been updated to reflect the patient population included in the study. In addition, the indication is now more consistent with recommendations for treatment stated in recent literature. According to guideline for screening examination of premature infants with ROP (Fierson, et al, Dec 2018), treatment should be initiated for Zone I ROP (any stage with plus disease); Zone I ROP stage 3 (no plus disease); as well as Zone II (stage 2 or 3 with plus disease).

Thus, the revised indication appears to be acceptable at this stage. However, positive results from the IA2 and the final report would be considered highly relevant for a continued positive benefit/risk balance of the product for this indication.

Initially, the MAH proposed to provide efficacy and safety results of IA2 as post approval commitment, as well as the submission of the final report submission in Q2 2023 (both Category 3).

However, given that the initial efficacy assessment is based on surrogate endpoints, this would require verification of the impact of the intervention on clinical outcome or disease progression or confirmation of previous efficacy assumptions. Accordingly, during the 2nd RSI, it was considered that the results of the IA2 and the final report for H2301E1 should be subject to a Category 1 commitment (Annex II D condition) as a PAES, interventional, with a due date Q2 2023, and including other relevant milestones.

In response to the second RSI, the MAH has agreed to this request. The submitted RMP version 18.2 includes this PAES, classified as a Category 1 commitment with due dates of 30 June 2020 for the results of IA2 and 30 June 2023 for the final CSR.

The doses administered using the 1-ml Plastipak™ syringe from Becton Dickinson in the RAINBOW study appeared to be higher than the target doses of 10 and 20 microliter. The Low volume high accuracy syringe intended for clinical use is likely to deliver a dose closer to this target dose. However, the slight discrepancy between the dose to be used in clinical practice and the actual doses tested in the RAINBOW study is not considered to be of clinical concern. The MAH is proposing to provide the low-volume high-accuracy syringe in the standalone device kit proposed by the MAH. In this respect it should be noted that adults and preterm infants represent very different target populations with different needs (the number of candidates and the frequency of treatment is much higher in the adult than in the preterm population). In addition, the use of the commercially available vial for preterm infants implies discarding a relevant part of the total volume of the product. Finally, the product information for this indication/population will partially differ from the currently approved one. With this in mind, developing a specific pre-filled low volume syringe would have been a preferred option to minimize medication errors. It will allow providing the suitable dose/volume of 0.02 ml with its own product information (specific to the preterm infants). However, the company has provided sufficient additional justification that the low volume high accuracy syringe is a safe and suitable option for this patient population.

3.5.3. Conclusions on the clinical efficacy

The results of the IA2 and the final report for H2301E1 have been implemented as a Category 1 commitment (Annex II D condition) as a PAES, interventional. In addition, the MAH has agreed to take measures to reduce bias in the visual acuity assessments in the ongoing extension study and has sufficiently addressed other outstanding concerns.

Accordingly, the benefit–risk for ranibizumab for the treatment of retinopathy of prematurity (ROP) in preterm infants can be considered positive from a clinical efficacy point of view.

3.6. Clinical safety

3.6.1. Introduction

Lucentis (ranibizumab) has been marketed in the EU since the International Birth Date (IBD) of 22 Jan 2007 with the nAMD indication. Lucentis is currently indicated in four adult indications. Total post-marketing patient exposure based on the number of ranibizumab vials and ranibizumab pre-filled syringes (PFS) sold worldwide since the IBD of the product is estimated to be approximately 3,771,644 patient-treatment years (PTY) (PSUR 13). The overall safety profile of Lucentis in adults is well characterised.

The majority of adverse reactions reported following administration of Lucentis are related to the intravitreal injection procedure. From the previously conducted clinical trials, the most frequently reported (very common) ocular adverse reactions are:

Vitritis, vitreous detachment, retinal haemorrhage, visual disturbance, eye pain, vitreous floaters, conjunctival haemorrhage, eye irritation, foreign body sensation in eyes, lacrimation increased, blepharitis, dry eye, ocular hyperaemia, eye pruritus.

The most frequently reported (very common) non-ocular adverse reactions are nasopharyngitis, headache, arthralgia and intraocular pressure (IOP) increased.

Less frequently reported (common), but more serious, ocular adverse reactions include retinal detachment, retinal tear and iatrogenic traumatic cataract.

Less frequently reported (common) non ocular adverse reactions are urinary tract infection, anaemia, hypersensitivity, anxiety, cough, nausea and allergic reactions.

Rarely reported (uncommon) ocular adverse reactions include endophthalmitis, blindness, hypopyon, hyphamia, keratopathy, iris adhesion, corneal deposits, corneal oedema, corneal striae, injections site pain, injection site irritation, abnormal sensation in eye and eyelid irritation.

There is a theoretical risk of arterial thromboembolic events, including stroke and myocardial infarction, following intravitreal use of VEGF inhibitors. In the wet AMD phase III studies, non-ocular haemorrhages, an adverse event potentially related to systemic VEGF (vascular endothelial growth factor) inhibition, was slightly increased in ranibizumab-treated patients, without a consistent pattern among the different haemorrhages. An increased risk for death, CVA and vascular death following monthly dosing of ranibizumab (0.5 mg) in DME patients compared to sham and laser treatment, has been reported (studies RIDE and RISE).[1]

These issues for the adult indications were raised and thoroughly assessed during the PAM (EMEA/H/C/715 LEG 071. However, no change to the product information was made and it was concluded that the current SmPC text remains appropriate.

Though, ranibizumab is expected to have low systemic exposure following intravitreal injection, the distinct possibility of its systemic effects cannot be ruled out in the preterm infants with immature, and often impaired, blood-retinal barrier (Law, J AAPOS 2010;14:6-10). Furthermore, a recent Cochrane review (Sankar et al, 2018) pointed to the fact that long-term systemic adverse effects of VEGF-inhibitors are unknown.

3.6.2. Clinical data

The summary of clinical safety is based on the Core Study H2301 (completed) and the interim analysis of the Extension Study H2301E (ongoing), as presented in the in Table 4. Patients who had successfully completed the 24-week Core Study H2301 were invited to participate in the open-label Extension Study (Study H2301E1) to collect long-term efficacy and safety data up to the patient's 5th birthday.

Analysis	Age at assessment	Calendar time
Interim 1	17 months	Cut off 31 Dec 2017
Interim 2	2 years corrected age	Data expected early 2019
Final	5 years	Planned Q4 2022

The 24-week study is part of clinical development programme and was carried out according to the Paediatric Investigation Plan of Lucentis, and described in a full clinical study report (EMA/H/C/715/P46).

[1] Avery et al (2015) JAMA Ophthalmology, 1-9

Study H2301 was a randomised, multicenter, open-label, 3-arm, parallel-group, superiority study evaluating the efficacy and safety of intravitreal ranibizumab 0.2 mg, intravitreal ranibizumab 0.1 mg, and laser therapy for the treatment of ROP.

The study population consisted of male and female preterm infants with a birth weight of <1500 g and with bilateral ROP with 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 retinopathy of prematurity (AP-ROP).

Patients were randomised in a 1:1:1 ratio to one of the following 3 treatment arms to receive at Baseline:

- Intravitreal ranibizumab 0.2 mg to both eyes
- Intravitreal ranibizumab 0.1 mg to both eyes
- Laser therapy to both eyes

Additional information on study design is provided in Clinical efficacy section.

Overall analysis plan

All analyses were based on the Safety analysis set, except for disposition, demographic and other characteristics at Baseline, which were based on the Randomised Set (see efficacy section).

The Safety Set consisted of all patients who received at least one application of study treatment and had at least one post baseline safety assessment. The statement that a patient had no AEs also constituted a safety assessment. Reports using the Safety Set were by initial treatment received at Baseline.

In addition to the pre-planned analyses specified for the CSR, post-hoc analyses were performed for exposure and ocular and non-ocular AEs/SAEs by subgroups.

The submitted efficacy and safety data covers a total study period of 40 weeks and includes infants who were on average 26 gestational weeks of age at inclusion.

During the review period, supplementary data (supp-IA) was submitted including included 177 patients followed-up for more than 18 months, among them 125 patients followed-up for more than two years

The Extension Study H2301E1 is still ongoing and the final evaluation of efficacy is planned for the patients' 5th birthday.

3.6.3. Exposure

3.6.3.1. Exposure to treatment

Core Study

The number of ranibizumab injections in Study H2301 received per patient during the safety observation period is summarised in Table 23.

Table 20. Number of ranibizumab injections received per patient during the safety observation period (Study H2301, Safety Set).

Statistic	Ranibizumab 0.2 mg N=73	Ranibizumab 0.1 mg N=76	Laser N=69
n	73	76	13
Mean	2.4	2.5	2.2
SD	0.93	1.03	0.93
Min	2	2	1
Median	2.0	2.0	2.0
Max	6	6	4
Q1, Q3	2.0, 2.0	2.0, 2.0	2.0, 2.0
Frequency – n (%)			
1	0	0	2 (2.9)
2	57 (78.1)	59 (77.6)	8 (11.6)
3	4 (5.5)	3 (3.9)	1 (1.4)
4	10 (13.7)	9 (11.8)	2 (2.9)
5	0	3 (3.9)	0
6	2 (2.7)	2 (2.6)	0

Patients in ranibizumab groups received bilateral treatment (2 injections) at Baseline.
n= number of patients meeting the criterion (for categorical variables); number of patients with non-missing assessment (for continuous variables), SD= standard deviation.
Note: There was one patient (), randomised to the ranibizumab 0.1 mg group, who received ranibizumab at a dose of 1.0 mg as initial treatment. This patient was included in the ranibizumab 0.1 mg group for all analysis sets. Furthermore, one patient was randomised to the ranibizumab 0.1 mg group and received ranibizumab 0.2 mg at the time of first re-treatment.

In the ranibizumab groups, the majority received only one initial bilateral ranibizumab treatment (i.e., 2 injections, one in each eye), 78.1 % in the ranibizumab 0.2 mg group and 77.6 % in the ranibizumab 0.1 mg group.

The mean number of injections per patient was similar in the two ranibizumab groups (2.4 injections vs. 2.5 injections), which includes the initial bilateral ranibizumab treatment.

The mean number of ranibizumab injections received by eye was 1.2 and 1.3 in the ranibizumab 0.2 mg and 0.1 mg groups, respectively, and 1.2 in in the laser group who switched to ranibizumab.
A total of 13/69 (18.8%) patients in the laser group switched to ranibizumab and received at least 1 injection of ranibizumab 0.2 mg. Most patients in the laser group switching to ranibizumab, received 2 injections (11.6%).

A summary of laser treatment is provided in Table 24.

Table 21. Number of days laser treatment received by patient during the safety observation period (Study H2301, Safety Set).

Statistic	Ranibizumab 0.2 mg N=73	Ranibizumab 0.1 mg N=76	Laser N=69
Number of days laser treatment received			
n	11	10	69
Mean	1.0	1.1	1.2
SD	0.00	0.32	0.43
Min	1.0	1.0	1.0
Median	1.0	1.0	1.0
Max	1.0	2.0	3.0
Q1, Q3	1.0	1.0, 1.0	1.0, 1.0

n = number of patients meeting the criterion (for categorical variables); number of patients with non-missing assessment (for continuous variables).
Number of days laser treatment received: each laser treatment received on a distinctive day is counted as 1 day, bilateral laser treatment received on the same day is also counted as 1 day.
Duration of laser treatment: date of last laser treatment – date of first laser treatment +1.

