Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Lucentis

Active ingredient: Ranibizumab

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

May 2023

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADR	Adverse drug reaction
AE	Adverse event
AMD	Age-related macular degeneration
AP-ROP	Aggressive posterior retinopathy of prematurity
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
$AUC_{0\text{-inf}}$	Area under the concentration-time curve from time zero to infinity
CAT	Cardiff Acuity test
C_{max}	Maximum plasma drug concentration
CMI	Consumer medicine information
CRYO-ROP	Cryotherapy for Retinopathy of Prematurity (Study)
DLP	Data lock point
EMA	European Medicines Agency (European Union)
EU	European Union
IA	Interim analysis
PD	Pharmacodynamic(s)
PI	Product Information
PK	Pharmacokinetic(s)
popPK/PD	Population pharmacokinetic(s) / pharmacodynamic(s)
RMP	Risk management plan
ROP	Retinopathy of prematurity
SAE	Serious adverse event
SOC	System organ class

Abbreviation	Meaning
TGA	Therapeutic Goods Administration
VA	Visual acuity
Vd	Volume of distribution
VEGF	Vascular endothelial growth factor

Product submission

Submission details

Type of submission:	Extension of indications
Product name:	Lucentis
Active ingredient:	Ranibizumab
Decision:	Approved
Date of decision:	2 February 2022
Date of entry onto ARTG:	7 February 2022
ARTG number:	148325
▼ *Black Triangle Scheme:*[1]	Yes This product will remain in the scheme for 5 years, starting on the date the new indication was approved
Sponsor's name and address:	Novartis Pharmaceuticals Australia Pty Ltd 54 Waterloo Road, Macquarie Park, NSW 2113
Dose form:	Solution for injection
Strength	2.3 mg/0.23 mL
Container:	Vial
Pack size:	One
Approved therapeutic use:	*Lucentis is indicated in preterm infants for: the treatment of retinopathy of prematurity (ROP) with Zone I (Stage 1+, 2+, 3 or 3+), Zone II (Stage 3+) or AP-ROP (aggressive posterior ROP) disease.*
Route of administration:	Intravitreal
Dosage:	Single-use vial for preterm infants for intravitreal use only. Use of more than one injection from a vial can lead to product contamination and subsequent ocular infection. For preterm infants, both 0.2 mg and 0.1 mg doses of Lucentis have demonstrated efficacy (see Section 5.1 *Pharmacodynamic Properties, Clinical trials* of the Product Information).

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

	The recommended dose for Lucentis in preterm infants is 0.2 mg given as an intravitreal injection. This corresponds to an injection volume of 0.02 mL Alternatively, a dose of 0.1 mg corresponding to an injection volume of 0.01 mL can be given. Treatment should be initiated and monitored by paediatric ophthalmologists experienced in the treatment of retinopathy of prematurity (ROP). Treatment of ROP is initiated with a single injection per eye and may be given bilaterally on the same day. In total, up to three injections per eye may be administered within six months of treatment initiation if there are signs of disease activity. The administration of more than three injections per eye has not been studied. The interval between two doses injected into the same eye should be at least four weeks. For further information, including *dose and method of administration*, and *instructions for use and handling*, refer to the Product Information.
Pregnancy category:	D Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the submission by Novartis Pharmaceuticals Australia Pty Ltd (the sponsor) to register Lucentis (ranibizumab (rbe)) 2.3 mg/0.23 mL solution for injection for the following proposed extension of indication:

> *Lucentis is indicated in preterm infants for the treatment of retinopathy of prematurity (ROP) with Zone I (Stage 1+, 2+, 3 or 3+), Zone II (Stage 3+) or AP-ROP (aggressive posterior ROP) disease.*

Retinopathy of prematurity (ROP) is a developmental proliferative vascular disorder and a leading cause of childhood blindness worldwide.[2] Infants born prematurely have an immature retina with a peripheral avascular zone and ROP develops if there is disruption of angiogenesis in this zone. Retinopathy of prematurity is a biphasic disease comprising

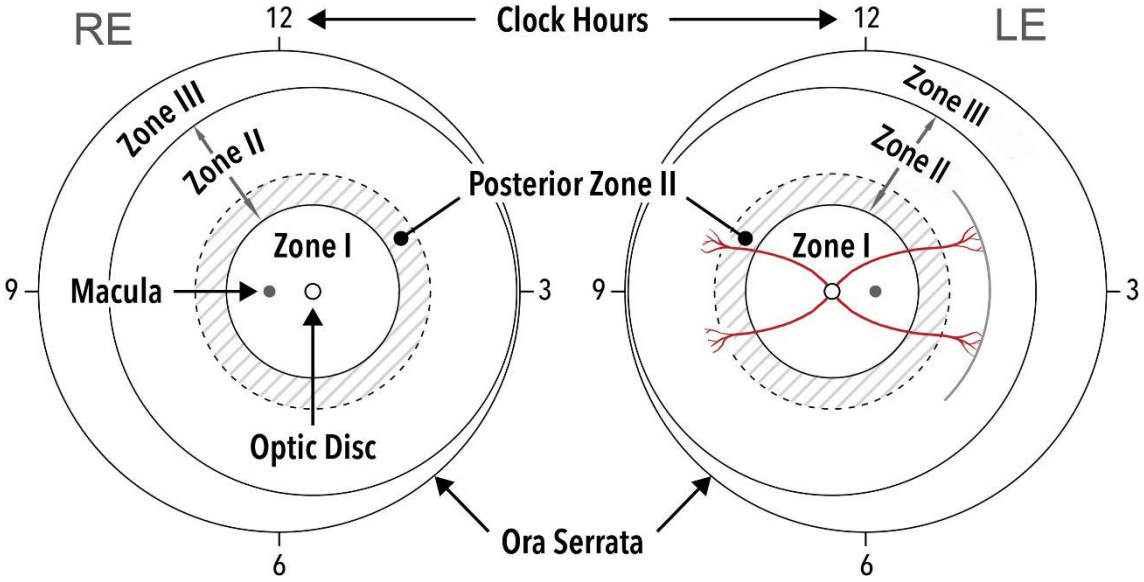
[2] Gilbert C. Retinopathy of prematurity: a global perspective of the epidemics, population of babies at risk and implications for control. *Early Hum Dev.* 2008;84(2):77-82.

an initial phase of vessel loss and a second phase of vessel proliferation.[3] In most cases the vascular changes of retinopathy regress with time, however, in some cases, can lead to fibrous scar formation, visual distortion, retinal detachment, and blindness if left untreated.

Retinopathy of prematurity is often classified as per the International Classification of Retinopathy of Prematurity.[4,5] The extent and severity of ROP is described by:

- *Location*: Zones I to III, defining the extent of vascularisation from the central zone (Zone I) to the outer crescent (Zone III) (see Figure 1, below).
- *Severity*: Stage 1 to 5. Stage 1 is characterised by a thin demarcation line between vascularised and non-vascularised retina, Stage 2 by a ridge, Stage 3 by extraretinal fibrovascular proliferation, Stage 4 by partial retinal detachment, and Stage 5 by total retinal detachment.
- *'Plus' disease*: refers to the presence (rather than extent) of vascular dilatation and tortuosity of the posterior retinal vessels involving at least two quadrants of the retina.

Figure 1: Chiang et al. (2021); Zone borders and clock hour sectors used to describe location of vascularisation and extent of retinopathy



Schema of right eye (RE) and left eye (LE) showing zone borders and clock hour sectors used to describe the location of vascularisation and extent of retinopathy. Solid circles represent borders of Zones I through III, and dotted circles represent borders of posterior zone II (2 disc diameters beyond zone I). A hypothetical example of examination findings is shown in LE, representing approximately 3 clock hours of stage 1 disease in zone II (note single line on drawing to document presence of stage 1 disease).

Figure adapted from Chiang MF, Quinn GE, Fielder AR, et al. International Classification of Retinopathy of Prematurity, Third Edition. Ophthalmology. 2021;128(10):e51-e68.

Aggressive posterior retinopathy of prematurity (AP-ROP) is an uncommon, rapidly progressive, severe form (mainly in Zone I, and to a lesser extent in Zone II), mainly characterised by posterior location, flat neovascularisation, and 'plus' disease.

[3] Rivera, J.C., Holm, M., Austeng, D. et al. Retinopathy of prematurity: inflammation, choroidal degeneration, and novel promising therapeutic strategies. *J Neuroinflammation* 14, 165 (2017).
[4] Chiang MF, Quinn GE, Fielder AR, et al. International Classification of Retinopathy of Prematurity, Third Edition. *Ophthalmology*. 2021;128(10):e51-e68.
[5] International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity Revisited. *Archives of Ophthalmology*. 2005, 123(7):991-9

A further classification system distinguishes high-risk and low risk pre-threshold ROP:

- *Type 1 (high risk):* Zone I (Stage 1+, 2+, 3 or 3+), Zone II (Stage 2+ or 3+); and
- *Type 2 (low risk):* Zone I (Stage 1 or 2), Zone II (Stage 3).

The incidence and severity of ROP increase with the degree of prematurity at birth, with low gestational age and low birth weight being the main risk factors. Among infants with a gestational age of less than 31 weeks and/or a birth weight of less than 1,250 grams registered with the Australian and New Zealand Neonatal Network in 2018 who were examined for ROP, 7.5% had Stage 3 or 4 eye disease.[6]

Current treatment options

At the time the submission was under consideration, there was no registered products on the Australian Register of Therapeutic Goods (ARTG) for the treatment of retinopathy of prematurity (ROP).

Treatment is usually required for more advanced ROP, including: any Zone I ROP with plus disease, Zone I Stage 3 without plus disease, Zone II Stage 3 ROP with plus disease and aggressive posterior retinopathy of prematurity (AP-ROP).

The main treatment modalities are laser photocoagulation or intravitreal anti-vascular endothelial growth factor (VEGF) injection therapy (in Australia, anti-VEGF medicines are not currently indicated for ROP). Surgical intervention is usually indicated for Stage 4 and Stage 5 ROP. Breast milk appears to be the only preventative treatment.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG);[7] on 27 February 2007 for the treatment of neovascular (wet) age-related macular degeneration (AMD) in adults. The indications approved in Australia at the time of this submission were:

Lucentis (ranibizumab) is indicated in adults for:

- *the treatment of neovascular (wet) age-related macular degeneration (AMD)*
- *the treatment of visual impairment due to diabetic macular oedema (DME)*
- *treatment of proliferative diabetic retinopathy (PDR)*
- *the treatment of visual impairment due to choroidal neovascularisation*
- *the treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia (PM)*
- *the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (RVO)*

A previous submission;[8] to extend the indication for use in preterm infants for the treatment of ROP was withdrawn, following Advisory Committee on Medicines (ACM)

[6] Chow, SSW, Creighton, P, Chambers, GM, Lui, K. 2020. Report of the Australian and New Zealand Neonatal Network 2018. Sydney: ANZNN.
[7] Therapeutic goods must be entered in the Australian Register of Therapeutic Goods (ARTG) before they can be lawfully supplied in or exported from Australia, unless exempt from being entered in the ARTG, or otherwise authorised by the TGA. For further information visit: https://www.tga.gov.au/australian-register-therapeutic-goods.
[8] AusPAR for Lucentis (ranibizumab) Novartis Pharmaceuticals Australia Pty Ltd; Submission PM-2018-04902-1-5. Published 10 September 2020. Available at: https://www.tga.gov.au/resources/auspar/auspar-ranibizumab-rbe

advice that did not recommend approval. The submission was based on data from the single pivotal Study H2301 (RAINBOW trial) and early results from the extension Study H2301E1 (RAINBOW extension trial).

