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Human Medicines Division

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

Lucentis

Ranibizumab

Procedure no: EMEA/H/C/000715/P46/078

Note

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

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1. Introduction

On March 15, 2024, the MAH submitted a completed paediatric study CRFB002H1401 for Lucentis (ranibizumab), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

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

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study CRFB002H1401 (hereafter referred to as H1401) was a non-interventional, post- marketing surveillance (PMS) study to evaluate the safety and efficacy of Lucentis® (ranibizumab) in retinopathy of prematurity (ROP) patients in the clinical practice setting in Japan. Study H1401 enrolled 120 preterm infants with ROP and concluded on 25-Sep-2023. The results of this study are now submitted to the CHMP as a standalone submission in accordance with Article 46.

The MAH stated that this study is a stand-alone study which includes patient population of Japan and was not included in a development program.

The MAH describes the objective of their Critical Expert Overview (CEO) as to provide a summary of the findings from Study H1401, and any impact these data may have on the Sponsor's understanding of the safety and efficacy profile of ranibizumab.

2.2. Information on the pharmaceutical formulation used in the study

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

2.3. Clinical aspects

2.3.1. Introduction

Ranibizumab is a recombinant humanized immunoglobulin G1 kappa (IgG1□) isotype monoclonal antibody fragment that selectively binds VEGF-A. It binds with high affinity to the receptor binding site of active forms of VEGF-A, including the biologically active, cleaved form of this molecule, VEGF110. VEGF-A has been shown to cause neovascularization and leakage in models of ocular angiogenesis. The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation.

Ranibizumab in a dose of 0.5 mg for intravitreal injection is approved in Europe and indicated in adults for the treatment of:

- neovascular (wet) age-related macular degeneration (nAMD)
- visual impairment due to diabetic macular edema (DME)
- visual impairment due to macular edema secondary to retinal vein occlusion (RVO); (branch RVO or central RVO)

- visual impairment due to choroidal neovascularization (CNV)
- diabetic retinopathy (DR), or proliferative diabetic retinopathy (PDR) and/or moderately severe to severe non-proliferative diabetic retinopathy (NPDR)

Ranibizumab in a dose of 0.2 mg is indicated in preterm infants for the treatment of:

- ROP with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 3+) or AP-ROP (aggressive posterior ROP) disease.

The MAH submitted a final report for:

- CRFB002H1401, a multicentre, single-arm, open-label, PMS study evaluating the safety and efficacy of ranibizumab when administered in a clinical practice setting, in ROP patients in Japan.

2.3.2. Clinical study

Study CRFB002H1401

Description

Methods

Study participants

The study population consisted of 120 male and female preterm infants who were treated with ranibizumab in a clinical practice setting.

Overall, 120 pediatric patients with ROP from 39 sites in Japan were enrolled in Study H1401. A total of 11 patients (9.2%) discontinued from the study – 8 patients (6.7%) discontinued from the study as observation could not continue due to moving or transfer to another hospital, etc., 2 patients (1.7%) discontinued due to death, and 1 patient (0.8%) discontinued for other reasons.

Of the enrolled patients, 55.8% were male and 44.2% were female. The mean gestational age at birth was 25.2 weeks (range: 22-35 weeks) and the mean corrected gestational age at the start of ranibizumab treatment was 35.0 weeks (range: 30-44 weeks).

The majority of patients (97.5%) had ROP in both eyes. ROP was present in Zone I in 42 patients (35.0%) and in Zone II in 77 patients (64.2%). Most patients (65.0%) had Stage 3 disease, and AP-ROP was reported for 24 patients (20.0%). Five patients (4.2%) had severe ROP at baseline.

Most patients (97.5%) had no prior ROP therapy, except for 3 patients (2.5%) who had previously had laser therapy for ROP treatment.

Treatments

Lucentis is a solution for intravitreal injection containing 0.2 mg of ranibizumab per 0.02 mL. It was administered in the clinical practice setting in accordance with the local package insert.

Objective(s)

Primary objectives

- To confirm the safety specifications and the occurrence of systemic adverse events related to the VEGF inhibitory action when Lucentis was administered in a clinical practice setting in ROP patients.

- To evaluate the safety of Lucentis in a clinical practice setting in ROP patients

Secondary objectives

- To explore factors that may affect the safety of ranibizumab in a clinical practice setting in ROP patients.

- To determine the effect of laser photocoagulation on the safety of ranibizumab in clinical practice setting in ROP patients.
- To confirm the efficacy of ranibizumab when administered in a clinical practice setting in ROP patients.

Outcomes/endpoints

Primary endpoint

Number of patients with AEs and the incidence during the 24-week observation period

Secondary endpoints

- Number of patients with AEs
- Overall assessment of ROP activity at Weeks 12 and 24 of the observation period
- Presence or absence of unfavorable ocular structural outcomes during the 24-week observation period

Sample size

Number of subjects to be studied
120 patients
[Rationale]
ROP patients are mostly unable to complain of subjective symptoms, thus it was speculated that the diagnosis of eye infections, etc. were possibly delayed after intravitreal administration of Lucentis. Therefore, it was decided to calculate the target sample size using "infectious endophthalmitis," which is an important identified risk potentially leading to blindness and is also a clinically important event, as the index. The incidence of "infectious endophthalmitis" as an adverse event was 2.6% in the ranibizumab group (76 patients) in Study H2301 (a 24-week randomized, controlled clinical trial comparing two doses of ranibizumab, 0.2 mg and 0.1 mg, to laser therapy for the treatment of ROP in preterm infants) and 114 patients (safety analysis set) were needed to detect an event occurring at a rate of 2.6% in at least 1 patient with a probability of ≥ 95% in the drug-use

investigation. Considering that a certain number of patients was going to be excluded from the safety analysis set, the target number of patients to be enrolled was set to be 120.

Statistical Methods

Statistical analysis

Data to be used for statistical analysis
In this study, only case report form data recorded by the investigator or sub investigator were used for statistical analysis.

