Report on the Deliberation Results

June 1, 2016
Evaluation and Licensing Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare

Brand Name	Hemangiol Syrup for Pediatric 0.375%
Non-proprietary Name	Propranolol Hydrochloride (JAN*)
Applicant	Maruho Co., Ltd.
Date of Application	September 25, 2015

Results of Deliberation

In its meeting held on May 27, 2016, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 10 years. The drug product is classified as a powerful drug. The product is not classified as a biological or specified biological product.

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

May 16, 2016
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency.

Brand Name	Hemangiol Syrup for Pediatric 0.375%
Non-proprietary Name	Propranolol Hydrochloride
Applicant	Maruho Co., Ltd.
Date of Application	September 25, 2015
Dosage Form/Strength	Oral solution containing 4.28 mg of propranolol hydrochloride (equivalent to 3.75 mg of propranolol) per 1 mL
Application Classification	Prescription drug, (4) Drug with a new indication, (5) Drug in a new dosage form
Items Warranting Special Mention	Orphan drug (Drug Designation No. 319 [*25 yaku*]; Notification No. 1115-7 dated November 15, 2013, issued by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug I

Results of Review

The Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the data submitted demonstrate the efficacy of the product in the treatment of infantile hemangioma and acceptable safety in view of benefits indicated by the data submitted, as shown in Attachment.

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition.

Indication	Infantile hemangioma
Dosage and Administration	The usual dosage is 1 to 3 mg/kg/day of propranolol administered orally in 2 divided doses under non-fasting conditions. The starting dose is 1 mg/kg/day, and the dose is increased in increments of 1 mg/kg at intervals of ≥2 days to 3 mg/kg/day as a maintenance dose. The dose may be adjusted according to the patient's condition.

Condition of Approval	The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

April 1, 2016

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Hemangiol Syrup for Pediatric 0.375%
Non-proprietary Name	Propranolol Hydrochloride
Applicant	Maruho Co., Ltd.
Date of Application	September 25, 2015
Dosage Form/Strength	Oral solution containing 4.28 mg of propranolol hydrochloride (equivalent to 3.75 mg of propranolol) per 1 mL
Proposed Indication	Infantile hemangioma
Proposed Dosage and Administration	The usual starting dose for patients aged ≥5 weeks is 1 mg/kg/day of propranolol, and the dose is increased to 3 mg/kg/day as a maintenance dose. Any daily dose is administered orally in 2 divided doses during or right after feeding.

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List of Abbreviations

Adverse drug reaction	An adverse event for which a causal relationship to the study drug cannot be ruled out
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CUP	Compassionate use program
CYP	Cytochrome P450
DMSO	Dimethyl sulfoxide
EMA	European Medicines Agency
FAS	Full analysis set
FDA	Food and Drug Administration
Guidelines	Clinical Practice Guidelines for Hemangioma and Vascular Malformation 2013 (first edition, March 2013, the Committee of Clinical Practice Guideline for Hemangioma and Vascular Malformation)
Hemangiol	Hemangiol Syrup for Pediatric 0.375%
HemECs	Human IH-derived endothelial cells
HIF	Hypoxia-inducible factor
HPLC	High performance liquid chromatography
IDMC	Independent data monitoring committee
IH	Infantile hemangioma
ITT	Intention to Treat
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MF	Master File
PCR	Polymerase chain reaction
PMDA	Pharmaceuticals and Medical Devices Agency
Propranolol	Propranolol hydrochloride
PSUR	Periodic Safety Update Report
RH	Relative humidity
UV	Ultraviolet absorption spectrum
VEGF	Vascular endothelial growth factor

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Infantile hemangioma (IH) is a benign vascular tumor characterized by the proliferation of vascular endothelial cells that occurs at or shortly after birth. In general, IH develops within the first 4 weeks of life and grows rapidly over the subsequent year. In ≥90% of patients, tumors involute gradually and spontaneously over years by 5 to 7 years of age. However, the clinical course of IH may vary depending on the size and location of lesions. Some lesions affect the vital organs or sensory organs, causing complications such as congestive cardiac failure, airway stenosis, stimulus deprivation amblyopia due to palpebral or orbital lesions, strabismus, astigmatism, external auditory canal atresia due to a parotid lesion, and ulceration with bleeding. IH leading to these conditions should be treated promptly. The incidence of IH in Japanese infants is 0.8% to 1.7%, and approximately 10% of IH affect vital organs or sensory organs (Clinical Practice Guidelines for Hemangioma and Vascular Malformation 2013 [first edition, March 2013, the Committee of Clinical Practice Guidelines for Hemangioma and Vascular Malformation]; hereinafter, the Guidelines).

Therapies including corticosteroids, interferon alfa, and vincristine sulfate have been used to treat patients with IH. However, these attempts failed to produce adequate evidence of efficacy, while concerns about adverse reactions to these drugs and the risk of therapy-related effects on the growth of infants remain (*Dermatol Ther,* 2005;18:151-159; *J Pediatr,* 1998;132:527-530; and others). In Japan, none of these drugs have been approved for the indication of IH. Other treatment options including laser therapy, cryotherapy, and surgery are available depending on the patient's condition. However, there are still issues associated with these procedures because of general anesthesia that is often required in infants and a risk of incomplete removal of hemangiomas.

Hemangiol Syrup for Pediatric 0.375% (Hemangiol) is an oral solution containing Propranolol Hydrochloride (propranolol) as the active ingredient. Propranolol is a non-selective beta-adrenergic receptor blocker, and it has been approved in Japan for essential hypertension, etc. Due to its vasoconstrictive effect and anti-angiogenic effect mediated by the suppression of the expression of angiogenic factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), propranolol is expected to be effective in the treatment of IH, particularly proliferating IH. Published papers in and outside Japan have reported the efficacy of propranolol in the treatment of IH. The Guidelines recommend propranolol as a treatment option for IH. The Japanese Society of Pediatric Hematology/Oncology submitted a request for the development of propranolol to the Study Group on Unapproved and Off-label Drugs of High Medical Need.

The applicant conducted a clinical study in Japanese patients with IH. Based on its claim that the study demonstrated the efficacy and safety of propranolol, the applicant has filed a marketing application for Hemangiol. Propranolol was designated as an orphan drug on November 15, 2013 for the intended indication of "infantile hemangioma" (Drug Designation No. 319 [*25 yaku*]).

Outside Japan, propranolol was approved for the indication of IH in March 2014 in the US and in April 2014 in Europe.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

Propranolol Hydrochloride, the drug substance, is listed in the Japanese Pharmacopoeia. The drug substance registered in the drug master file (DMF) (DMF registration [redacted]) is used for manufacture of the product and [redacted].

2.2 Drug product

2.2.1 Description and composition of the drug product and formulation development

The drug product is an oral solution containing 3.75 mg of propranolol per 1 mL. The excipients contained in the drug product are hydroxyethyl cellulose, saccharin sodium hydrate, [redacted], flavoring agent, citric acid hydrate, and purified water.

2.2.2 Manufacturing process

The drug product is produced through the manufacturing process comprising [redacted], packaging/labeling, testing, and storage. [redacted] was defined as a critical step, and process controls were specified for the step.

2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, description, identification (high performance liquid chromatography [HPLC]/ultraviolet absorption spectrum [UV]), [redacted], purity (related substances [HPLC]), [redacted], and assay (HPLC).

2.2.4 Stability of drug product

The results of stability testing of the drug product are presented in Table 1. The photostability testing was performed, and the drug product was shown to be photolabile.

Table 1. Stability testing of the drug product

Test	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term ([redacted])	3 pilot-scale batches	25°C	60% RH	Brown glass bottle	36 months
Long-term ([redacted])	[redacted] pilot-scale batches				
Accelerated ([redacted])	3 pilot-scale batches	40°C	75% RH		6 months
Accelerated ([redacted])	[redacted] pilot-scale batches				

Based on the above, a shelf-life of 3 years was defined for the drug product when stored at room temperature in a brown glass bottle protected from light.

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substance and the drug product is adequately controlled.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

There are no established animal models to evaluate the effect of propranolol on IH appropriately. For primary pharmacodynamics data, the applicant submitted data from published papers on *in vitro* studies investigating the beta-adrenergic receptor antagonist activity, vasoconstrictive effect, cytostatic effect, antiangiogenic effect, and apoptosis-inducing effect of propranolol. In this section, concentrations of propranolol are expressed as free base unless otherwise specified.

3.1 Primary pharmacodynamics

3.1.1 Beta-adrenergic receptor antagonist activity (CTD 4.2.1.1-2, *J Pharmacol Exp Ther,* 1970;171:52-61 [reference data])

Specimens of the right atrial myocardium, aortic smooth muscle, and gastric smooth muscle of the rabbit were used to investigate the antagonist activity of propranolol on receptor responses to isoproterenol, a non-selective beta-adrenergic receptor agonist. Propranolol produced the parallel shift to the right of the dose-response curves of isoproterenol in all specimens, showing an antagonist activity.

3.1.2 Vasoconstrictive effect (CTD 4.2.1.1-3, *J Pharmacol Exp Ther,* 1982;220:127-132 [reference data])

Propranolol at concentrations of 0.3 to 30 μmol/L was added to specimens of the left anterior descending coronary artery smooth muscle and left circumflex coronary artery smooth muscle of the dog. Both vascular smooth muscle specimens were constricted in a concentration-dependent manner.

3.1.3 Cytostatic effect on HemECs cells (CTD 4.2.1.1-5, *Plast Reconstr Surg,* 2012;130:1012-1021 [reference data])

Human hemangioma-derived endothelial cells (HemECs) were incubated with propranolol at concentrations of 50 and 100 μmol/L or vehicle (water) for 4 days to examine cell growth. Cell proliferation was significantly inhibited by propranolol (50 and 100 μmol/L) as compared with vehicle.

3.1.4 Inhibitory effects on lumen formation of HemECs and angiogenic factor expression (CTD 4.2.1.1-6, *Ann Surg,* 2012;256:146-156 [reference data])

HemECs were incubated with propranolol at concentrations of 0 to 300 μmol/L for 18 hours, and the length of the capillary-like lumen was measured. Propranolol inhibited lumen formation in a concentration-dependent manner.

HemECs were incubated with propranolol at concentrations of 0 to 300 μmol/L for 48 or 96 hours. Propranolol decreased the expression of vascular endothelial growth factor (VEGF)-A, VEGF-R1 and

VEGF-R2, and hypoxia-inducible factor (HIF)-1α[1)] in a concentration-dependent manner at both time points.

3.1.5 Apoptosis-inducing effect on HemECs (CTD 4.2.1.1-8, *J Pediatr Surg,* 2012;47:2216-2223 [reference data])

HemECs were incubated with propranolol at concentrations of 25, 50, and 100 μmol/L or vehicle (0.1% dimethyl sulfoxide [DMSO]) for 24 hours, and the proportion of apoptotic cells was measured by flow cytometry. The proportion of apoptotic cells increased in a concentration-dependent manner.

HemECs were incubated with propranolol at concentrations of 25, 50, and 100 μmol/L or vehicle (0.1% DMSO) for 24 hours to investigate the effect of propranolol on caspase activity. Propranolol (100 μmol/L) induced activation of caspase-9 and -3.

HemECs were incubated with propranolol at a concentration of 100 μmol/L or vehicle (0.1% DMSO) for 24 hours. Then, the expression levels of pro-apoptotic genes (p53 and Bax) and anti-apoptotic genes (Bcl-2 and Bcl-xL) were determined by real-time polymerase chain reaction (PCR). Propranolol (100 μmol/L) significantly increased the expression levels of p53 and Bax and significantly decreased that of Bcl-xL, as compared with vehicle. No changes in the expression level of Bcl-2 were reported in this literature. However, there is another article reporting a decrease in the expression level of Bcl-2 at 48 hours after addition of propranolol (*Oncol Rep,* 2015;33:3099-3107). The applicant therefore explained that the incubation of 24 hours may not have been long enough to detect a change in Bcl-2 expression.