On 31 July 2020, the TGA granted Lucentis a positive Orphan drug designation,[9] for the following indication:

'treatment of preterm infants with retinopathy of prematurity (ROP)'.

At the time the TGA considered the current re-submission to extend of the indications of ranibizumab to include treatment of retinopathy of prematurity, similar submissions had been approved in the European Union, United Kingdom, Japan, Singapore and Switzerland. A similar submission was under consideration in Canada. The following table summarises these submissions and provides the indications where approved.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
European Union	17 October 2018	Approved on 3 September 2019	*Lucentis is indicated in preterm infants for the treatment of retinopathy of prematurity (ROP) with Zone I (Stage 1+, 2+, 3 or 3+), Zone II (Stage 3+) or APROP (aggressive posterior ROP) disease.*
United Kingdom	17 October 2018	Approved on 3 September 2019	*Lucentis is indicated in preterm infants for: the treatment of retinopathy of prematurity (ROP) with Zone I (Stage 1+, 2+, 3 or 3+), Zone II (Stage 3+) or APROP (aggressive posterior ROP) disease.*
Japan	13 March 2019	Approved on 22 November 2019	*Retinopathy of Prematurity (eligible patients as described in Clinical Trial section: - Zone I with Stage 1+, 2+, 3+, or Stage 3; - Zone II with Stage 3+ stage; - Aggressive posterior (AP)-ROP)*
Singapore	4 December 2018	Approved on 20 November 2020	*Lucentis is indicated in preterm infants for: the treatment of retinopathy of prematurity (ROP) with Zone I (Stage 1+, 2+, 3 or 3+), Zone II (Stage 3+) or APROP (aggressive posterior ROP) disease.*

This AusPAR describes a withdrawn submission that had proposed to extend the indications of Lucentis to include the following indication: *Lucentis is indicated in preterm infants for the treatment of retinopathy of prematurity (ROP).*

[9] **'Orphan drugs'** are often developed to treat small and very specific patient populations who suffer from rare diseases and conditions. In order to facilitate orphan drug access to the Australian marketplace and help offset orphan drug development costs, the TGA waives application and evaluation fees for prescription medicine registration applications if a related orphan designation is in force. A medicine may be eligible for orphan drug designation if all orphan criteria set by the TGA are met. The orphan designation application precedes the registration application, and the designation is specific to the sponsor, orphan indication for which designation was granted and dosage form of the medicine

Region	Submission date	Status	Approved indications
Switzerland	4 December 2018	Approved on 1 October 2020	*Lucentis is indicated in preterm infants for the treatment of retinopathy of prematurity (ROP): ROP in Zone I (Stage 1+, 2+, 3 or 3+), Zone II (Stage 3+) or APROP (aggressive posterior ROP).*
Canada	November 2019	Under consideration	Under consideration

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Registration timeline

The following table captures the key steps and dates for this submission.

Table 2: Timeline for Submission PM-2020-04187-1-5

Description	Date
Positive designation (Orphan)	31 July 2020
Submission dossier accepted and first round evaluation commenced	30 September 2020
First round evaluation completed	22 February 2021
Sponsor provides responses on questions raised in first round evaluation	21 April 2021
Second round evaluation completed	16 June 2021
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	2 November 2021
Sponsor's pre-Advisory Committee response	16 November 2021
Advisory Committee meeting	2 December 2021
Registration decision (Outcome)	2 February 2022
Completion of administrative activities and registration on the ARTG	7 February 2022
Number of working days from submission dossier acceptance to registration decision*	198

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

Quality

There was no requirement for a quality evaluation for this submission. The quality of the currently approved product was deemed appropriate for the extension of indication.

Nonclinical

There was no requirement for a non-clinical evaluation for this submission.

Clinical

Summary of clinical studies

There are no new pharmacokinetic (PK) data provided in this submission. In the previous (and withdrawn) submission;**Error! Bookmark not defined.** the clinical dossier consisted of two studies:

- Study H2301 (RAINBOW trial): Ranibizumab compared with laser therapy for the treatment of infants born prematurely with retinopathy of prematurity. This was a pivotal Phase III study.[10]
- Study H2301E1 (RAINBOW extension trial): 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. Only the first interim results were submitted.[11]

In this submission, a new second pre-defined 2 year safety data interim analysis (IA) is provided for the RAINBOW extension trial.

Pharmacology

Pharmacokinetics

In the Study H2301 (the RAINBOW trial), sparse pharmacokinetic sampling (at Day 1, 15, and 29) was conducted in approximately half of the participants assigned to ranibizumab (those with an odd identification number).

After intravitreal administration, the highest serum concentrations of ranibizumab were detected at Day 1. Day 1 serum concentrations were approximately twice as high in the ranibizumab 0.2 mg group (n = 49; median 7.82 ng/mL) compared to the 0.1 mg group (n = 46; median = 4.35 ng/mL). At Day 29, concentrations were approximately 7-fold (1.07 ng/mL) and 8-fold (0.566 ng/mL) lower than Day 1 levels, for 0.2 mg and 0.1 mg, respectively (show in Table 3, below).

[10] Study (CRFB002)H2301: RAnibizumab Compared With Laser Therapy for the Treatment of INfants BOrn Prematurely With Retinopathy of Prematurity (RAINBOW trial).
ClinicalTrials.gov Identifier: NCT02375971; EudraCT Number: 2014-003041-10.
[11] Study (CRFB002)H2301E1: 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 (RAINBOW extension trial).
ClinicalTrials.gov Identifier: NCT02640664; EudraCT Number: 2014-004048-36.

Table 3: Study H2301 (RAINBOW trial) Summary of ranibizumab concentration in pharmacokinetic serum samples (ng/mL) (pharmacokinetic set)

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.

Pharmacodynamics

In the RAINBOW trial, sparse pharmacodynamic (PD) sampling (serum VEGF) (at Day 1, 15 and 29) was conducted (from study participants with even ID numbers in the ranibizumab groups and all patients in the laser group). The VEGF set comprised of 19, 26 and 51 patients in the ranibizumab 0.2 mg group, ranibizumab 0.1 mg group and laser group, respectively. The results are summarised in Table 4. The large sample collection windows likely contributed to the moderate and high inter-individual variability in free VEGF concentrations.

Table 4: Study H2301 (RAINBOW trial) Summary of systemic free VEGF concentration (pg/mL) (VEGF Set)

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

BLQ= below limit of quantification (< 1 pg/mL on plate; 5.99 pg/mL plasma), with imputation as 0.0 in source table; CV= coefficient of variation.
n= number of patients who had at least one valid VEGF concentration.
Treatment arm is based on actual treatment received at Day 1 (Baseline).
Systemic free VEGF levels were assessed in patients who received initial ranibizumab treatment and with an even patient identification number, and for all patients who received an initial laser treatment.
Day 1: Before the first administration of study treatment.
* Excluding the outlier value of 5900 pg/mL, Max is 153 pg/mL.

Population pharmacokinetic/pharmacodynamic data

Ranibizumab estimated pharmacokinetic parameters

Adults dosed at 0.5 mg ranibizumab in one eye were compared to premature infants dosed at 0.2 or 0.1 mg per eye. The population pharmacokinetic/pharmacodynamic (popPK/PD) data analysis showed:

- *Elimination:* elimination from the eye was 50% faster for premature infants than for adults (half-life = 5.6 days versus 8.7 days in adults with age-related macular degeneration) whilst elimination from serum was three fold lower for premature infants than in adults (half-life = 0.3 days versus 0.09 days). As the rate of vitreous elimination is the rate limiting step, the half-life of ranibizumab in serum after intravitreal administration is equivalent to the vitreous elimination half-life.
- *Volume of distribution and clearance*: the apparent systemic volume of distribution (Vd) is approximately, three-fold lower in preterm infants than in adults (median of 0.7 to 0.8 L versus 2.97 L) and the apparent clearance is more than ten-fold lower (median of 1.7 to 1.8 L/day versus 23.8 L/day).
- *Exposure:* when comparing median systemic ranibizumab peak concentration (C_{max}) in plasma and area under the concentration versus time curve from 0 time to infinity (AUC_{inf}) in plasma, the results were:
  - 16-fold and 12-fold greater, respectively in infants (at a dose of 0.2 mg per eye) compared to adults (0.5 mg ranibizumab in one eye).
  - 7.6-fold and 5-fold greater, respectively in infants (at a dose of 0.1 mg per eye) compared to adults (0.5 mg ranibizumab in one eye).

There was a variability of observed concentrations in preterm infants, with between-subject variability, particularly in estimated Vd, much greater than in adults. Further, the range of weight was much greater (approximately four-fold from lightest to heaviest infant) compared to the age-related macular degeneration population.

Vascular endothelial growth factors concentrations

The popPK/PD model was used to assess the relationship between serum ranibizumab concentration and systemic vascular endothelial growth factors (VEGF) levels. VEGF concentrations were stratified by actual dose administered (not assigned treatment); therefore, initial laser treatments rescued by ranibizumab were classified by the dose administered at the time of rescue. Vitreous VEGF concentrations were not assessed.

The popPK/PD model did not predict a relationship between systemic ranibizumab concentrations and systemic free VEGF concentrations but provided the following values: median C_{max} was 11.5 ng/mL (0.1 mg dose) and 24.3 ng/mL (0.2 mg dose). Both values were capable to inhibit VEGF receptors by 50% (range given in the Product Information: 11 to 27 ng/mL; based on *in vitro* data) with possible implications for safety and development in premature infants.

The clinical evaluator concluded that the pharmacokinetic/pharmacodynamics data are limited and potential systemic inhibition of VEGF following administration of intravitreal ranibizumab to premature infants cannot be determined.

Dosage selection

The 0.1 mg and 0.2 mg doses of ranibizumab used in the pivotal RAINBOW trial were selected based on results of a modelling and simulation analysis using predicted exposure levels and a PK model that was scaled for infants.

Efficacy

The clinical trial program uses the same Study H2301 (RAINBOW trial) as for the previous submission;[Error! Bookmark not defined.] (withdrawn by sponsor prior to a regulatory decision being made) together with 2-year follow up data from the second interim analysis for those patients enrolled in the subsequent extension Study H2301E1 (RAINBOW extension trial), to support use of ranibizumab 0.2 mg in preterm infants for the treatment of retinopathy of prematurity (ROP) affecting Zone I (Stage 1+, 2+, 3 or 3+), Zone II (Stage 3+) or preterm infants with aggressive posterior retinopathy of prematurity (AP-ROP).