A total of 21/149 (14.1 %) patients in the ranibizumab groups switched to laser and received at least 1 laser treatment (11 patients in the ranibizumab 0.2 mg group and 10 patients in the ranibizumab 0.1 mg group).

Extension Study

The number of ranibizumab injections received by eye and by patient up to the Week 40 visit for the Extension Safety Set is presented in Table 25.

Table 22. Number of ranibizumab injections received by eye and by subject up to 40 weeks post baseline visit of the core study (Extension Safety Set).

Statistic	Ranibizumab 0.2 mg N=50	Ranibizumab 0.1 mg N=51	Laser N=43
n	50	54	8
Mean	2.3	2.6	2.4
SD	0.64	1.12	1.06
Min	2	2	1
Median	2.0	2.0	2.0
Max	4	6	4
Q1, Q3	2.0, 2.0	2.0, 3.0	2.0, 3.0
Frequency – n (%)			
1	0	0	1 (2.3)
2	41 (82.0)	38 (74.5)	5 (11.6
3	4 (8.0)	2 (3.9)	0
4	5 (10.0)	7 (13.7)	2 (4.7)
5	0	2 (3.9)	0
6	0	2 (3.9)	0

The pattern of injections for patients during the extension phase was in line with that during the core study.

Out of the patients included in the Extension Study, on average, patients received 2.3 and 2.6 ranibizumab injections, in the 0.2 and 0.1 mg ranibizumab group, respectively. There were 8 patients

who received ranibizumab injections in the laser group; on average, these patients received 2.4 ranibizumab injections.

Study H2301 showed that 78.1% and 77.6% of patients in the ranibizumab 0.2 and 0.1 mg group, respectively, received the baseline bilateral injection (counted as two injections per patient, or one injection per eye). ROP recurrence beyond 24 weeks was not observed and repeated injection are not anticipated in this population. Only two patients in the each of the ranibizumab groups required three injection per eye (six injections per patient). No patient received more than three injections in either eye.

3.6.3.2. Re-treatment and rescue treatment (post-hoc analyses)

Re-treatment is discussed in the efficacy section.

Rescue treatment was defined in the study as a switch from ranibizumab to laser within less than 28 days from the last ranibizumab injection, whereas for laser it was defined as a switch occurring at any time after the initial laser (including supplemental laser). Rescue treatment was given to a lower proportion of patients in both ranibizumab groups than in the laser group: 7/73 (9.6 %) patients in the ranibizumab 0.2 mg group, 6/76 (7.9 %) patients in the ranibizumab 0.1 mg group, and13/69 (18.8 %) patients in the laser group.

3.6.3.3. Concomitant medication or treatments

Ocular and non-ocular medications and significant non-drug therapies prior to start of study treatment as well as used on or after the first study treatment administration were overall comparable between treatment groups with no clinically relevant differences. For details see Clinical Study Report of core study.

3.6.3.4. Patient disposition

Core Study H2301

Subject disposition in ranibizumab and laser treated patients are shown in Table 10 above.

A total of 225 patients from 87 sites in 26 countries were enrolled and randomised. The majority of patients (218 patients, 96.9 %) 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 also 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 %).

Seven patients were randomised but did not receive initial treatment and were discontinued from the study. These patients were not included in the Safety Set for safety analyses as they did not receive any study treatment but were included in the Full Analysis Set for efficacy analyses.

Extension Study H2301E1

In Extension Study H2301E1, at the time of the data cut-off for the first interim analysis, 144 patients had either completed Week 40 visit (143 patients) or had been discontinued in the Extension Study prior to Week 40 visit (1 patient discontinued due to death). The patient who discontinued due to death only received initial laser treatment at baseline in the core study.

The number of completers was high, >95 % in all three groups and the most common reason for discontinuation was death, 4 patients in each group.

No of discontinuations due to AE during treatment phase was one patient in the laser group and one patient in the ranibizumab (0.2 mg) group during the follow up phase. Twelve patients discontinued due to death, four in each group.

3.6.3.5. Baseline demographics and disease characteristics

The baseline demographics and disease characteristics have been described above in the Efficacy section.

Growth parameters from supp-IA (cut-off 06-Feb-2019, submitted in Applicant's response to RSI)
At Year 2, growth data (body weight, body height and head circumference) were available from 103 patients for body weight, from 80 patients for body height and from 83 patients for head circumferences [Appendix 5-Table ias–V1.1]. These growth parameters indicated a comparable growth of babies in all three treatment groups. The mean body weight gain at Year 2 visit relative to Baseline was 9867, 9421 and 10021 grams in the ranibizumab 0.2 mg, 0.1 mg and laser treatment groups, respectively, mean gain in body height was 49.9, 50.6, and 50.2 cm, respectively, and mean gain in head circumference was 22.5, 22.1 and 22.2 cm, respectively.

The preliminary data from the supplemental -IA (cut-off date of 06-Feb-2019) for patients at two years of age did not reveal any concerns regarding in growth parameters.

3.6.4. Adverse events

Ocular adverse events

Core Study

The reported ocular adverse events during the 24 week core study are shown in Table 26.

Table 23. Ocular adverse events regardless of study treatment or procedure relationship (greater than or equal to 2 % in any arm) by preferred term (Study H2301, Safety Set).

Preferred term	Ranibizumab 0.2 mg N=73 n (%)	Ranibizumab 0.1 mg N=76 n (%)	Laser* N=69 n (%)	Total N=218 n (%)
Any ocular AEs	**22 (30.1)**	**31 (40.8)**	**23 (33.3)**	**76 (34.9)**
Conjunctival haemorrhage	6 (8.2)	6 (7.9)	2 (2.9)	14 (6.4)
Retinal haemorrhage	6 (8.2)	10 (13.2)	7 (10.1)	23 (10.6)
Retinopathy of prematurity	2 (2.7)	2 (2.6)	4 (5.8)	8 (3.7)
Conjunctivitis	1 (1.4)	6 (7.9)	3 (4.3)	10 (4.6)
Conjunctival hyperaemia	0	0	2 (2.9)	2 (0.9)
Corneal opacity	0	0	2 (2.9)	2 (0.9)
Eye haemorrhage	0	2 (2.6)	1 (1.4)	3 (1.4)
Vitreous haemorrhage	0	4 (5.3)	0	4 (1.8)

AEs with start date on or after the date of first study treatment administration are counted.

Preferred terms are sorted in descending frequency of AEs in the ranibizumab 0.2mg arm. A patient with multiple AEs is counted only once in the "number of patients" row.

A patient with multiple AEs with the same preferred term is counted only once for that preferred term.

* In the laser group, 13 patients (18.8 % received ranibizumab (i.e. were switched to ranibizumab treatment)

Severity

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).

Relation to study treatment/procedure

Overall, during the core study 76 patients (34.9 %) experienced ocular AEs, 30.1 %; 40.8 %; 33.3 % in respective group (Ranibizumab 0.2 mg; 0.1 mg; Laser).

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. Out of the five severe ocular AES, 4 patients had severe events of ROP (1 patient in each ranibizumab 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).

Ocular AEs suspected to be related to study treatment were as expected more common in the ranibizumab groups (11 patients (15.1 %) for ranibizumab 0.2 mg, 12 patients (15.8 %) for ranibizumab 0.1 mg) than in the laser group (6 patients, 8.7 %).

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.

Extension Study

The incidence of ocular adverse events was overall low: 6/50 (12.0 %) patients in the ranibizumab 0.2 mg group, 8/51 (15.7 %) patients in the ranibizumab 0.1 mg group and 4/43 (9.3 %) patients in the laser group.

Overall the most frequently reported ocular AEs (preferred terms) were strabismus (4 patients) and conjunctivitis (4 patients). Most frequently reported ocular AEs (preferred terms) in the ranibizumab 0.2 mg and 0.1 mg and the laser groups, respectively, were strabismus (2, 1 and 1 patients) and conjunctivitis (1, 2 and 1 patients). ROP was reported as an AE preferred term in 1 patient in the ranibizumab 0.1 mg and in 1 patient in the laser group.

The majority of ocular AEs were mild in severity. Ocular adverse events assessed as severe were reported in 1 patient in each group (1 patient with severe strabismus in the ranibizumab 0.2 mg group, 1 patient with severe retinal detachment in the ranibizumab 0.1 mg group, and 1 patient with severe ROP in the laser group).

The adverse drug reactions reported are consistent with the known safety profile of Lucentis in adults.

However, the extension study H2301E1 is still ongoing and the final evaluation of efficacy is planned for the patients' 5th birthday. The preliminary data from a supplemental IA submitted as part of the RSI raised no new concerns regarding ocular and non-ocular safety.

A pooled presentation of ranibizumab groups as requested during the first RSI did not show any unexpected findings the ocular and non-ocular events.

Furthermore, post-baseline interventions due to ROP recurrence were necessary in 26.0 % of patients in the ranibizumab 0.2 mg group, in 35.3 % of patients in the ranibizumab 0.1 mg group and in 18.6 % of patients in the laser group (i.e. in 165 % more subjects in ranibizumab groups that the laser group).

The issue of repeated injection raised in the first RSI with regard to increased exposure as well as increased risk of ocular infections was alleviated by the Applicant by showing that a large majority (almost 80%) of the patients received only one injection/eye and the frequency of endophthalmitis was similar to that in adult indications.

Non-ocular adverse events

Core Study

The reported non-ocular adverse events during the 24-week core study are shown in table below.

Table 24. Non-ocular adverse events regardless of study treatment or procedure relationship (greater than or equal to 3 % in any arm) by preferred term (Study H2301, Safety Set).

