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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Ranibizumab

Trial Indication(s)

Retinopathy of Prematurity (ROP)

Protocol Number

CRFB002HKR01

Protocol Title

Regulatory Post-Marketing Surveillance(PMS) Study for Lucentis®(Ranibizumab) in Patients with Retinopathy of Prematurity

Clinical Trial Phase

Phase IV

Phase of Drug Development

Full Development

Study Start/End Dates

Study Start Date: June 22, 2022 (Actual)

Primary Completion Date: January 11, 2025 (Actual)
Study Completion Date: January 11, 2025 (Actual)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was an open-label, multicenter, single arm, post-marketing surveillance study under routine care setting with no mandated treatments, visits or assessments.

The investigators collected approximately 4 weeks of safety and effectiveness data from patients who were prescribed with Lucentis® injection for ROP after informed consent. However, according to the result of the phase 3 clinical study of Lucentis® injection for ROP (RAINBOW study, CRFB002H2301), ranibizumab could be administered up to three times, but it was found that only about 30% of subjects received two or more doses (Stahl A, et al. 2019). Based on this, it is expected that less than approximately 30% of the subjects who received a single dose of Lucentis® injection will show signs of disease activity in the actual clinical settings, in which case Lucentis® will be rechallenged. Therefore, for the purpose of this study, subjects who received Lucentis® at least once and whose safety and effectiveness data were collected for 12 weeks were defined as subjects with long-term use to perform a separate analysis of 12-week safety and effectiveness data. In addition, a separate analysis was performed for subjects who received a single dose.

Lucentis® injection was prescribed according to the approved label. The decision on the treatment method for subjects was made according to the approved indication within the current real-world care settings and regardless of participation in the surveillance. No additional diagnostic or monitoring procedures were required for this surveillance other than the procedures in the routine care settings.

Centers

Korea, Republic of(6)

Objectives:

This was a regulatory post-marketing surveillance study mandated by the Korean health authority to evaluate the safety and effectiveness of Lucentis® injection for the treatment of ROP as the approved indication under routine care setting.

Test Product (s), Dose(s), and Mode(s) of Administration

Lucentis® Injection 10 mg/ml (ranibizumab, genetic recombinant)

Statistical Methods

The number of subjects who experienced AEs/ADRs, serious AEs/ADRs (SAEs/SADRs), unexpected AEs/ADRs (UAEs/UADRs), and unexpected SAEs/SADRs (USAEs/USADRs), incidence rate, and frequencies are presented along with the 95% Wald or Clopper-Pearson confidence interval (CI) for the incidence rate. The number of subjects who experienced AEs/ADRs, SAEs/SADRs, UAEs/UADRs, and USAEs/USADRs, incidence rate, and frequencies are summarized according to the system organ classes (SOCs) and preferred terms (PTs) of MedDRA.

Effectiveness analysis: The number and percentage of subjects who had successful treatment as evaluated by the investigator are presented with the 95% CIs.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

1) Premature infants with retinopathy of prematurity (ROP)

2) Patients (infants) prescribed with Lucentis® injection according to the product approval information in the Republic of Korea

3) In the case that the legal guardian of the patient (infant) provided a written consent to participate in this study

Exclusion Criteria:

1) In the case that the legal guardian of the patient (infant) does not want participation in this study

2) In the case that it falls under any of the contraindications listed in local prescribing information of Lucentis® injection

- Patients with hypersensitivity to the active substance or to any of the excipients
- Patients with an active or suspected ocular or periocular infection.
- Patients with active intraocular inflammation

Participant Flow Table

Item	Overall (N=71) N(%)
Completed[f]	69 (97.18)
Prematurely discontinued[f]	2 (2.82)