3.R Outline of the review conducted by PMDA

The applicant's explanation on the pharmacological action of propranolol:

IH is a benign vascular tumor resulting from tumorigenesis of vascular endothelial cells. Beta-1 and beta-2 adrenergic receptors are expressed in vascular endothelial cells of IH lesions (*Exp Ther Med,* 2012;4:594-604). During the proliferative phase, activation of the receptors promotes vascular endothelial cell proliferation and enhancement of angiogenesis, thereby forming a mass of tissue (the Guidelines).

Propranolol is expected to have efficacy in the treatment of proliferating IH by inhibiting the activation of beta adrenergic receptors through the following mechanisms of actions:

- A vasoconstriction effect that decreases blood flow to IH lesions
- Inhibition of vascular endothelial cell proliferation and angiogenesis by decreasing the expression of VEGF and HIF-lα
- An apoptosis-inducing effect on vascular endothelial cells of IH lesions

1) The increased expression of HIF-1α in the proliferative phase of IH contributes to an increase in the production of angiogenic growth factors (*J Hematol Oncol*, 2014;7:7-13).

PMDA's view:

The submitted primary pharmacodynamic data and the above discussion of the applicant demonstrate the promising efficacy of propranolol in the treatment of proliferating IH.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Because propranolol is an approved active ingredient, its non-clinical pharmacokinetics have already been evaluated. Thus no data relating to non-clinical pharmacokinetic studies were submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

Because propranolol is intended for use in infants, the evaluation data submitted were produced from a toxicity study in juvenile rats.

5.1 Toxicity study in juvenile rats (CTD 4.2.3.5.4-1, Study 39331RSR)

Male and female rats aged 4 days received propranolol 10, 20, or 40 mg/kg/day (as free base) or vehicle (reverse osmosis deionized water) orally for 18 days. No propranolol-related changes were observed in the development of organs or their functions, fertility, or cardiac function. Therefore, no observed adverse effect level (NOAEL) for these indices was determined to be 40 mg/kg/day. Meanwhile, 1 of 16 males in the 40 mg/kg/day group was sacrificed moribund due to emaciation, hypothermia, and dehydration. According to the applicant, whether these changes were related to propranolol was unknown. The NOAEL for general toxicity was determined to be 20 mg/kg/day.

5.R Outline of the review conducted by PMDA

PMDA finds no toxicologically significant problems in the results of the toxicity study in juvenile rats.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

In this section, the dose of propranolol are expressed as free base unless otherwise specified.

6.1 Summary of biopharmaceutic studies and associated analytical methods

Plasma concentrations of propranolol and its metabolite 4-OH propranolol were determined by liquid chromatography/tandem mass spectrometry with a lower limit of quantification (LLOQ) of 0.50 ng/mL.

6.2 Clinical pharmacology

6.2.1 Foreign phase I study (CTD 5.3.3.2-1, Study V00400SB102, [redacted] to [redacted])

A multicenter open-label study was conducted at 4 centers in foreign countries to investigate primarily the pharmacokinetics and safety of propranolol in patients with proliferating IH requiring systemic therapy (e.g., function-threatening or large facial IH) (target sample size, 20 subjects [10 subjects aged 35 to 90 days in Group 1 and 10 subjects aged 91 to 150 days in Group 2]).

Propranolol was administered orally for 12 weeks, at 1 mg/kg/day from Day 1 to Day 6, 2 mg/kg/day from Day 7 to Day 13, and 3 mg/kg/day from Day 14 onward (all in 2 divided doses).

The pharmacokinetic parameters of propranolol were measured pre-dose (trough time point) on Days 7 and 14 during the dose titration period in both Groups 1 and 2. Further measurement was performed pre-dose on Day 28 in Group 1, and pre-dose and at 1, 2, 4, 6, and 9 hours post-dose on Day 84 in Group 2.

A total of 23 subjects (10 in Group 1 and 13 in Group 2) received the study drug. Of these, 4 subjects were excluded from the pharmacokinetic analysis because 2 subjects in Group 2 failed to undergo blood sampling as per protocol, and 3 subjects (2 in Group 1 and 1 in Group 2) failed to receive the study drug at pre-specified intervals before blood sampling (one subject was counted twice). The remaining 19 subjects were included in the pharmacokinetic analysis population. All 23 subjects were included in the safety and efficacy analysis populations.

Table 2 shows the plasma (trough) concentrations of propranolol at each dose level during the dose titration period. Because some subjects had plasma trough concentrations of 4-OH propranolol below the LLOQ, no median, maximum, or minimum plasma levels of 4-OH propranolol were calculated. Plasma concentrations of 4-OH propranolol were quantifiable in 2 subjects (0.7 and 0.8 ng/mL) in Group 1 at 1 mg/kg/day, 2 subjects (1.3 and 1.4 ng/mL) in Group 1 at 2 mg/kg/day, 5 subjects (0.7-2.1 ng/mL) in Group 1 at 3 mg/kg/day, and 2 subjects (0.5 and 0.6 ng/mL) in Group 2 at 3 mg/kg/day.

Table 2. Plasma trough concentrations of propranolol at each dose

Dose	Treatment group (Day of measurement)	N	Plasma concentration (ng/mL)
1 mg/kg/day	Group 1 (Day 7)	8	4.6 [1.2, 12.5]
	Group 2 (Day 7)	10	3.7 [1.1, 29.9]
2 mg/kg/day	Group 1 (Day 14)	8	9.4 [4.1, 15.8]
	Group 2 (Day 14)	8	6.8 [2.3, 25.5]
3 mg/kg/day	Group 1 (Day 28)	8	22.4 [7.3, 36.8]
	Group 2 (Day 84)	11	10.1 [4.4, 47.4]

Median [minimum, maximum]

The plasma pharmacokinetic parameters of propranolol and 4-OH propranolol are shown in Table 3.

Table 3. Plasma pharmacokinetic parameters of propranolol and 4-OH propranolol

Propranolol					
Dose	**Treatment group (Day of measurement)**	**N**	**C_{max} (ng/mL)**	**AUC_{τ} (h•ng/mL)**	**t_{max} (h)**
3 mg/kg/day	**Group 1 (Day 28)**	**8**	**74 [48, 119]**	**555 [360, 804]**	**2.0 [1.0, 9.0]**
	Group 2 (Day 84)	**11**	**88 [21, 448]**	**438 [116, 1193]**	**2.0 [1.0, 4.0]**
4-OH propranolol					
Dose	**Treatment group (Day of measurement)**	**N**	**C_{max} (ng/mL)**	**AUC_{9h} (h•ng/mL)**	**t_{max} (h)**
3 mg/kg/day	**Group 1 (Day 28)**	**8**	**5.7 [2.9, 14.4]**	**25.2 [16.8, 53.8]**	**1.1 [1.0, 2.0]**
	Group 2 (Day 84)	**10**	**5.0 [0.9, 10.9]**	**19.4 [5.3, 23.8]**	**2.0 [1.0, 4.0]**

τ = 12 hours; median [min, max]

Safety results showed that the incidence of adverse events was 80.0% (8 of 10 subjects) in Group 1 and 92.3% (12 of 13 subjects) in Group 2.The incidence of adverse drug reactions was 70.0% (7 of 10 subjects) in Group 1 and 61.5% (8 of 13 subjects) in Group 2. The adverse events occurring in ≥2 subjects in either group are summarized in Table 4. The adverse drug reactions occurring in ≥2 subjects in either group were diarrhoea (0% in Group 1 versus 15.4% [2 of 13 subjects] in Group 2), nightmare (30.0% [3 of 10 subjects] vs. 30.8% [4 of 13 subjects]), and peripheral coldness (30.0% [3 of 10 subjects] vs. 7.7% [1 of 13 subjects]). While serious adverse events (crying, pallor, and otitis media acute) occurred in 1 subject, a causal relationship with the study drug was ruled out for the events.

Table 4. Adverse events occurring in ≥2 subjects in either group

	Group 1 (N = 10)	**Group 2 (N = 13)**
Any adverse event	**80.0% (8)**	**92.3% (12)**
Nasopharyngitis	**30.0% (3)**	**23.1% (3)**
Bronchitis	**10.0% (1)**	**15.4% (2)**
Diarrhoea	**20.0% (2)**	**38.5% (5)**
Toothache	**0% (0)**	**23.1% (3)**
Nightmare	**30.0% (3)**	**30.8% (4)**
Pyrexia	**30.0% (3)**	**30.8% (4)**
Peripheral coldness	**30.0% (3)**	**7.7% (1)**
Conjunctivitis	**30.0% (3)**	**7.7% (1)**
Cough	**10.0% (1)**	**23.1% (3)**
Decreased appetite	**20.0% (2)**	**0% (0)**

MedDRA/J ver.13.0
% (n)

6.2.2 Japanese phase III study (CTD 5.3.5.2-1, Study M703101-01, [redacted] to [redacted])

A multicenter, open-label, uncontrolled study was conducted at 13 centers in Japan to investigate the efficacy, safety, and pharmacokinetics of propranolol in patients with IH. For the details of the study design and the efficacy and safety results, see "7.1 Japanese phase III study."

Pharmacokinetic parameters were measured at 1, 2, 3, 4, or 6 hours post-dose (assigned at enrollment) in the morning on Day 2 and 2 hours post-dose in the morning at Week 12. A total of 32 subjects received the study drug and all the subjects treated were included in the pharmacokinetic analysis population.

The plasma pharmacokinetic parameters of propranolol and 4-OH propranolol are shown in Table 5.

Table 5. Plasma concentrations of propranolol and 4-OH propranolol

Propranolol				
Dose	**Measurement day**		**n**	**Plasma concentration (ng/mL)**
3 mg/kg/day	**3 mg/kg/day Day 2**	**1 h post-dose**	**7**	**72.3 [13.2, 161.0]**
		3 h post-dose	**6**	**171.5 [45.9, 299.0]**
		6 h post-dose	**6**	**104.9 [27.2, 168.0]**
	Week 12	**2 h post-dose**	**31 [a)]**	**67.4 [15.4, 177.0]**
4-OH propranolol				
Dose	**Measurement day**		**n**	**Plasma concentration (ng/mL)**
3 mg/kg/day	**3 mg/kg/day Day 2**	**1 h post-dose**	**7**	**6.9 [2.5, 7.8]**
		3 h post-dose	**6**	**3.9 [2.3, 9.8]**
		6 h post-dose	**6**	**2.3 [1.3, 3.8]**
	Week 12	**2 h post-dose**	**31 [a)]**	**5.1 [1.2, 11.6]**

Median [min, max]

[a)] One subject was excluded because of not undergoing blood sampling for PK measurement at Week 12.

6.R Outline of the review conducted by PMDA

The applicant's explanation on the pharmacokinetics of propranolol in Japanese and non-Japanese patients with IH:

CYP2D6, CYP1A2, and CYP2C19 are involved in the metabolism of propranolol, and CYP2D6 and CYP1A2 contribute to approximately 80% of propranolol metabolism (*Drug Met Disp,* 1985;13:204-209). While CYP2D6 is known to be polymorphic, no noteworthy difference in changes in plasma propranolol concentrations was observed among the polymorphic variants of CYP2D6 (*Pharmacotherapy,* 1997;17:1305-1310).

Plasma concentrations of propranolol and 4-OH propranolol in patients treated with propranolol 3 mg/kg/day in the Japanese phase III study and the foreign phase I study were compared by age group. The results are shown in Table 6. The data used in the comparison represented the plasma concentrations at 2 hours post-dose at Week 12 in any age group for the Japanese phase III study, and those at 2 hours post-dose at Week 4 in patients aged 35 to 90 days and at Week 12 in patients aged 91 to 150 days for the foreign phase I study.