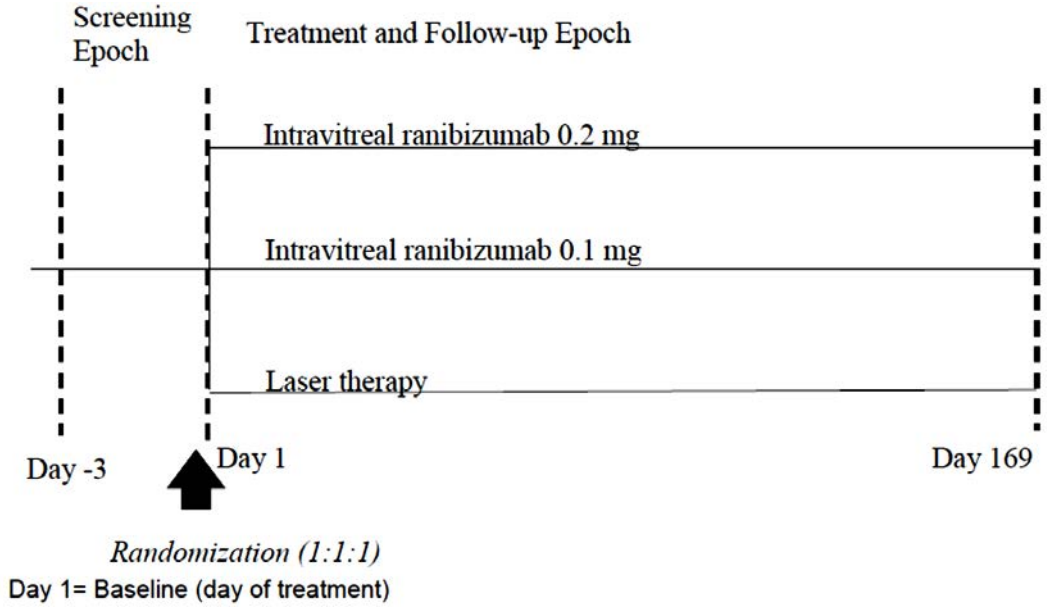
Study H2301 (RAINBOW trial)

Design

The study design was a pivotal, 24 week, Phase III, randomised, open label, multi-centre (87 centres in 26 countries), three arm parallel group (1:1:1), actively controlled superiority study to assess the efficacy and safety of ranibizumab in 225 preterm infants with ROP. The study was conducted between 30 December 2015 and 14 December 2017.

The treatments were intravitreal ranibizumab 0.2 mg, intravitreal ranibizumab 0.1 mg or laser therapy (see Figure 2, below). Up to 2 additional retreatments at least 28 days apart with the same ranibizumab dose were permitted to either eye for worsening ROP. Switching treatments was allowed if randomised treatment had been ineffective.

Figure 2: Study H2301 (RAINBOW trial) Study design schema



The study included preterm infants with birth weight less than 1500 g and bilateral ROP with one of the following retinal findings in each eye: Zone I Stage 1+, 2+, 3 or 3+ disease, Zone II Stage 3+ disease or AP-ROP. Exclusion criteria included previous surgical or non-surgical treatment for ROP (for example, ablative laser therapy, cryotherapy or vitrectomy), previous exposure to any intravitreal or systemic anti-VEGF agent (patient or mother during pregnancy).

The primary objective was to demonstrate that intravitreal ranibizumab 0.2 mg is superior to laser therapy as measured by the absence of active ROP and absence of unfavourable structural outcomes in both eyes 24 weeks after starting treatment.

The key secondary objectives were: (i) to demonstrate intravitreal ranibizumab 0.1 mg is superior to laser therapy in the treatment of ROP and (ii) to demonstrate that intravitreal ranibizumab 0.2 mg is superior to intravitreal ranibizumab 0.1 mg in the treatment of ROP, measured as described for the primary objective.

The primary efficacy outcome (binary variable) measure was:

- 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
- Treatment failure

Secondary efficacy variables included:

- individual components of the primary endpoint (death, active ROP, unfavourable structural outcomes and intervention with treatment modality other than the first treatment (that is. switched treatment));
- recurrence of ROP receiving any post-baseline intervention at or before 24 weeks; and
- time to death, treatment switch or first occurrence of unfavourable structural outcomes in either eye up to 24 weeks.

Magnitude of the treatment effect and its clinical significance

Baseline treatment was received by 218 preterm infants received baseline treatment. Baseline disease characteristics were generally comparable across groups (including disease severity), apart from an imbalance in birth weight groups observed at Baseline: mean birth weight was lower in the ranibizumab 0.2 mg group (790.6 g) than in the 0.1 mg group (885.6 g) and laser group (830.6 g). Most patients were Caucasian (59.1%). Mean gestational age was 26.1 weeks and mean chronological age was 10.9 weeks.

For ROP extent and severity, 38.2% had ROP Zone I and 61.3% ROP Zone II which was similar across the treatment groups. Zone II Stage 3+ (60.0%) the most common ROP classification at Baseline. AP-ROP was reported for 30 (13.3%) patients (n = 10 patients in each group) (Table 5).

Table 5: Study H2301 (RAINBOW trial) Proportion of patients at Week 24 and second interim analysis (IA2) by Baseline disease classification.

Baseline disease classification	Proportion of patients (%) at Week 24 (FAS)	Proportion of patients (%) at IA2 (ESS)
Zone I (Stage 1+)	1.3	1.1
Zone I (Stage 2+)	4.0	4.4
Zone I (Stage 3)	3.6	4.4
Zone I (Stage 3+)	16.4	16.1
Zone II (Stage 3+)	60.0	60.6
AP-ROP (zone I)	12.9	12.2
AP-ROP (Zone II)	0.4	0.6

Abbreviations: ESS = extension safety set; FAS = full analysis set; IA2 = interim analysis 2.

Primary endpoint results

Treatment success

The proportions of patients achieving treatment success were 80.0%, 75.0% and 66.2%, for the ranibizumab 0.2 mg, ranibizumab 0.1 mg and laser therapy groups, respectively (see Table 6). The differences were not statistically significant.

Table 6: Study H2301 (RAINBOW trial) Treatment success proportions at Week 24 after the first study treatment by treatment group and ROP Zone (full analysis set)

	Ranibizumab 0.2 mg N=74		Ranibizumab 0.1 mg N=77		Laser N=74	
ROP Zone	**n/M (%)**	**95% CI**	**n/M (%)**	**95% CI**	**n/M (%)**	**95% CI**
All patients	56/70 (80.0)	(0.6873, 0.8861)	57/76 (75.0)	(0.6374, 0.8423)	45/68 (66.2)	(0.5368, 0.7721)
Zone I	19/28 (67.9)	(0.4765, 0.8412)	21/30 (70.0)	(0.5060, 0.8527)	14/23 (60.9)	(0.3854, 0.8029)
Zone II	37/42 (88.1)	(0.7437, 0.9602)	36/46 (78.3)	(0.6364, 0.8905)	31/45 (68.9)	(0.5335, 0.8183)

CI= confidence interval, M= the 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 unfavorable structural outcome in both eyes 24 weeks after the first study treatment, ROP= retinopathy of prematurity
The 95% CI is using Clopper-Pearson exact method.
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.
ROP zone information is obtained from CRF.

Ocular structural abnormalities

The proportion of patients with unfavourable structural outcomes in either eye at or before 24 weeks (an individual component of the primary efficacy variable), was lower for the 0.2 mg (1.4%) compared to the 0.1mg (6.7%) group and laser group (10.1%).

Comparison using odds ratio

When comparing the ranibizumab 0.2 mg group against the laser group, the odds ratio was 2.19 (95% confidence interval (CI): 0.9932, 4.8235) with p = 0.0254. The odds ratio for the comparison of ranibizumab 0.1 mg versus laser and for ranibizumab 0.2 mg versus ranibizumab 0.1 mg were 1.57 (95% CI: 0.7604, 3.2587) and 1.35 (95% CI: 0.6101, 2.9810), respectively.

Risk difference and risk ratio do not appear to have been reported.

The primary endpoint subgroup analysis (Week 24) stratified by baseline disease classification is shown in Table 7.

Table 7: Study H2301 (RAINBOW trial) Proportion of patients with absence of active ROP and unfavourable structural outcomes in both eyes at the Week 24 visit by core study baseline ROP disease (extension study safety set).

Baseline ROP disease	Ranibizumab 0.2 mg N = 61 n/M (%)	Ranibizumab 0.1 mg N = 65 n/M (%)	Laser N = 54 n/M (%)
ZONE I/AP-ROP	4/ 7 (57.1)	5/ 8 (62.5)	5/ 7 (71.4)
ZONE II/AP-ROP	0/ 0	0/ 0	0/ 1 (0.0)
ZONE I/STAGE 3+	9/ 10 (90.0)	9/ 11 (81.8)	4/ 8 (50.0)
ZONE I/STAGE 3	3/ 3 (100)	4/ 4 (100)	1/ 1 (100)
ZONE I/STAGE 2+	3/ 3 (100)	0/ 1 (0.0)	4/ 4 (100)
ZONE I/STAGE 1+	0/ 0	1/ 1 (100)	0/ 1 (0.0)
ZONE II/STAGE 3+	35/ 38 (92.1)	32/ 39 (82.1)	23/ 32 (71.9)
ZONE II/STAGE 3	0/ 0	1/ 1 (100)	0/ 0

Abbreviations: n: Number of subjects with absence of active ROP and absence of unfavourable structural outcomes in both eyes 24 weeks after the first study treatment (including imputed values); M: The total number of subjects with non-missing value on primary efficacy outcome (including imputed values).

Notes: If a subject died or switched study treatment before or at week 24, then the subject will be considered as having active ROP and unfavourable structural outcomes at week 24.

As the primary endpoint did not reach statistical significance, the key secondary endpoints were not tested.

Post-Baseline intervention

The proportion of patients with recurrence of ROP requiring any post-Baseline intervention at or before 24 weeks was higher in the ranibizumab groups (31.1% for 0.2 mg) than in the laser group (18.9%).

Study H2301E1 (RAINBOW extension trial)

Ranibizumab re-treatment was permitted up to Week 40 (that is, up to 40 weeks after the baseline treatment in Study H2301 (the RAINBOW trial)). One patient in the ranibizumab 0.1 mg group received ranibizumab re-treatment at the extension study Baseline visit, with no additional patients requiring ranibizumab re-treatment during the extension study.

Magnitude of the treatment effect and its clinical significance

Study H2301E1 (RAINBOW extension trial) had 180 patients (89.6%) entering the study from Study H2301 (the RAINBOW trial, discussed above). Of these 180 patients, 166 (92.2%) patients were still in the study at the time of data cut-off for the pre-specified second interim analysis (IA2).

In each of the ranibizumab groups (that is 0.1 mg, and 0.2 mg ranibizumab dose groups), 77% of patients received initial bilateral treatment only.

Primary endpoint results

At the 2-year visit, treatment success proportions (absence of all ocular structural abnormalities) were 98.3% in the ranibizumab 0.2 mg group, 93.8% in the 0.1 mg group and 88.7% in the laser group (see Table 8, below). There were no cases of recurrence of ROP in any treatment group after 40 weeks and no cases of active ROP at the 2-year visit. Detailed data on absence of individual ocular structural abnormalities are shown in Table 9.

Table 8: Study H2301/E1 (RAINBOW trial and extension trial) Treatment success proportions at different timepoints by treatment group (full analysis set or extension safety set)

	Ranibizumab 0.2 mg	Ranibizumab 0.1 mg	Laser therapy	Comments
Week 24 (FAS)	56/70 (80.0%) (0.6873, 0.8861)	57/76 (75.0%) (0.6374, 0.8423)	45/68 (66.2%) (0.5368, 0.7721)	
Week 40 (ESS)	55/55 (100.0%) (0.9351, 1.0000)	58/58 (100.0%) (0.9384, 1.0000)	46/46 (100.0%) (0.9229, 1.0000)	40 weeks post core baseline.
2 years (ESS)	59/60 (98.3%) (0.9106, 0.9996)	61/65 (93.8%) (0.8499, 0.9830)	47/53 (88.7%) (0.7697, 0.9573)	At or before subjects' 2 years' corrected age visit.