Definition of analysis sets
Patients with finalized enrollment
Patients for whom the enrollment form had been received and who became eligible were defined as patients with finalized enrollment.
Patients with locked case report forms
When the case report forms of a patient were locked, the patient was to be regarded as a patient with locked case report forms.
Safety analysis set
The safety analysis set was defined as patients with locked case report forms who did not meet any of the following conditions for exclusion from the safety analysis.
• Observation outside the contract period
• Administration occurred prior to the contract.
• Treatment started outside the enrollment period.
• No signature or seal of the physician
• Enrollment outside the enrollment period
• Previous use of Lucentis
• Non-indicated disease/disease not subject to the study of Lucentis
• Protocol violation
• Duplicate patients
• Patients not enrolled
• Patients whose enrollment is not finalized
• Lucentis not administered
• Start date of Lucentis unknown/not specified
• Presence or absence of adverse events unknown/not specified
• Other (patients judged to be excluded from the safety analysis for reasons other than the above)
Efficacy analysis set
The efficacy analysis set was defined as patients in the safety analysis set who did not meet any of the following conditions for exclusion from the efficacy analysis.
• Efficacy evaluation in the eye treated on the day of the first dose not measured/not specified
• Other (patients judged to be excluded from the efficacy analysis set for reasons other than the above)

Handling of patient data
Handling of deviated values
Handling of deviated values followed the criteria specified in the SAP.
Missing data
Imputation of missing data was specified in the SAP.

Analysis methods
When the number of patients with locked case report forms reached 1/3 or more of the target sample size, the following analyses were performed.
Patient composition
A patient composition chart was prepared for the number of enrolled patients, the number of patients whose case report form had been collected, the number of patients analyzed for safety and efficacy, the number of patients excluded from analysis, and the reasons for exclusion. In addition, a list of

patients excluded from the safety analysis or efficacy analysis was prepared.
Discontinuation status of the study
Regarding the discontinuation status of the study, the number and proportion of discontinued patients were calculated by reason for discontinuation.
Administration status of Lucentis
A frequency table of the number of doses was prepared for the administration status of Lucentis.
Demographic and other characteristics
Proportions were calculated for categorical variables, and summary statistics were calculated for continuous variables.

Safety endpoints, assessment methods, and analysis methods
The safety evaluation was based mainly on adverse events.
Adverse events
The incidence of adverse events was calculated by SOC and PT. Serious adverse events (SAEs) were defined as adverse events that are described as serious and have a fatal outcome, and similar tabulation to adverse events was performed for SAEs also.
For adverse events, listings of events included in and excluded from the tabulation were prepared.
• The incidence of adverse events was calculated by SOC and PT.
• For adverse events leading to treatment discontinuation, the incidence of adverse events was calculated by SOC and PT.
• Regarding the time of the first onset of adverse events, the number of patients with adverse events was calculated by SOC and PT for each predetermined period. Details for each period were provided in the SAP. Regarding the outcome of adverse events, the incidence of adverse events was calculated by SOC and PT. When the statistical analysis was performed collectively for each PT, patients with multiple outcomes were counted only once in a category in order of priority of "death, sequelae, not recovered, recovering, recovered, and unknown."
Adverse reactions
Among adverse events, those for which a causal relationship with Lucentis could not be ruled out (including adverse events due to the intravitreal injection procedure) and those not listed were defined as adverse reactions, and the following analysis was performed.
• The incidence of adverse reactions was calculated by SOC and PT.
Safety specifications
For adverse events specified in the safety specifications, the following analysis was performed.
• The incidence was calculated by safety specification and by PT.

Efficacy endpoints, examination methods, and analysis methods
ROP activity
The proportion of patients with each overall assessment of ROP activity was calculated by evaluation time point. In addition, the proportion of responders (defined as "improved + minimally improved") was also calculated.

Unfavourable ocular structural outcomes
The proportion was calculated for the presence or absence of unfavourable ocular structural outcomes.

Methods used to examine subgroups and interactions
Subgroup analyses by major background factors were performed for ROP activity and adverse events.

Results

Baseline data

Patient characteristics

Of the 120 patients in the safety analysis set, 55.8% (67 patients) were male and 44.2% (53 patients) were female. The mean (standard deviation) gestational age at birth was 25.2 (2.70) weeks.

ROP affected both eyes in 97.5% (117 patients), only the left eye in 1.7% (2 patients), and only the right eye in 0.8% (1 patient) of the patients.

The mean (standard deviation) weight at birth was 744.5 (300.27) g, with 66.7% (80 patients) weighing ≤ 750 g, 19.2% (23 patients) weighing > 750 to < 1000 g, and 11.7% (14 patients) weighing ≥ 1000 g.

The zone was Zone II in 64.2% (77 patients) and Zone I in 35.0% (42 patients).

The stage was Stage 3 in 65.0% (78 patients), Stage 2 in 22.5% (27 patients), Stage 1 in 5.8% (7 patients), and Stage 4 in 4.2% (5 patients). AP-ROP was "present" in 20.0% (24 patients). The severity of ROP was "other than mild and severe" in 69.2% (83 patients). Prior treatment for ROP was "present" in 2.5% (3 patients) and was laser photocoagulation in all of these patients.

Concomitant drugs and therapies for ROP were "present" in 46.7% (56 patients), including laser photocoagulation in 54 patients and vitreous surgery in 6 patients (overlapped count).

Table 10-2 Demographic and Disease Characteristics (safety analysis set)

Background factors	Safety analysis set N=120
Sex - n (%)	
Male	67 (55.8)
Female	53 (44.2)
Gestational age at birth (weeks)	
Number of patients	120
Mean (standard deviation)	25.2 (2.70)
Median	24.0
Min - Max	22 - 35
Gestational age at birth - n (%)	
≤ 24 weeks	64 (53.3)
> 24 weeks and < 27 weeks	25 (20.8)
≥ 27 weeks	31 (25.8)
Corrected gestational age (weeks) at the start of treatment with Lucentis	
Number of patients	120
Mean (standard deviation)	35.0 (2.77)
Median	35.0
Min - Max	30 - 44
Reason for use of Lucentis - n (%)	
Retinopathy of prematurity	120 (100.0)
Other	0 (0.0)
Eye affected by ROP – n (%)	
Right eye	1 (0.8)
Left eye	2 (1.7)
Both eyes	117 (97.5)
Height at birth (cm)	
Number of patients	67
Mean (standard deviation)	31.66 (4.309)
Median	31.00
Min - Max	23.0 - 46.0
Height at birth - n (%)	
< 20 cm	0 (0.0)
≥ 20 cm - < 40 cm	63 (52.5)
≥ 40 cm	4 (3.3)
Unknown/not specified	53 (44.2)