Given the extent of variability in the results, the values shown in Table 6 indicate similarity in the plasma concentrations of propranolol and 4-OH propranolol between Japanese and non-Japanese patients with IH.

Table 6. Plasma concentrations of propranolol and 4-OH propranolol

Dose	Age group	35-90 days old		91-150 days old	
	Study	Foreign phase I study	Japanese phase III study	Foreign phase I study	Japanese phase III study
	N	8	11	11	20
3 mg/kg/day	Propranolol				
	Plasma concentration (ng/mL)	62 [34, 119]	65 [15, 146]	74 [21, 125]	86 [27, 177]
	4-OH propranolol				
	Plasma concentration (ng/mL)	5.0 [1.8, 8.8]	3.5 [1.2, 9.0]	3.9 [0.8, 6.7]	5.5 [2.1, 11.6]

Median [min, max]

PMDA's view:

Based on the above explanation of the applicant, there is currently no noteworthy difference in the pharmacokinetics of propranolol between Japanese and non-Japanese patients with IH.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

7.1 Japanese phase III study (CTD 5.3.5.2-1, Study M703101-01, [redacted] to [redacted])

A multicenter, open-label, uncontrolled study was conducted at 13 centers in Japan to investigate the efficacy, safety, and pharmacokinetics of propranolol in patients with IH [see Table 7] (target sample size, 30 subjects).

Table 7. Main inclusion and exclusion criteria

Main inclusion criteria
Aged 35 to 150 days at enrollment
A proliferating IH with largest diameter of ≥1.5 cm
Main exclusion criteria
Congenital hemangioma
Life-threatening IH
Kasabach-Merritt syndrome
Bronchial asthma and/or bronchospasm
Hypoglycaemia (<40 mg/dL or at risk)
Hypotension (systolic pressure <50 mmHg, diastolic pressure <30 mmHg)
Bradycardia (<80 bpm)
Uncontrolled heart failure, etc.

Propranolol was administered orally twice daily for 24 weeks in titrated doses. Subjects were hospitalized to start propranolol at a dose of 1 mg/kg/day. While tolerability was checked by the investigator, the dose was titrated up every 2 days in increments of 1 mg/kg/day to 2 mg/kg/day on Day 3 and to 3 mg/kg/day on Day 5. Subjects stayed hospitalized until the day after dose increase to 3 mg/kg/day. The dose was not increased if the investigator deemed it inappropriate. Patients who could not tolerate an increased dose received the previous dose throughout the rest of the study. After the

completion of study treatment, patients were followed at Weeks 24, 28, 32, and 36 to evaluate the post-treatment course and treatment response.

All 32 subjects enrolled in the study were included in the full analysis set (FAS). The FAS was used for the efficacy and safety analyses. No subjects discontinued the study. The 32 subjects were all treated with propranolol at the maintenance dose of 3 mg/kg/day after the specified titration period.

The primary efficacy endpoint was the treatment success rate at Week 24 compared to baseline. Treatment success rates were determined based on the assessment of photographs of the target IH lesion at Week 24 compared to baseline (Day 1). Each subject was assessed either as "success (complete or nearly complete resolution)" or "failure." "Nearly complete resolution" was defined as a minimal degree of telangiectasia, erythema, skin thickening, soft tissue swelling, and/or distortion of anatomic landmarks.

The treatment success rate [95% confidence interval] at Week 24 compared to baseline was 78.1% (25 of 32 subjects) [60.0%-90.7%]. The lower limit of the 95% confidence interval was higher than the pre-specified threshold for treatment success (12%).

Safety results showed that the incidence of adverse events and adverse drug reactions was 96.9% (31 of 32 subjects) and 31.3% (10 of 32 subjects), respectively. The adverse events occurring in ≥2 subjects are shown in Table 8. Of these, adverse drug reactions were diarrhoea in 4 subjects, and alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, blood pressure diastolic decreased, and blood pressure systolic decreased in 2 subjects each.

Table 8. Adverse events occurring in ≥2 subjects

	Propranolol group (N = 32)		Propranolol group (N = 32)
Any adverse event	**96.9% (31)**	**Rhinorrhoea**	**9.4% (3)**
Nasopharyngitis	**31.3% (10)**	**Dry skin**	**9.4% (3)**
Diarrhoea	**28.1% (9)**	**Erythema**	**9.4% (3)**
Eczema infantile	**25.0% (8)**	**Constipation**	**6.3% (2)**
Pyrexia	**18.8% (6)**	**ALT increased**	**6.3% (2)**
Upper respiratory tract inflammation	**18.8% (6)**	**AST increased**	**6.3% (2)**
Eczema	**12.5% (4)**	**Blood pressure diastolic decreased**	**6.3% (2)**
Conjunctivitis	**9.4% (3)**	**Blood pressure systolic decreased**	**6.3% (2)**
Excoriation	**9.4% (3)**	**Urticaria**	**6.3% (2)**

MedDRA/J ver.18.0;
% (n)

There were no deaths, serious adverse events, or adverse events leading to study discontinuation.

7.2 Foreign phase II/III study (CTD 5.3.5.1-1 and 5.3.5.1-2, Study V00400SB201, February 2010 to November 2013)

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study was conducted at 56 centers in 16 countries to investigate the dose, efficacy, and safety of propranolol in patients with IH [see Table 9] (target sample size, up to 450 subjects).

Table 9. Main inclusion and exclusion criteria

Main inclusion criteria
Aged 35 to 150 days at enrollment
Presence of a proliferating IH requiring systemic therapy with largest diameter of ≥1.5 cm
Main exclusion criteria
Congenital IH
One or more of the following types of IH:
Life threatening IH
Function-threatening IH (e.g., those causing impairment of vision or respiratory impairment)
Ulcerated IH with pain and lack of response to simple wound care measures
The patient was born prematurely and had not yet reached his/her term-equivalent age
Kasabach-Merritt syndrome
Bronchial asthma and/or bronchospasm
Hypoglycaemia (<40 mg/dL or at risk)
Hypotension (systolic <50 mmHg, diastolic <30 mmHg)
Bradycardia (<80 bpm)
Uncontrolled heart failure, etc.

Either placebo or propranolol was administered orally twice daily for 24 weeks as per the dosage regimens shown in Table 10. The treatment period was followed by a 72-week follow-up period (until Week 96).

Table 10. Dosage regimens

Placebo group: Placebo for 24 weeks
1 mg 3M group: Propranolol 1 mg/kg/day for 3 months followed by placebo from Month 4 to Month 6
1 mg 6M group: Propranolol 1 mg/kg/day for 6 months
3 mg 3M group: Propranolol 3 mg/kg/day for 3 months followed by placebo from Month 4 to Month 6
3 mg 6M group: Propranolol 3 mg/kg/day for 6 months
*** In the 3 mg 3M group and the 3 mg 6 M group, the starting dose of 1 mg/kg/day was administered for the first 6 days, 2 mg/kg/day from Day 7 to Day 13, and 3 mg/kg/day on and after Day 14.**
(Dummy titration was used for patients assigned to the placebo group or propranolol 1 mg groups)

This study was a 2-stage, adaptive design study.

In Stage 1, subjects were randomized to the placebo, 1 mg 3 months (3M), 1 mg 6 months (6M), 3 mg 3M, or 3 mg 6M group at a ratio of 1:2:2:2:2. An interim analysis was planned to be performed when 40 subjects in the propranolol groups and 20 subjects in the placebo group had completed the 24-week study treatment or discontinued study treatment prematurely.

The Independent Data Monitoring Committee (IDMC) consisting of 3 specialists (a pediatric dermatologist specializing in IH, a pediatric cardiovascular specialist, and a statistician) performed an

unblinded interim analysis. Based on the interim analysis, the IDMC had to select one of the following 3 preplanned options to make a decision on the study design and recommend it to the sponsor:

(a) The study should be discontinued due to safety concerns or a lack of efficacy.
(b) Of the 4 dosing regimens of propranolol, 1 or 2 best treatment regimens with no safety concerns are selected, and the study is continued only with the selected propranolol regimen(s) and placebo.
(c) If the power to demonstrate the superiority of the selected propranolol regimen to placebo is lower than 80%, the target sample size should be re-specified (increased).

If Option (b) was recommended by the IDMC after the interim analysis, subjects were to be randomized to receive placebo or the selected propranolol regimen(s) (based on the results of the interim analysis) at a ratio of 1:2 in Stage 2. Enrollment of subjects were to be continued until the placebo group had 50 randomized subjects including those in Stage 1 and the selected propranolol regimen group(s) had 100 subjects per group including those in Stage 1.

In Stage 1, of 190 subjects randomized, 188 subjects received the study drug (25 in the placebo group, 41 in the 1 mg 3M group, 40 in the 1 mg 6M group, 39 in the 3 mg 3M group, and 43 in the 3 mg 6M group). In the interim analysis, the 188 subjects treated were included in the intent-to-treat (ITT) population, which was defined as the efficacy analysis population and the safety analysis population for the interim analysis. The treatment success rate (proportion of subjects with IH that was centrally assessed as "complete or nearly complete resolution"[2)]) at Week 24 compared to baseline is shown in Table 11.

Table 11. Interim analysis results: treatment success rate at Week 24 (ITT population)

	Placebo (N = 25)	1 mg 3M (N = 41)	1 mg 6M (N = 40)	3 mg 3M (N = 39)	3 mg 6M (N = 43)
Treatment success rate (n)	8.0% (2)	9.8% (4)	37.5% (15)	7.7% (3)	62.8% (27)

The interim analysis revealed the highest treatment success rate in the propranolol 3 mg 6M group with no notable safety concerns. The IDMC concluded that the results were applicable to Option (b) and advised the sponsor to continue the study only with the propranolol 3 mg 6M regimen and placebo. Meanwhile, because the enrollment of subjects for randomization to the placebo group and the 4 propranolol groups was continued during the analysis by the IDMC, the number of subjects enrolled had reached the target sample size by the time the IDMC came to the decision. The enrollment was then terminated.

In Stages 1 and 2, of 460 subjects randomized, 456 subjects received the study drug (55 in the placebo group, 98 in the 1 mg 3M group, 102 in the 1 mg 6M group, 100 in the 3 mg 3M group, and 101 in the 3 mg 6M group). In the final analysis of pooled data of Stages 1 and 2, the 456 subjects were included in the ITT population, which was defined as the efficacy analysis population and the safety analysis

2) The definition of "nearly complete resolution" was the same as that in the Japanese study.

population for the final analysis. A total of 133 subjects[3] (36 in the placebo group, 35 in the 1 mg 3M group, 14 in the 1 mg 6M group, 35 in the 3 mg 3M group, and 13 in the 3 mg 6M group) discontinued study treatment.

Table 12 shows the treatment success rate at Week 24 compared to baseline (the primary endpoint) in the placebo group and the propranolol 3 mg 6M group, demonstrating the superiority of the propranolol 3 mg 6M regimen to placebo (one-sided significance level of 0.5%; combination test by Posch et al. [*Stat Med*, 2005;24:3697-3714]).

Table 12. Final analysis results: treatment success rate at Week 24 (ITT population)

	Placebo (N = 55)	**3 mg 6M (N = 101)**
Treatment success rate (n)	**3.6% (2)**	**60.4% (61)**
Adjusted *P*-value (one-sided)[a]	**< 0.0001**	

[a] Combination test by Posch et al. (*Stat Med*, 2005;24:3697-3714)

Safety results showed that the incidence of adverse events was 72.7% (40 of 55 subjects) in the placebo group, 90.8% (89 of 98 subjects) in the 1 mg 3M group, 88.2% (90 of 102 subjects) in the 1 mg 6M group, 91.0% (91 of 100 subjects) in the 3 mg 3M group, and 95.0% (96 of 101 subjects) in the 3 mg 6M group. The incidence of adverse drug reactions was 29.1% (16 of 55 subjects) in the placebo group, 44.9% (44 of 98 subjects) in the 1 mg 3M group, 32.4% (33 of 102 subjects) in the 1 mg 6M group, 35.0% (35 of 100 subjects) in the 3 mg 3M group, and 34.7% (35 of 101 subjects) in the 3 mg 6M group. The adverse events and adverse drug reactions occurring in ≥5.0% of subjects in any group are shown in Table 13 and Table 14, respectively.