Abbreviations: FAS = Full analysis set; ESS = extension safety set

Results given as proportion (number), and percentage of participants with treatment success/total number of participants per group, followed by 95% confidence intervals.

Table 9: Study H2301E1 (RAINBOW extension trial) Absence of individual ocular structural abnormality at or before subjects' 2 years corrected age visit at the second interim analysis (IA2) (extension safety set).

Variable	n/M (%)	95% CI	n/M (%)	95% CI	n/M (%)	95% CI
Absence of substantial temporal retinal vessel dragging causing abnormal structural features/ macular ectopia	59/ 60 (98.3)	(0.9106, 0.9996)	63/ 65 (96.9)	(0.8932, 0.9963)	49/ 53 (92.5)	(0.8179, 0.9791)
Absence of Retrolental membrane obscuring the view of the posterior pole	60/ 60 (100)	(0.9404, 1.0000)	65/ 65 (100)	(0.9448, 1.0000)	52/ 53 (98.1)	(0.8993, 0.9995)
Absence of posterior retinal fold involving the macula	59/ 60 (98.3)	(0.9106, 0.9996)	65/ 65 (100)	(0.9448, 1.0000)	51/ 53 (96.2)	(0.8702, 0.9954)
Absence of retinal detachment involving the macula	60/ 60 (100)	(0.9404, 1.0000)	63/ 65 (96.9)	(0.8932, 0.9963)	50/ 53 (94.3)	(0.8434, 0.9882)
Absence of retinal detachment not involving the macula	60/ 60 (100)	(0.9404, 1.0000)	62/ 65 (95.4)	(0.8710, 0.9904)	50/ 53 (94.3)	(0.8434, 0.9882)
Absence of pre-retinal fibrosis	58/ 60 (96.7)	(0.8847, 0.9959)	59/ 65 (90.8)	(0.8098, 0.9654)	48/ 53 (90.6)	(0.7934, 0.9687)
Absence of optic disc pallor	60/ 60 (100)	(0.9404, 1.0000)	65/ 65 (100)	(0.9448, 1.0000)	53/ 53 (100)	(0.9328, 1.0000)
Absence of optic disc swelling	60/ 60 (100)	(0.9404, 1.0000)	65/ 65 (100)	(0.9448, 1.0000)	53/ 53 (100)	(0.9328, 1.0000)
Absence of pigmentary disturbance in the macula	60/ 60 (100)	(0.9404, 1.0000)	64/ 65 (98.5)	(0.9172, 0.9996)	52/ 53 (98.1)	(0.8993, 0.9995)
Absence of atrophic changes in macula	60/ 60 (100)	(0.9404, 1.0000)	65/ 65 (100)	(0.9448, 1.0000)	52/ 53 (98.1)	(0.8993, 0.9995)

Abbreviations: 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.

Note: The 95% confidence interval for the proportion using Clopper-Pearson exact method.

A direct statistical comparison of efficacy data between groups is difficult to make and may be misleading, as there are missing data at all timepoints, in particular within the RAINBOW extension trial. But there appears to be a reasonable proportion of treatment success in all treatment groups.

The primary endpoint subgroup analysis stratified by baseline disease classification is shown in Table 10 for ROP status at the 2 years visit (corrected age), Table 7 (see above) for the Week 24 visit, and Table 11 (below) for Week 40 visit.

Table 10: Study H2301E1 (RAINBOW extension trial) Proportion of patients with absence of unfavourable structural outcomes in both eyes up to the subjects' 2 years corrected age visit by core study baseline ROP disease (extension study safety set)

Baseline ROP disease	Ranibizumab 0.2 mg N = 61 n/M (%)	Ranibizumab 0.1 mg N = 65 n/M (%)	Laser N = 54 n/M (%)
ZONE I/AP-ROP	4/ 7 (57.1)	6/ 8 (75.0)	5/ 7 (71.4)
ZONE II/AP-ROP	0/ 0	0/ 0	0/ 1 (0.0)
ZONE I/STAGE 3+	9/ 10 (90.0)	9/ 11 (81.8)	3/ 8 (37.5)
ZONE I/STAGE 3	3/ 3 (100)	4/ 4 (100)	1/ 1 (100)
ZONE I/STAGE 2+	3/ 3 (100)	0/ 1 (0.0)	4/ 4 (100)
ZONE I/STAGE 1+	0/ 0	1/ 1 (100)	0/ 1 (0.0)
ZONE II/STAGE 3+	34/ 37 (91.9)	32/ 39 (82.1)	23/ 32 (71.9)
ZONE II/STAGE 3	0/ 0	1/ 1 (100)	0/ 0

Abbreviations: Number of subjects with absence of unfavourable structural outcomes in both eyes up to subjects 2 years corrected age visit (including imputed values); M: The total number of subjects with non-missing value on primary efficacy outcome (including imputed values).

Note: If a subject died or switched study treatment before or at 2 years' corrected age visit, then the subject will be considered as having unfavourable structural outcomes at 2 years' corrected age visit.

Table 11: Study H2301 (RAINBOW trial) Proportion of patients with absence of active ROP and unfavourable structural outcomes in both eyes at the Week 40 visit by core study baseline ROP disease (extension study safety set)

Baseline ROP disease	Ranibizumab 0.2 mg N = 61 n/M (%)	Ranibizumab 0.1 mg N = 65 n/M (%)	Laser N = 54 n/M (%)
ZONE I/AP-ROP	4/ 7 (57.1)	6/ 8 (75.0)	5/ 7 (71.4)
ZONE II/AP-ROP	0/ 0	0/ 0	0/ 1 (0.0)
ZONE I/STAGE 3+	9/ 10 (90.0)	9/ 11 (81.8)	3/ 8 (37.5)
ZONE I/STAGE 3	3/ 3 (100)	4/ 4 (100)	1/ 1 (100)
ZONE I/STAGE 2+	3/ 3 (100)	0/ 1 (0.0)	4/ 4 (100)
ZONE I/STAGE 1+	0/ 0	1/ 1 (100)	0/ 1 (0.0)
ZONE II/STAGE 3+	34/ 37 (91.9)	32/ 39 (82.1)	22/ 32 (68.8)
ZONE II/STAGE 3	0/ 0	1/ 1 (100)	0/ 0

Abbreviations: Number of subjects with absence of active ROP and absence of unfavourable structural outcomes in both eyes 40 weeks after the first study treatment (including imputed values); M: The total number of subjects with non-missing value on primary efficacy outcome (including imputed values).

Note: If a subject died or switched study treatment before or at week 40, then the subject will be considered as having active ROP and unfavourable structural outcomes at week 40.

There were no cases of recurrence of ROP in any treatment group after 40 weeks and no cases of active ROP at the 2 year visit, noting one patient in ranibizumab 0.1 mg group had active ROP at Week 52, which was reported to have resolved at the 2-year visit.

Additional endpoints

Additional endpoints were based on visual function outcomes.

Unblinded visual acuity (VA) measurements for a small subgroup at the 2-year corrected age visit did not demonstrate a negative impact of ranibizumab on vision (see Table 12,

below). It is noted that for Cardiff Acuity test LogMAR;[12,13] a lower value is more favourable. The planned 5-year VA assessment will be masked (as per the European Medicines Agency (EMA) request).

Table 12: Study H2301E1 (RAINBOW extension trial) Summary of visual function outcomes (second interim analysis (IA2))

	Ranibizumab 0.2 mg N=61	Ranibizumab 0.1 mg N=65	Laser N=54
n	58	57	50
Visual reception of the Mullen scale (T score, mean (SD)) at Year 2	40.5 (13.54)	39.6 (14.39)	37.2 (13.89)
n	22	26	19
Cardiff Acuity Test (CAT, mean (SD)) [a]	0.377 (0.3007)	0.431 (0.3159)	0.474 (0.2806)
n	14	13	15
Vision function rating – visual acuity [a]	12 normal 1 minor impairment 0 major impairment 1 Not available	12 normal 1 minor impairment 0 major impairment 0 Not available	11 normal 3 minor impairment 1 major impairment 0 Not available
n	12	19	11
Vision function rating – peripheral vision [a]	7 normal 1 minor impairment 0 major impairment 4 Not available	11 normal 1 minor impairment 0 major impairment 7 Not available	8 normal 2 minor impairment 1 major impairment 0 Not available

[a] Binocular results presented, for visual acuity from Cardiff Acuity test at Year 2, summary statistics in LogMAR; for vision function rating, results from the IA2 analysis are presented. N represents the number of enrolled patients in Study H2301E1. n represents the number of patients with available data for specified assessments.

Safety

Exposure

Study H2301 (RAINBOW trial)

The mean safety observation period was 161.7 to 162.7 days across treatment groups. The mean number of injections per patient was 2.4 in the 0.2 mg group and 2.5 in the 0.1 mg group. Thirteen (18.8%) patients from the laser treatment group switched to ranibizumab, receiving a mean 2.2 injections each.

Study H2301E1 (RAINBOW) extension trial

For the 180 enrolled patients, the mean number of injections per patient up to Week 40 was 2.5 for each of the ranibizumab groups, with 77% of patients receiving initial treatment at the baseline of Study H2301 (Rainbow trial) only. Eleven patients who

[12] The **Cardiff Acuity test** (**CAT**) is based on the principle of vanishing optotypes and is a set of six cards with six easily recognisable shapes (including house, fish, dog, duck, train) positioned either at the top or bottom half of a card. The cards are calibrated to give visual acuity of equivalent of 20/20 to 20/200 at one metre viewing distance. The child is comfortably seated and the cards are presented at eye level at a distance of one meter. The examiner watches the eye movements towards the shape. If the child is looking at the shape, then the next card is presented. This procedure is continued until no definite fixation is observed. The test is performed at 1 metre distance but altered to 0.5 metres if the child is unable to see the first card. The identification score and Snellen's equivalent of each card is mentioned at the back of card.
[13] Logarithm of the Minimum Angle of Resolution (LogMAR) scoring used for assessing visual acuity.

received laser treatment switched to ranibizumab, receiving a mean 2.4 ranibizumab injections each. Over 96% patients had a safety follow-up period of more than 24 months.

Adverse events

Study H2301 (RAINBOW trial)

The adverse event (AE) profile was generally comparable between the 0.2 mg and 0.1 mg treatment groups with no definite dose-related trends observed in the clinical trial program. Non-ocular AEs and serious adverse events (SAE) in the pivotal study were reported most frequently in the infections and infestations, respiratory, thoracic and mediastinal disorders and gastrointestinal disorders System Organ Classes (SOC) and in line with co-morbidities in a premature infant patient population.

Non-ocular adverse events were experienced by 84.9%, 81.6% 76.8% of the patients in the ranibizumab 0.2 mg, 0.1 mg, and laser groups, respectively. The most common AE was pyrexia (8.7%), nasopharyngitis and anaemia (8.3% each).

An imbalance relating to hearing disorders (6.8% for ranibizumab 0.2 mg versus 1.4% for laser) had various time to onset after treatment and was not considered treatment-related by the sponsor.