Preferred term	Ranibizumab 0.2 mg N=73 n (%)	Ranibizumab 0.1 mg N=76 n (%)	Laser* N=69 n (%)	Total N=218 n (%)
Any non-ocular AE	**62 (84.9)**	**62 (81.6)**	**53 (76.8)**	**177 (81.2)**
Pyrexia	9 (12.3)	6 (7.9)	4 (5.8)	19 (8.7)
Dermatitis diaper	8 (11.0)	6 (7.9)	4 (5.8)	18 (8.3)

Nasopharyngitis	7 (9.6)	7 (9.2)	4 (5.8)	18 (8.3)
Upper respiratory tract infection	6 (8.2)	3 (3.9)	1 (1.4)	10 (4.6)
Anaemia	5 (6.8)	8 (10.5)	5 (7.2)	18 (8.3)
Gastrooesophageal reflux disease	5 (6.8)	6 (7.9)	5 (7.2)	16 (7.3)
Pneumonia	5 (6.8)	1 (1.3)	8 (11.6)	14 (6.4)
Bronchopulmonary dysplasia	4 (5.5)	5 (6.6)	5 (7.2)	14 (6.4)
Cough	4 (5.5)	2 (2.6)	1 (1.4)	7 (3.2)
Diarrhoea	4 (5.5)	2 (2.6)	1 (1.4)	7 (3.2)
Inguinal hernia	4 (5.5)	2 (2.6)	2 (2.9)	8 (3.7)
Urinary tract infection	4 (5.5)	2 (2.6)	2 (2.9)	8 (3.7)
Bronchiolitis	3 (4.1)	4 (5.3)	2 (2.9)	9 (4.1)
Bronchitis	3 (4.1)	3 (3.9)	2 (2.9)	8 (3.7)
Bronchospasm	3 (4.1)	0	1 (1.4)	4 (1.8)
Escherichia urinary tract infection	3 (4.1)	1 (1.3)	0	4 (1.8)
Rhinitis	3 (4.1)	0	2 (2.9)	5 (2.3)
Viral infection	3 (4.1)	1 (1.3)	1 (1.4)	5 (2.3)
Anaemia neonatal	2 (2.7)	4 (5.3)	1 (1.4)	7 (3.2)
Bradycardia	2 (2.7)	5 (6.6)	1 (1.4)	8 (3.7)
Flatulence	2 (2.7)	3 (3.9)	2 (2.9)	7 (3.2)
Vomiting	2 (2.7)	5 (6.6)	4 (5.8)	11 (5.0)
Apnoea	1 (1.4)	6 (7.9)	3 (4.3)	10 (4.6)
Constipation	1 (1.4)	3 (3.9)	2 (2.9)	6 (2.8)
Necrotising colitis	1 (1.4)	3 (3.9)	1 (1.4)	5 (2.3)
Pneumonia bacterial	1 (1.4)	0	3 (4.3)	4 (1.8)
Respiratory failure	1 (1.4)	4 (5.3)	1 (1.4)	6 (2.8)
Sepsis	1 (1.4)	1 (1.3)	5 (7.2)	7 (3.2)
Malnutrition	0	3 (3.9)	0	3 (1.4)
Osteopenia	0	4 (5.3)	2 (2.9)	6 (2.8)
Pneumonia aspiration	0	3 (3.9)	2 (2.9)	5 (2.3)
Umbilical hernia	0	3 (3.9)	2 (2.9)	5 (2.3)

AEs with start date on or after the date of first study treatment administration are counted.
Preferred terms are sorted in descending frequency of AEs in the ranibizumab 0.2 mg arm.
A patient with multiple AEs is counted only once in the “number of patients” row.
A patient with multiple AEs with the same preferred term is counted only once for that preferred term.
* In the laser group, 13 patients (18.8 %) received ranibizumab (i.e., were switched to ranibizumab treatment),

Severity

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.

Relation to study treatment/procedure

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 (discussed below).

Overall during the core study, 177 patients (81.2 %) experienced non-ocular AEs, 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 %).

The non-ocular events were few, primarily mild in severity. This applies also to the patients switching to treatment modality.

The somewhat higher reporting rate of cardiovascular events (bradycardia 6.6% vs 1.4%) and respiratory events (upper respiratory tract infection (8.2% vs 1.4%) was further analysed in the first RSI.

However, due to limited data in general and a high prevalence of co-morbidities, the data is not conclusive.

Extension Study

The incidence of non-ocular AEs was numerically lower in both ranibizumab groups than in the laser group (58.0 %, 58.8 % and 72.1 % in the ranibizumab 0.2 mg and 0.1 mg and the laser groups, respectively).

The most commonly affected System Organ Classes were infections and infestations (46.0 %, 37.3 % and 39.5 % of patients in the ranibizumab 0.2 mg and 0.1 mg and the laser groups, respectively, of which the most frequent event (preferred term) was nasopharyngitis, 12.0 %, 15.7 % and 11.6 %, respectively); respiratory, thoracic and mediastinal disorders (20.0 %, 13.7 % and 25.6 %, respectively, of which the most frequent event was cough, 4.0 %, 5.9 % and 7.0 %, respectively); and metabolism and nutrition disorders (10.0 %, 7.8 % and 9.3 %, respectively, with no specific event being reported in more than 1 patient per group). Most AEs were reported in single or very few patients only.

The majority of non-ocular AEs were reported as mild or moderate in severity. Severe non-ocular AEs were reported in 7.6 % of overall patients, with no major differences between treatment groups: 3/50 (6.0 %) patients in the ranibizumab 0.2 mg group, 4/51 (7.8 %) patients in the ranibizumab 0.1 mg group, and 4/43 (9.3 %) patients in the laser group. Each of the severe AEs were reported in not more than 1 patient overall.

The non-ocular events were few, primarily mild in severity during Extension Study. There were no major differences between treatment groups regarding the frequency of particular preferred terms during the 40-week study.

No evident differences were found between treatment groups during the core and Extension Study with the most frequently reported non-ocular adverse events of pyrexia, dermatitis diaper, nasopharyngitis. No new non-ocular AEs were identified during the 40-week study and in general data is in agreement with the known safety profile of ranibizumab in adults.

Serious adverse event/deaths/other significant events

The proportion of patients who died or experienced SAEs or AEs leading to permanent discontinuation of study treatment are shown in Table 28.

Overall, 12 patients (5.5 %) died during the study; 74 patients (33.9 %) experienced SAEs, and 16 patients (7.3 %) discontinued study treatment due to SAEs. One patient (ranibizumab 0.1 mg group; 1.3 %) discontinued study treatment due to a non-serious AE (mild conjunctivitis in both eyes, not suspected by the Investigator to be related to study treatment or procedure).

Table 25. Number of patients with deaths, SAEs or AEs leading to permanent discontinuation of study treatment (Safety set).

Patients with serious or other significant events	Ranibizumab 0.2 mg N=73 n (%)	Ranibizumab 0.1 mg N=76 n (%)	Laser N=69 n (%)	Total N=218 n (%)

Death	4 (5.5)	4 (5.3)	4 (5.8)	12 (5.5)
SAE(s)	26 (35.6)	24 (31.6)	24 (34.8)	74 (33.9)
Discontinued study treatment due to any AE(s)	6 (8.2)	6 (7.9)	5 (7.2)	17 (7.8)
Discontinued study treatment due to non-serious AE(s)	0	1 (1.3)	0	1 (0.5)
Discontinued study treatment due to any SAE(s)	6 (8.2)	5 (6.6)	5 (7.2)	16 (7.3)

Deaths

Core Study

Table 26. Primary reasons for deaths by preferred term (Safety Set).

Preferred term	Ranibizumab 0.2 mg N=73 n (%)	Ranibizumab 0.1 mg N=76 n (%)	Laser N=69 n (%)	Total N=218 n (%)
Number of patients who died	**4 (5.5)**	**4 (5.3)**	**4 (5.8)**	**12 (5.5)**
Aspiration	1 (1.4)	0	0	1 (0.5)
Bronchopulmonary dysplasia	1 (1.4)	0	1 (1.4)	2 (0.9)
Klebsiella sepsis	1 (1.4)	0	0	1 (0.5)
Pneumonia	1 (1.4)	0	0	1 (0.5)
Cardiac arrest	0	0	1 (1.4)	1 (0.5)
Hepatic failure	0	0	1 (1.4)	1 (0.5)
Necrotising colitis	0	1 (1.3)	0	1 (0.5)
Pulmonary vein stenosis	0	0	1 (1.4)	1 (0.5)
Renal failure	0	1 (1.3)	0	1 (0.5)
Respiratory failure	0	1 (1.3)	0	1 (0.5)
Sepsis	0	1 (1.3)	0	1 (0.5)

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).

The event of respiratory failure was suspected by the Investigator to be related to study treatment. For all other event, no causality to study treatment or procedure was suspected by the Investigator.

Of the patients who switched treatment modality, 1 patient (in the ranibizumab 0.2 mg group) died due to an event of pneumonia. All other deaths occurred in patients who did not switch treatment modality

Extension Study

There was one death reported in the Extension Safety Set (a patient in the laser group). At the time of enrolment in the Extension Study the patient's historical conditions included (reported terms) Sepsis heterolytic staphylococcus and Sepsis pseudomonas aeruginosa. Current conditions included bronchopulmonary dysplasia, myocardial hypertrophy, apnea, periventricular leukomalacia and CMV (cytomegalovirus) infection. The patient had not received any study medication as part of the

Extension Study. The death was due to septic shock and the investigator assessed the event septic shock as not suspected to study treatment.

During the Core Study twelve deaths (four patients in each treatment group) were reported, with the most commonly affected primary SOC Respiratory, thoracic and mediastinal disorders (5 patients (2.3 %) overall), followed by infections and infestations (3 patients (1.4 % overall).

Except for one event of respiratory failure, none of the events leading to death was suspected by the Investigator to be related to study treatment. However, this conclusion that the majority of the deaths were not considered related to study treatment is difficult to fully evaluate, considering the uncertainty regarding the role of VEGF as well as comorbidities in this sensitive population.

Ocular SAEs

Core Study

Table 27. Number (%) of patients with ocular serious adverse events regardless of study treatment or procedure relationship by preferred term (Safety Set)

Preferred term	Ranibizumab 0.2 mg N=73 n (%)	Ranibizumab 0.1 mg N=76 n (%)	Laser N=69 n (%)	Total N=218 n (%)
Number of patients with any ocular SAE	**4 (5.5)**	**1 (1.3)**	**4 (5.8)**	**9 (4.1)**
Retinopathy of prematurity	2 (2.7)	1 (1.3)	3 (4.3)	6 (2.8)
Cataract	1 (1.4)	0	0	1 (0.5)
Nystagmus	1 (1.4)	0	0	1 (0.5)
Conjunctivitis	0	0	1 (1.4)	1 (0.5)
Endophthalmitis	0	1 (1.3)	0	1 (0.5)
Exophthalmos	0	1 (1.3)	0	1 (0.5)
Eye disorder	0	1 (1.3)	0	1 (0.5)
Orbital infection	0	1 (1.3)	0	1 (0.5)

AEs with start date on or after the date of first study treatment administration are counted.

Preferred terms are sorted in descending frequency of AEs in the ranibizumab 0.2 mg arm. w. the same preferred term is counted only once for that preferred term.

The incidence of ocular SAEs was low (9 patients (4.1 %) overall) and the most frequent ocular SAE by PT was ROP, 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 3 patients (4.3 %) in the laser group. All other ocular SAEs (cataract, nystagmus, conjunctivitis, endophthalmitis, exophthalmos, eye disorder, and orbital infection) were each reported for only 1 patient (0.5 %) overall.

The SAE of cataract was suspected by the Investigator to be related to study procedure but not to study treatment, and the SAEs of endophthalmitis, exophthalmos and orbital infection that occurred in one patient were suspected by the Investigator to be related to study procedure and to study treatment.

The Investigator commented that "the relationship between the SAEs and both the study procedure and treatment was suspected because of the short time interval to the onset of SAE". All other ocular SAEs were not suspected by the Investigator to be related to study procedure/study treatment.

Extension Study

The incidence of serious ocular AEs in the Extension Safety Set was 2.8 % overall (4 patients). ROP was reported as an SAE preferred term in 1 patient (2.0 %) in the ranibizumab 0.1 mg group and in 1

patient (2.3 %) in the laser group. Serious retinal detachment and nystagmus was reported in 1 patient each in the ranibizumab 0.1 mg group. No ocular SAEs were reported in the ranibizumab 0.2 mg group.