[3] Main reasons for discontinuation (some subjects had more than 1 reason): insufficient efficacy in 103 subjects (32 in the placebo group, 30 in the 1 mg 3M group, 7 in the 1 mg 6M group, 25 in the 3 mg 3M group, and 9 in the 3 mg 6M group); request from the parent in 37 subjects (7 in the placebo group, 9 in the 1 mg 3 M group, 5 in the 1 mg 6M group, 12 in the 3 mg 3M group, and 4 in the 3 mg 6M group); safety reasons unrelated to study treatment in 8 subjects (2 in the placebo group, 1 in the 1 mg 3M group, 1 in the 1 mg 6M group, 3 in the 3 mg 3M group, and 1 in the 3 mg 6M group)

Table 13. Adverse events occurring in ≥5.0% of subjects in any group

Treatment group	Placebo (N = 55)	1 mg 3M (N = 98)	1 mg 6M (N = 102)	3 mg 3M (N = 100)	3 mg 6M (N = 101)
Mean treatment duration[a)]	82.6 days	142.7 days	156.9 days	146.6 days	161.0 days
Any adverse event	72.7% (40)	90.8% (89)	88.2% (90)	91.0% (91)	95.0% (96)
Nasopharyngitis	18.2% (10)	29.6% (29)	16.7% (17)	32.0% (32)	33.7% (34)
Diarrhoea	7.3% (4)	16.3% (16)	13.7% (14)	16.0% (16)	27.7% (28)
Pyrexia	9.1% (5)	20.4% (20)	19.6% (20)	22.0% (22)	26.7% (27)
Teething	10.9% (6)	17.3% (17)	21.6% (22)	15.0% (15)	20.8% (21)
Bronchitis	1.8% (1)	5.1% (5)	7.8% (8)	11.0% (11)	16.8% (17)
Upper respiratory tract infection	7.3% (4)	6.1% (6)	12.7% (13)	19.0% (19)	13.9% (14)
Vomiting	5.5% (3)	13.3% (13)	11.8% (12)	10.0% (10)	12.9% (13)
Cough	7.3% (4)	14.3% (14)	14.7% (15)	16.0% (16)	11.9% (12)
Gastroenteritis	3.6% (2)	2.0% (2)	5.9% (6)	4.0% (4)	10.9% (11)
Peripheral coldness	1.8% (1)	8.2% (8)	7.8% (8)	1.0% (1)	9.9% (10)
Toothache	3.6% (2)	5.1% (5)	2.0% (2)	7.0% (7)	8.9% (9)
Bronchiolitis	5.5% (3)	6.1% (6)	6.9% (7)	6.0% (6)	8.9% (9)
Dermatitis diaper	3.6% (2)	4.1% (4)	4.9% (5)	4.0% (4)	8.9% (9)
Vaccination complication	3.6% (2)	6.1% (6)	8.8% (9)	6.0% (6)	7.9% (8)
Conjunctivitis	3.6% (2)	4.1% (4)	7.8% (8)	2.0% (2)	7.9% (8)
Sleep disorder	1.8% (1)	12.2% (12)	4.9% (5)	1.0% (1)	6.9% (7)
Middle insomnia	5.5% (3)	6.1% (6)	3.9% (4)	7.0% (7)	5.0% (5)
Rash	1.8% (1)	3.1% (3)	2.9% (3)	3.0% (3)	5.0% (5)
Nightmare	1.8% (1)	3.1% (3)	2.0% (2)	3.0% (3)	5.0% (5)
Constipation	1.8% (1)	9.2% (9)	5.9% (6)	9.0% (9)	4.0% (4)
Ear infection	0% (0)	7.1% (7)	3.9% (4)	7.0% (7)	4.0% (4)
Rhinitis	9.1% (5)	10.2% (10)	11.8% (12)	5.0% (5)	4.0% (4)
Insomnia	5.5% (3)	2.0% (2)	1.0% (1)	2.0% (2)	4.0% (4)
Rhinorrhoea	3.6% (2)	3.1% (3)	2.9% (3)	8.0% (8)	3.0% (3)
Condition aggravated	3.6% (2)	3.1% (3)	1.0% (1)	5.0% (5)	2.0% (2)
Gingival pain	1.8% (1)	3.1% (3)	0% (0)	5.0% (5)	2.0% (2)
Irritability	5.5% (3)	5.1% (5)	5.9% (6)	1.0% (1)	2.0% (2)
Decreased appetite	1.8% (1)	4.1% (4)	1.0% (1)	5.0% (5)	1.0% (1)
Eczema	1.8% (1)	8.2% (8)	3.9% (4)	2.0% (2)	1.0% (1)
Somnolence	1.8% (1)	6.1% (6)	3.9% (4)	1.0% (1)	1.0% (1)

MedDRA/J ver.13.1;
% (n)
[a)] The treatment duration for the 1 mg 3M and 3 mg 3M groups include treatment with placebo from Month 4 to Month 6.

Table 14. Adverse drug reactions occurring in ≥5.0% of subjects in any group

Treatment group	Placebo (N = 55)	1 mg 3M (N = 98)	1 mg 6M (N = 102)	3 mg 3M (N = 100)	3 mg 6M (N = 101)
Mean treatment duration[a)]	82.6 days	142.7 days	156.9 days	146.6 days	161.0 days
Any adverse drug reaction	29.1% (5)	44.9% (44)	32.4% (33)	35.0% (35)	34.7% (35)
Peripheral coldness	0% (0)	8.2% (8)	7.8% (8)	1.0% (1)	8.9% (9)
Diarrhoea	3.6% (2)	5.1% (5)	4.9% (5)	4.0% (4)	7.9% (8)
Sleep disorder	1.8% (1)	10.2% (10)	2.0% (2)	1.0% (1)	6.9% (7)
Nightmare	1.8% (1)	3.1% (3)	2.0% (2)	3.0% (3)	5.0% (5)
Middle insomnia	5.5% (3)	5.1% (5)	3.9% (4)	7.0% (7)	4.0% (4)
Insomnia	5.5% (3)	2.0% (2)	1.0% (1)	1.0% (1)	3.0% (3)
Somnolence	0% (0)	5.1% (5)	2.9% (3)	1.0% (1)	1.0% (1)

MedDRA/J ver.13.1;
% (n)
[a)] The treatment duration for the 1 mg 3M and 3 mg 3M groups include treatment with placebo from Month 4 to Month 6.

There were no deaths in the study. The incidence of serious adverse events was 5.5% (3 of 55 subjects) in the placebo group, 5.1% (5 of 98 subjects) in the 1 mg 3M group, 2.9% (3 of 102 subjects) in the 1 mg 6M group, 9.0% (9 of 100 subjects) in the 3 mg 3M group, and 5.9% (6 of 101 subjects) in the

3 mg 6M group. Serious adverse drug reactions occurred in 1 subject (condition aggravated) in the placebo group, 1 subject (atrioventricular block second degree) in the 1 mg 3M group, and 3 subjects (condition aggravated, bradycardia, and bronchitis in 1 subject each) in the 3 mg 3M group. The outcomes of all these serious adverse drug reactions were "resolved." The incidence of adverse events leading to the discontinuation of study treatment was 10.9% (6 of 55 subjects) in the placebo group, 4.1% (4 of 98 subjects) in the 1 mg 3M group, 2.0% (2 of 102 subjects) in the 1 mg 6M group, 7.0% (7 of 100 subjects) in the 3 mg 3M group, and 3.0% (3 of 101 subjects) in the 3 mg 6M group.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical data package

The Japanese phase III study was conducted as an open-label uncontrolled study. The clinical data package consisted of data from this study and the foreign phase II/III study.

The applicant's explanation of the clinical data package:

Due to the rareness of IH, propranolol has been designated as an orphan drug for the indication of IH in the US and Europe. In Japan, the incidence of IH is 0.8% to 1.7% (the Guidelines) and is even lower than that in the US or Europe. Given that the Japanese population aged <1 year was 1.04 million when the clinical study was being planned (Ministry of Internal Affairs and Communications Statistics Bureau, Population Estimates, Table 1, October 1, 2012), an estimated 8300 to 17,700 Japanese infants had proliferating IH. According to the literature, 85% to 90% of IH regress spontaneously, leaving only 5% to 10% requiring treatment (*Eur J Pediatr*, 2015;174:855-865). Considering that the watchful waiting-approach is taken for many cases of IH with no aggressive medical intervention, the number of patients requiring treatment with propranolol is even more limited.

A placebo-controlled study involving infants was expected to have difficulty in obtaining informed consent, for the following reasons: (1) several data on the efficacy of propranolol in the treatment of IH are available from publications in and outside Japan (e.g., *Pediatrics*, 2011;128:e259-e266; *The Journal of Japan Pediatric Society*, 2012;116:1351-1356); (2) propranolol had already been used off-label in Japan; and (3) the Japanese phase III study would include high-risk patients who were ineligible for the foreign phase II/III study.

Meanwhile, the foreign phase II/III study was a placebo-controlled study and investigated the optimal dose, efficacy, and safety of propranolol in patients with IH. Therefore, the applicant examined whether the results of this study could be used for regulatory submission. Because the Japanese Guidelines follow the International Society for the Study of Vascular Anomalies (ISSVA) Classification, there are no differences between Japan and foreign countries in diagnostic criteria in terms of extrinsic ethnic factors. Apart from propranolol being approved for the indication of IH in the US and Europe, other available therapies for IH, such as corticosteroid and laser therapies, are similar in foreign countries and Japan. The foreign phase II/III study employed a photograph-based efficacy assessment by a third party, and use of the same assessment method in the Japanese phase III study would allow for comparison of the

2 studies. In terms of intrinsic ethnic factors, CYP2D6 and other genes involved in the metabolism of propranolol are known to be polymorphic. However, there were no marked differences in plasma concentrations of propranolol and its metabolite 4-OH propranolol between Japanese and non-Japanese infants receiving the oral dose of propranolol 3 mg/kg/day [see "6.R Outline of the review conducted by PMDA"], indicating the practicability of the inclusion of the results of the foreign phase II/III study in the clinical data package.

Based on the above, the Japanese phase III study was conducted as an open-label uncontrolled study and demonstrated no marked differences in the efficacy and safety profiles of propranolol between the study and the foreign phase II/III study. Therefore, this application has been filed using the clinical data package consisting of the data from these 2 studies.

PMDA's view:
Because of the small number of patients with IH and their treatment environment in Japan, and based on the applicant's explanation on the intrinsic and extrinsic ethnic factors, there are no particular problems with the Japanese phase III study designed as an open-label uncontrolled study and the clinical data package comprising the data from both the Japanese phase III study and the foreign phase II/III study.

7.R.2 Efficacy

Based on the discussions in Sections 7.R.2.1 through 7.R.2.5, PMDA considers that the Japanese phase III study and the foreign phase II/III study demonstrated the efficacy of propranolol in patients with IH.

The decision on the efficacy of propranolol will be finalized, taking into account the comments made in the Expert Discussion.

7.R.2.1 Primary endpoint

The applicant's explanation on the primary endpoint of the Japanese phase III study and the foreign phase II/III study:
In both studies, treatment outcomes were judged based on the centralized photograph-based assessment, either as success (complete or nearly complete resolution) or failure. "Nearly complete resolution" was defined as a minimal degree of telangiectasia, erythema, skin thickening, soft tissue swelling, and/or distortion of anatomic landmarks. Digital photographs of the front and side of target IH lesions were taken in accordance with a standardized procedure. The efficacy assessment committee evaluated the treatment effect in individual subjects by comparing photographs taken at baseline and Week 24. The efficacy assessment committee members of the Japanese phase III study were trained by the evaluators of the foreign phase II/III study, using real photographs of lesions of subjects participating in the foreign phase II/III study so that visual examination would be standardized between the 2 studies.