[f] Percentage calculated based on the subjects whose CRF was collected

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Baseline Characteristics

Item	Category and statistics	Overall (N=69)
Corrected age (week)	N	69
	Mean ± SD	-2.90 ± 2.98
	Median	-4.00
	[Min – Max]	[-9.00, 7.00]
Sex	Male, N(%)	42 (60.87)
	Female, N(%)	27 (39.13)
Height (cm)	N	40
	Mean ± SD	41.18 ± 4.55
	Median	40.75
	[Min – Max]	[31.00, 52.00]
Weight (kg)	N	69
	Mean ± SD	2.32 ± 0.57
	Median	2.30
	[Min – Max]	[1.30, 4.10]
Renal impairment	Yes, N(%)	5 (7.25)
	No, N(%)	64 (92.75)
Hepatic impairment	Yes, N(%)	6 (8.70)
	No, N(%)	63 (91.30)

Note) Corrected age: Age based on expected date of delivery (chronological age – weeks of prematurity)

Primary Outcome Result(s)

Refer to Safety Results section for primary outcome result.

Secondary Outcome Result(s)

Treatment success rate at 4 weeks after treatment (Effectiveness Set)

Category and statistics	Overall (N=61)
N	54
Treatment success, N(%)	51 (94.44)
95% CI [a] [Lower, Upper]	[84.61, 98.84]

[a] 95% Clopper-Pearson Confidence Interval

Treatment success rate at 4 weeks after treatment in special subjects (Effectiveness Set)

Population	Category and statistics	
Renal impairment	N	5
(N=5)	Treatment success, N(%)	4 (80.00)
	95% CI [a] [Lower, Upper]	[28.36, 99.49]
Hepatic impairment	N	5
(N=6)	Treatment success, N(%)	5 (100.00)

Population	Category and statistics	
	95% CI [a] [Lower, Upper]	[47.82, 100.00]

[a] 95% Clopper-Pearson Confidence Interval

Treatment success rate at 4 weeks after treatment for subjects with long-term use (Long-term Effectiveness Set)

Category and statistics	Overall (N=40)
N	33
Treatment success at 4 weeks, N(%)	30 (90.91)
95% CI [a] [Lower, Upper]	[75.67, 98.08]

[a] 95% Clopper-Pearson Confidence Interval

Treatment success rate at 12 weeks after treatment for subjects with long-term use (Long-term Effectiveness Set)

Category and statistics	Overall (N=40)
N	40
Treatment success at 12 weeks, N(%)	39 (97.50)
95% CI [a] [Lower, Upper]	[86.84, 99.94]

[a] 95% Clopper-Pearson Confidence Interval

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

No data identified.

Safety Results

Summary of adverse events (Safety Set)

Item	Overall (N=69) N (%) [N][f]	95% CI [Lower, Upper]
Adverse events	13 (18.84) [27]	[9.61, 28.07][a]
Adverse drug reactions	3 (4.35) [3]	[0.91, 12.18][b]
Serious adverse events	3 (4.35) [3]	[0.91, 12.18][b]
Serious adverse drug reactions	2 (2.90) [2]	[0.35, 10.08][b]
Unexpected adverse events	11 (15.94) [25]	[7.30, 24.58][a]
Unexpected adverse drug reactions	3 (4.35) [3]	[0.91, 12.18][b]
Unexpected serious adverse events	3 (4.35) [3]	[0.91, 12.18][b]
Unexpected serious adverse drug reactions	2 (2.90) [2]	[0.35, 10.08][b]

[a] 95% Clopper-Pearson Confidence Interval
[b] 95% Clopper-Pearson Confidence Interval
[f] N (%), where [N] refers to the number of subjects (prevalence) [number of events], with duplicate counting

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Incidence status of adverse events/adverse drug reactions by System Organ Class and Preferred Term (Safety Set)

System Organ Class Preferred Term	Adverse events N (%) [N][j]	Adverse drug reactions N (%) [N][j]
Overall	**13 (18.84) [27]**	**3 (4.35) [3]**
Nervous system disorders	**5 (7.25) [5]**	**1 (1.45) [1]**
Intraventricular haemorrhage	2 (2.90) [2]	1 (1.45) [1]
Periventricular leukomalacia	2 (2.90) [2]	--
Headache	1 (1.45) [1]	--
Respiratory, thoracic and mediastinal disorders	**3 (4.35) [3]**	**1 (1.45) [1]**