Overall, at least one ocular SAE was experienced by 9 patients (4.1%) in the core study and 4 patients (2.8%) in the Extension Study. The most frequent ocular SAE was ROP (6 patients, 2.8 % overall in the core study).

Although the number of patients experiencing ocular SAEs were similar in the ranibizumab groups compared to the laser group, more ocular events were reported in the ranibizumab treated patients, which is consistent with the known safety profile in adults. Cataract, endophthalmitis, exophthalmos, and orbital infection were suspected by investigator to be related to study treatment or causality, this is agreed.

In the first review round, the potential risk of frequent injections and increased risk of endophthalmitis was discussed.

In study H2301, 78.1% and 77.6% of the patients in the ranibizumab 0.1 mg and 0.1 mg, respectively received only baseline bilateral injection (counted as two injections per patient or one injection per eye). Only two patients in each ranibizumab groups required three injections per eye (six injections per patient). No patient received more than three injections per eye. Thus, the expected duration of treatment in clinical practice for patients with ROP was clarified in the SmPC (section 4.2).

This together with a summary presenting similar endophthalmitis in the paediatric population as in the approved adult indication, alleviates this concern of an increased risk of endophthalmitis in this population.

As treatment is contraindicated in patients with ocular and periocular infection the MAH was requested to discuss the possible need for defining a strategy for ROP patients with a concurrent systemic infection. Overall, there currently appears to be no data indicating an increased risk in relation to ranibizumab treatment in ROP patients with ongoing systemic infections or an increased risk of exogenous infectious endophthalmitis in such patients.

Non-ocular SAEs

Core Study

Table 28. Number (%) of patients with non-ocular serious adverse events regardless of study treatment or procedure relationship (greater than or equal to 2 % in any arm) by preferred term (Safety Set).

Preferred term	Ranibizumab 0.2 mg N=73 n (%)	Ranibizumab 0.1 mg N=76 n (%)	Laser N=69 n (%)	Total N=218 n (%)
Number of patients with any non-ocular SAE	**24 (32.9)**	**24 (31.6)**	**22 (31.9)**	**70 (32.1)**
Pneumonia	4 (5.5)	0	2 (2.9)	6 (2.8)
Brain oedema	2 (2.7)	0	0	2 (0.9)
Bronchiolitis	2 (2.7)	4 (5.3)	0	6 (2.8)
Bronchopulmonary dysplasia	2 (2.7)	2 (2.6)	2 (2.9)	6 (2.8)
Incarcerated inguinal hernia	2 (2.7)	0	0	2 (0.9)
Inguinal hernia	1 (1.4)	2 (2.6)	0	3 (1.4)
Apnoea	0	2 (2.6)	2 (2.9)	4 (1.8)
Cardio-respiratory arrest	0	2 (2.6)	0	2 (0.9)
Diarrhoea	0	2 (2.6)	0	2 (0.9)

Nasopharyngitis	0	2 (2.6)	0	2 (0.9)
Necrotising colitis	0	3 (3.9)	0	3 (1.4)
Perinatal brain damage	0	0	2 (2.9)	2 (0.9)
Respiratory failure	0	3 (3.9)	1 (1.4)	4 (1.8)
Sepsis	0	1 (1.3)	2 (2.9)	3 (1.4)
Vomiting	0	1 (1.3)	2 (2.9)	3 (1.4)

AEs with start date on or after the date of first study treatment administration are counted. Preferred terms are sorted in descending frequency of AEs in the ranibizumab 0.2 mg arm.

A patient with multiple AEs is counted only once in the 'number of patient' row.

A patient with multiple AEs with the same preferred term is counted only once for that preferred term.

Overall, 70 patients (32.1 %) experienced non-ocular SAEs. The most commonly affected primary SOCs were infections and infestations (31 patients, 14.2 % overall), respiratory, thoracic and mediastinal disorders (22 patients, 10.1 % overall), and gastrointestinal disorders (18 patients, 8.3 % overall).

The most common non-ocular SAEs by PT were pneumonia, bronchiolitis, and bronchopulmonary dysplasia (all 6 patients (2.8 %) overall), followed by apnea and respiratory failure (both 4 patients (1.8 %) overall).

There was 1 patient in the ranibizumab 0.1 mg group (1.3 %) with a non-ocular SAE (respiratory failure) that was suspected by the Investigator to be related to study treatment or procedure. This severe event had a fatal outcome and was reported for a patient who did not switch treatment modality during the study.

There were no clinically relevant differences in the incidence of non-ocular SAEs for patients who switched treatment modality and for patients who did not switch treatment modality.

Extension Study

The incidence of serious non-ocular AEs was comparable across treatment groups (11 patients in each group, corresponding to 22.0 %, 21.6 % and 25.6 % in the ranibizumab 0.2 mg and 0.1 mg groups and the laser group, respectively).

The most frequent serious non-ocular AEs in the ranibizumab 0.2 mg, 0.1 mg and laser group, respectively, were bronchitis (1, 1 and 3 patients) and pneumonia (1, 1 and 2 patients). Apart from these, most of the serious non-ocular AEs were reported for 1 or 2 patients overall.

Taken together, the non-ocular serious AEs in the core study and Extension Study were similar across treatment groups with the primarily affected SOCs were 'Infections and infestations', 'Respiratory, thoracic and mediastinal disorders', and 'Gastrointestinal disorders'. The most common non-ocular SAE (n>5) were pneumonia, bronchitis and bronchopulmonary dysplasia.

Although there was a slight imbalance of higher reporting of respiratory-related events in the ranibizumab groups compared to laser, however, due to confounding factors as and medical history, the data is inconclusive.

Overall, a trend of higher AE incidences reported for patients with lower gestational age (<27 weeks) as well as lower birthweight (≤ 750 g) was observed in the ranibizumab pooled group and the laser group.

This was also reflected in Respiratory, thoracic, and mediastinal disorders (<27 weeks resp <1000g). The same pattern applied to serious AEs with even fewer patients. However, due to the small sample size, this should be interpreted with caution.

Other significant events

Hospitalisation [Study H2301-Table 14.2-11.1] and requirement of respiratory support [Study H2301-Table 14.3-6.1a] and [Study H2301-Table 14.3-6.1b] were analyzed as additional exploratory safety parameters. According to Applicant, no clinically relevant differences were observed between treatment groups.

Laboratory findings

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

Discontinuation due to adverse events

The overall discontinuations in the core study are shown in Table 28.

The ocular events leading to permanent discontinuation of study treatment in the Core Study are shown in Table 32.

Table 29. Ocular adverse events leading to permanent discontinuation of study treatment by preferred term (Study H2301, Safety Set).

Preferred term	Ranibizumab 0.2 mg N=73 n (%)	Ranibizumab 0.1 mg N=76 n (%)	Laser N=69 n (%)	Total N=218 n (%)
Any ocular AE leading to permanent discontinuation of study treatment	1 (1.4)	2 (2.6)	1 (1.4)	4 (1.8)
Retinopathy of prematurity	1 (1.4)	1 (1.3)	1 (1.4)	3 (1.4)
Conjunctivitis	0	1 (1.3)	0	1 (0.5)

AEs with start date on or after the date of first study treatment administration are counted. Preferred terms are sorted in descending frequency of AEs in the ranibizumab 0.2 mg arm.

A patient with multiple AEs is counted only once in the “number of patients” row.

A patient with multiple AEs with the same preferred term is counted only once for that preferred term.

In the core study, there were no ocular AEs leading to permanent study discontinuation.

Overall, 13 patients (6.0 %) had non-ocular AEs leading to permanent discontinuation of study treatment, with a similar proportion of patients across treatment groups (5 patients (6.8 %) in the ranibizumab 0.2 mg group, 4 patients (5.3 %) in the ranibizumab 0.1 mg group, and 4 patients (5.8 %) in the laser group).

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). For the other 12 patients, the reason for discontinuing study treatment in the follow-up phase was death.

In the Extension Study, there were no discontinuations in the ranibizumab groups during the extension, but one patient discontinued in the laser group due to death.

Overall the discontinuations were few and mainly non-ocular events and related to the comorbidity of ROP patients.

Long term safety data from supp-IA (cut-off 06-Feb-2019, submitted in Applicant's response to RSI)

Ocular and non-ocular AEs were assessed for all 180 patients participating in Study H2301E1. Of all 180 patients, three patients discontinued (two patients due to consent withdrawal and one patient due to death) the study before reaching 18 months of safety observation. Therefore, the supp-IA included 177 patients followed-up for more than 18 months, among them 125 patients followed-up for more than two years [Appendix 5-Table ias-S3].

Ocular AEs in Study H2301E1 were reported for 13.1%, 18.5% and 16.7% of patients in the ranibizumab 0.2 mg, ranibizumab 0.1 mg and laser groups, respectively (Table 1-2). Most frequent were strabismus and conjunctivitis, with no major differences between treatment groups. Myopia was reported as AE in a total of 5 patients (1.6%, 1.5% and 5.6% of patients in the ranibizumab 0.2 mg, ranibizumab 0.1 mg and laser groups, respectively). All other events were reported in single patients per treatment arm.

The incidence of ocular SAEs was low; none were reported for the ranibizumab 0.2 mg and the laser groups, and three (4.6%) in the ranibizumab 0.1 mg group (one patient each with retinal detachment, retinopathy of prematurity (AE verbatim progression of retinopathy of prematurity) and nystagmus).

Table 1-2 Ocular adverse events regardless of study treatment or procedure relationship, with onset date on/after extension baseline by preferred term (Study H2301E1, Extension Safety Set)

Preferred term	Ranibizumab 0.2 mg N=61 n (%)	Ranibizumab 0.1 mg N=65 n (%)	Laser N=54 n (%)	Total N=180 n (%)
Patients with any ocular AE	**8 (13.1)**	**12 (18.5)**	**9 (16.7)**	**29 (16.1)**
Strabismus	3 (4.9)	5 (7.7)	3 (5.6)	11 (6.1)
Conjunctivitis	2 (3.3)	2 (3.1)	2 (3.7)	6 (3.3)
Astigmatism	1 (1.6)	1 (1.5)	0	2 (1.1)
Hypermetropia	1 (1.6)	0	0	1 (0.6)
Myopia	1 (1.6)	1 (1.5)	3 (5.6)	5 (2.8)
Swelling of eyelid	1 (1.6)	0	0	1 (0.6)
Eyelid injury	1 (1.6)	0	0	1 (0.6)
Amblyopia	0	1 (1.5)	0	1 (0.6)
Amblyopia strabismic	0	0	1 (1.9)	1 (0.6)
Corneal scar	0	1 (1.5)	0	1 (0.6)
Exposure keratitis	0	1 (1.5)	0	1 (0.6)
Lenticular opacities	0	1 (1.5)	0	1 (0.6)
Maculopathy	0	1 (1.5)	0	1 (0.6)
Retinal detachment	0	1 (1.5)	0	1 (0.6)
Retinopathy of prematurity	0	1 (1.5)	1 (1.9)	2 (1.1)
Rash pustular	0	1 (1.5)	0	1 (0.6)
Nystagmus	0	1 (1.5)	0	1 (0.6)

AEs that start on/after extension baseline are counted.
Preferred terms are sorted in descending frequency of AEs in the ranibizumab 0.2 mg arm.
A patient with multiple AEs is counted only once in the "Patients with any ocular AE" row.
A patient with multiple AEs with the same preferred term is counted only once for that preferred term.
Source: [Appendix 5-Table ias-S1.1a]

Non-ocular AEs were reported for 62.3%, 56.9% and 72.2% of patients in the ranibizumab 0.2 mg and 0.1 mg groups and the laser group, respectively (Table 1-3). Most frequent were nasopharyngitis (14.3% overall), pyrexia (10.6%) and bronchitis (8.9%). Generally, no major differences were noted across the three treatment groups.