The evaluation period of the Japanese phase III study was 24 weeks, as in the foreign phase II/III study. The evaluation period of the foreign phase II/III study was determined by referring to foreign published papers (e.g., *New England Journal of Medicine,* 2008;358:2649-2651) on studies investigating the efficacy and safety of propranolol in patients with IH, who had been treated for approximately 24 weeks.

The treatment success rate [95% confidence interval] at Week 24 based on the centralized assessment in the Japanese phase III study was 78.1% (25 of 32 subjects) [60.0%-90.7%], showing that the lower limit of the 95% confidence interval was higher than the pre-specified threshold for treatment success (12%). The treatment success rate at Week 24 (final analysis) based on the centralized assessment in the foreign phase II/III study was 3.6% (2 of 55 subjects) in the placebo group and 60.4% (61 of 101 subjects) in the 3 mg 6M group, demonstrating the superiority of the 3 mg 6M regimen over placebo ($P < 0.001$, combination test by Posch et al.). The treatment success rate in the Japanese phase III study was not inferior to that in the foreign phase II/III study. Furthermore, the treatment success rate assessed by the investigator at Week 24 in the Japanese phase III study was 78.1% (25 of 32 subjects), which was the same as the result of the centralized assessment.

The above findings indicate the efficacy of propranolol in patients with IH.

PMDA accepted the applicant's explanation.

7.R.2.2 Treatment success rate by age in days and by lesion site

The treatment success rates by age in days and by lesion site in the Japanese phase III study and the foreign phase II/III study are shown in Table 15.

Table 15. Treatment success rate at Week 24 by age in days and by lesion site based on the centralized assessment

		Foreign phase II/III study		Japanese phase III study
		Placebo (N = 55)	3 mg 6M (N = 101)	Propranolol 3 mg/kg (N = 32)
Age in days	35-90 days old	10.0% (2/20)	67.6% (25/37)	72.7% (8/11)
	≥91 days old	0% (0/35)	56.3% (36/64)	81.0% (17/21)
Target lesion site	Facial[a)]	5.0% (2/40)	60.6% (43/71)	80.0% (16/20)
	Non-facial[a)]	0% (0/15)	60.0% (18/30)	75.0% (9/12)

Foreign phase II/III study, ITT population; Japanese phase III study, FAS

[a)] In the Japanese phase III study, target lesion sites were categorized into either the head and neck region or other regions.

PMDA's conclusion:

The treatment success rate by age in days in the Japanese phase III study was non-inferior to that in the foreign phase II/III study.

In addition, a comparison of the Japanese and foreign studies showed that the treatment success rates did not differ markedly between facial and non-facial lesions.

7.R.2.3 Changes in target lesions

The applicant's explanation on the changes in target lesions:

The target IH lesion was centrally assessed at every visit as improved, unchanged, or worsened by comparing with the previous condition.

In the Japanese phase III study, all subjects were assessed as "improved" at Week 5, based on the first centralized assessment. From Week 8 through Week 20, approximately 50% of the subjects were assessed as "improved" and the other half was "stabilized." At Week 24, 10 of 32 subjects (31.3%) were assessed as "improved" and 22 of 32 subjects (68.8%) as "stabilized." At Weeks 8 and 16, one subject each was assessed as "worsened" as compared to the previous visit.

In the foreign phase II/III study, the proportion of subjects achieving improvement as compared to the previous visit (based on the centralized assessment) in the placebo group was 5.4% (2 of 37 subjects) at Week 5 (the first assessment), and 3.8% to 4.8% at and after Week 8, and the proportion of subjects achieving improvement in the 3 mg 6M group was 88.0% (88 of 100 subjects) at Week 5 and 85.9% to 96.7% at and after Week 8.

PMDA confirmed that most subjects had "improved" or "stabilized" condition as compared to the previous visit and that no subjects experienced worsening in the Japanese phase III study.

7.R.2.4 Changes in the area, largest diameter, and color of target lesions

The applicant's explanation on changes in the area, largest diameter, and color of target lesions based on centralized assessments:

Table 16 shows the changes in the area, largest diameter, and color of target lesions based on centralized assessment in the Japanese phase III study and the foreign phase II/III study.

In the foreign phase II/III study, while the area and largest diameter of target lesions in the 3 mg 6M group tended to decrease as compared to the placebo group, there were no clear differences between the treatment groups. The change from baseline was greater in color in the 3 mg 6M group than in the placebo group.

The changes in the area, largest diameter, and color of target lesions were greater in the Japanese phase III study than in the foreign phase II/III study.

Table 16. Changes from baseline at Week 24 based on centralized assessment

	Foreign phase II/III study		Japanese phase III study
	Placebo (N = 55)	3 mg 6M (N = 101)	Propranolol 3 mg/kg (N = 32)
Area (cm^2)	0.464 ± 1.804 (19)	–1.207 ± 2.439 (88)	–5.242 ± 10.866 (31)
Largest diameter (cm)	–0.028 ± 0.743 (19)	–0.179 ± 0.731 (88)	–1.195 ± 2.096 (31)
Color difference (dE*2000)	–0.054 ± 4.824 (19)	–7.369 ± 7.430 (88)	–13.53 ± 13.36 (31)

Mean ± standard deviation (n)
Foreign phase II/III study, ITT population; Japanese phase III study, FAS

PMDA confirmed that the changes in the area, largest diameter, and color of target lesions in the 3 mg 6M group showed improvement as compared to the placebo group in the foreign phase II/III study and that the outcomes in the Japanese phase III study were non-inferior to those in the foreign phase II/III study.

7.R.2.5 Time course after the completion of the treatment with propranolol

The applicant's explanation on the time course of IH after the completion of the 24-week treatment with propranolol in the Japanese phase III study and the foreign phase II/III study:

In the Japanese phase III study, 32 subjects completed the 24-week treatment with propranolol and all the subjects were followed until Week 36 (12 weeks after the end of treatment) to ascertain if reintroduction of treatment was required. Of 25 subjects who were centrally assessed as "success" at Week 24, 18 subjects (72.0%) required no additional treatment while 7 subjects (28.0%) required it. Additional treatments in these 7 subjects were oral doses of propranolol (6 subjects) and pulsed dye laser therapy (1 subject).

In the foreign phase II/III study, the ITT population was followed until Week 96 (72 weeks after the end of treatment) to ascertain the efficacy of propranolol. A total of 61 subjects treated with the 3 mg 6M regimen were assessed as "success" in achieving complete/nearly complete resolution at Week 24 (the primary endpoint) and entered in the follow-up period. Of these, 54 subjects were centrally assessed for the efficacy of treatment at Week 96. Of the 54 subjects, 35 (64.8%) were also assessed as "success" at Week 96 without reintroduction of treatment during the follow-up period. In the placebo group, 2 subjects were assessed as "success" at Week 24 and enter in the follow-up period, and they were also assessed as "success" at Week 96 without additional treatment.

PMDA confirmed that, despite different duration and focus of follow-up in the Japanese phase III study and the foreign phase II/III study, 60% to 70% of subjects who achieved treatment success after the 24-week treatment remained free from reintroduction of treatment for a certain period.

7.R.3 Safety

PMDA's view:

Based on the discussions in the subsections below, the safety of propranolol is acceptable if the following requirements are met: (1) a physician with expertise in the treatment of IH should assess the benefits

and risks of propranolol in a patient with IH before deciding whether to use it; (2) once the use of propranolol has been decided, the patient should be carefully monitored during the treatment; and (3) the parent(s) of the patient should be fully informed of the importance of adequate treatment adherence. Because the Japanese phase III study had limited number of subjects, safety data from patients receiving propranolol in clinical settings should be collected via post-marketing surveillance.

The decision on the safety of propranolol will be finalized taking into account the comments made in the Expert Discussion.

7.R.3.1 Summary of adverse events reported in Japanese and foreign clinical studies

The applicant's explanation on adverse events reported in Japanese and foreign studies:

Table 17 summarizes adverse events occurring in the Japanese phase III study and the foreign phase II/III study. In the foreign phase II/III study, adverse events or adverse drug reactions occurred more frequently in the propranolol groups than in the placebo group, but there was no clear difference in the incidence of serious adverse events among treatment groups. Adverse events leading to study drug discontinuation occurred most frequently in the placebo group. The individual adverse events reported [see Tables 8 and 13] were either non-specific events that are commonly observed in infants or known adverse reactions to propranolol [for known adverse reactions to propranolol, see "7.R.3.2 Known events that require special attention"].

Table 17. Adverse events occurring in the Japanese phase III study or the foreign phase II/III study

Study	Japanese phase III study (M703101-01)	Foreign phase II/III study (V00400SB201)				
Treatment group	Propranolol 3 mg/kg (N = 32)	Placebo (N = 55)	1 mg 3M (N = 98)	1 mg 6M (N = 102)	3 mg 3M (N = 100)	3 mg 6M (N = 101)
Mean duration of treatment[a)]	168.3 days	82.6 days	142.7 days	156.9 days	146.6 days	161.0 days
Any adverse event	96.9% (31)	72.7% (40)	90.8% (89)	88.2% (90)	91.0% (91)	95.0% (96)
Adverse drug reactions	31.3% (10)	29.1% (16)	44.9% (44)	32.4% (33)	35.0% (35)	34.7% (35)
Serious adverse events	0% (0)	5.5% (3)	5.1% (5)	2.9% (3)	9.0% (9)	5.9% (6)
Serious adverse drug reactions	0% (0)	1.8% (1)	1.0% (1)	0% (0)	3.0% (3)	0% (0)
Adverse events leading to study drug discontinuation	0% (0)	10.9% (6)	4.1% (4)	2.0% (2)	7.0% (7)	3.0% (3)
Adverse drug reactions leading to study drug discontinuation	0% (0)	1.8% (1)	2.0% (2)	1.0% (1)	5.0% (5)	0.0% (0)

% (n)

a) The treatment duration of the 1 mg 3M and the 3 mg 3M groups include treatment with placebo from Month 4 to Month 6.

Table 18 shows the serious adverse events occurring in Japanese and foreign clinical studies. No serious adverse events were reported in the Japanese phase III study or the foreign extension study (V00400SB301, reference data). There was no tendency toward increased incidence of any specific

serious adverse events in the foreign phase I study and the foreign phase II/III study. Although serious adverse drug reactions occurred in 4 subjects [see "7.2 Foreign phase II/III study"], all eventually resolved.

Table 18. Serious adverse events occurring in Japanese and foreign clinical studies[a)]

Treatment group	Serious adverse events ("*" indicates adverse drug reactions)
Placebo for 6 months	Condition aggravated* in 2 subjects (*1 subject), and drug ineffective in 1 subject
1 mg/kg for 3 months + placebo for 3 months	Bronchiolitis, cataract operation, drug ineffective, cystitis, and atrioventricular block second degree* in 1 subject each
1 mg/kg for 6 months	Ileostomy closure and inguinal hernia repair; epilepsy; and bronchopneumonia and gastroenteritis in 1 subject each
3 mg/kg for 3 months + placebo for 3 months	Gastrooesophageal reflux disease in 2 subjects; and pyelonephritis, apathy and cyanosis, dehydration and viral infection, bronchitis and rotavirus infection, condition aggravated,* bronchiolitis, and bradycardia* and enterocolitis in 1 subject each
3 mg/kg for 3 months	Crying, pallor, and otitis media acute in 1 subject
3 mg/kg for 6 months	Head injury, apathy, drug ineffective, bronchiolitis, and bronchitis in 1 subject each

[a)] Japanese phase III study (M703101-01), foreign phase I study (V00400SB102), foreign phase II/III study (V00400SB201), foreign extension study (V00400SB301)

7.R.3.2 Known events that require special attention

Bradycardia, hypotension, bronchospasm, and hypoglycaemia are the known adverse reactions to propranolol. The applicant classified these as adverse events of special interest in Japanese and foreign clinical studies, requiring monitoring at the start of treatment and at every dose increase in 3 foreign studies and the Japanese phase III study [see Table 19]. Measures to be taken at the onset of these adverse events [see Table 20] were also specified in 3 foreign studies but not in the Japanese phase III study, in which subjects were required to be hospitalized until the day after dose increase to 3 mg/kg/day. In the 3 foreign studies, parents received a letter of safety precautions, which contained the following advice: (a) discontinue the treatment with the study drug immediately and contact the investigator if the subject presents with symptoms such as fatigue, altered mood, difficulty in awakening, muscular weakness and fatiguability, feeding difficulty, pallor, cough, dyspnea, and tachypnea; (b) the subject must be fed before treated with the study drug to avoid the risk of hypoglycaemia. Temporarily stop the treatment if vomiting, etc. occurs; and (c) administer sugar-containing oral solution if a symptom of hypoglycaemia develops. Consult with the investigator if the symptom persists.