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System Organ Class Preferred Term	Adverse events N (%) [N][j]	Adverse drug reactions N (%) [N][j]
Bronchopulmonary dysplasia	2 (2.90) [2]	1 (1.45) [1]
Pulmonary hypertension	1 (1.45) [1]	--
Infections and infestations	**2 (2.90) [4]**	**--**
Sepsis	1 (1.45) [2]	--
Bacterial sepsis	1 (1.45) [1]	--
Urinary tract infection	1 (1.45) [1]	--
General disorders and administration site conditions	**2 (2.90) [3]**	**--**
Catheter site swelling	1 (1.45) [1]	--
Extravasation	1 (1.45) [1]	--
Pyrexia	1 (1.45) [1]	--
Eye disorders	**2 (2.90) [2]**	**1 (1.45) [1]**
Vitreous haemorrhage	1 (1.45) [1]	--
Vitreous opacities	1 (1.45) [1]	1 (1.45) [1]
Musculoskeletal and connective tissue disorders	**2 (2.90) [2]**	**--**
Myositis	1 (1.45) [1]	--
Rickets	1 (1.45) [1]	--
Injury, poisoning and procedural complications	**1 (1.45) [2]**	**--**
Femur fracture	1 (1.45) [1]	--
Humerus fracture	1 (1.45) [1]	--
Congenital, familial and genetic disorders	**1 (1.45) [1]**	**--**
Hydrocele	1 (1.45) [1]	--
Gastrointestinal disorders	**1 (1.45) [1]**	**--**
Inguinal hernia	1 (1.45) [1]	--
Hepatobiliary disorders	**1 (1.45) [1]**	**--**
Cholestasis	1 (1.45) [1]	--
Investigations	**1 (1.45) [1]**	**--**
SARS-CoV-2 antibody test positive	1 (1.45) [1]	--
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (1.45) [1]**	**--**
Infantile haemangioma	1 (1.45) [1]	--
Skin and subcutaneous tissue disorders	**1 (1.45) [1]**	**--**
Eczema	1 (1.45) [1]	--

[j] N (%), where [N] refers to the number of subjects (prevalence) [number of events], with duplicate counting
Note) Coded using the MedDRA (version 27.1) System Organ Class and Preferred Term

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Incidence status of unexpected adverse events/adverse drug reactions by System Organ Class and Preferred Term (Safety Set)

System Organ Class Preferred Term	Overall (N=69) Unexpected adverse events N (%) [N][j]	Unexpected adverse drug reactions N (%) [N][j]
Overall	**11 (15.94) [25]**	**3 (4.35) [3]**
Nervous system disorders	**4 (5.80) [4]**	**1 (1.45) [1]**
Intraventricular haemorrhage	2 (2.90) [2]	1 (1.45) [1]
Periventricular leukomalacia	2 (2.90) [2]	--
Respiratory, thoracic and mediastinal disorders	**3 (4.35) [3]**	**1 (1.45) [1]**
Bronchopulmonary dysplasia	2 (2.90) [2]	1 (1.45) [1]
Pulmonary hypertension	1 (1.45) [1]	--
General disorders and administration site conditions	**2 (2.90) [3]**	**--**
Catheter site swelling	1 (1.45) [1]	--
Extravasation	1 (1.45) [1]	--
Pyrexia	1 (1.45) [1]	--
Infections and infestations	**2 (2.90) [4]**	**--**
Sepsis	1 (1.45) [2]	--
Bacterial sepsis	1 (1.45) [1]	--
Urinary tract infection	1 (1.45) [1]	
Musculoskeletal and connective tissue disorders	**2 (2.90) [2]**	**--**
Myositis	1 (1.45) [1]	--
Rickets	1 (1.45) [1]	--
Injury, poisoning and procedural complications	**1 (1.45) [2]**	**--**