Non-ocular SAEs were reported for 29.5%, 29.2% and 33.3% of patients in the ranibizumab 0.2 mg and 0.1 mg groups and the laser group, respectively (Table 1-4). Most frequent overall were bronchitis (0%, 4.6% and 9.3% of patients in the ranibizumab 0.2 mg and 0.1 mg groups and the laser group, respectively) and pneumonia (3.3%, 1.5% and 5.6%, respectively).

Table 1-3 **Non-ocular adverse events regardless of study treatment or procedure relationship (greater than or equal to 4% in any arm), with onset date on/after extension baseline by preferred term (Study H2301E1, Extension Safety Set)**

Preferred term	Ranibizumab 0.2 mg N=61 n (%)	Ranibizumab 0.1 mg N=65 n (%)	Laser N=54 n (%)	Total N=180 n (%)
Patients with any non-ocular AE	**38 (62.3)**	**37 (56.9)**	**39 (72.2)**	**114 (63.3)**
Nasopharyngitis	10 (16.4)	9 (13.8)	7 (13.0)	26 (14.4)
Pyrexia	6 (9.8)	6 (9.2)	7 (13.0)	19 (10.6)
Otitis media	4 (6.6)	1 (1.5)	3 (5.6)	8 (4.4)
Bronchitis	3 (4.9)	6 (9.2)	7 (13.0)	16 (8.9)
Ear infection	3 (4.9)	2 (3.1)	1 (1.9)	6 (3.3)
Pneumonia	3 (4.9)	1 (1.5)	3 (5.6)	7 (3.9)
Respiratory tract infection viral	3 (4.9)	2 (3.1)	1 (1.9)	6 (3.3)
Cough	3 (4.9)	4 (6.2)	4 (7.4)	11 (6.1)
Constipation	2 (3.3)	4 (6.2)	1 (1.9)	7 (3.9)
Diarrhoea	2 (3.3)	4 (6.2)	2 (3.7)	8 (4.4)
Developmental delay	2 (3.3)	0	3 (5.6)	5 (2.8)
Bronchiolitis	2 (3.3)	4 (6.2)	0	6 (3.3)
Upper respiratory tract infection	2 (3.3)	2 (3.1)	5 (9.3)	9 (5)
Gastroenteritis viral	1 (1.6)	0	3 (5.6)	4 (2.2)
Pharyngitis	0	3 (4.6)	4 (7.4)	7 (3.9)
Viral upper respiratory tract infection	0	3 (4.6)	0	3 (1.7)
Vomiting	0	5 (7.7)	1 (1.9)	6 (3.3)

AEs that start on/after extension baseline are counted.
Preferred terms are sorted in descending frequency of AEs in the ranibizumab 0.2 mg arm.
A patient with multiple AEs is counted only once in the "Patients with any ocular AE" row.
A patient with multiple AEs with the same preferred term is counted only once for that preferred term.
Source: [Appendix 5-Table ias-S1.01b]

Table 1-4 **Non-ocular serious adverse events regardless of study treatment or procedure relationship (greater than or equal to 2% in any arm), with onset date on/after extension baseline by preferred term (Study H2301E1, Extension Safety Set)**

Preferred term	Ranibizumab 0.2 mg N=61 n (%)	Ranibizumab 0.1 mg N=65 n (%)	Laser N=54 n (%)	Total N=180 n (%)
Patients with any non-ocular SAE	**18 (29.5)**	**19 (29.2)**	**18 (33.3)**	**55 (30.6)**
Developmental delay	2 (3.3)	0	0	2 (1.1)
Pyrexia	2 (3.3)	0	1 (1.9)	3 (1.7)

Preferred term	Ranibizumab 0.2 mg N=61 n (%)	Ranibizumab 0.1 mg N=65 n (%)	Laser N=54 n (%)	Total N=180 n (%)
Pneumonia	2 (3.3)	1 (1.5)	3 (5.6)	6 (3.3)
Dehydration	2 (3.3)	1 (1.5)	0	3 (1.7)
Bronchiolitis	1 (1.6)	3 (4.6)	0	4 (2.2)
Febrile convulsion	1 (1.6)	2 (3.1)	0	3 (1.7)
Asthma	0	2 (3.1)	2 (3.7)	4 (2.2)
Bronchitis	0	3 (4.6)	5 (9.3)	8 (4.4)
Gastroenteritis viral	0	0	2 (3.7)	2 (1.1)
Nasopharyngitis	0	2 (3.1)	0	2 (1.1)
Pharyngitis	0	2 (3.1)	0	2 (1.1)
Pneumonia respiratory syncytial viral	0	2 (3.1)	0	2 (1.1)
Vomiting	0	3 (4.6)	0	3 (1.7)

AEs that start on/after extension baseline are counted.
Preferred terms are sorted in descending frequency of AEs in the ranibizumab 0.2 mg arm.
A patient with multiple AEs is counted only once in the "Patients with any ocular AE" row.
A patient with multiple AEs with the same preferred term is counted only once for that preferred term.
Source: [Appendix 5-Table ias-S1.2b]

The most frequent ocular AEs were strabismus (n=3, n=5, n=3 in the ranibizumab 0.2 mg and 0.1 mg groups and the laser group, respectively) and conjunctivitis (n=2 in the ranibizumab 0.2 mg and 0.1 mg groups and the laser group, respectively).

Three serious ocular AE was reported in the 0.1 mg ranibizumab group (retinal detachment, retinopathy of prematurity, nystagmus).

Most frequent non-ocular AEs were bronchitis (0%, 4.6% and 9.3% of patients in the ranibizumab 0.2 mg and 0.1 mg groups and the laser group, respectively) and pneumonia (3.3%, 1.5% and 5.6%, respectively).

In summary, no clinically significant differences were observed for ocular and non-ocular AEs and SAEs across the treatment groups.

Post marketing experience

Post-marketing exposure for ranibizumab is limited to approved indications in adults. Lucentis (ranibizumab) has been marketed since the International Birth Date (IBD) of 30 Jun 2006 with the nAMD indication. Total post-marketing patient exposure based on the number of ranibizumab vials and ranibizumab pre-filled syringes (PFS) sold worldwide since the IBD of the product is estimated to be approximately 5 million patient treatment years (PTY).

The PSUR cycle was recently changed to 3 years.

During the last PSUR reporting period no new safety concerns were evoked. Routine pharmacovigilance was regarded as sufficient. The risk-benefit balance remained unchanged and there was no need for changes of the risk management plan (RMP) at the time.

3.6.5. Discussion on clinical safety

CRFB002H2301E1 (RAINBOW) is a currently ongoing multicentre open-label Extension Study evaluating the long-term efficacy and safety of ranibizumab treatment in preterm infants with ROP.

Patients who had successfully completed the 24-week Core Study CRFB002H2301 were offered to participate in the Extension Study. Ranibizumab as study treatment was permitted for eligible eyes up to and including the Week 40 visit (Epoch 1), corresponding to 40 weeks after a patient received the first study treatment in the Core Study. Treatment with ranibizumab was permitted, either as retreatment for patients who had received ranibizumab as the last treatment prior to joining the Extension Study or as switch treatment for patients who only received laser therapy in the Core Study CRFB002H2301 and required additional treatment in the Extension Study.

A maximum of 3 ranibizumab injections in each eye were allowed during the combined time period of the Core Study plus Epoch 1 of the Extension Study. The remainder of the Extension Study (Epoch 2) is observational.

This is the first of the three planned interim analyses planned for RAINBOW. Interim analysis 2 will be conducted on all patients at 2 years' corrected age, and the final analyses will be conducted at the completion of the study when the patients are 5 years of age. During review period, the Applicant submitted preliminary data (sub IA, cut off 6 Feb 2019) including 177 patients followed-up for more than 18 months, among them 125 patients followed-up for more than two years.

Of the 225 patients who were randomised into the Core Study, 218 patients were treated and 201 patients completed the Core Study. The safety set included 76 patients treated with ranibizumab 0.1 mg; 73 patients with 0.2 mg and 69 patients treated with laser.

At the time of the data cut-off for this interim analysis (initial submission), 144 patients had either completed Week 40 visit (143 patients) or had been discontinued in the Extension Study prior to Week 40 visit (1 patient discontinued due to death).

A majority of patients (66.1 %) completed up to 40 weeks post baseline (time point of data cut-off for the first interim CSR).

Exposure and Demography

During the Core Study, 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 0.1 mg and 0.2 mg ranibizumab groups, respectively, who switched to laser.

During the Extension Study, of the 144 patients, only one patient received ranibizumab 0.1 mg re-treatment in both eyes at the Extension baseline visit.

The mean number of injections/patient was similar in the two ranibizumab groups (2.4 injections in the ranibizumab 0.2 mg group vs 2.5 injections in the ranibizumab 0.1 mg group) during the core study as well as during the extension phase (2.3 vs 2.6).

The study was generally balanced between the ranibizumab and laser treatment groups with regards to baseline demographics and ROP baseline characteristics with the majority classified with non-ROP status (86.2 %) and Zone II, stage 3+ (60.0 %).

As the included population is heterogeneous in terms of gestational age, birth weight and country of origin, it should be taken into account that the population of infants with severe disease in emerging economies is very different from that in industrialized countries and the risks under different conditions (standard of care, timing of treatment, etc). The Applicant presented a specific analysis of the safety profile in each population. The observation of higher frequencies of (S)AEs being reported in Region 1 than Region 2 is expected, as Region 1 included a much higher proportion of patients with severe prematurity as indicated by low GA and lower birth weight. According the MAH, the observed differences in frequencies of ocular and non-ocular (S)AEs between Region 1 and Region 2 can be attributed to a higher proportion of patients with severe prematurity in Region 1 than in Region 2, which appears reasonable.

Core Study
Overall, during the core study 76 patients (34.9 %) experienced ocular AEs, the most commonly reported ocular AEs overall was retinal haemorrhage, followed by conjunctival haemorrhage, conjunctivitis, and ROP. A higher reporting in any ranibizumab group vs laser was found for the following: Conjunctival haemorrhage (8.2% n=6 vs 2.9% n=2); Retinal haemorrhage (13.2% n=10 vs 10.1% n=7); Conjunctivitis (7.9% n=6 vs 4.3% n=3). The adverse drug reactions reported are consistent with the known safety profile of Lucentis in adults. No new safety concerns are evoked.