Background factors	Safety analysis set N=120
Body weight at birth (g)	
Number of patients	117
Mean (standard deviation)	744.5 (300.27)
Median	670.0
Min - Max	299 - 2108
Body weight at birth - n (%)	
≤ 750 g	80 (66.7)
> 750 g - < 1000 g	23 (19.2)
≥ 1000 g	14 (11.7)
Unknown/not specified	3 (2.5)
Body weight at the start of treatment with Lucentis (g)	
Number of patients	88
Mean (standard deviation)	1573.8 (523.46)
Median	1435.0
Min - Max	642 - 3190
Status of ROP: Zone*1 - n (%)	
ZoneI	42 (35.0)
ZoneII	77 (64.2)
ZoneIII	0 (0.0)
Unknown/not specified	1 (0.8)
Status of ROP: Stage*1 - n (%)	
Stage1	7 (5.8)
Stage2	27 (22.5)
Stage3	78 (65.0)
Stage4	5 (4.2)
Stage5	0 (0.0)
Unknown/not specified	3 (2.5)
Status of ROP: AP-ROP*1 - n (%)	
Absent	91 (75.8)
Present	24 (20.0)
Unknown/not specified	5 (4.2)
Severity of ROP*1 - n (%)	
Mild	31 (25.8)
Other than mild and severe	83 (69.2)
Severe	5 (4.2)
Unknown/not specified	1 (0.8)
Complication - n (%)	
Absent	55 (45.8)
Present	63 (52.5)
Unknown/not specified	2 (1.7)

Background factors	Safety analysis set N=120
Medical history - n (%)	
Absent	70 (58.3)
Present	48 (40.0)
Unknown/not specified	2 (1.7)
Prior treatment for ROP – n (%)	
Absent	117 (97.5)
Present	3 (2.5)
Details of prior treatment for ROP*2 - n	
Laser photocoagulation	3
Vitreous surgery	0
Buckling	0
Cryotherapy	0
Other	0
Prior laser therapy for ROP*3 - n (%)	
Absent	117 (97.5)
Present	3 (2.5)
Concomitant drugs and therapies for ROP - n (%)	
Absent	63 (52.5)
Present	56 (46.7)
Unknown/not specified	1 (0.8)
Details of concomitant drugs and therapies for ROP*2 - n	
Laser photocoagulation	54
Vitreous surgery	6
Buckling	0
Cryotherapy	0
Anti-VEGF agent (other than Lucentis)	0
Other	0

Source: DM_T001

*1 The eyes treated with Lucentis on the start day of the treatment are assessed. In the case of bilateral administration, the status of ROP is assessed in the eye that is worse.

*2 Duplicated counting

*3 The eyes treated with Lucentis on the start day of the treatment are assessed. Patients with a treatment history with laser photocoagulation for the eyes treated with Lucentis on the start day of treatment are defined as those for whom prior therapy is “present.”

Efficacy results

Efficacy was evaluated in Study H1401 by i) assessing the overall ROP activity in patients at Weeks 12 and 24, and ii) by assessing the proportion of patients with absence of unfavorable ocular structural outcomes at Week 24.

Overall assessment of ROP activity at Weeks 12 and 24

- ROP activity was evaluated at 12 and 24 weeks, with the proportion of responders defined as those whose ROP activity had ‘improved’ or ‘minimally improved’ at that timepoint compared to baseline.

- An improvement in ROP activity was observed in the majority of patients. A total of 109/112 patients (97.3%) were assessed as responders at Week 12, and 100/102 patients (98.1%) were assessed as responders at Week 24 (or at discontinuation)

- As most patients were assessed as responders, subgroup analyses of ROP activity by sex, gestational age at birth, body weight at birth, ROP zone, presence/absence of AP-ROP, and ROP severity did not reveal any meaningful differences between subgroups.

Safety results

- Most patients (88/120, 73.3%) received 2 doses of ranibizumab (one per eye) during the study period. Seven patients (5.8%) received a single dose, one patient (0.8%) received 3 ranibizumab doses, and 24 patients (20.0%) received 4 or more.

- Overall, 9 patients (7.5%) experienced AEs (both ocular and non-ocular)

- There was no trend observed in the occurrence of AEs by timing of initial onset

- Subgroup analyses revealed a higher incidence of AEs in females, patients with lower gestational age at birth, patients with lower body weight (≤ 750 g) at birth, and patients with complications. However, due to the overall low number of patients experiencing AEs during the study, these results should be interpreted with caution.

- In the subset of patients previously treated with laser therapy, no AEs were reported. However, as the number of patients with prior laser therapy for ROP was low (3/120 patients), these results should be interpreted with caution.

- The safety specifications (adverse events related to known safety risks) for this study were infectious endophthalmitis, intraocular inflammation, intraocular pressure increased, and arterial thromboembolic events. No AEs corresponding to these safety specifications were reported during the study.

Ocular AEs

- Ocular AEs were reported in 6 patients (5.0%). The only ocular AE that occurred in ≥2 patients was reported as ROP (worsening of the primary condition), occurring in 3 patients (2.5%). One ocular AE of therapeutic response decreased was assessed by the Investigator as related to study treatment, and the patient was recovering at the time of reporting. None of the reported ocular AEs led to study treatment discontinuation.

- Three ocular SAEs were reported in one patient each, all of which were considered by the Investigator as unrelated to study treatment. One patient experienced an SAE reported as ROP (aggravation of the primary condition) and was recovering; another patient with an SAE reported as ROP (deterioration of the primary condition) had an unknown outcome. One patient with an SAE of vitreous haemorrhage did not recover.

- Non-ocular AEs were reported in 3 patients (2.5%). Two non-ocular AEs (both occurring in the same patient) were reported as related to VEGF inhibition: one AE of renal vein thrombosis and one of vena cava thrombosis. Both AEs were non-serious, assessed by the

Investigator as related to study treatment with an unknown outcome, and no specific safety measures in relation to these AEs were considered necessary.

- Two non-ocular SAEs were reported – one of systemic inflammatory response syndrome and one of respiratory failure, occurring in one patient each. The SAE of systemic inflammatory response led to study treatment discontinuation.

- Two deaths were reported during the 24-week observation period, both due to worsening of an AE. One patient to whom ranibizumab was administered in both eyes at 18 weeks of age, had a worsening of the AE of systemic inflammatory response syndrome on Day 58 of the treatment with ranibizumab, and the patient died on the same day. The other patient was administered ranibizumab in both eyes at 13 weeks of age. The patient had a worsening of the AE of respiratory failure on Day 4 of the treatment with ranibizumab and died on the same day. Both of these deaths were assessed by the Investigator as not related to the study treatment.