Table 19. Monitoring of heart rate, blood pressure, bronchospasm, and blood glucose at the start of treatment and dose increase

	3 foreign studies	Japanese phase III study
Vital signs (heart rate, blood pressure, respiratory rate, body temperature)	Days of the start of treatment and dose increase (Days 7 and 14) Every 1 hour for 4 hours post-dose Breath sound auscultation included.	Days of the start of treatment and dose increase (Days 3 and 5) AM; pre-dose and 1, 2, and 4 hours post-dose PM; pre-dose and 2 and 4 hours post-dose Days after the first dose and dose increase AM; pre-dose and 2 and 4 hours post-dose
Blood glucose	Days of the start of treatment and dose increase (Days 7 and 14) Pre-dose and 2 and 4 hours post-dose	Days of the start of treatment and dose increase (Days 3 and 5) AM; pre-dose and 2 and 4 hours post-dose
ECG	Days of the start of treatment and dose increase (Days 7 and 14) Pre-dose and 2 and 4 hours post-dose	Days of the start of treatment and dose increase (Days 3 and 5) AM; pre-dose and 2 and 4 hours post-dose
Other		Hospitalization until the day after dose increase to 3 mg/kg/day (Day 6 or later)

Table 20. Measures to be taken for heart rate, blood pressure, and blood glucose (3 foreign studies)

Pre-dose on Day 1	Before dose increase on Days 7 and 14	Post-dose	Measures
Heart rate <80 bpm, blood pressure <50/30 mmHg, or blood glucose <40 mg/dL	Heart rate <60 bpm, blood pressure <50/30 mmHg, or blood glucose <40 mg/dL		Discontinue study treatment and continue monitoring at the study site.
Heart rate <80 bpm, blood pressure <50/30 mmHg, or blood glucose <40 mg/dL after additional monitoring	1) Heart rate <60 bpm, blood pressure <50/30 mmHg, or blood glucose <40 mg/dL after additional monitoring 2) Heart rate <50 bpm or blood glucose <30 mg/dL at any pre-dose time point	1)Heart rate <60 bpm, blood pressure <50/30 mmHg, or blood glucose <40 mg/dL after additional monitoring (after 4 hours as specified) 2) Heart rate <50 bpm or blood glucose <30 mg/dL at any post-dose time point	Discontinue study treatment permanently and continue monitoring at the study site.

The applicant's explanation on adverse events related to bradycardia, hypotension, bronchospasm, or hypoglycaemia observed in the 3 foreign studies and Japanese phase III study, and monitoring methods for the events:

(a) Bradycardia

In the foreign phase II/III study, bradycardia occurred in 1 subject (3 mg 3M group) during the dose titration period and 1 subject (1 mg 6M group) during the maintenance dose period. The subject who had bradycardia in the dose titration period had been in poor condition since birth after a 25-week gestation. During the administration of the 1 mg/kg/day dose on Day 6, the subject experienced enterocolitis with an increase the pulse rate (90 to 100 per minute). The treatment was discontinued and the event resolved 3 days later. The other case of bradycardia that occurred during the maintenance dose (1 mg/kg/day) period was mild and asymptomatic, and resolved with no change in the study drug regimen. Bradycardia was not observed in other foreign studies or the Japanese phase III study.

(b) Hypotension

The occurrence of hypotension in the foreign phase II/III study was as follows: 1 subject in the placebo group; 1 subject on the 1 mg/kg/day dose on Day 1 and 2 subjects on the day of dose increase from 1 mg/kg/day to 2 mg/kg/day in the 3 mg 3M group; 2 subjects in the 1 mg 3M group; and 1 subject in

the 1 mg 6M group. All the events were asymptomatic and resolved with no change in study drug regimens. Hypotension was not observed in other foreign studies. In the Japanese phase III study, blood pressure systolic decreased occurred in 2 subjects (on Day 6 during treatment at 3 mg/kg/day), blood pressure diastolic decreased occurred in 2 subjects (1 subject on the 3 mg/kg/day dose on Days 5 and 6, and 1 subject both on the 2 mg/kg/day dose on Day 3 and on the 3 mg/kg/day dose on Days 5 and 15), and blood pressure decreased occurred in 1 subject (on the maintenance dose of 3 mg/kg/day on Day 15). All the events were mild and resolved without dose adjustment or any measures taken against the symptoms.

(c) Bronchospasm

In the foreign phase II/III study, bronchospasm occurred in 2 subjects on placebo, 1 subject on the maintenance dose (3 mg/kg/day) in the 3 mg 3M group, and 1 subject on the 2 mg/kg/day dose (the dose titration period) in the 3 mg 6M group. The bronchospasm occurring in the subject on the 2 mg/kg/day dose (the dose titration period) resolved with no change in the study drug regimen, and the other one occurring in the subject on the maintenance dose (3 mg/kg/day) resolved after temporary discontinuation of the study drug. Bronchospasm was not observed in other foreign studies or the Japanese phase III study.

(d) Hypoglycaemia

In the foreign phase II/III study, hypoglycaemia occurred in 2 subjects in the dose titration period (1 subject on the 2 mg/kg/day dose in the 1 mg 6M group and 1 subject on the 2 mg/kg/day dose in the 3 mg 6M group). Both events were mild and asymptomatic, and resolved within a day without dose adjustment. Hypoglycaemia was not observed in other foreign studies or the Japanese phase III study.

As mentioned above, the onset of bradycardia, hypotension, bronchospasm, and hypoglycaemia was reduced by appropriate precautionary advice and monitoring. Subjects experiencing these events were promptly cared and most of them were able to continue the treatment without dose adjustment.

The applicant's view on precautionary advice in the package insert about monitoring for bradycardia, hypotension, bronchospasm, and hypoglycaemia:

Vital signs were measured for up to 4 hours post-dose in Japanese and foreign studies [see Table 18]. Most of changes in vital signs occurred within 2 hours post-dose, and they were minor and resolved without requiring dose interruption or treatment. No clinically relevant changes in vital signs occurred during the period from 2 to 4 hours post-dose. Outside Japan, there are a number of published papers on clinical studies of propranolol in patients with IH. The European Consensus Guidelines (*Eur J Pediatr,* 2015;174:855-865) established based on knowledge from these papers recommend monitoring particularly for the first 2 hours after the first dose or dose increase. Since the market release in foreign countries, no safety issues requiring regulatory measures have been reported for the use of propranolol in the outpatient setting. Therefore, the package insert in Japan will include a precautionary statement that monitoring should be performed for ≥2 hours after the first dose and dose increase.

7.R.3.3 Safety information overseas

The applicant's explanation on safety information on propranolol outside Japan:

The following safety data are available from a compassionate use program (CUP) in France covering from [redacted] to July [redacted], 2014, 60 published reports[4] included in the marketing applications submitted to the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), and Periodic Safety Update Reports (PSURs).

In France, 1661 patients participated in the CUP to receive propranolol. Adverse drug reactions occurred in 161 of 1661 patients (9.7%), including serious ones noted in 40 of 1661 patients (2.4%). Death occurred in 3 patients. The fatal events in 2 of these 3 patients (asphyxia due to aspiration of food in 1 patient, and atrioventricular block complete/cardiac failure acute[5] in 1 patient) were assessed as unrelated to propranolol, and one in the other 1 patient (lack of efficacy; off-label use for treating multifocal lymphangioendothelioma 3 days after birth) was not evaluable. The adverse drug reactions occurring in ≥5 patients were bronchiolitis in 38 patients (serious in 12 patients), insomnia and sleep disorder in 39 patients (serious in 0 patients), agitation in 8 patients (serious in 0 patients), decreased appetite in 8 patients (serious in 1 patient), hypoglycaemia in 7 patients (serious in 4 patients), bronchitis in 7 patients (serious in 0 patients), bronchospasm in 6 patients (serious in 6 patients), cough and peripheral coldness in 6 patients each (serious in 0 patients), malaise in 5 patients (serious in 4 patients), hypotonia and pallor in 5 patients each (serious in 1 patient), and diarrhoea in 5 patients (serious in 0 patients) (some patients had more than 1 event). Data were obtained from 697 patients who had discontinued treatment. The reasons for discontinuation included "good efficacy" (83.8%, 584 patients) and "adverse drug reactions" (4.2%, 29 patients). Adverse drug reactions leading to discontinuation noted in >1 patient were bronchiolitis in 20 patients, nightmare in 4 patients, bronchospasm in 4 patients, sleep disorder and asthma in 3 patients each, and bradycardia, cough, hypoglycaemia, respiratory distress, and failure to thrive in 2 patients each (some patients had more than 1 event).

According to the 60 published articles (involving 1367 patients) included in the marketing applications submitted to FDA and EMA, most patients were treated with propranolol 2 mg/kg/day for ≤30 months. No unknown serious adverse drug reactions were reported. The main adverse drug reactions were sleep disorder in 20 patients, hypotension in 18 patients, and diarrhoea in 13 patients. While many published articles did not mention the severity of adverse drug reactions, 13 patients were reported to have discontinued treatment due to adverse drug reactions including bradycardia, hypotension, respiratory

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4) Pierre Fabre Dermatologie, the developer of propranolol, searched 13 databases ([redacted]) using "propranolol" and "hemangioma" as search words on [redacted]. Then, they began to search 5 databases ([redacted]) regularly to cross-check the results of this search against the results of a search started on [redacted] (databases, [redacted]; search words, "propranolol" and "newborn, infant, or child"). From the results of these searches cut-off on [redacted], Pierre Fabre chose 60 articles containing any safety information (at least 1 adverse event). None of these articles were on the drug product manufactured by Pierre Fabre.

5) The patient had biliary atresia with portal hypertension. The adverse events occurred after administration of drugs (such as Lauromacrogol) for endoscopic sclerotherapy for treating esophageal varices.

disorder, and hypoglycaemia. Events leading to a dose reduction or interruption of propranolol also included these events as well as sleep disorder, fatigue, restlessness, and gastrointestinal disorder.

A total of 3 PSURs of propranolol were submitted by March 2016 (the first report, April 23, 2014 through October 23, 2014; the second report, October 24, 2014 through April 23, 2015; and the third report, April 24, 2015 through October 23, 2015). In the second PSUR, "hyperkalaemia in patients with giant ulcerated infantile hemangioma" was added as an important identified risk of propranolol based on a published paper reporting that hyperkalaemia occurred in patients with giant ulcerated infantile hemangioma following administration of propranolol. Propranolol induces apoptosis of capillary endothelial cells, and thus propranolol-associated tumor lysis syndrome may lead to hyperkalaemia in patients with large IH.