Ocular adverse events were experienced by 30.1%, 40.8% and 33.3% of the patients in the ranibizumab 0.2 mg, 0.1 mg and laser groups, respectively. Adverse events were most commonly retinal haemorrhage (10.6%), conjunctival haemorrhage (6.4%), conjunctivitis (4.6%) and ROP (3.7%).

Adverse events suspected to be related to study drug treatment or procedure were more frequent in the ranibizumab groups (15.1 to 15.8% versus 8.7% for laser), most commonly conjunctival haemorrhage. These AE were consistent with the known adult safety profile.

The key safety issues were the lack of long-term safety data for intravitreal ranibizumab in premature infants with ROP and important potential risk of neurodevelopmental delay.

Study H2301E1 (RAINBOW extension trial)

First interim analysis (IA1) safety data (up to Week 40) from the Study H2301AE (RAINBOW extension trial) were considered consistent with Study H2301 (core RAINBOW trial) safety data.

Non-ocular adverse events were experienced by 72.3 to 79.6% of patients across the groups. The most common AEs were nasopharyngitis, pyrexia and bronchitis, with no treatment specific trends noted.

Ocular adverse events were experienced by 4.6%, 33.8% and 35.2% of patients in the 0.2 mg, 0.1 mg, and laser groups, respectively. The most frequent AEs were strabismus, myopia, astigmatism and conjunctivitis. Severe AEs occurred in 3.3% of patients. The ocular AE profile in the extension study was consistent with the known ocular AE profile observed in the core part of Study H2301 (RAINBOW trial), with no new ocular safety concerns identified.

The overall ocular and non-ocular AE profiles of ranibizumab 0.2 mg and 0.1 mg at the 2-year corrected age visit were similar.

Treatment-related adverse event

Treatment-related adverse events (potential adverse drug reactions (ADR)) for the ROP indication were identified based on the established adult ADR profile and on AEs reported in 4 or more patients in either ranibizumab group with a difference of 3% or greater in either ranibizumab group (0.1 mg or 0.2 mg) versus the laser treatment group. They appear to be consistent with the known adult ocular safety profile.

Deaths

Study H2301 (RAINBOW trial)

Twelve deaths occurred in the study: four patients in each group, with one death due to respiratory failure in the ranibizumab 0.1 mg group suspected to be related to study medication.

Study H2301E1 (RAINBOW extension trial)

There were two deaths with both patients in the laser group. Neither death was considered related to study treatment or procedure.

Serious adverse events

Study H2301 (RAINBOW trial)

The number of patients with non-ocular serious adverse events (SAEs) was comparable across the treatment groups (31.6 to 32.9%), with pneumonia, bronchiolitis, and bronchopulmonary dysplasia the most frequent (2.8% each).

Four patients (5.5 to 5.8%) each in the ranibizumab 0.2 mg and laser groups with ROP the most frequent ocular SAE (2.8%). There was one ocular SAE of endophthalmitis suspected to be related to study treatment and study procedure in the ranibizumab 0.1 mg group. Endophthalmitis is a known important risk of ranibizumab.

Study H2301E1 (RAINBOW extension trial)

Non-ocular SAEs occurred in 32.8%, 32.3% and 42.6% of patients in the 0.2 mg, 0.1 mg and laser groups, respectively. The most common SAEs were bronchitis (5.6%), pneumonia (4.4%) and bronchiolitis in accordance with the known co-morbidities of the patient population.

Seven (3.9%) patients experienced ocular SAE, including two SAEs of retinal detachment in the ranibizumab 0.1 mg group. No patients in the ranibizumab 0.2 mg group had ocular SAEs.

Adverse events of special interest and long-term safety

Neurodevelopmental impairment is an important potential risk of ranibizumab for the ROP indication, and a recognised complication of prematurity with the risk increasing with decreasing gestational age.

The sponsor provided an analysis of neurodevelopmental impairment for the RAINBOW extension trial (to the second interim analysis (IA2) cut off) using two approaches:

- A broader medical review of all relevant AE reported in Study H2301E1 (RAINBOW extension trial), up to the IA2 cut-off) that may be considered related to overall developmental impairment associated with central nervous system (CNS) disorders was conducted.

  The review revealed:

  – 37 patients: 14 (23.0%), 9 (13.9%), and 14 (25.9%) patients in the ranibizumab 0.2 mg, 0.1 mg and laser groups, respectively.

    Of those:

  – 11 out of 14 versus 6 out of 9 versus 12 out of 14 patients were less than 28 weeks gestational age, with birth weight ≤ 1,000 g for 29 patients, and ≤ 750 g for 21 patients (11 versus 3 versus 7) amongst the ranibizumab 0.2 mg, 0.1 mg and laser treated patients, respectively.

  – Twenty-five patients had AE relating to CNS haemorrhage or lesions prior to baseline treatment in the core study (9 out of 14 versus 5 out of 9 versus 11 out of

14) amongst the ranibizumab 0.2 mg, 0.1 mg and laser treated patients, respectively.

- A review of results from a search strategy as defined in the risk management plan (RMP) version 20.0 for the potential risk of neurodevelopmental impairment (ROP).

  From this review, relevant AEs were identified for seven (11.5%), 3 (4.6%) and 9 (16.7%) patients in the ranibizumab 0.2 mg, ranibizumab 0.1 mg and laser groups, respectively (see Table 13).

The results of these two reviews differ, presumably as the RMP review appeared to have been a subset of the broader review.

Table 13: Study H2301E1 (RAINBOW extension trial) Risk management plan search strategy; adverse events related to non-ocular safety risks up to the second interim analysis (IA2) cut-off (extension safety set)

Risk Category Preferred term	Ranibizumab 0.2 mg N = 61 n(%)	Ranibizumab 0.1 mg N = 65 n(%)	Laser N = 54 n(%)
Neurodevelopmental impairment (ROP)	7 (11.5)	3 (4.6)	9 (16.7)
Developmental delay	4 (6.6)	0	3 (5.6)
Deafness	3 (4.9)	0	1 (1.9)
Motor developmental delay	2 (3.3)	0	0
Deafness transitory	1 (1.6)	0	0
Language disorder	1 (1.6)	0	0
Cerebral palsy	0	1 (1.5)	1 (1.9)
Cognitive disorder	0	1 (1.5)	0
Deafness bilateral	0	0	1 (1.9)
Developmental coordination disorder	0	1 (1.5)	1 (1.9)
Hypoacusis	0	0	1 (1.9)
Intellectual disability	0	0	1 (1.9)
Motor dysfunction	0	1 (1.5)	1 (1.9)
Psychomotor retardation	0	1 (1.5)	0
Psychomotor skills impaired	0	1 (1.5)	0

Note: Multiple occurrences of the same event in a subject were counted only once.

However, developmental (including cognitive) and other outcome measures were collected separately (see Table 14, below). Summary statistics were provided for the 2-year visit results for the following:

- *Mullen Scales of Early Learning*:[14] observed distribution of the T-score was in the lower range of the cognitive scale typical for a premature, extremely low birth weight population with corresponding co-morbidities, but scores were comparable between groups.
- *Children Visual Function Questionnaire*:[15] based on 4 domains; scores were comparable between groups.
- *Gross Motor Function Classification System (GMFCS - E&R):*[16] The GMFCS-E&R was adapted by the sponsor to include Level 0 where Level 0: No evidence of neurological abnormality and normal gross motor ability as described in Level 1. Level 1: Abnormal neurological status but normal gross motor ability.
- *Respiratory function:* not included in Table 14, as not a validated scoring system; however, the provided results were comparable between groups.

[14] Mullen Scales of Early Learning (MSEL; Mullen, 1995) is a standardized developmental test for children ages 3 - 60 months that with five scale scores representing developmental ages.
[15] The Children Visual Function Questionnaire is a vision specific quality of life questionnaire, designed for use with parents of infants and young children.

[16] Gross Motor Function Classification System (GMFCS - E&R) categorises the gross motor function of children and young people into five levels.

- *Hearing:* Proportion with normal or near normal hearing.
- *Mean duration of hospitalisation*: from birth to first hospital discharge home.
- *Growth parameters*: Mean body weight, standing height and head circumference were comparable between the three treatment groups, with similar mean change from Baseline across the groups for each of these growth parameters. Not included in Table 14.
- *Impaired vital organ development:* renal and liver function test data at the patients 2-years corrected age were available for a small number of subjects (10 subjects or less per group for most parameters) and reference intervals not provided. No conclusions can be drawn from these data. Not included in Table 14.

Table 14: Study H2301E1 (RAINBOW extension trial) Selected clinical and cognitive outcomes (second interim analysis IA2)

	Ranibizumab 0.2 mg	Ranibizumab 0.1. mg	Laser therapy
Neurodevelopmental impairment adverse events			
Broad medical review: proportion of patients	23.0%	13.9%	25.9%
RMP review: proportion of patients	11.5%	4.6%	16.7%
Mullen Scales of Early Learning			
Visual Reception t-score (SD)	40.5 (13.5)	39.6 (14.4)	37.2 (13.9)
Receptive Language t-score (SD)	41.7 (12.2)	39.0 (13.3)	38.6 (13.0)
Expressive Language t-score (SD)	36.9 (11.3)	34.2 (11.9)	35.2 (12.2)
Children Visual Function Questionnaire			
Mean composite score (SD)	80.9 (12.0)	78.6 (12.3)	76.2 (11.5)
Gross Motor Function Classification System (GMFCS-E&R, adapted)			
Proportion at Level 0 or 1 (%)	75.4	75.3	64.8
Hearing function			
Proportion with normal or near normal hearing (%)	86.9	76.9	81.5
Hospitalisations			
Mean duration of hospitalisation (from birth to first hospital discharge home)	111.1	118.0	97.5

Abbreviation: SD = standard deviation; AE = adverse event

Post-market experience

Specifically in patients treated for ROP only, limited ROP-specific post-market data were provided in periodic safety update reports (PSUR).[17] They did not reveal any new relevant safety information

[17] A **periodic safety update report (PSUR)** is a systematic review of the global safety data of an approved medicine that becomes available during a defined time period. PSURs are also referred to as periodic benefit–risk evaluation reports (PBRERs).

Risk management plan

The most recent European Union (EU) RMP was version 20.0 (dated 13 August 2019; data lock point (DLP) 24 January 2018 for clinical trial data, and 31 May 2018 for post-marketing data) and Australia-specific annex (ASA),[18] version 11.2 (dated 24 June 2021).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 15.[19] Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach.

Table 15: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Infectious endophthalmitis	✓*	–	✓	✓†
	Retinal detachment and retinal tear	✓	–	✓	✓†
	Intraocular inflammation	✓	–	✓	✓†
	Intraocular pressure increase	✓	–	✓	✓†
Important potential risks	Neurodevelopmental impairment (ROP)	✓	–	–	–
Missing information	Long term effects on the progression of the condition CNV (other than nAMD)	✓	–	✓	–
	Visudyne (verteporfin-PDT) given in combination with ranibizumab (PM)	✓	–	✓	–
	Long term safety of ranibizumab in the condition ROP	✓*	–	✓	–

*Targeted follow up form; † Patient booklet

[18] **The Australian specific annex (ASA)** enables the European Union-risk management plan (EU-RMP), or, if no current EU-RMP exists, then a core or global RMP, to be adapted to the Australian context.
The ASA is required because global activities proposed in the EU-RMP may differ from those planned for Australia. For example, the sponsor may propose different wording for the Australian PI than that proposed in the EU-RMP for the European Summary of Product Characteristics (SmPC).
The ASA should provide Australian-specific information that is important in assessing the risk in Australia (and therefore appropriateness of proposed plans/activities) and the relevance of product vigilance and risk minimisation activities to Australia, and identify and explain the reasons for any differences from activities planned overseas (this includes product information statements). If an RMP activity to be conducted overseas will not include Australian data, the ASA should address the applicability of that activity to the Australian context.