Occurrence of adverse events

The occurrence of adverse events in the safety analysis set is shown in Table 10-7, and the occurrence of adverse events by outcome is shown in Table 10-8. The incidence of adverse events was 7.5% (9 / 120 patients), and the only adverse event that occurred in $\geqslant$ 2 patients was retinopathy of prematurity (2.5%, 3 / 120 patients). A total of 10 adverse events occurred in 9 patients. The outcome of the 10 adverse events was "recovering" and "unknown" in 3 events each, "death" in 2 events, and "recovered" and "not recovered" in 1 event each.

Table 10-7 Occurrence of Adverse Events (by SOC and PT) (safety analysis set)

SOC PT	Safety analysis set N=120 n (%)
Total	9 (7.5)
Eye disorders	5 (4.2)
Retinopathy of prematurity	3 (2.5)
Conjunctival haemorrhage	1 (0.8)
Vitreous haemorrhage	1 (0.8)
Vascular disorders	1 (0.8)
Vena cava thrombosis	1 (0.8)
Respiratory, thoracic and mediastinal disorders	1 (0.8)
Respiratory failure	1 (0.8)
Renal and urinary disorders	1 (0.8)
Renal vein thrombosis	1 (0.8)
General disorders and administration site conditions	2 (1.7)
Therapeutic response decreased	1 (0.8)
Systemic inflammatory response syndrome	1 (0.8)

Source: AE_T001-1

A patient who experienced the same event (PT) more than once is counted as one patient.

SOC is shown in internationally agreed order, PT is shown in descending order of incidence -> order of PT code

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Table 10-8 Occurrence of Adverse Events by Outcome (by SOC and PT) (safety analysis set)

	Safety analysis set N=120						
SOC PT	All n (%)	Recovered n (%)	Recovering n (%)	Not recovered n (%)	Sequelae n (%)	Death n (%)	Unknown n (%)
Total	10	1	3	1	0	2	3
Eye disorders	5 (4.2)	1 (0.8)	2 (1.7)	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.8)
Retinopathy of prematurity	3 (2.5)	0 (0.0)	2 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Conjunctival haemorrhage	1 (0.8)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vitreous haemorrhage	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Vena cava thrombosis	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Respiratory, thoracic and mediastinal disorders	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Respiratory failure	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Renal and urinary disorders	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Renal vein thrombosis	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
General disorders and administration site conditions	2 (1.7)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)

Therapeutic response decreased	1 (0.8)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Systemic inflammatory response syndrome	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)

Source: AE_T013-1

Total: Number of events

A patient who experienced the same event (PT) more than once is counted as one patient.

SOC is shown in internationally agreed order, PT is shown in descending order of incidence in the "All" column -> order of PT code

A patient who experienced the same event (PT) more than once with different outcome is counted for the worst outcome.

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Occurrence of adverse events by timing of initial onset

The occurrence of adverse events by timing of initial onset (≤ 4 weeks, > 4 to ≤ 8 weeks, > 8 to< 12 weeks, ≥ 12 weeks) in the safety analysis set is shown in Table 10-9. The number of patients with adverse events by timing of initial onset was 3 each for ≤ 4 weeks and > 8 to < 12 weeks, and 2 for ≥ 12 weeks.

Table 10-9 Occurrence of Adverse Events by Timing of Initial Onsetnset (by SOC and PT) (safety analysis set)

		Timing of initial onset (weeks)				
	All	≤ 4 weeks	> 4 to ≤ 8 weeks	> 8 weeks and < 12 weeks	≥ 12 weeks	Unknown timing of onset
SOC	N=120	N=120	N=120	N=115	N=114	
PT	n (%)	n	n	n	n	n
Total	9 (7.5)	3	0	3	2	1
Eye disorders	5 (4.2)	2	0	1	2	0
Retinopathy of prematurity	3 (2.5)	0	0	1	2	0
Conjunctival haemorrhage	1 (0.8)	1	0	0	0	0
Vitreous haemorrhage	1 (0.8)	1	0	0	0	0
Vascular disorders	1 (0.8)	0	0	0	0	1
Vena cava thrombosis	1 (0.8)	0	0	0	0	1
Respiratory, thoracic and mediastinal disorders	1 (0.8)	1	0	0	0	0
Respiratory failure	1 (0.8)	1	0	0	0	0
Renal and urinary disorders	1 (0.8)	0	0	0	0	1
Renal vein thrombosis	1 (0.8)	0	0	0	0	1
General disorders and administration site conditions	2 (1.7)	0	0	2	0	0
Therapeutic response decreased	1 (0.8)	0	0	1	0	0
Systemic inflammatory response syndrome	1 (0.8)	0	0	1	0	0

Source: AE_T008-1

N: Number of patients being observed (safety analysis period) during each period

Total: A patient who experienced more than one PT was counted as one patient for the period corresponding to the PT with the earliest onset date.

Each SOC: A patient who experienced more than one PT within the same SOC was counted as one patient for the period corresponding to the PT with the earliest onset date.

Each PT: A patient who experienced the same PT more than once was counted as one patient only for the period of initial onset.

SOC is shown in internationally agreed order, PT is shown in descending order of overall incidence -> order of PT code

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Occurrence of serious adverse events

Occurrence of serious adverse events in the safety analysis set is shown in Table 10-13. The incidence of serious adverse events was 4.2% (5/120 patients). These events were retinopathy of prematurity (1.7%, 2/120 patients), vitreous haemorrhage, respiratory failure, and systemic inflammatory response syndrome (0.8%, 1/120 patients each).

Table 10-13 Occurrence of Serious Adverse Events (by SOC and PT) (safety analysis set)

SOC PT	Safety analysis set N=120 n (%)
Total	5 (4.2)
Eye disorders	3 (2.5)
Retinopathy of prematurity	2 (1.7)
Vitreous haemorrhage	1 (0.8)
Respiratory, thoracic and mediastinal disorders	1 (0.8)
Respiratory failure	1 (0.8)
General disorders and administration site conditions	1 (0.8)
Systemic inflammatory response syndrome	1 (0.8)

Source: AE_T001-3

A patient who experienced the same event (PT) more than once is counted as one patient.