PMDA's view on the applicant's explanation in Sections 7.R.3.1 through 7.R.3.3:
While bradycardia, hypotension, bronchospasm, and hypoglycaemia are known adverse reactions to propranolol, none of these events caused particular concern in the Japanese phase III study or foreign studies, in which the monitoring of these events was required after the first dose and dose increase. Safety data obtained from the CUP and available Japanese and foreign published papers indicate that the safety of both Hemangiol and propranolol in patients with IH is generally equivalent to the known safety profile of propranolol.

The use of propranolol in patients with IH will require attention to the occurrence of known adverse drug reactions including bradycardia, hypotension, bronchospasm, and hypoglycaemia. Therefore, physicians should be reminded of these adverse drug reactions. Further, (a) monitoring of vital signs for ≥2 hours after the first dose and dose increase at medical institutions and (b) treatment discontinuation and other appropriate actions to be taken for severe events including bradycardia and hypotension should be adequately advised in the package insert or educational materials for healthcare professionals [see "7.R.3.2 Known events that require special attention"].

In addition to the known adverse reactions to propranolol, hyperkalaemia in patients with ulcerated IH should also be mentioned in the package insert in Japan as in foreign countries.

7.R.4 Indication
The applicant's rationale for the proposed indication:
The foreign phase II/III study and the Japanese phase III study were conducted in patients with proliferating IH and demonstrated the efficacy and safety of propranolol. Accordingly, "infantile hemangioma" has been proposed as the indication of propranolol.

Study treatment was initiated in infants aged 35 to 150 days in the foreign phase II/III study and the Japanese phase III study. Based on the foreign phase II/III study, the foreign package inserts state that treatment should be started at 5 weeks to 5 months of age. The CUP data included 1645 patients for

whom the age at the start of treatment was recorded. Of these, 59 patients (3.6%) were aged <5 weeks. The CUP, because of its objectives, did not collect sufficient data for efficacy or safety evaluation but examined the reasons for discontinuation of treatment in relevant patients. The reasons for discontinuation were obtained from a total of 686 patients including 18 patients aged <5 weeks. Of the 18 patients, 16 (88.9%) discontinued treatment due to "good efficacy" but none discontinued due to "insufficient efficacy" or adverse events. These results indicate no clinically significant issues in terms of the efficacy or safety of propranolol administered to patients aged <5 weeks for the proposed indication. However, given that currently available information on safety in patients aged <5 weeks is insufficient, propranolol should be used in patients aged ≥5 weeks in principle.

In the CUP, 538 of 1645 patients (32.7%) receiving propranolol were aged >150 days at the start of treatment. Of the 686 patients who gave a reason for discontinuation, 213 patients were aged >150 days. Of the 213 patients, 162 (76.1%) discontinued treatment due to "good efficacy," 22 (10.3%) due to "insufficient efficacy," and 7 (3.3%) due to adverse events. A literature review of articles published in and outside Japan was performed for 16 Japanese patients (9 reports) and 33 non-Japanese patients (9 reports) who were aged >150 days at the start of treatment and whose clinical course was detailed. The literature review showed treatment success in 42 of these 49 patients. The safety summary in published articles revealed vomiting occurring in 1 patient aged 10 months in Japan and mild blood pressure decreased in 1 patient outside Japan. These findings suggest propranolol have some degree of efficacy also in patients aged >150 days at the start of treatment without no particular safety concerns. Furthermore, given that propranolol is expected to be used in patients with proliferating IH, the age at the start of treatment does not need to be limited to ≤150 days.

PMDA's view:
Based on the results of Japanese and foreign clinical studies, the proposed indication of propranolol (i.e., "infantile hemangioma") will raise no particular issue. However, since propranolol is expected to have efficacy in treating proliferating IH based on its mechanism of action [see "3.R Outline of the review conducted by PMDA"], the applicant should provide precautionary advice stating that propranolol be used only in patients with proliferating IH. In addition, because of the risks of propranolol [see "7.R.3 Safety"], the applicant should also give precautionary advice to the effect that propranolol be administered only when a physician with expertise in in the treatment of IH considers that the expected benefits will outweigh the risks to the patient.

The foreign CUP involved a substantial number of patients aged <5 weeks or >150 days at the start of treatment, suggesting that patients of these age groups may need to be treated with propranolol. At present, efficacy and safety data from the foreign CUP and Japanese and foreign published papers shows no particular concern in patients aged <5 weeks or >150 days. Therefore, it is not necessary to limit the patient's age at the start of treatment strictly, provided that propranolol therapy is chosen at the discretion of a physician with expertise in the treatment of IH and administered appropriately under the supervision of the physician. However, in light of the lack of experience with use of propranolol in patients aged <5

weeks or >150 days in Japanese and foreign clinical studies, data on the efficacy and safety of propranolol in patients of these age groups should be collected through the post-marketing surveillance, etc.

A final decision on the indication of Hemangiol will be made, taking account of comments from the Expert Discussion.

7.R.5 Dosage and administration

The applicant's rationale for the proposed dosage and administration of propranolol:

(a) Dose, dose increase, etc.

Propranolol has been used for years for the treatment of arrhythmia, hypertension, etc. in infants at a dose of 1 to 4 mg/kg/day with confirmed efficacy and safety. Most published papers on IH showed that propranolol was administered at ≤3 mg/kg/day. Thus, the maximum dose in clinical studies was determined to be 3 mg/kg/day. The foreign phase II/III study had 3-month and 6-month dosing groups for each of 1 mg/kg/day and 3 mg/kg/day of propranolol, and the study demonstrated that the treatment success rate was highest in patients treated with propranolol 3 mg/kg/day for 6 months. Partly because of the recommended dose of propranolol for pediatric patients with arrhythmia, an approved indication, being consistent in Japan, the US, and Europe, the Japanese phase III study employed the dosage regimen of 3 mg/kg/day for 6 months. This was the dosage regimen that demonstrated efficacy in the foreign phase II/III study. The efficacy and safety of propranolol was also proved in Japanese patients with IH. Therefore, 3 mg/kg/day has been proposed as the maintenance dose of propranolol.

The proposed starting dose (1 mg/kg/day) and the dose increment size(1 mg/kg/day) were determined according to the dosing regimens for the 3 mg/kg/day group in both the foreign phase II/III study and the Japanese phase III study.

The maximum daily dose per patient was 32.9 mg/body in Japanese and foreign clinical studies and 87 mg/body (the maximum body weight of 29 kg and the oldest age of 6.4 years at the start of treatment; mean, 32.5 mg/body) in the CUP in France. In Japan, according to the dosage and administration for pediatric patients for the approved indications, the maximum daily dose of propranolol hydrochloride is 90 mg/body (79 mg/body as propranolol) for "premature contraction (supraventricular or ventricular), prevention of paroxysmal tachycardia, atrial fibrillation with rapid ventricular response (bradycardic effect), sinus tachycardia, new atrial fibrillation, or prevention of paroxysmal atrial fibrillation." However, it does not mention the maximum daily dose for infants and young children "to reduce hypoxic episodes due to right ventricular outflow tract stenosis." The target population of Hemangiol (propranolol) for the proposed indication is infants and young children, and therefore most patients will not need a daily dose exceeding 90 mg/body (79 mg/body as propranolol base), which is the maximum daily dose of propranolol for the approved indications in Japan. Furthermore, the maximum daily dose per patient is not mentioned in approved labels of propranolol outside Japan. Therefore, the maximum daily dose per patient is not defined in the "Dosage and Administration" section.

The dose was increased at intervals of 1 week in the foreign phase II/III study. However, the data from the foreign phase I study (V00400SB102) suggested that plasma propranolol concentration would reach steady state after the third dose (given in the morning on Day 2) or subsequent doses. Some Japanese published papers report that propranolol with dose increase at intervals of <1 week poses no safety issues (*PEPARS,* 2012;71:26-35; *The Journal of Japan Pediatric Society,* 2012;116:1351-1356). The dose increase interval in the Japanese phase III study was determined to be 2 days. In the Japanese phase III study, the dose was increased in all subjects every 2 days as specified, while none of them experienced a dose reduction due to safety concerns. Consequently, the dose increase interval has been set as ≥2 days.

(b) Dosing timing

Due to the potential risk of hypoglycaemia, healthcare professionals should be advised that propranolol should be administered during or right after feeding, the dose should be skipped if the patient is not eating or is vomiting. The recommended daily dose of propranolol should be administered in 2 divided doses as in the foreign phase II/III study and the Japanese phase III study. Healthcare professionals should also be advised that doses be administered ≥9 hours apart.

(c) Duration of treatment

Because the highest treatment success rate was achieved in patients receiving propranolol 3 mg/kg/day for 6 months (24 weeks) in the foreign phase II/III study, the duration of treatment in the Japanese phase III study was also 6 months (24 weeks).

In the CUP, the mean and maximum durations of treatment with propranolol were 8.6 months and 36.8 months, respectively. The above CUP findings and publications in and outside Japan indicate that the duration of propranolol therapy exceeding 6 months (24 weeks) is required in some patients depending on their condition. The foreign extension study (V00400SB301, reference data) enrolled patients who had participated in the foreign phase I study or the foreign phase II/III study and who were judged to require reintroduction of propranolol even after completion of these studies. In the foreign extension study, some subjects were treated for >24 weeks (the total duration of treatment in 7 subjects was >24 weeks [169 to 346 days]). The main adverse events that occurred during the foreign extension study included infection and gastrointestinal disorder. The incidence of adverse events was similar to those in the Japanese phase III study and the foreign phase II/III study, with no serious adverse events. Target IH lesions in all 11 subjects enrolled in the foreign extension study improved from baseline.

As discussed above, at this point, no new events arousing safety concerns were observed in patients with IH treated with propranolol for longer periods, and no specific rules have been set to limit treatment duration in foreign countries. Therefore, there is no need to prohibit treatment with propranolol for a period of >24 weeks. The package insert of propranolol will advise that the recommended duration of

treatment is 24 weeks and that the use of propranolol for >24 weeks should be determined based on medical necessity.

PMDA's view:
Because the efficacy of propranolol was demonstrated in the Japanese phase III study [see "7.R.2 Efficacy"] and because the safety of propranolol is acceptable when the drug is used under such conditions that the associated risks are monitored and managed appropriately [see "7.R.3 Safety"], there should be no problem with selecting the same dosage regimen employed in the Japanese phase III study. There is also no problem with the applicant's explanation on the treatment duration.

The protocol of the Japanese phase III study required that the dose be increased at the discretion of the investigator and that an increased dose be reduced to the previous dose if the increased dose was not well tolerated by the patient. The "Dosage and Administration" section of the package insert should also state that the dose may be adjusted according to the patient's condition.

A final decision on the dosage and administration of propranolol will be made taking account of comments from the Expert Discussion.

7.R.6 Measures for proper use

The parent(s) of the patient must measure the right amount of the Hemangiol (propranolol) oral solution with the provided pipette, according to the patient's body weight. The patient(s) should monitor the patient for hypotension, hypoglycaemia, and other adverse events, and should discontinue treatment or take any appropriate measures depending on the patient's condition. For these reasons, parents should be informed of potential risks associated with the use of propranolol. In France, 1661 patients participated in the CUP of propranolol. Among these patients, drug administration errors occurred in 8 patients (including 2 patients with serious cases). The 2 patients with the serious cases received propranolol under fasting conditions and later developed hypoglycaemia (one of them also experienced vomiting due to gastroenteritis when receiving propranolol). Of the remaining 6 non-serious cases, 2 involved inappropriate use of the pipette.[6)]

Known adverse reactions to propranolol are bradycardia, hypotension, bronchospasm, and hypoglycaemia, and the use of propranolol in patients with IH requires attention to these adverse reactions. Given that patients with IH are usually treated by plastic surgeons, propranolol may not necessarily be prescribed by cardiovascular specialists. Healthcare professionals treating IH should be well informed of the possible adverse reactions to propranolol and advised to perform monitoring at the start of treatment and dose increase as well as to take measures for managing bradycardia, hypotension, or other events. Such information and advice should be adequately included in the package insert and educational materials for healthcare professionals [see "7.R.3 Safety"].