[19] **Routine risk minimisation** activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

The summary of safety concerns contains two safety concerns relating to ROP. It aligns with the European Union RMP, and the safety concerns relating to ROP remain unchanged since they were considered acceptable by the RMP evaluator for the withdrawn ROP submission. The summary of safety concerns is acceptable.

Routine pharmacovigilance is proposed for all safety concerns. No additional pharmacovigilance is proposed in the EU or in Australia.

The sponsor has agreed to utilise paediatric follow-up forms in Australia as a routine pharmacovigilance activity for the safety concern 'Long term safety of ranibizumab in the condition ROP', as requested.

The pharmacovigilance plan is acceptable.

No routine or additional risk minimisation activities are proposed for safety concerns relating to ROP; however, a dedicated ROP information leaflet has been implemented in the EU. Upon request the sponsor has committed to implementing a similar leaflet for guardians of premature infants in Australia. Changes to the 'Information for guardians of babies born prematurely' leaflet and inclusion of this routine risk minimisation activity in the ASA, were largely implemented at the third round of evaluation. A letter will be sent to prescribers to inform them of the inclusion of an information for guardian's leaflet in the product packaging.

The PI and Consumer medicine information (CMI) were revised as requested in the first round of RMP evaluation with further changes to the CMI that were recommended at the second round of the RMP evaluation process implemented at the third round of evaluation.

The risk minimisation plan is acceptable at the third round of RMP evaluation, although minor revisions have been requested to the CMI and to the 'Information for guardians of babies born prematurely' leaflet.

Recommended conditions of registration

The recommended RMP and PSUR wording is:

> *The Lucentis EU-Risk Management Plan (RMP) (version 20.0, dated 13 August 2019, data lock point DLP 24 Jan 2018 for clinical trial data, 31 May 2018 for post-marketing data), with Australian Specific Annex (version 11.2, dated 24 June 2021), included with submission PM-2020-04187-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*
>
> *An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).*
>
> *Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.*
>
> *The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.*

As the indications for Lucentis are being extended into a significantly different population it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

> *Lucentis (ranibizumab) is to be included in the Black Triangle Scheme. The PI and CMI for Lucentis must include the black triangle symbol and mandatory*

accompanying text for five years, which starts from the date the new indication is registered.

Risk-benefit analysis

In 2018, the sponsor made a similar submission to extend the indications of Lucentis (ranibizumab) to allow *for use in preterm infants for the treatment of ROP*. **Error! Bookmark not defined.** This submission was withdrawn by the sponsor in January 2020 prior to the TGA making a regulatory decision regarding approval.

For the previous submission, the TGA's clinical evaluation, Delegate's considerations, and the Advisory Committee on Medicines (ACM) did not recommend approval.

The previous submission was based on data from a single pivotal Study H2301 (the RAINBOW trial) and early results from the Study H2301E1 (the RAINBOW extension trial).

In this submission, a new, second pre-defined 2 year safety data interim analysis (IA) is provided for the RAINBOW extension trial.

Delegate's considerations

The Delegate for the current submission has listed the previous concerns from the previous (and withdrawn) submission;[8] so they can be considered against this newly submitted data.

Outcomes of the previous submission

Delegate's conclusions on the previous submission

The Delegate for the past submission concluded their evaluation of that submission by stating the following:

> 'at this stage, it is uncertain whether the efficacy benefits for intravitreal ranibizumab outweigh the lack of long-term safety data and potential risk of neurodevelopmental delay. At this stage the Delegate is of the opinion that the submission should be rejected until the long-term outcomes of visual acuity, visual function and developmental outcomes are known.'

Advisory Committee on Medicines advice

The previous ACM Ratified Resolution stated:

> 'Lucentis had an overall negative benefit-risk profile for the proposed extension of indications, as the evidence submitted did not satisfactorily establish the safety of the product.
>
> The ACM was of the view that the long-term safety of the product is unclear; other similar products are used/available for this purpose; and that infants with ROP will not be disadvantaged if the current application is not approved.'

The ACM previously raised issues concerning the following:

- Proposed indication – considered too broad
- Long term visual outcomes
- Lack of long-term safety data
- Increased rate of ROP recurrence and need for monitoring
- Need for specialist use restriction and education for longer term monitoring

Efficacy

There are many practical difficulties in performing clinical studies in preterm infants. Studies H2301/E1 (the RAINBOW trial and its extension trial) were reasonably well designed. The primary endpoint set a rather high bar, as infants were required to have no ROP or adverse structural outcomes.

Baseline demographics and disease characteristics of patients in the RAINBOW trial were generally comparable across the treatment groups, with the exception of birth weight. The impact of the imbalance in birth weight across the three treatment groups at Baseline (lower in the 0.2 mg group) is uncertain.

Endpoints, analysis, and clinical relevance

At Week 24, the proportions of patients achieving treatment success were 80.0%, 75.0% and 66.2%, for the ranibizumab 0.2 mg, ranibizumab 0.1 mg and laser therapy groups, respectively (see Table 6, above). The primary endpoint differences were not statistically significant.

However, ranibizumab had numerically higher treatment success over laser (odds ratio of 2.19). Expressing the difference between treatment groups with an odds ratio is rather questionable. Using 'risk difference' or 'risk ratio' would have been more appropriate.

Although the study did not demonstrate statistical significance for the primary endpoint, it is acknowledged that preterm infants are a vulnerable study population and the statistical challenges in paediatric studies. Further, the composite endpoint 'treatment success' was rather stringent, with death, treatment switch, any active ROP or unfavourable structural outcomes all considered as treatment failure.

However, the structural outcomes are not necessarily correlated with visual function, but likely a reasonable surrogate endpoint for neonates. Visual function itself was measured at the 2-year visit (see Table 12, above), but only for a subgroup, unmasked, and using a limited range of tests.

Overall, the results are considered to be clinically relevant. Sensitivity analyses were generally supportive of the primary analysis.

Main limitations of the clinical trial program

There was only one pivotal efficacy and safety study (Study H2301, or the RAINBOW trial), and a second pivotal study may have provided additional data that would further support registration for the proposed indication. The extension part of the pivotal RAINBOW trial is still ongoing (Study H2301E1 (RAINBOW extension trial).

There was an imbalance in birth weight across the three treatment groups at Baseline with uncertain impact (lower birth weight in in the ranibizumab 0.2 mg group).

There are only rather limited data for Zone I (Stage 1+, 2+, or 3) disease.

Predictors of non-response

There appear to be no potential predictors of non-response to ranibizumab, that is, no identifiable demographic or disease characteristics (for example, location or severity of ROP), but the study was not powered for such assessments, especially for the lower stages of Zone I disease.

Limited longer-term data

There are no long-term data (beyond 2 year corrected age) on visual outcomes or developmental outcomes.

Limited visual acuity data

There were only limited visual acuity data (small subgroup sample size in Study H2301E1 (RAINBOW extension trial) at the 2-year corrected age visit.

The long-term effect of ranibizumab on visual function however remains unknown, and it is unclear if data relating to the absence of ocular structural abnormalities correlate with long term visual outcomes.

Comparator issues

Laser therapy is an appropriate comparator per se, but there have been concerns that the success rates found in the RAINBOW trial are inferior to those typically found in an Australian context, and that the comparison may therefore be less informative than desirable. However, even a non-active comparator for example, placebo would likely be acceptable in a clinical trial program.

Safety

Ocular adverse events were reported for 34.9% patients in the RAINBOW trial (Study H2301); and 31.1% patients in the extension trial. The ocular adverse event profile appears to be consistent with the known ocular adverse event profile of ranibizumab in adults. The incidence of endophthalmitis was low; one patient in the ranibizumab 0.1 mg group during the RAINBOW trial. Endophthalmitis is an important identified risk of ranibizumab and described in the PI. The incidence of ocular serious adverse events was relatively low in the core RAINBOW trial (4.1%) and RAINBOW extension trial (3.9%). There were no patients in the ranibizumab 0.2 mg group with serious ocular adverse events in the extension study.

Non-ocular adverse events were reported for 81.2% patients in RAINBOW trial and 75.0% patients in RAINBOW extension trial. Non-ocular adverse events were most commonly reported in the infection and infections disorders and respiratory, thoracic and mediastinal disorders System Organ Classes and are generally consistent with co-morbidities of a premature infant patient population.

Issues for consideration for the current submission

Further relevant issues (including safety issues) are discussed below.

Long-term visual outcomes

For the previous application;**Error! Bookmark not defined.** with regard to the 24-week ocular outcomes (primary analysis time point in the core RAINBOW trial (Study H2301E1) the ACM considered there was a low correlation between structural changes at 24 weeks and long-term visual outcomes. The ACM noted case reports of patients with recurrent ROP at 2 years after bevacizumab treatment, and the findings of the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study;[20] indicating there is a risk of retinal detachment in treated eyes at 15 years follow-up.

For the current submission, the mean visual acuity scores were generally comparable across the treatment groups, but the available data were limited (that is, 19 to 26 patients per group). There are limitations to the Cardiff Acuity test (CAT);[12] and another method (for example, Teller Acuity test);[21] could have been employed. It is noted that the 5-year tests will be masked as per the EMA request.

[20] Study NEI-32: Cryotherapy for Retinopathy of Prematurity (CRYO-ROP trial) - Outcome Study of Cryotherapy for Retinopathy of Prematurity. ClinicalTrials.gov Identifier: NCT00000133.
[21] The **Teller Acuity test**, is preferential-looking test, an exam carried out to assess, objectively and quantitatively, the visual acuity of patients, mainly children, who are unable to collaborate in subjective visual tests because they cannot yet speak or have psychomotor difficulties impeding them from doing so. The Teller

Retinopathy of prematurity recurrence

For the previous submission;[Error! Bookmark not defined.] the ACM considered the increased rate of ROP recurrence with ranibizumab and the need for retreatment an important negative outcome, noting similar trends observed with bevacizumab. Infants will require frequent close follow up for many months after initial treatment to assess potential reoccurrence.

In the core RAINBOW trial (Study H2301) recurrence of ROP was higher for ranibizumab treated patients (31.1 to 31.2%) versus laser patients (18.9%).

For the current submission, in the RAINBOW extension trial (Study H2301E1), no patients required additional treatment with ranibizumab after the baseline visit of the extension study. One patient in the ranibizumab 0.1 mg had active ROP at the 52 week visit. At the 2 year corrected age visit there were no cases of active ROP.

Patients receiving initial ranibizumab treatment for ROP may need longer term monitoring for disease recurrence. Appropriate information in the PI or otherwise (for example, prescriber education) should be provided.