Overall, 9 patients (4.1 %) experienced at least one ocular SAE. The most frequent ocular SAE was ROP (6 patients, 2.8 % overall). There were no clinically relevant differences between treatment groups. There were no ocular AEs leading to permanent study discontinuation. All other ocular SAEs (cataract, nystagmus, conjunctivitis, endophthalmitis, exophthalmos, eye disorder, and orbital infection) were each reported for 1 patient only (0.5 %).

Overall, in the core study, 177 patients (81.2 %) experienced non-ocular AEs (mostly mild, moderate), 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 %).

Extension Study
The most frequently reported ocular AEs (majority mild) were strabismus (4 patients) and conjunctivitis (4 patients), and a somewhat increased reporting of eye disorders in the ranibizumab groups (10.0 % and 9.8 %) compared to the laser group (7.0 %).

Serious ocular AEs was only reported in the 0.1 mg dose group, in 4 patients, including ROP (n=1); Serious retinal detachment (n=1) and Nystagmus (n=1). In the laser group one case of ROP was reported.

The incidence of non-ocular AEs (primarily mild) was lower in both ranibizumab groups than in the laser group (58.0 %, 58.8 % and 72.1 % in the ranibizumab 0.2 mg and 0.1 mg and the laser groups, respectively). The most commonly affected System Organ Classes were Infections and infestations, Respiratory, thoracic and mediastinal disorders and Metabolism and nutrition disorders.

Deaths
Overall, 12 patients (5.5 %) died during the core study, with similar proportions across treatment groups (4 patients in each group). One patient died during the extension study. The most commonly affected system organ class was respiratory, thoracic and mediastinal disorders (5 patients (2.3 %), followed by infections and infestations (3 patients (1.4 %). Thus, deaths included the primarily the system organ classes related to comorbidity of ROP. However, in this context, it is noted that there is an imbalance in systemic serious adverse effects (including death) related to the respiratory organ system in the ranibizumab groups compared to laser treatment, however, due to confounding factors, the data is inconclusive.

Overall, in the analysis during the review round, a trend of higher AE incidences reported for patients with lower gestational age (<27 weeks) as well as lower birthweight (≤ 750 g) was observed in the ranibizumab pooled group and the laser group. This was also reflected in Respiratory, thoracic, and mediastinal disorders (<27 weeks resp <1000g). The same pattern applied to serious AEs with even fewer patients. However, due to the small sample size, this should be interpreted with caution.

The plasma analysis showed ranibizumab concentrations considerably higher (10-15 times) compared to adult levels, however, the VEGF were at the same level regardless of treatment (ranibizumab or

laser). The significance of this is currently unknown. High plasma levels of bevacizumab resulting in reduced levels of VEGF have previously been shown in preterm ROP patients (Sato et al, 2012).

However, in the current application, a PK/PD analysis showed no clear relationship between systemic ranibizumab concentrations and systemic VEGF concentrations.

Long term safety data from the supp-IA (cut off 06 Feb 2019)

Ocular and non-ocular AEs were assessed for all 180 patients participating in Study H2301E1. Of all 180 patients, three patients discontinued (two patients due to consent withdrawal and one patient due to death) the study before reaching 18 months of safety observation. Therefore, the supp-IA included 177 patients followed-up for more than 18 months, among them 125 patients followed-up for more than two years

Ocular AEs were reported for 13.1%, 18.5% and 16.7% of patients in the ranibizumab 0.2 mg, ranibizumab 0.1 mg and laser groups, respectively

The most frequent ocular AEs were strabismus (n=3, n=5, n=3 in the ranibizumab 0.2 mg and 0.1 mg groups and the laser group, respectively) and conjunctivitis (n=2 in the ranibizumab 0.2 mg and 0.1 mg groups and the laser group, respectively). Myopia was reported as AE in a total of 5 patients (1.6%, 1.5% and 5.6% of patients in the ranibizumab 0.2 mg, ranibizumab 0.1 mg and laser groups, respectively). All other events were reported in single patients per treatment arm.

Three serious ocular AE was reported in the 0.1 mg ranibizumab group (retinal detachment, retinopathy of prematurity, nystagmus).

Non-ocular AEs were reported for 62.3%, 56.9% and 72.2% of patients in the ranibizumab 0.2 mg and 0.1 mg groups and the laser group, respectively. Most frequent non-ocular AEs were bronchitis (0%, 4.6% and 9.3% of patients in the ranibizumab 0.2 mg and 0.1 mg groups and the laser group, respectively) and pneumonia (3.3%, 1.5% and 5.6%, respectively).

Non-ocular SAEs were reported for 29.5%, 29.2% and 33.3% of patients in the ranibizumab 0.2 mg and 0.1 mg groups and the laser group, respectively. Most frequent overall were bronchitis (0%, 4.6% and 9.3% of patients in the ranibizumab 0.2 mg and 0.1 mg groups and the laser group, respectively) and pneumonia (3.3%, 1.5% and 5.6%, respectively).

Taken together, in the core study and Extension Study (including preliminary supp-IA data), no new ocular AEs or non-ocular AEs were identified during the 40-week study and data is in general in agreement with the known safety profile of ranibizumab in adults and with the comorbidity of the preterm population. However, the intended patient population is particularly vulnerable undergoing critical organ development. Although the limited long-term safety data from the supp-IA showed no clinically significant differences for ocular and non-ocular AEs and SAEs across the treatment groups, the long-term effects are uncertain.

Furthermore, there could possibly be increased risk of endophthalmitis due to frequent injections in this infection-prone population.

However, almost 80% of the patients received no more than one baseline bilateral injection and the frequency of endophthalmitis was similar to that for approved adult indications. Section 4.2 of the SmPC was proposed to be updated with this information which is agreed. In addition, the Applicant has agreed to enrich the collection of relevant data for future PSUR discussions by collecting prior history of periocular infection for events of endophthalmitis.

As treatment with ranibizumab is contraindicated for patients with ocular and periocular infections, the potential need of a strategy for patients with concurrent systemic infections was discussed by the

Applicant. However, currently there are no indications of increased risk for ranibizumab treatment in ROP patients with concurrent systemic infections and the SmPC is considered adequate at this time.

3.6.6. Conclusions on clinical safety

Overall, the safety profile of Lucentis appears to be in line with that reported in adults in the previously approved indications. However, considering this sensitive preterm infant population and the important role of VEGF during development, there are uncertainties related to long-term safety in this population.

3.6.7. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Based on the fact that the ROP population is very different from the adult population with regard to the critical role of VEGF in organogenesis in the pre-term infants, the CHMP is of the opinion that the already existing entry in the EURD list for ranibizumab needs to be amended as follows: the PSUR cycle for the medicinal product should follow a yearly cycle.

4. Risk management plan

4.1. Summary of updates of the RMP

The MAH submitted an updated RMP version 18.1, sign off 2019-03-20, in support of new indication of treatment of retinopathy of prematurity in preterm infants. The (main) proposed RMP changes were the following:

Important identified risks	No change
Important potential risks	*Proposed for addition:* Neurodevelopment impairment (ROP) Impaired bone growth and toxicity (ROP) Impaired vital organ development (ROP)
Missing information	*Proposed for addition:* Long term safety of ranibizumab in the condition ROP
Pharmacovigilance activities:	Addition of study CRFB002H2301E1
Risk minimisation activity:	No change, addition, or deletion made since V17.2.

The RMP has been updated with the important potential risks:

- Neurodevelopment impairment (ROP)

- Impaired bone growth and toxicity (ROP)

- Impaired vital organ development (ROP)

During the review period, RMP 18.0 (not approved) was updated to v 18.1 with the specific risks of impaired bone growth and toxicity respectively vital organ development (ROP). However, the detailed risks 'impaired bone growth and toxicity' and 'impaired vital organ development' were questioned and the Applicant was requested to further explain and justify the inclusion of these particular potential risks. In response, the Applicant agreed to remove these risks ('impaired bone growth and toxicity' and

'vital organ development') as they were insufficiently supported by current study data and/or literature-based sources.

This is agreed at present (for details see response to LoQ).

In addition, the safety concern of 'Neurodevelopment impairment' was requested to be further discussed and justified by the Applicant in the previous round. Thus, the assessment of impairment of cognitive function, language development and motor function in the extension study was described in detail as well as the anticipated outcome (For details see response to LoQ). The concern is considered adequately addressed and inclusion of 'Neurodevelopmental impairment is agreed.

In addition, the MAH has agreed to include a dedicated discussion on this topic in future PSURs.

The RMP has been updated to include the following Missing information:

Long-term safety of ranibizumab in the condition ROP

This is considered acceptable.

Following the 2nd RSI, the RMP was updated to version 18.2 which included revisions to the safety specification.

Summary of safety concerns	
Important identified risks	Infectious endophthalmitis Intraocular inflammation Retinal detachment and retinal tear Intraocular pressure increase
Important potential risks	Neurodevelopment impairment (ROP)
Missing information	Potential effect on Diabetic Retinopathy of stopping periodic anti-VEGF injections (DME) Visudyne (verteporfin-PDT) given in combination with ranibizumab (PM) Long-term effects on the progression of the condition CNV (other than nAMD) Long-term safety of ranibizumab in the condition ROP

The revised safety specification is acceptable.

4.2. Pharmacovigilance plan

For the paediatric ROP indication, the long-term efficacy and safety Extension Study H2301E1 was initially added as additional pharmacovigilance study. Long-term data will be collected up to the patients' 5th birthday, with an interim analysis at the corrected age of 2 years.

The collection of additional safety data from this study is supported. Furthermore, additional visual outcome data will be obtained from this study. These visual data are considered key to the evaluation of long-term benefit of ranibizumab in the treatment of ROP.

The Applicant has acknowledged the request that the results of the IA2 and the final report for H2301E1 be subject to a Category 1 commitment as a PAES (Annex IID condition) (For details see response to second RSI).

Planned and ongoing post-authorization efficacy studies that are conditions of the marketing authorization or that are specific obligations

Study Status	Summary of Objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorization				
RFB002H2301E1 (RAINBOW extension study) Title: 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. (ongoing)	To evaluate the visual function of patients, by assessing the visual acuity in the better-seeing eye at the patient's fifth birthday. To evaluate the safety outcomes by analyzing the type, frequency and severity of ocular and non- ocular AEs.	Long-term efficay of ranibizumab in the condition ROP Additional safety uncertainties addressed: Neurodevelopmental impairment (ROP) Long-term safety of ranibizumab in the condition ROP	FPFV	16-Jun-2016
			Interim analysis 2 (IA2) submission (planned)	30-Jun-2020
			LPLV (Planned)	31-Dec-2022
			Final report submission (Planned)	30-Jun-2023

Overall conclusions on the PhV Plan

The MAH has added the Extension Study H2301E1 as a category 1 study into the RMP. This is acceptable.

4.3. Risk Minimisation Measures

To ensure that patients are adequately informed about the potential to develop intraocular pressure increase, intraocular inflammation, retinal detachment and retinal tear and infectious endophthalmitis after an intravitreal injection of ranibizumab, a patient information booklet (also available in spoken form in audio-CD format) was developed. The booklets are provided to the physician for distribution to the patient after ranibizumab is prescribed to them.