SOC is shown in internationally agreed order, PT is shown in descending order of incidence -> order of PT code

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Occurrence of serious ocular adverse events

Occurrence of serious ocular adverse events in the safety analysis set is shown in Table 10-14. The incidence of serious ocular adverse events was 2.5% (3 / 120 patients). These events were retinopathy of prematurity (1.7%, 2 / 120 patients) and vitreous haemorrhage (0.8%, 1 / 120 patients).

Table 10-14 Occurrence of Serious Ocular Adverse Events (by SOC and PT) (safety analysis set)

SOC PT	Safety analysis set N=120 n (%)
Total	3 (2.5)
Eye disorders	3 (2.5)
Retinopathy of prematurity	2 (1.7)
Vitreous haemorrhage	1 (0.8)

Source: AE_T001-7

A patient who experienced the same event (PT) more than once is counted as one patient.

SOC is shown in internationally agreed order, PT is shown in descending order of incidence -> order of PT code

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Occurrence of adverse reactions

Occurrence of adverse reactions in the safety analysis set is shown in Table 10-15. The incidence of adverse reactions was 2.5% (3 / 120 patients), and conjunctival haemorrhage, vena cava thrombosis, renal vein thrombosis, and therapeutic response decreased occurred at an incidence of 0.8% (1 / 120 patients) each. The outcome was "recovered" (conjunctival haemorrhage), "recovering" (therapeutic response decreased), and unknown (vena cava thrombosis and renal vein thrombosis) (Table 10-8).

Table 10-15 Occurrence of Adverse Reactions (by SOC and PT) (safety analysis set)

SOC PT	Safety analysis set N=120 n (%)
Total	3 (2.5)
Eye disorders	1 (0.8)
Conjunctival haemorrhage	1 (0.8)
Vascular disorders	1 (0.8)
Vena cava thrombosis	1 (0.8)
Renal and urinary disorders	1 (0.8)
Renal vein thrombosis	1 (0.8)
General disorders and administration site conditions	1 (0.8)
Therapeutic response decreased	1 (0.8)

Source: AE_T001-2

A patient who experienced the same event (PT) more than once is counted as one patient.

SOC is shown in internationally agreed order, PT is shown in descending order of incidence -> order of PT code

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Adverse events leading to treatment discontinuation

Occurrence of adverse events leading to treatment discontinuation in the safety analysis set is shown in Table 10-17. The incidence of adverse events leading to treatment discontinuation was 0.8% (1 / 120 patients). The event that occurred was systemic inflammatory response syndrome. The details are provided in Section 10.4.5 Deaths.

Table 10-17 Occurrence of Adverse Events leading to Treatment Discontinuation (by SOC and PT) (safety analysis set)

SOC PT	Safety analysis set N=120 n (%)
Total	1 (0.8)
General disorders and administration site conditions	1 (0.8)
Systemic inflammatory response syndrome	1 (0.8)

Deaths

A list of adverse events leading to death is shown in Table 10-18.

Table 10-18 List of Adverse Events leading to Death (safety analysis set)

Patient number	Sex	Event term (term entered by physician/PT)	Site of onset	Timing of onset (Day)	Number of days to death	Outcome	Causality
[redacted]	Male	Worsening of systemic inflammatory response syndrome/ Systemic inflammatory response syndrome	Non-eye	58	1	Death	Not related
[redacted]	Male	Worsening of respiratory failure/ Respiratory failure	Non-eye	4	1	Death	Not related

Source: AE_L002

Timing of onset: The start day of treatment with Lucentis was considered Day 1.

Number of days to death: The number of days to death when the day of onset of adverse events is considered Day 1

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Of the 2 patients who died, 1 patient was a male whose gestational age at birth was 24 weeks and whose body weight was 648 g. He had ROP in both eyes. The status in both eyes was Zone I, Stage 1, and with plus disease, and the severity was other than mild and severe. Complications were anaemia neonatal, asthma, circulatory collapse, disseminated intravascular coagulation, ileus, jaundice neonatal, neonatal asphyxia, neonatal respiratory distress syndrome, patent ductus arteriosus, skin infection, small intestinal perforation, chylothorax, systemic inflammatory response syndrome, and motor developmental delay (all non-ocular). There was no past medical history. Lucentis was administered in both eyes at 18 weeks of age. Systemic inflammatory response syndrome worsened on Day 58 of the treatment with Lucentis, and the patient died on the same day. The investigator ruled out the causal relationship with Lucentis.

The other patient was a male, whose gestational age at birth was 23 weeks and whose body weight was 58 g. He had ROP in both eyes. The status in both eyes was Zone II, Stage 3, and with plus disease. The severity was other than mild and severe. He had a complication of respiratory failure and no past medical history. Lucentis was administered in both eyes at 13 weeks of age. Respiratory failure

worsened on Day 4 of the treatment with Lucentis, and the patient died on the same day. The investigator ruled out the causal relationship with Lucentis.

Safety specifications

The 4 safety specifications in this study are infectious endophthalmitis, intraocular inflammation, intraocular pressure increased, and arterial thromboembolic events. The definition of each specification is shown in Table 15-1. Adverse events corresponding to these were not reported in 120 patients in the safety analysis set.

Occurrence of systemic adverse events related to VEGF inhibition

The definition of systemic adverse events related to VEGF inhibition in the safety analysis set is shown in Table 15-2, and their occurrence is shown in Table 10-19. The incidence of systemic adverse events related to VEGF inhibition was 0.8% (1 / 120 patients). Causal relationship with Lucentis was not ruled out for these events. The outcome was unknown for all events.

Table 10-19 Occurrence of Systemic Adverse Events related to VEGF inhibition (by event and PT) (safety analysis set)

Event PT	Safety analysis set N=120 n (%)
Total	1 (0.8)
Venous thromboembolism	1 (0.8)
Renal vein thrombosis	1 (0.8)
Vena cava thrombosis	1 (0.8)

Safety analysis by patient factor

Evaluation is limited by the small number of patients with adverse events. The results are described in the following subsections. Unknown cases are not included in the tabulation.

Occurrence of adverse events by sex

The incidence of adverse events by sex was 4.5% (3 / 67 patients) in males and 11.3% (6 / 53 patients) in females (Table 10-20).