Lack of long-term safety data beyond 2 year visit

In the previous submission;[Error! Bookmark not defined.] the lack of long-term safety data was a significant concern for the ACM, particularly with uncertainties regarding effects on mortality and neurodevelopment, as well as effects on other body systems such as renal (including hypertension) and respiratory outcomes. The ACM previously stated:

> 'Given the safety concerns raised, particularly in relation to neurodevelopmental defects, the ACM was of the view that it would be preferable to have at least the 2-year safety outcomes of the RAINBOW trial before Lucentis were considered for registration, or ideally the 5-year outcomes. At a minimum, the ACM was of the view that safety data from a second pre-defined interim analysis (IA2) of the ongoing extension Study H2301E1 (due for submission in Q2 2020) should be provided before registration were considered.'

In the current submission, ocular adverse events at the 2-year corrected age visit were generally consistent with the known profile of ranibizumab in adults. Non-ocular adverse events at the 2-year corrected age visit were generally consistent with co-morbidities associated with a premature infant patient population.

Growth parameters at the 2-year corrected age visit (weight, head circumference, standing height and leg length) were comparable across the three treatment groups.

Respiratory function data were limited and not evaluated using a validated assessment tool.

Impaired vital organ development was a non-approved potential risk subsequently removed from the current RMP in consultation with the EMA.

Longer term safety (beyond 2 years) remains uncertain. Study H2301E1 (the Rainbow extension) is ongoing and will provide additional long term safety data at the patient's fifth birthday.

Systemic ranibizumab exposure and potential effect on VEGF

Systemic ranibizumab exposure in premature infants was 12- to 16-fold higher following intravitreal ranibizumab 0.2 mg per eye (and 5- to 7.6-fold higher following intravitreal ranibizumab 0.1 mg per eye) compared with adults receiving ranibizumab 0.5 mg per eye. However, no definite relationship with VEGF was demonstrated in

acuity card procedure provides a quantitative measure of grating acuity in infants and young children and has been used in clinical and laboratory settings.

pharmacokinetic/pharmacodynamics analyses. There were no definite ranibizumab dose related trends observed for adverse events in the RAINBOW or RAINBOW extension trials.

However, the ranibizumab C_{max} values found in the population PK/PD analysis were capable of inhibiting VEGF receptors by 50% (range given in the PI: 11 to 27 ng/mL; based on *in vitro* data) with possible implications for safety and development in premature infants. In response, the sponsor stated that serum ranibizumab concentration would be predicted to decline below 50% inhibitory concentration (IC_{50}) in approximately one week following a 0.2 mg dose (based on apparent half-life); and ranibizumab treatment would be of low frequency with low exposure, and thus VEGF inhibition would not likely be prolonged, with a likelihood to affect safety outcomes.

There is mixed evidence on VEGF. Furthermore, measuring VEGF is rather difficult, comparing levels between studies may not be meaningful (for example, due to different assays), and VEGF levels may be affected by factors other than ranibizumab exposure.

Premature infants have an immature blood retinal barrier. Potential suppression of VEGF cannot be excluded. The effects of systemic VEGF suppression on neurodevelopmental and vital organ development in premature infants are uncertain.

Over 77% ranibizumab treated patients required initial bilateral treatment only, therefore further exposure to ranibizumab was not required for most patients.

Potential risk of neurodevelopmental impairment

The clinical evaluation drew attention to the inconsistency in the literature regarding adverse neurodevelopmental outcomes among infants with ROP treated with anti-VEGF agents.

Neurodevelopmental impairment is an important potential risk for ranibizumab in the ROP population. In the RAINBOW extension trial (Study H2301E1), in the broad medical review, neurodevelopmental impairment adverse events occurred in 23.0% (ranibizumab 0.2 mg), 13.9% (ranibizumab 0.1 mg) and 25.9% (laser therapy) of patients. Most of these infants were less than 28 weeks gestational age with birth weights less than 1,000 g and had CNS co-morbidities at Baseline. There were no notable differences between ranibizumab and laser treated patients regarding the types of neurodevelopmental impairment adverse events.

Cognitive status was assessed at the 2-year corrected age visit using the Mullen Scales for Early Learning;[14] a validated endpoint in children within the study age group. The mean T-scores for each of the three subscales were comparable across the treatment groups.

The types of adverse events of neurodevelopmental impairment were variable with no notable differences between groups. From the data provided there do not appear to be any temporal trends observed in time to onset of relevant adverse events and ranibizumab treatment or re-treatment. The adverse event profile retrieved using the risk management plan search strategy was consistent with the broader review.

The long-term effects (beyond the study period) of ranibizumab on neurodevelopmental outcomes are unknown. Whilst the ongoing RAINBOW extension trial will provide additional long-term data regarding neurodevelopmental impairment at the patient's fifth birthday, the study cohort is small. Larger patient numbers would likely be needed to address confounding issues and fully characterise this risk.

Translating clinical trial data into an indication

Intravitreal anti-VEGF injection therapy may offer some benefits over laser photocoagulation, including a quicker, less technically challenging procedure and potentially requiring less sedation and anaesthetic. Intravitreal anti-VEGF injection agents provide another option of treatment for ROP.

For the previous submission;[Error! Bookmark not defined.] the ACM noted that in the RAINBOW trial, the proportion of infants with Zone I and aggressive posterior retinopathy of prematurity (AP-ROP) was larger than typically observed in an Australian context.

The then proposed indication was:

> *Lucentis (ranibizumab) is indicated in preterm infants for: the treatment of retinopathy of prematurity (ROP).*

The ACM noted that the proposed indication using the clinical criteria as per the RAINBOW trail could result in more infants being treated with Lucentis compared to those currently exposed to anti-VEGF agents in Australia.

Considerations of the current submission

Proposed indication based on inclusion criteria

In the current submission, the proposed indication is restricted to:

- ROP in Zone I (Stage 1+, 2+, 3 or 3+);
- Zone II (Stage 3+); or
- AP-ROP disease.

It no longer includes the lower risk Type 2 ROP: Zone I (Stage 1 or 2), or Zone II (Stage 3). This means that only forms that include 'plus' disease (with the exception of Zone I (Stage 3) disease) are included in the indication.

The inclusion criteria in Study H2301 (the RAINBOW trial) and the proposed indication are still slightly broader than typical criteria used in Australia for off-label use of anti-VEGF medicines, but to a much lesser extent compared to the previous application (see Table 17, below).

Clinical trial data mainly from certain subgroups

Most data (approximately 90% of patients) in Study H2301 (the RAINBOW trial) are derived from patients with Zone II (Stage 3+) disease, Zone I (Stage 3+) disease and AP-ROP (zone I) disease. Furthermore, a distinction between anterior and posterior disease appears not to have been made in the trial (except for AP-ROP which is defined as posterior disease). There are only rather limited data for Zone I (Stage 1+, 2+, or 3) disease. Extrapolation from AP-ROP (zone I) disease to AP-ROP (Zone II) disease would not be unreasonable. Extrapolation to other 'plus' disease states could be considered reasonable.

Results by baseline disease classification

The primary (or other) endpoint subgroup analyses were not originally stratified by baseline disease classification other than by zone. This has been requested from the sponsor and the stratified primary efficacy endpoint results shown in Tables 7, 10, and 11 (above).

Ranibizumab 0.2 mg was effective in both ROP zone subgroups, with 67.9% of patients with Zone I disease and 88.1% of patients with Zone II disease achieving treatment success at Week 24.

Comparison of the proposed indication to Australian guidance

With regard to ROP classification, the Australia and New Zealand ROP Group Consensus on Avastin (bevacizumab) in ROP;[22] appears to recommend Avastin for Zone I disease and AP-ROP, but not Zone II disease, whereas the more recent 2021 Australasian Neonatal

[22] The Royal Australian and New Zealand College of Ophthalmolgists. Retinopathy of prematurity (ROP) screening and treatment guidelines. Available from: https://ranzco.edu/

Medicines Formulary (ANMF) monograph;[23] appears to nearly match the sponsor-proposed ROP indication, with the exception of Zone II (Stage 2+) and anterior Zone II (Stage 3+) disease (see Table 17). The ANMF guidance does not state why it restricts the Zone II classifications to posterior disease only. However, this it likely due to posterior disease typically being more severe than anterior disease, and the more posterior the disease, the more severe and likely the progression may be. The inclusion criteria and the proposed indication are silent with regard to laser therapy.

Table 16: Classification of retinopathy: comparison of consensus group guidance, study inclusion criteria, and proposed indication.

Australia and New Zealand ROP Group Consensus on Avastin in ROP*	Australasian Neonatal Medicines Formulary (ANMF) consensus group guidance (2021)	RAINBOW inclusion criteria	Sponsor-proposed indication
Zone I (Stage 1+, 2+, 3 or 3+)	Zone I (Stage 1+, 2+, 3 or 3+)	Zone I (Stage 1+, 2+, 3 or 3+)	Zone I (Stage 1+, 2+, 3 or 3+)
--	Zone II (Stage 2+ or 3+) (posterior)	Zone II (Stage 3+)	Zone II (Stage 3+)
AP-ROP	AP-ROP	AP-ROP	AP-ROP
Failed laser therapy Cases for which laser therapy is not possible due to poor view of retina or baby too unwell to tolerate laser therapy	Failed laser therapy Cases for which laser therapy is not possible due to media opacity	--	--
*Specific to Avastin, but in the past commonly used for all anti-VEGF agents			

Guidance referenced:

[23] Australasian Neonatal Medicines Formulary (ANMF) monograph: ranibizumab - Lucentis. ANMF consensus group; 2021. Archived version available at: ranibizumab-lucentis-20052021-1.0.pdf (anmfonline.org)

The Royal Australian and New Zealand College of Ophthalmolgists. Retinopathy of prematurity (ROP) screening and treatment guidelines. Available from: https://ranzco.edu/

Australasian Neonatal Medicines Formulary (ANMF) monograph: ranibizumab - Lucentis. ANMF consensus group; 2021. Archived version available at: ranibizumab-lucentis-20052021-1.0.pdf (anmfonline.org)

It could be considered to restrict the indication (for example, to higher risk forms of ROP). Potential major indication options are outlined in Table 18.

Table 17: Potential indication options for this submission

Selected potential indication options	Comment
Zone I (Stage 1+, 2+, 3 or 3+) Zone II (Stage 3+) AP-ROP	Sponsor-proposed, as per Study H2301 (RAINBOW trial) inclusion criteria.
Zone I (Stage 3+) Zone II (Stage 3+) AP-ROP (Zone I)	Restriction to disease classifications with most clinical trial data

Dosing

Two ROP dosing regimens are under consideration based on clinical trial data: 0.2 mg or 0.1 mg (per eye by intravitreal injection). The sponsor proposes the use of the 0.2 mg dose.

A dose lower than 0.2 mg appears not to have been considered in the previous submission by the Delegate, partly due to the at least numerically (but not statistically different) more favourable efficacy results from the 0.2 mg dose compared to the 0.1 mg dose.

In the current application, there may be a reasonable justification for either dose, or even both. It is noted that other regulators have recommended different doses: The EMA and Health Sciences Authority (HSA) Singapore have chosen the 0.2 mg dose, whereas Swissmedic have chosen the 0.1 mg dose (see Table 1, above).

The efficacy data from second interim analysis (IA2) of the Study H2301E1 (Rainbow extension trial) appears to favour a 0.2 mg dose. A numerically higher proportion in the 0.2 mg group (versus 0.1 mg) had absence of ocular abnormalities (98.3% versus 93.8%) and full peripheral vascularisation of the retina (56.9% versus 44.8%) at the 2-year corrected age visit. The differences were not statistically significant. However, for the small group of AP-ROP patients, the 0.1 mg dose was numerically favourable for the primary outcome for all timepoints (24 weeks, 40 weeks, and 2 years (see Table 10, above)), but the sample size was extremely small, and the differences would not be statistically significant.