No additional risk minimisation measures are proposed for the paediatric ROP patients. Specifically, no educational materials are proposed to parents/guardians of paediatric patients receiving ranibizumab for the treatment of ROP. The majority of the ROP patients will be hospitalised in neonatal intensive care and regularly supervised by health care professionals and thus no educational material for caregivers as proposed by the Applicant is considered acceptable.

Parents/guardians can obtain relevant information on the use of ranibizumab for the treatment of ROP from the PL.

Annexes

The targeted follow-up (TFU) checklists in Annex 4 of the RMP was updated to collect relevant information for discussion in future PSURs. Newly included queries are Gestational age and Birth weight for all reported AEs from ROP patients treated with ranibizumab. For reported events of Endophthalmitis, prior history of periocular infection will be queried in addition to the existing follow-up request.

Overall conclusions on Risk Minimisation Measures

No additional risk minimisation measures are proposed for ROP patients. The fact that the caregivers are provided with the PL and that the vast majority of the patients are hospitalised is in this regard considered adequate.

4.4. Overall conclusion on the RMP

Overall, the collection of additional safety data from the extension study H2301E1 is supported.

No educational material as a risk minimisation measure is proposed for the ROP patients, this is acceptable.

The RMP version 18.2 is acceptable.

PRAC Outcome on RMP version 18.1 (dated 20 March 2019)

During the plenary meeting held on 13-16 May 2019, the PRAC fully supported the assessment of the pharmacovigilance plan and risk minimisation measures (RMMs) as detailed in the assessment report (AR) and agreed that the RMP for Lucentis (ranibizumab) in the proposed indication could be acceptable provided that an update to RMP version 18.1 and satisfactory responses to the questions detailed in the joint CHMP-PRAC JAR are submitted.

Additionally, the PRAC agreed that it is not required for Lucentis to be included in the additional monitoring list.

5. Changes to the Product Information

The following sections of the SmPC are suggested to be updated; 2, 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 6.5 and 6.6, and the Package Leaflet and Labelling have been updated accordingly.

Please refer to Attachment 1.

5.1.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found partially acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Lucentis currently approved PL. The bridging report submitted by the MAH has been found acceptable for content but unacceptable for layout. A focus test on the layout was requested to make sure that the reader easily finds the correct information (i.e. the correct side of the double-sided PL) and to test the increased leaflet dimension.

The Applicant submitted the results of the focus test with the responses to the second RSI.

The applicant has submitted a focus test to ascertain the readability of layout of the PL for Lucentis vial presentation. An assessment of technical and procedural aspects of the user test is not performed by the Rapporteur. The Rapporteur has focused the assessment of the user test on the Summary of results/Conclusions including feedback from participants.

The general impression of the leaflet (content, layout and language) was mostly positive according to the responses given on the general questions.

As stated in the applicant´s report conclusion, the results of User Testing demonstrated that all participants were able to find the correct side of the leaflet. The results also demonstrated that for both sides of the leaflet, at least 90% of the participants were able to find each point of information and at least 90% of those were able to understand it.

The test met the success criteria.

In conclusion, the user test is considered acceptable. The Rapporteur suggested some additional changes to the PL due to the result of the user test. These are considered to further improve readability and have been implicated by the applicant.

6. Benefit–Risk Balance

6.1. Therapeutic Context

6.1.1. Disease or condition

The applied new indication is the treatment of retinopathy of prematurity (ROP).

The pathophysiology of ROP is characterised by abnormal neovascularisation. The disruption of angiogenesis in preterm infants with ROP typically occurs in two postnatal phases. In the vaso-obliterative phase (phase 1), the normally high arterial oxygen saturation in the postnatal life, coupled with hyperoxia secondary to oxygen supplementation, leads to involution and loss of formed blood vessels. In the vaso-proliferative phase (phase 2), the relatively hypoxic environment due to ischaemia caused by vessel loss coupled with the high metabolic demands of the avascular retina leads to upregulation of various angiogenic factors, resulting in abnormal neovascularisation (Sankar et al, 2018). The extent and severity of ROP are traditionally described in terms of location (zones; I to III), severity (stages; 1 to 5), extent (clock hours; 1 to 12), and vascular dilatation and tortuosity (plus disease) according to the International Classification of ROP definitions. In 2005, the classification was revised to include aggressive posterior ROP (AP-ROP), pre-plus disease, and a practical way to estimate the extent of zone I with the indirect ophthalmoscope (Arch Ophthalmol. 2005).

Vascular endothelial growth factor (VEGF) is a key regulator of angiogenesis in foetal life. In the normally developing retina, VEGF is released in response to the higher oxygen demand of the retinal tissue, which leads to the development of blood vessels from the optic nerve to the periphery. In preterm infants with disrupted angiogenesis, however, the expression and levels of VEGF differ markedly in the two different phases. While the levels are suppressed in the vaso-obliterative phase, there is an overproduction/ expression of VEGF, leading to abnormal vascular proliferation in the vaso-proliferative phase (Sankar et al 2018). The vascular changes may be mild and may regress with time or may continue to progress, leading to total retinal detachment, and severe visual impairment or blindness (Hardy et al, 2004).

Incidence and severity of ROP were found to rise with the degree of prematurity at birth, with low gestational age and low birth-weight being the main risk factors (Hartnett and Penn 2012, Fierson et al 2013). According to the Global Burden of Disease (GBD) study, in 2015 there were about 50,000 children aged 5-14 years and about 42,000 children aged <5 years blind from ROP worldwide (GBD Collaborative Network 2016).

6.1.2. Available therapies and unmet medical need

Left untreated, ROP may lead to strabismus, myopia, glaucoma, cataract, retinal detachment and blindness early or later in life. The current treatment strategy for ROP involves peripheral ablation of the retina by laser coagulation (laser therapy). The established retina ablation techniques result in a significant improvement in long-term visual function, however, 10 % to 15 % of the patients with high-risk disease experience progression to tractional retinal detachment. Further, the retina ablation techniques may also cause myopia and loss of peripheral visual field. In addition, the laser treatment per se often requires sedation or general anaesthesia. Thus, there is a need for additional treatment strategies.

VEGF, a regulator of angiogenesis, plays a key role in the progression of ROP and is involved in both phases of ROP pathophysiology. Thus, there is a scientific rationale for targeting elevated ocular VEGF in the treatment of ROP in preterm infants.

6.1.3. Main clinical studies

A randomised, open-label, 3-arm parallel-group study was submitted to determine if intravitreal ranibizumab (0.1 mg, n=76 and 0.2 mg, n=73) is superior to laser ablation therapy (n=69) in the treatment of ROP in infants born prematurely with retinopathy of prematurity (Study H2301, RAINBOW). A total of 225 preterm infants (mean gestational age 26.1 weeks) with ROP were randomised of whom 218 received investigational treatment. Patients should have 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. Treatment success, the primary efficacy variable, was defined as the absence of active ROP and absence of unfavourable structural outcomes before or at 24 weeks. A 3-step sequential superiority testing procedure was used for primary (ranibizumab 0.2 mg against laser) and 2 key secondary comparisons (ranibizumab 0.1 mg against laser and ranibizumab 0.2 mg against 0.1 mg). The FAS population included 225 patients.

Study H2302E1 (RAINBOW extension) is a currently ongoing Extension Study evaluating the long-term efficacy and safety of ranibizumab 0.2 mg and 0.1 mg compared with laser therapy. Ranibizumab treatment was permitted for eligible eyes up to and including the Week 40 visit.. The remainder of the Extension Study up to the age of 5 years is observational.

Both studies are part of the Paediatric Investigation Plan (PIP-EMEA-000527-PIP04-13-M01) for ranibizumab.

The initial submission consisted of the final results of the pivotal 24-week Study H2301, supplemented by the results of a predefined first interim analysis of the extension Study H2301E1. At the time point, 144 patients had either completed the Week 40 visit in the Extension Study.

6.2. Favourable effects

In the Core Study, 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. Superiority of 0.2 mg ranibizumab over laser ablation therapy was not formally demonstrated as the one-sided p-value 0.0254 was marginally above the significance level of 0.025 (OR: 2.19, CI: 0.9932, 4.8235). The remaining key efficacy comparisons were assessed descriptively; the ORs for the comparison of ranibizumab 0.1 mg vs. laser and ranibizumab 0.2 mg vs. ranibizumab 0.1 mg were 1.57 (95% CI [0.7604, 3.2587]) and 1.35 (95% CI [0.6101, 2.9810]), respectively. The conducted sensitivity analyses were supportive of the primary analysis.

Regarding individual components of primary efficacy variable, active ROP in either eye at the 24-week assessment visit was reported only in the ranibizumab 0.1 mg group (3 patients, 4.3%) but not in the ranibizumab 0.2 mg and laser groups.

A lower proportion of patients in both ranibizumab groups compared to 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 study treatment received at Baseline: 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. Most patients (78%) received a single injection per eye (2 injections in total) without the need for retreatment. No patient in the ranibizumab 0.2 mg group was re-treated beyond Week 24.

Fewer patients 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 had one or more unfavourable structural outcomes in either eye at or before 24 weeks.

In the ongoing Extension Study H2301E1, the absence of ocular structural abnormalities at Week 40 was 49/50 patients (98.0 %) in the ranibizumab 0.2 mg group and 50/51 patients (98.0 %) in the ranibizumab 0.1 mg group as compared with 38/43 patients (88.4 %) in the laser group.

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No cases of active ROP were detected at 40 weeks post baseline visit.

6.3. Uncertainties and limitations about favourable effects

The medicinal product should be administered to preterm infants with the new low-volume, high-accuracy syringe specifically referred to in the SmPC. While the doses in the clinical study were administered with a different syringe than the above-mentioned low-volume high-accuracy syringe intended for clinical use, there is no expected negative impact on efficacy by the small volume difference between these syringes.

No statistical significance was demonstrated for the primary endpoint. Nevertheless, it appears from the data that ranibizumab is at least as effective as laser therapy with regard to the primary endpoint even if a non-inferiority test was not planned in the study and a non-inferiority margin not defined.

No follow-up data are yet available to conclude on long-term visual outcomes. The protocol to the Extension Study introduces measures to assess visual acuity at the child's 2 and 3 years' corrected age (Cardiff Acuity test) and 5 years (ETDRS visual acuity test), refraction in each eye and visual function as per a vision function form (qualitative assessment) at a supplemental visit to capture visual function and peripheral vision at the patient's fifth birthday. In addition, in response to the RSI, the MAH submitted a supplementary interim analysis containing additional results of vision function outcomes and safety from the ongoing H2301E1 study that have become available. The data is too limited to draw firm conclusions, but there are no indications of a negative effect on visual function.

The study design and the criteria for re-treatment of unresponsive patients do not allow to draw firm conclusions on the effect of re-treatment and on the best strategy to follow. However, the majority of patients needed no more than one injection in each eye.