Table 10-20 Occurrence of Adverse Events by Sex (by SOC and PT) (safety analysis set)

Sex: male	
SOC PT	N=67 n (%)
Total	3 (4.5)
Vascular disorders	1 (1.5)
Vena cava thrombosis	1 (1.5)
Respiratory, thoracic and mediastinal disorders	1 (1.5)
Respiratory failure	1 (1.5)
Renal and urinary disorders	1 (1.5)
Renal vein thrombosis	1 (1.5)
General disorders and administration site conditions	1 (1.5)
Systemic inflammatory response syndrome	1 (1.5)

Sex: female	
SOC PT	N=53 n (%)
Total	6 (11.3)
Eye disorders	5 (9.4)
Retinopathy of prematurity	3 (5.7)
Conjunctival haemorrhage	1 (1.9)
Vitreous haemorrhage	1 (1.9)
General disorders and administration site conditions	1 (1.9)
Therapeutic response decreased	1 (1.9)

Occurrence of adverse events by gestational age at birth

The incidence of adverse events by gestational age at birth was 10.9% (7 / 64 patients) for ⩽ 24 weeks and 8.0% (2 / 25 patients) for > 24 to < 27 weeks. No adverse events were observed for ⩾ 27 weeks (Table 10-21).

Table 10-21 Occurrence of Adverse Events by Gestational Age at Birth (by SOC and PT) (safety analysis set)

Gestational age at birth: ≤ 24 weeks	
SOC	N=64
PT	n (%)
Total	7 (10.9)
Eye disorders	4 (6.3)
Retinopathy of prematurity	3 (4.7)
Vitreous haemorrhage	1 (1.6)
Vascular disorders	1 (1.6)
Vena cava thrombosis	1 (1.6)
Respiratory, thoracic and mediastinal disorders	1 (1.6)
Respiratory failure	1 (1.6)
Renal and urinary disorders	1 (1.6)
Renal vein thrombosis	1 (1.6)
General disorders and administration site conditions	1 (1.6)
Systemic inflammatory response syndrome	1 (1.6)

Gestational age at birth: > 24 to < 27 weeks	
SOC	N=25
PT	n (%)
Total	2 (8.0)
Eye disorders	1 (4.0)
Conjunctival haemorrhage	1 (4.0)
General disorders and administration site conditions	1 (4.0)
Therapeutic response decreased	1 (4.0)

Gestational age at birth: ≥ 27 weeks	
SOC	N=31
PT	n (%)
Total	0 (0.0)

Occurrence of adverse events by body weight at birth

The incidence of adverse events by body weight at birth was 8.8% (7 / 80 patients) for ⩽ 750 g and 4.3% (1 / 23 patients) for > 750 to < 1000 g. No adverse events were observed for ⩾ 1000 g (Table 10-22).

Table 10-22 Occurrence of Adverse Events by Body Weight at Birth (by SOC and PT) (safety analysis set)

Body weight at birth: ≤ 750 g	
SOC	N=80
PT	n (%)
Total	7 (8.8)
Eye disorders	4 (5.0)
Retinopathy of prematurity	2 (2.5)
Conjunctival haemorrhage	1 (1.3)
Vitreous haemorrhage	1 (1.3)
Vascular disorders	1 (1.3)
Vena cava thrombosis	1 (1.3)
Respiratory, thoracic and mediastinal disorders	1 (1.3)
Respiratory failure	1 (1.3)
Renal and urinary disorders	1 (1.3)
Renal vein thrombosis	1 (1.3)
General disorders and administration site conditions	1 (1.3)
Systemic inflammatory response syndrome	1 (1.3)

Body weight at birth: > 750 to < 1000 g	
SOC	N=23
PT	n (%)
Total	1 (4.3)
General disorders and administration site conditions	1 (4.3)
Therapeutic response decreased	1 (4.3)

Body weight at birth: ≥ 1000 g	
SOC	N=14
PT	n (%)
Total	0 (0.0)

Occurrence of adverse events by presence or absence of complications

The incidence of adverse events by presence or absence of complications was 5.5% (3 / 55 patients) in patients without complications and 9.5% (6 / 63 patients) in patients with complications (Table 10-23).

Table 10-23 Occurrence of Adverse Events by Presence or Absence of Complications (by SOC and PT) (safety analysis set)

Complication: absent	
SOC	N=55
PT	n (%)
Total	3 (5.5)
Eye disorders	2 (3.6)
Retinopathy of prematurity	2 (3.6)
General disorders and administration site conditions	1 (1.8)
Therapeutic response decreased	1 (1.8)

Complication: present	
SOC	N=63
PT	n (%)
Total	6 (9.5)
Eye disorders	3 (4.8)
Conjunctival haemorrhage	1 (1.6)
Retinopathy of prematurity	1 (1.6)
Vitreous haemorrhage	1 (1.6)
Vascular disorders	1 (1.6)
Vena cava thrombosis	1 (1.6)
Respiratory, thoracic and mediastinal disorders	1 (1.6)
Respiratory failure	1 (1.6)
Renal and urinary disorders	1 (1.6)
Renal vein thrombosis	1 (1.6)
General disorders and administration site conditions	1 (1.6)
Systemic inflammatory response syndrome	1 (1.6)

Occurrence of adverse events by severity of ROP

The incidence of adverse events by severity of ROP was 9.7% (3 / 31 patients) for mild, 4.8% (4 / 83 patients) for other than mild and severe, and 20.0% (1 / 5 patients) for severe (Table 10- 24).

Table 10-24 Occurrence of Adverse Events by Severity of ROP (by SOC and PT) (safety analysis set)

Severity of ROP: mild	
SOC	N=31
PT	n (%)
Total	3 (9.7)
Eye disorders	2 (6.5)
Conjunctival haemorrhage	1 (3.2)
Retinopathy of prematurity	1 (3.2)
General disorders and administration site conditions	1 (3.2)
Therapeutic response decreased	1 (3.2)

Severity of ROP: other than mild and severe	
SOC	N=83
PT	n (%)
Total	4 (4.8)
Eye disorders	1 (1.2)
Vitreous haemorrhage	1 (1.2)
Vascular disorders	1 (1.2)
Vena cava thrombosis	1 (1.2)
Respiratory, thoracic and mediastinal disorders	1 (1.2)
Respiratory failure	1 (1.2)
Renal and urinary disorders	1 (1.2)
Renal vein thrombosis	1 (1.2)
General disorders and administration site conditions	1 (1.2)
Systemic inflammatory response syndrome	1 (1.2)

Severity of ROP: severe	
SOC	N=5
PT	n (%)
Total	1 (20.0)
Eye disorders	1 (20.0)
Retinopathy of prematurity	1 (20.0)

Source: AE_T005-5

A patient who experienced the same event (PT) more than once is counted as one patient.
SOC is shown in internationally agreed order, PT is shown in descending order of incidence -> order of PT code

The severity of ROP was assessed in the eyes treated on the start day of treatment with Lucentis. In the case of bilateral administration, the status of ROP was assessed in the eye that was worse.