System Organ Class Preferred Term	Overall (N=69) Unexpected adverse events N (%) [N][j]	Unexpected adverse drug reactions N (%) [N][j]
Femur fracture	1 (1.45) [1]	--
Humerus fracture	1 (1.45) [1]	--
Congenital, familial and genetic disorders	**1 (1.45) [1]**	**--**
Hydrocele	1 (1.45) [1]	--
Eye disorders	**1 (1.45) [1]**	**1 (1.45) [1]**
Vitreous opacities	1 (1.45) [1]	1 (1.45) [1]
Gastrointestinal disorders	**1 (1.45) [1]**	**--**
Inguinal hernia	1 (1.45) [1]	--
Hepatobiliary disorders	**1 (1.45) [1]**	**--**
Cholestasis	1 (1.45) [1]	--
Investigations	**1 (1.45) [1]**	**--**
SARS-CoV-2 antibody test positive	1 (1.45) [1]	--
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (1.45) [1]**	**--**
Infantile haemangioma	1 (1.45) [1]	--
Skin and subcutaneous tissue disorders	**1 (1.45) [1]**	**--**
Eczema	1 (1.45) [1]	--

[j] N (%), where [N] refers to the number of subjects (prevalence) [number of events], with duplicate counting
Note) Coded using the MedDRA (version 27.1) System Organ Class and Preferred Term

All-Cause Mortality

There was no death in this study

Serious Adverse Events

Incidence status of adverse events/adverse drug reactions by System Organ Class and Preferred Term (Safety Set)

System Organ Class Preferred Term	Overall (N=69) Serious adverse events N (%) [N][∫]	 Serious adverse drug reactions N (%) [N][∫]
Overall	**3 (4.35) [3]**	**2 (2.90) [2]**
Gastrointestinal disorders	**1 (1.45) [1]**	**--**
Inguinal hernia	1 (1.45) [1]	--
Nervous system disorders	**1 (1.45) [1]**	**1 (1.45) [1]**
Intraventricular haemorrhage	1 (1.45) [1]	1 (1.45) [1]
Respiratory, thoracic and mediastinal disorders	**1 (1.45) [1]**	**1 (1.45) [1]**
Bronchopulmonary dysplasia	1 (1.45) [1]	1 (1.45) [1]

[∫] N (%), where [N] refers to the number of subjects (prevalence) [number of events], with duplicate counting
Note: Coded using the MedDRA (version 27.1) System Organ Class and Preferred Term

Incidence status of unexpected serious adverse events/adverse drug reactions by System Organ Class and Preferred Term (Safety Set)

System Organ Class Preferred Term	Overall (N=69) Unexpected serious adverse events N (%) [N][∫]	Unexpected serious adverse drug reactions N (%) [N][∫]
Overall	**3 (4.35) [3]**	**2 (2.90) [2]**
Gastrointestinal disorders	**1 (1.45) [1]**	**--**
Inguinal hernia	1 (1.45) [1]	--
Nervous system disorders	**1 (1.45) [1]**	**1 (1.45) [1]**
Intraventricular haemorrhage	1 (1.45) [1]	1 (1.45) [1]
Respiratory, thoracic and mediastinal disorders	**1 (1.45) [1]**	**1 (1.45) [1]**
Bronchopulmonary dysplasia	1 (1.45) [1]	1 (1.45) [1]

[∫] N (%), where [N] refers to the number of subjects (prevalence) [number of events], with duplicate counting
Note: Coded using the MedDRA (version 27.1) System Organ Class and Preferred Term

Other Relevant Findings

Not applicable

Conclusion:

In conclusion, there were no signals suggesting specific safety or effectiveness concerns observed for Lucentis® during this re-examination period.

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Date of Clinical Trial Report

11 April 2025