Long term visual outcomes (beyond 2 years) based on dose remain uncertain.

With regard to safety (in particular non-ocular safety results, including neurodevelopmental effects), the sample size is too small to draw meaningful conclusions between dose groups.

As stated above, systemic ranibizumab exposure in premature infants was 12- to 16-fold higher following intravitreal ranibizumab 0.2 mg per eye (and 5- to 7.6-fold higher following intravitreal ranibizumab 0.1 mg per eye) compared with adults receiving ranibizumab 0.5 mg per eye. The significance of this is unknown.

There are no clinical data available to differentiate the dose based on disease severity, disease location, age, repeat dose, or other factors.

For practical considerations, in the off-label usage guidance by the Australasian Neonatal Medicines Formulary (ANMF) Consensus group states that any dose under 0.12 mg is difficult to draw up.[23] This should not affect any decision regarding dose, as this can potentially be addressed with amending the product presentation, if required.

The sponsor has provided information on dosing in Switzerland, where the 0.1 mg dose is used. The same 1 mL syringe with 0.01 mL graduations is typically used for this (as it was in the clinical trial), and there appear to be no reports of dosing errors with the smaller dose since registration.

Dosing options include (dose per eye by intravitreal injection):

- Recommending a 0.2 mg dose
- Recommending a 0.1 mg dose
- Recommending a 0.1 mg or 0.2 mg dose
- Recommending a 0.1 mg to 0.2 mg dose

However, giving prescribers a choice of dosing in the absence of clear clinical data may cause confusion in some prescribers.

Specialist use restriction and education

For the previous application, the ACM was concerned that the ease of administration of intravitreal injections may lead to less skilled clinicians using this treatment, who may not be aware of the need for close observation over several months to monitor for possible recurrence of disease.

For the current application, concerns over use by less skilled clinicians have been noted, and these should be able to be mitigated with specialist use restriction, and prescriber and referrer education and training. It is desirable that only clinicians highly skilled and experienced in the treatment of ROP in conjunction with Australian best practice guidelines would use Lucentis for treatment. Frequent follow up in addition yearly follow up by a paediatrician or other appropriate specialist to screen for potential developmental abnormalities is recommended.

Proposed action

Based on the evidence available, the Delegate deemed it would not be unreasonable to register Lucentis for a ROP indication, as long as appropriate conditions are in place to retain a positive benefit risk balance. These conditions include but are not limited to; an appropriate indication, an appropriate dosing schedule, appropriate prescriber restriction and education, and appropriate reporting of the remaining clinical study data.

Advisory Committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

The ACM advised the following in response to the Delegate's specific request for advice:

1. Can the ACM comment on systemic ranibizumab exposure and the potential associated suppression of vascular endothelial growth factor (VEGF)?

The ACM was of the view that there are several findings from the Study H2301 (the RAINBOW trial) cohort that provide some reassurance regarding suppression of VEGF following ranibizumab. Within this cohort the reduction of ranibizumab levels in the systemic circulation occurred over a relatively short time period, with a median half-life elimination of 5.6 days. The ACM also noted that no statistically significant differences in plasma free VEGF concentrations were apparent between groups on Days 15 or 29 within the study.

This view was further supported by the CARE-ROP trial;[24.25] which found VEGF plasma levels were not systemically altered in ranibizumab 0.12 mg or 0.20 mg groups, however low patient numbers within this study (n = 19) were noted by the ACM.

In Study H2301 (the RAINBOW trial), based on VEGF level plots on Day 1, 15 or 29, there was no apparent difference between ranibizumab groups compared with laser. The ACM concluded that while there is potential for systemic suppression of VEGF, this is unlikely to contribute to a significant increase in clinically significant non-ocular adverse outcomes.

2. Can the ACM comment on whether the available safety data are sufficient to support registration of the proposed indication?

The ACM commented that Study H2301E1 (the Rainbow extension trial) is the first study to provide visual function and developmental outcome data from a randomised sample of children receiving ranibizumab versus laser treatment and noted that the data provided is the interim analysis at 2 years, with primary outcome data planned for 5 year assessment.

The ACM were reassured by the ocular outcomes from the RAINBOW extension data that showed fewer occurrences of high myopia which is important to help reduce the risk of retinal detachments later in life. There appeared to be no significant difference in the incidence of strabismus, nystagmus or abnormal ocular fixation, but early risks including endophthalmitis, cataract and haemorrhage need to be considered.

The ACM were further reassured by the 2 year interim safety data on development and non-ocular adverse outcomes, as it demonstrated no evidence of trends to adverse outcomes.

The ACM also commented that anti-VEGF treatment has become standard in many places around the world and is increasingly being used in Australia as standard treatment, particularly for those children with posterior ROP, and that ranibizumab may potentially be associated with less risk than other medications currently being used.

The RAINBOW extension trial has not shown significant neurodevelopmental changes. Compared to laser treatment, the ACM noted no significant difference in developmental outcomes including visual reception, receptive language, and expressive language. No

[24] Stahl A, Krohne TU, Eter N, Oberacher-Velten I, Guthoff R, Meltendorf S, et al. Comparing alternative ranibizumab dosages for safety and efficacy in retinopathy of prematurity: a randomized clinical trial. *Jama, Pediatr.* 2018;172(3):278-86.
[25] CARE-ROP trial: Comparing Alternative Ranibizumab Dosages for Safety and Efficacy in Retinopathy of Prematurity. ClinicalTrials.gov Identifier: NCT02134457

significant difference in outcomes for motor function, hearing impairment, growth, respiratory symptoms, or mean systolic or diastolic blood pressure were noted either.

The ACM agreed that the interim data at 2 years appears reasonably predictive of the 5 year data and in general the data is reasonably robust at the 2 year mark. The ACM did, however, note that the final study containing the 5 year assessment data should be provided to the TGA once available.

3. Can the ACM comment on the proposed indication, in particular in the context of the disease subgroups less represented in the RAINBOW study?

The ACM was of the view that treatment requiring Zone I disease of any stage can benefit greatly from intravitreal anti-VEGF and there is no evidence to suggest that children with Zone I, Stage 1+, 2+ or 3 disease should have a higher risk of non-ocular adverse events.

The ACM noted that the alternative is laser treatment which ablates the retina so that there cannot be development of peripheral retinal vessels. The ACM noted from the ET ROP trial;[26,27] that the outcomes from treatment requiring Zone I disease after laser treatment were generally poor.

4. Assuming Lucentis were registered for the sponsor-proposed or a similar indication, can the ACM comment on the most appropriate dosing option?

The ACM highlighted that the aim of treatment is to minimise the reactivation of ROP. The ACM also acknowledged the importance of minimising re-injection, noting that every intervention is associated with a level of risk and these risks must be a significant consideration in treatment options.

During discussion the ACM acknowledged the CARE-ROP trial, which showed that 0.12 mg was effective in treating ROP without suppressing systemic VEGF levels. [25]

The ACM noted that the data provided do not indicate that 0.2 mg carries a significantly higher risk of non-ocular adverse outcomes when compared to the 0.1 mg dose. Additionally, noting that clinical expertise is suggestive that a dose of 0.2 mg/0.02 mL (40% of the adult dose) may minimise repeated injections.

The ACM was of the view that the current presentation of the medicine makes precise infant dosing difficult. The pre-filled syringe for intravitreal injection has only the adult dose of 0.5 mg/0.05 mL on the barrel and there is no lower dose marked. The ACM commented that it is difficult to draw up a dose of less than 0.02 mL from the 2.3 mg/0.23 mL vial and noted that a syringe with appropriate dosage markings for infant doses would be beneficial.

On balance, the ACM agreed that either the 0.1 mg or 0.2 mg dose could be appropriate and were of the view that the decision to utilise 0.1 mg or 0.2 mg should be made by the treating ophthalmologist. In making this recommendation the ACM noted that prescribing is limited to a subset of ophthalmologists with expertise in ROP.

5. Assuming Lucentis were registered for the sponsor proposed or a similar indication, can the ACM comment on the need for specific prescriber restriction and education?

The ACM highlighted the importance of restricting use to paediatric ophthalmologists who regularly treat ROP, as these prescribers are aware of the treatment risks, the need for longer and more frequent follow up, and the potential need for re-treatment.

[26] Good WV; Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial. Trans Am Ophthalmol Soc. 2004;102:233-250.
[27] The Early Treatment for Retinopathy of Prematurity Study (ETROP trial). ClinicalTrials.gov Identifier: NCT00027222

The ACM also endorsed the use of an informed parental consent process and ongoing prescriber and referrer education and training.

6. The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

The ACM commented that laser treatment appears to be the preferred treatment for ROP except in specific circumstances. Lucentis may also have a role in Type 1 ROP where the infant is too unwell to cope with laser surgery or where there is a risk of re-activation of ROP after adequate laser treatment. The ACM noted that this could be considered in relation to the wording of the indication.

Conclusion

The ACM considered this product to have an overall positive benefit risk profile for the indication:

> *Lucentis is indicated in preterm infants for the treatment of retinopathy of prematurity (ROP) with Zone I (Stage 1+, 2+, 3 or 3+), Zone II (Stage 3+) or AP-ROP (aggressive posterior ROP) disease.*

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Lucentis ranibizumab (rbe) 2.3 mg/0.23 mL solution for injection vial indicated for the following extension of indications:

In preterm infants for:

- *the treatment of retinopathy of prematurity (ROP) with Zone I (Stage 1+, 2+, 3 or 3+), Zone II (Stage 3+) or AP-ROP (aggressive posterior ROP) disease*

As such, the full indications at this time were:

Lucentis (ranibizumab) is indicated in adults for:

- *the treatment of neovascular (wet) age-related macular degeneration (AMD)*
- *the treatment of visual impairment due to diabetic macular oedema (DME)*
- *treatment of proliferative diabetic retinopathy (PDR)*
- *the treatment of visual impairment due to choroidal neovascularisation*
- *the treatment of visual impairment due to choroidal neovascularisation (CNV)secondary to pathologic myopia (PM)*
- *the treatment of visual impairment due to macular oedema secondary to retinal veinocclusion (RVO)*

Lucentis is indicated in preterm infants for:

- *the treatment of retinopathy of prematurity (ROP) with Zone I (Stage 1+, 2+, 3 or 3+),Zone II (Stage 3+) or AP-ROP (aggressive posterior ROP) disease*

The above extension of indications are inclusive of the previous approved indications.

Specific conditions of registration applying to these goods

- Lucentis (ranibizumab) is to be included in the Black Triangle Scheme. The PI [Product Information] and CMI [Consumer Medicine Information] for Lucentis must include the

black triangle symbol and mandatory accompanying text for five years, which starts from the date the new indication is registered.

- The final Clinical study report (CSR) for Study RFB002H2301E1 (RAINBOW extension study) should be submitted to the TGA, once available (planned completion: 30 June 2023).
- The Lucentis EU-Risk Management Plan (RMP) (version 20.0, dated 13 August 2019, data lock point DLP 24 Jan 2018 for clinical trial data, 31 May 2018 for post-marketing data), with Australia specific annex (version 11.2, dated 24 June 2021), included with submission PM-2020-04187-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.
- For all injectable products the Product Information must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Lucentis approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

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