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Occurrence of adverse events by presence or absence of prior laser therapy for ROP

Three patients had received prior therapy for ROP, all of whom had received prior laser therapy. The incidence of adverse events by presence or absence of prior laser therapy for ROP was 7.7% (9 / 117

patients) in patients without prior laser therapy, and no adverse events were observed in patients with prior laser therapy (Table 10-25).

Table 10-25 Occurrence of Adverse Events by Presence or Absence of Prior Laser Therapy for ROP (by SOC and PT) (safety analysis set)

Prior laser therapy for ROP: absent	
SOC	N=117
PT	n (%)
Total	9 (7.7)
Eye disorders	5 (4.3)
Retinopathy of prematurity	3 (2.6)
Conjunctival haemorrhage	1 (0.9)
Vitreous haemorrhage	1 (0.9)
Vascular disorders	1 (0.9)
Vena cava thrombosis	1 (0.9)
Respiratory, thoracic and mediastinal disorders	1 (0.9)
Respiratory failure	1 (0.9)
Renal and urinary disorders	1 (0.9)
Renal vein thrombosis	1 (0.9)
General disorders and administration site conditions	2 (1.7)
Therapeutic response decreased	1 (0.9)
Systemic inflammatory response syndrome	1 (0.9)

Prior laser therapy for ROP: present	
SOC	N=3
PT	n (%)
Total	0 (0.0)

Source: AE_T005-7

A patient who experienced the same event (PT) more than once is counted as one patient.

SOC is shown in internationally agreed order, PT is shown in descending order of incidence -> order of PT code

Prior laser therapy for ROP was assessed in the eyes treated on the start day of treatment with Lucentis. Patients with a treatment history with laser photocoagulation for the eyes treated with Lucentis on the start day of treatment were defined as those for whom prior therapy was "present."

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Occurrence of adverse events by presence or absence of concomitant drugs and therapies for ROP

The incidence of adverse events by presence or absence of concomitant drugs and therapies for ROP was 6.3% (4 / 63 patients) in patients without concomitant drugs and therapies and 8.9% (5 / 56 patients) in patients with concomitant drugs and therapies (Table 10-26).

Table 10-26 Occurrence of Adverse Events by Presence or Absence of Concomitant Drugs and Therapies for ROP (by SOC and PT) (safety analysis set)

Concomitant drugs and therapies for ROP: absent	
SOC	N=63
PT	n (%)
Total	4 (6.3)
Eye disorders	2 (3.2)
Conjunctival haemorrhage	1 (1.6)
Retinopathy of prematurity	1 (1.6)
Respiratory, thoracic and mediastinal disorders	1 (1.6)
Respiratory failure	1 (1.6)
General disorders and administration site conditions	1 (1.6)
Systemic inflammatory response syndrome	1 (1.6)

Concomitant drugs and therapies for ROP: present	
SOC	N=56
PT	n (%)
Total	5 (8.9)
Eye disorders	3 (5.4)
Retinopathy of prematurity	2 (3.6)
Vitreous haemorrhage	1 (1.8)
Vascular disorders	1 (1.8)
Vena cava thrombosis	1 (1.8)
Renal and urinary disorders	1 (1.8)
Renal vein thrombosis	1 (1.8)
General disorders and administration site conditions	1 (1.8)
Therapeutic response decreased	1 (1.8)

Occurrence of adverse events by total number of doses of Lucentis

The incidence of adverse events by total number of doses of Lucentis was 14.3% (1 / 7 patients) for 1, 5.7% (5 / 88 patients) for 2, 0.0% (0 / 1 patients) for 3, and 12.5% (3 / 24 patients) for ⩾ 4 (Table 10-27).

Table 10-27 Occurrence of Adverse Events by Total Number of Doses of Lucentis (by SOC and PT) (safety analysis set)

Total number of doses of Lucentis: 1	
SOC	N=7
PT	n (%)
Total	1 (14.3)
Vascular disorders	1 (14.3)
Vena cava thrombosis	1 (14.3)
Renal and urinary disorders	1 (14.3)
Renal vein thrombosis	1 (14.3)

Total number of doses of Lucentis: 2	
SOC	N=88
PT	n (%)
Total	5 (5.7)
Eye disorders	2 (2.3)
Conjunctival haemorrhage	1 (1.1)
Retinopathy of prematurity	1 (1.1)
Respiratory, thoracic and mediastinal disorders	1 (1.1)
Respiratory failure	1 (1.1)
General disorders and administration site conditions	2 (2.3)
Therapeutic response decreased	1 (1.1)
Systemic inflammatory response syndrome	1 (1.1)

Total number of doses of Lucentis: 3	
SOC	N=1
PT	n (%)
Total	0 (0.0)

Total number of doses of Lucentis: ≥ 4	
SOC	N=24
PT	n (%)
Total	3 (12.5)
Eye disorders	3 (12.5)
Retinopathy of prematurity	2 (8.3)
Vitreous haemorrhage	1 (4.2)

Source: AE_T005-9

A patient who experienced the same event (PT) more than once is counted as one patient.

SOC is shown in internationally agreed order, PT is shown in descending order of incidence -> order of PT code

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2.3.3. Discussion on clinical aspects

The results of study H1401, a non-interventional, post- marketing surveillance (PMS) study to evaluate the safety and efficacy of Lucentis® (ranibizumab) in 120 retinopathy of prematurity (ROP) patients in the clinical practice setting in Japan, have been submitted as a standalone submission in accordance with Article 46.

Of the 120 enrolled patients all were included in the safety analysis set but only 114 of those were included in the efficacy set because in 6 patients efficacy evaluation in the eye treated on the day of the first dose was not specified.

A slightly higher number of patients were male (67), and the mean gestational age was low at 25.2 weeks. Mean birth weight was also low at 744.5 g, with 80 patients weighing $\leq$ 750 g. The low mean birth weight and gestational age indicate a general vulnerability of this patient group. The severity of ROP at baseline was predominantly "other than mild and severe" (83 patients) with five patients having severe ROP. 3 patients had prior treatment of ROP in form of laser photocoagulation while 56 patients received concomitant drugs and therapies for ROP, including laser photocoagulation in 54 patients and vitreous surgery in 6 patients.