6.4. Unfavourable effects

During the core study 76 patients (34.9 %) experienced ocular AEs, the most commonly reported ocular AEs was retinal haemorrhage, followed by conjunctival haemorrhage, conjunctivitis, and ROP. The reported events in ranibizumab group vs laser were: Conjunctival haemorrhage (8.2% n=6 vs 2.9% n=2); Retinal haemorrhage (13.2% n=10 vs 10.1% n=7); Conjunctivitis (7.9% n=6 vs 4.3% n=3).

The risk of infectious endophthalmitis remains an identified risk for the adult indications. One case of endophthalmitis (serious) was reported in Core Study in the 0.1 mg ranibizumab dose group only.

The most frequently reported ocular AEs in the extension phase were strabismus (4 patients) and conjunctivitis (4 patients). Serious ocular AEs was only reported in the 0.1 mg dose group, in 4 patients, including ROP (n=1); Serious retinal detachment (n=1) and Nystagmus (n=1). In the laser group one case of ROP was reported.

The most frequent ocular AEs reported in the interim analysis were strabismus (n=3, n=5, n=3 in the ranibizumab 0.2 mg and 0.1 mg groups and the laser group, respectively) and conjunctivitis (n=2 in the ranibizumab 0.2 mg and 0.1 mg groups and the laser group, respectively).

Three serious ocular AE was reported in the 0.1 mg ranibizumab group (retinal detachment, retinopathy of prematurity, nystagmus).

Most frequent non-ocular AEs were bronchitis (0%, 4.6% and 9.3% of patients in the ranibizumab 0.2 mg and 0.1 mg groups and the laser group, respectively) and pneumonia (3.3%, 1.5% and 5.6%, respectively).

In summary, no clinically significant differences were observed for ocular and non-ocular AEs and SAEs across the treatment groups.

6.5. Uncertainties and limitations about unfavourable effects

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The initially submitted efficacy and safety data covers a total study period of 40 weeks and included infants who were on average 26 gestational weeks of age at inclusion. During the review round, long term safety data from an interim analysis with a cut-off 6 Feb 2019 was submitted, including 177 patients followed-up for more than 18 months, among them 125 patients followed-up for more than two years.

The additional safety data and growth data provided did not indicate any detrimental effects up to three years.

A somewhat higher reporting rate of adverse events was noted in the Core Study, in either ranibizumab group compared to laser group (ranibizumab vs laser) related to cardiovascular events (bradycardia 6.6% vs 1.4%) and respiratory events (upper respiratory tract infection 8.2% vs 1.4%).. The plasma analysis showed ranibizumab concentrations considerably higher (10-15 times) compared to adult levels. However, this is considered to be of low concern considering that the majority of patients need only one injection.

6.6. Effects Table

Table 30. Effects Table for Lucentis in the treatment of ROP.

Effect	Short Description	Unit	Ranibizumab	Laser	Uncertainties/ Strength of evidence
Favourable Effects					
ROP	Treatment success: absence of structural abnormalities in the eye fundus	Descriptive	Core study 80.0 % success with ranibizumab 0.2 mg 75.0 % success with ranibizumab 0.1 mg	66.2 % success with laser ablation therapy	Core study result not statistically significant, but likelihood of treatment success with ranibizumab 0.2 mg twice more likely than with laser. Repeat injections were necessary. Long term follow-up missing. No data on visual acuity.
	Structural abnormalities at Week 40 post baseline	Descriptive	Extension Study No abnormalities in 49/50 patients (98.0 %) in the	No abnormalities in 38/43 patients (88.4 %)	Long term follow-up missing.

Effect	Short Description	Unit	Ranibizumab	Laser	Uncertainties/ Strength of evidence
			ranibizumab 0.2 mg group or in 50/51 patients (98.0 %) in ranibizumab 0.1 mg group		
	Absence of active ROP at Week 40 post baseline	Descriptive	No cases	No cases	Long term follow-up missing.
Unfavourable Effects (Core Study)					
			0.2 mg		
Ocular risks in study eye	Conjunctival haemorrhage	N (%)	6 8.2	2 2.9	
	Conjunctivitis	N (%)	6 7.9*	3 4.3	*0.1 mg
	Retinal haemorrhage	N (%)	19 13.2*	7 10.1	*0.1 mg
	Endophtalmitis	N (%)	1 1.3*	0 0	*0.1 mg Identified risk of RMP
Non-ocular risks	Upper respiratory tract infection	N (%)	6 8.2	1 1.4	Comorbidities in pre-term population. Long term follow-up missing.
	Bradycardia	N (%)	5* 6.6	1 1.4	Comorbidities in pre-term population. Long term follow-up missing.
	Respiratory failure	N (%)	4* 5.3	1 1.4	*0.1 mg Comorbidities in pre-term population. Long term follow-up missing.

Abbreviations: ROP; retinopathy of prematurity

6.7. Benefit–risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

In the treatment of Type 1 ROP, laser photocoagulation is currently the treatment of choice. However, it may in some cases be associated with ocular complications and the risks derived from sedation or general anaesthesia. It is also a time and technical-demanding procedure. Ranibizumab may be a less destructive treatment and can be administered directly to the vitreous without requiring sedation or anaesthesia.

The medicinal product should be administered to preterm infants with the new low-volume, high-accuracy syringe specifically referred to in the SmPC.

Results from Study H2301 showed higher rates of treatment success (absence of active ROP and unfavourable structural outcomes) for ranibizumab compared with laser therapy up to 24 weeks after treatment initiation. The majority of patients received only one initial bilateral ranibizumab treatment (i.e., 2 injections, one in each eye), 78.1 % in the ranibizumab 0.2 mg group and 77.6 % in the ranibizumab 0.1 mg group. No eye required more than 3 injections (as per protocol). Late recurrence beyond 40 weeks after initial treatment was not observed.

No detrimental effects in vision function with ranibizumab treatment were identified in limited follow-up data from a supplementary analysis that included visual reception of Mullen scale of early learning, CAT at two years of corrected age, and vision function rating (VA and peripheral vision, respectively) at a supplementary visit. However, the provided data concerned only few patients and are insufficient to draw conclusions on long-term benefit in terms of visual outcome. More data will be submitted post approval.

The plasma analysis showed ranibizumab concentrations considerably higher (10-15 times) compared to adult levels, however, levels of VEGF were at the same level regardless of treatment (ranibizumab or laser).. A PK/PD analysis conducted by the MAH showed no clear relationship between systemic ranibizumab concentrations and systemic VEGF concentrations. Thus, the overall relevance of the relatively higher systemic ranibizumab exposure in premature infants for safety is currently unknown. However, it could be considered as somewhat reassuring that the vast majority of the patients in the study needed only one initial bilateral ranibizumab treatment (i.e., 2 injections, one in each eye).

The available short-term safety data showed that the most commonly reported ocular AEs were retinal haemorrhage, conjunctival haemorrhage and conjunctivitis, which is consistent with the known safety profile of ranibizumab. The non-ocular events (respiratory events and infections) were mainly related to the comorbidity of the population and medical history and no clinically relevant difference compared to laser was observed.

With respect to long-term safety, the MAH has submitted data from an interim analysis with a cut-off 6 Feb 2019, including 177 patients followed-up for more than 18 months, among them 125 patients followed-up for more than two years. These additional safety data do not raise any new issues; however, the intended patient population is particularly vulnerable and long-term follow-up data are limited.

6.7.2. Balance of benefits and risks

Results from the single pivotal study H2301 for ranibizumab showed higher treatment success rates (absence of active ROP and unfavourable structural outcomes) as compared with laser up to 24 weeks after initial treatment and fewer patients had unfavourable structural outcomes at or before Week 24. No patient in the ranibizumab 0.2 mg group received re-treatment in the Extension Study H2301E1,

indicating no recurrence after 40weeks post baseline treatment with ranibizumab 0.2 mg. The safety data available to date is in general in agreement with the known safety profile of ranibizumab in adults and with the comorbidity of the preterm population and do not raise new concerns. However, the data on long term efficacy and safety is still limited.

The beneficial effects are considered to outweigh the risks.

6.7.3. Additional considerations on the benefit-risk balance

The initially proposed indication (*treatment of ROP in premature infants*) was broader compared with the study population, which included patients with bilateral ROP with 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 AP-ROP (aggressive posterior retinopathy of prematurity). The MAH was requested to justify and explain why the benefit/risk balance would be positive also in subgroups not studied or propose a restricted target population.

In response, the MAH revised the proposed indicated population which now reflects the study population, including only patients with bilateral ROP with 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 AP-ROP (aggressive posterior retinopathy of prematurity).

This revised indication is more consistent with treatment recommendations in current literature. According to a recent guideline for screening examination of premature infants with ROP (Fierson, et al, Dec 2018), treatment should be initiated for Zone I ROP (any stage with plus disease); Zone I ROP stage 3 (no plus disease); as well as Zone II (stage 2 or 3 with plus disease).

As the revised indication reflects clinical practice guidelines and the population studied in H2301 and given that the benefit-risk observed in this population appears to be favourable at the current stage, this revised indication seems to be appropriate.

Most patients have received a single injection per eye without the need for retreatment. As no patient in the ranibizumab 0.2 mg group was re-treated beyond Week 24, the MAH has proposed a more structured SmPC statement concerning frequency and duration of treatment, using a limit of up to 3 injections per eye to be administered within 6 months. This is considered acceptable.

A primary objective of the H2301 extension study is visual acuity at the patient's 5th birthday, using the Lea symbols chart. In addition to visual acuity to be assessed at 5 years of age, a VA assessment using the Cardiff Acuity Test will be performed during the scheduled Year 2 and Year 3 visits. In addition, a Vision Function Form (VFF) will be used to collect qualitative data on VA and peripheral vision at a supplementary visit as part of standard clinical practice. Cognitive status including visual reception using the Mullen Scales of Early Learning will be assessed at 2 and 5 years of age. To reduce possible bias, the MAH has agreed to an additional protocol amendment for Study H2301E1 to require the person performing the visual outcome assessments at Year 5 to be blinded to the assigned treatment allocation in the core study.

The second predefined interim analysis (IA2) of the study is planned after the last patient has completed the visit at the corrected age of two years. The purpose of the IA2 is to evaluate the absence of any ocular structural abnormalities, as well as visual acuity, safety and cognitive outcomes. The IA2 results are planned to be available in Q2 2020. The final study report is expected in Q2 2023.

Regarding the subsequent submissions, the MAH initially proposed to provide the results of IA2 as a post approval commitment. RMP v18.1 submitted in response to the RSI has been updated accordingly and includes IA2 of the ongoing Study H2301E1 as a Category 3 milestone commitment (planned

submission 31 March 2020). This is in addition to the already included milestone for submission of the final report submission in Q2 2023.

However, given that the initial efficacy assessment is based on surrogate endpoints, this would require verification of the impact of the intervention on clinical outcome or disease progression or confirmation of previous efficacy assumptions. Accordingly, the MAH has agreed to the request that the results of the IA2 and 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 June 2023, and including other relevant milestones including IA2 (due date 30 June 2020). This is endorsed. In addition, the remaining other concerns including remaining comments to the product information have now been adequately addressed.

6.8. Conclusions

The benefit risk balance is positive