Regarding the administration status the most common total number of doses was 2 (88 patients), followed by $\geq$ 4 doses (24 patients) and in view of 117/120 patients suffering from ROP in both eyes, this appears reasonable. The study was discontinued in 11 patients with the reasons for discontinuation being "Observation cannot be continued because of moving, transfer to another hospital, etc." in 8 patients, "Death" in 2 patients and "Other" in 1 patient.

The mean duration of safety analysis was 171.2 days.

Regarding safety, the incidence of adverse events was 7.5% (9⁄120 patients), and the most common adverse event was ROP (2.5%, 3⁄120 patients, outcome "recovering" in 2 and "unknown" in 1 patient).

The incidence of adverse reactions was 2.5% (3⁄120 patients), and conjunctival haemorrhage (outcome recovered, a common adverse reaction), vena cava thrombosis and renal vein thrombosis (both in same patient, outcome unknown), and therapeutic response decreased (outcome recovering with no specific safety measures considered necessary) occurred at an incidence of 0.8% (1⁄120 patients) each.

Vena cava thrombosis and renal vein thrombosis were regarded as unknown systemic adverse reactions related to VEGF inhibition where causal relationship could not be ruled out. The MAH concludes that because both AEs were non-serious and occurred in the same patient, no specific safety measures were considered necessary and ongoing collection of information on these events was regarded necessary. However, due to the observational character of this study without control group, a causal relationship can be debated, with current literature indicating that about 2% to 4% of neonates die due to venous thromboembolism, i.e., the incidence of VTE in this study is not unexpected. Furthermore, both AEs had an unknown timing of onset in this male patient with a low gestational age at birth of <=24 weeks, with a low body weight of <=750 g, with complications present and with concomitant drugs and therapies present, at the occurrence of these AEs, i.e., this patient had already a higher risk profile for complications such as VTE. Vena cava thrombosis and renal vein thrombosis are therefore not regarded as new signals.

The MAH states that there was no consistent tendency in the timing of onset of adverse events which is agreed.

The incidence of adverse events leading to treatment discontinuation (systemic inflammatory response syndrome with outcome death) was 0.8% (1⁄120 patients). The investigator ruled out the causal relationship with Lucentis.

The adverse events resulting in death were systemic inflammatory response syndrome (see above) and respiratory failure in 1 patient each. The investigator ruled out the causal relationship with Lucentis for both of these events. This is agreed when looking at the patient histories. Gestational ages were 23 and 24 weeks and birth weight were 648 grs and 658 grs in these two male patients. One of these patients had multiple severe complications and the other had respiratory failure as severe complication. One of the patients died 4 days after bilateral administration and the other 58 days after bilateral administration. In conclusion, both patients were very vulnerable with low gestational age and very low birth weight with severe concomitant complications present and with very little chance of survival. It is therefore agreed that no causal relationship to the treatment with Lucentis can be observed.

It is agreed with the MAH that although the incidence of adverse events is higher in female patients, the group of patients with lower gestational age, the group of patients with lower body weight at birth, the group of patients with complications, and the group of patients with higher number of doses, no patient factors that may affect the safety could be identified because of the small number of patients with events in all these groups.

It is regarded reasonable that because most patients whose case report forms were collected had no prior treatment for ROP, safety was not compared between patients with and without prior treatment for ROP or between patients with and without prior laser treatment for ROP.

Concluding on safety it is agreed with the MAH that when compared with the Japanese population in Study H2301 ((a 24-week randomized, controlled clinical trial comparing two doses of ranibizumab, 0.2 mg and 0.1 mg, to laser therapy for the treatment of ROP in preterm infants), there are no apparent differences in the reported adverse events, and the incidence of adverse events and adverse reactions is low.

Of the 114 patients in the efficacy analysis set, 98.1% (104⁄106 patients) of the patients whose overall assessment of ROP activity at Week 24 (or at discontinuation) was available were assessed as responders in the overall assessment. It can be agreed with the MAH that because most of the patients responded, no clear difference can be observed in the overall assessment of ROP activity in subgroup analyses.

In the overall assessment, 97.3% (109⁄112 patients) of the patients were assessed as "responders" by Week 12, i.e., a very high responder rate.

At Week 24 (or at discontinuation), unfavourable ocular structural outcomes were "absent" in 98.1% (102⁄104 patients) of the patients, again a very satisfactory outcome.

100.0% (73⁄73 patients) of the patients with severity of ROP "other than mild and severe" were assessed as responders at Week 24 (or at discontinuation). All patients with mild disease were judged to be responders.

Although both patients with severe ROP showed improvement in the overall assessment at Week 12, 1 patient was assessed as "worsened" at Week 24 (or at discontinuation). It is agreed that evaluation is difficult and no conclusions on effect in severe ROP can be made due to the low number of patients with severe ROP.

ROP was considered to have been successfully cured in 88.6% (101⁄114 patients) of the patients which is line with previous treatment results.

It is agreed that because this was an observational study without control group, and information on patients not exposed to Lucentis was not collected, the relationship between the results obtained and the effects of exposure to Lucentis cannot be clarified, i.e. the scope for interpretation of the results is limited.

Overall, the MAH concludes that the results of this study showed neither tendencies different from the known safety profile nor particular concerns in terms of the safety of Lucentis administered to ROP patients in clinical practice settings and that based on the results of this study, it was considered unnecessary to take additional measures and this is agreed. The MAH further concludes that a certain level of efficacy of Lucentis was also demonstrated, and it is agreed that there are natural limitations due to the observational character of the study with for example, low numbers of severe ROP patients. The MAH reassures that collection of safety information will continue through regular pharmacovigilance activities specified in the Risk Management Plan, and that if any new safety concern is identified, appropriate measures will be taken.

3. Rapporteur's overall conclusion and recommendation

It is agreed with the MAH that the results of this stand-alone observational study without control group in Japan, with its inherent limitations, did not raise any new safety concern in ROP patients, that efficacy has been confirmed with limitations and no additional measures are considered necessary. Therefore, with no new safety signals observed, safety information collected through regular pharmacovigilance activities specified in the Risk Management Plan for Lucentis is regarded as sufficient.

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

☒ **Fulfilled:**

No regulatory action required.