6) One patient received propranolol measured with a pipette for a different product. The other patient received propranolol measured incorrectly due to confusion of the units ("mg" vs. "mL").

PMDA asked the applicant to explain how to provide precautionary advice, including the preparation of educational materials for parents and healthcare professionals.

The applicant's response:
The educational materials for parents will contain comprehensible information and advice that help them understand how to administer propranolol (including how to use the pipette), points to consider, adverse drug reactions that require special attention, and measures to be taken.

The educational materials for healthcare professionals will contain details of adverse reactions to propranolol and advice on monitoring at the start of treatment and dose increase and measures to be taken for managing bradycardia, hypotension, or other events. Prior to treatment, parents of patients should be fully informed by physicians to ensure their good understanding of the treatment. The educational materials for healthcare professionals will thus include guidelines on prior explanation to parents.

PMDA considers that the applicant's explanation is generally acceptable. However, a final decision on the measures for proper use of Hemangiol (propranolol) will be made, taking account of the comments from the Expert Discussion.

7.R.7 Post-marketing investigations
The applicant has a plan of a drug use-results survey shown in Table 21.

Table 21. Outline of use-results survey (draft)

Objectives	**To collect data on the long-term safety and efficacy of propranolol in patients with IH in routine clinical practice and to identify factors that may have an impact on the safety and efficacy of propranolol**
Survey period	**3 years**
Planned number of patients	**300 patients**
Planned survey sites	**All medical institutions to which Hemangiol (propranolol) is supplied**
Target patients	**Patients with IH**
Observation period	**76 weeks after the start of treatment (including the post-treatment follow-up period)**
Main survey items	• **Patient characteristics (sex, date of birth, height at birth, body weight, head circumference, duration of gestation period, complications, medical history, time to onset, lesion site, etc.)** • **Status of treatment with Hemangiol (dose, reason for dose change, reason for permanent or temporary discontinuation of treatment)** • **Concomitant medications and/or therapies** • **Vital signs, height, body weight, head circumference, and chest circumference** • **Adverse events (onset date, seriousness, action taken, outcome, causal relationship to propranolol, etc.)** • **Time course of hemangioma**

PMDA considers that information on the following issues should also be collected and studied in the drug use-results survey. However, post-marketing investigations will be finalized based on the comments made at the Expert Discussion.

- Safety at the start of treatment and at dose increase
- Safety and efficacy in patients treated with propranolol for >24 weeks
- Safety and efficacy in patients who required reintroduction of propranolol therapy
- Safety and efficacy of propranolol in patients aged <35 days or >150 days at the start of treatment

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection and assessment revealed no noteworthy issues. PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion on the results of on-site GCP inspection

The new drug application data (5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection revealed no noteworthy issues. PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

PMDA has concluded that the data submitted demonstrate the efficacy of propranolol (Hemangiol) in the treatment of infantile hemangioma and acceptable safety in view of the benefits indicated by the data submitted. Hemangiol is the first pharmaceutical product indicated for infantile hemangioma and is of clinical significance. PMDA has concluded that the application may be approved if propranolol is not considered to have any particular problems with the efficacy, safety, indication, dosage and administration, measures for proper use, or post-marketing investigations based on comments from the Expert Discussion.

Review Report (2)

May 16, 2016

Product Submitted for Approval

Brand Name	Hemangiol Syrup for Pediatric 0.375%
Non-proprietary Name	Propranolol Hydrochloride
Applicant	Maruho Co., Ltd.
Date of Application	September 25, 2015

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

At the Expert Discussion, the expert advisors supported PMDA's conclusions on "7.R.2 Efficacy" and "7.R.6 Measures for proper use" out of the issues presented in the Review Report (1), while making the following comments on "7.R.3 Safety," "7.R.4 Indication," "7.R.5 Dosage and administration," and "7.R.7 Post-marketing investigations."

1.1 Safety

In response to PMDA's conclusion described in the Review Report (1), the expert advisors made the following comments:

- Hemangiol (propranolol) is intended to be used in newborns and infants. Careful attention should thus be paid to adverse drug reactions such as bradycardia, hypotension, and hypoglycaemia, which are hard to identify in this population. Plastic surgeons, dermatologists, or other specialists who are not routinely engaged in the systemic treatment of young children are also expected to be involved in the treatment of infantile hemangioma (IH). In such a case, plastic surgeons and dermatologists should seek collaboration with a pediatrician at least for the first dose and every dose increase.

Based on the comments of the expert advisors, PMDA sees the need of inclusion of the following precautionary advice in the "Important Precautions" section of the package insert.

"Heart rate, blood pressure, respiratory condition, blood glucose, etc. should be monitored every hour for ≥2 hours after the first dose and dose increase in cooperation with a pediatrician."

PMDA instructed the applicant to take an action accordingly. The applicant responded to the instruction appropriately, and PMDA accepted it.

1.2 Indication

In response to PMDA's conclusion described in the Review Report (1), the expert advisors made the following comments:

- Use of propranolol is desirable for the treatment of IH that is highly likely to cause functional impairment (e.g., deprivation amblyopia, feeding disorder, airway obstruction) or that poses a risk of permanent scarring or disfigurement. Not all patients with IH are eligible for the treatment with propranolol. The indication of propranolol should be clearly defined as proliferating IH requiring systemic therapy with oral medication.
- Due to its variety, the diagnosis of so-called hemangioma may be difficult for non-specialists. Use of propranolol should be considered only in patient with confirmed IH. Therefore, as proposed by PMDA in the Review Report (1), the applicant should provide the precautionary advice to the effect that propranolol should be administered only when a physician with expertise in the treatment of IH considers that the expected benefits will outweigh the risks to the patient.
- The treatment with propranolol should be made available for patients with IH aged <5 weeks or >150 days. However, because only a limited number of patients in these age groups were treated with propranolol, relevant data should be collected through the post-marketing surveillance, as proposed by PMDA in the Review Report (1).

PMDA's view on the comments of the expert advisors:

Given that the location of IH and IH-related functional impairment vary from patient to patient, the necessity of treatment with propranolol should be determined by a physician with expertise in the treatment of IH according to the condition of individual patients. Therefore, the "Indication" and "Precautions for Indication" sections should be described as below. Healthcare professionals should be informed of specific cases of IH to be treated with propranolol through the educational materials for healthcare professionals.

Indication

Infantile hemangioma

Precautions for Indication

- Hemangiol (propranolol) should be administered only when a physician with expertise in the treatment of infantile hemangioma considers that the expected benefits will outweigh the risks to the patient.
- As a rule, Hemangiol (propranolol) should be used to treat proliferating infantile hemangioma requiring systemic therapy.

The above comments by PMDA were supported by the expert advisors. PMDA instructed the applicant to take necessary actions accordingly, and the applicant responded as per the instruction. PMDA accepted the applicant's response.

1.3 Dosage and administration

The conclusion of PMDA presented in the Review Report (1) was supported by the expert advisors. Furthermore, the following comments were raised by the expert advisors:

- Because IH has a clinical course characterized by rapid proliferation followed by slow involution, the use of propranolol should not be continued unnecessarily.
- Some patients will presumably respond well to a dose <3 mg/kg. The dosage and administration should be defined in such a way that the dose can be adjusted according to the patient's condition and at the discretion of the physician.
- Because feeding practice greatly depends on the infant's condition and surroundings, the infant may not always be fed in a timely manner. Therefore, specific measures for dosing should be communicated appropriately. For example, parents should be advised to skip the dose if the infant is not being fed. Even if it actually happens, a single skipped dose will not increase the risk of rapid growth of IH.

Based on the comments of the expert advisors, PMDA considered that the "Dosage and Administration," "Precautions for Dosage and Administration," and "Important Precautions" sections of the package insert should be presented as shown below. Further, measures to be taken for dosing in the infant not being fed should be communicated to parents in a comprehensible manner through the educational materials for parents.

Dosage and Administration

The usual dosage is 1 to 3 mg/kg/day of propranolol, administered orally in 2 divided doses under non-fasted conditions. The starting dose is 1 mg/kg/day, and the dose is increased in increments of 1 mg/kg at intervals of ≥2 days to 3 mg/kg/day as a maintenance dose. The dose may be adjusted according to the patient's condition.

Precautions for Dosage and Administration

- Any daily doses shown in the following table should be administered in 2 divided doses ≥9 hours apart. The dose should be adjusted according to the patient's body weight.

Reference – Daily dose of drug product to be given in 2 divided doses

		Daily dose of propranolol (as free base)		
		1 mg/kg	2 mg/kg	3 mg/kg
Body weight	2 kg	0.5 mL	1.1 mL	1.6 mL
	3 kg	0.8 mL	1.6 mL	2.4 mL
	4 kg	1.1 mL	2.1 mL	3.2 mL
	5 kg	1.3 mL	2.7 mL	4.0 mL
	6 kg	1.6 mL	3.2 mL	4.8 mL
	7 kg	1.9 mL	3.7 mL	5.6 mL
	8 kg	2.1 mL	4.3 mL	6.4 mL
	9 kg	2.4 mL	4.8 mL	7.2 mL
	10 kg	2.7 mL	5.3 mL	8.0 mL

- To reduce the risk of hypoglycaemia, propranolol should be administered during or right after feeding under non-fasting conditions. The dose should be skipped if the patient is not eating or is vomiting.

Important Precautions

Patients treated with propranolol should be carefully monitored. The efficacy of propranolol should be evaluated 24 weeks after the start of treatment to determine whether to continue the treatment.

PMDA instructed the applicant to take an action accordingly. The applicant responded to the instruction, and PMDA accepted the applicant's response.

1.4 Risk management plan (draft)

The conclusion of PMDA described in "7.R.7 Post-marketing investigations" in the Review Report (1) was supported by the expert advisors. PMDA instructed the applicant to further investigate the following issues through the post-marketing surveillance, and the applicant followed the instruction accordingly.

- Safety at the start of treatment and every dose increase
- Safety and efficacy in patients treated with propranolol for >24 weeks
- Safety and efficacy in patients who required the re-introduction of propranolol
- Safety and efficacy in patients aged <35 days or >150 days

Based on the comments by the expert advisors, PMDA concluded that the safety and efficacy specifications listed in Table 22 should be included in the current risk management plan (draft), the additional pharmacovigilance activities and risk minimization activities listed in Table 23 should be implemented, and a specified use-results survey should be conducted as per Table 24.

Table 22. Safety and efficacy specifications in the risk management plan (draft)

Safety specifications		
Important identified risks	**Important potential risks**	**Important missing information**
• Bradycardia • Atrioventricular block • Hypotension • Hypoglycaemia and associated symptoms • Bronchospasm and bronchial hyperreactivity (aggravation of wheezing, bronchitis, and bronchiolitis) • Hyperkalaemia	• Stroke from PHACES syndrome with central nervous system disorder • Agranulocytosis	• Long-term influence including that on growth
Efficacy specifications		
• Efficacy in routine clinical use		

Table 23. Summary of additional pharmacovigilance activities and risk minimization activities in the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey	• Dissemination of information/data collected through early post-marketing phase vigilance • Provision of educational materials for parents

Table 24. Outline of specified use-results survey plan (draft)

Objectives	Safety and efficacy of propranolol in routine clinical use
Survey period	3 years
Planned number of patients	300 patients
Planned number of survey sites	Approximately 60 medical institutions
Target patients	Patients with IH
Observation period	76 weeks after the start of treatment (including the post-treatment follow-up period)
Main survey items	• Patient characteristics (sex, date of birth, height at birth, body weight, head circumference, duration of gestation period, complications, medical history, time of onset, lesion site, etc.) • Status of treatment with Hemangiol (dose, reason for dose change, reason for permanent or temporary discontinuation of treatment) • Concomitant medications and/or therapies • Vital signs, height, body weight, head circumference, and chest circumference • Adverse events (onset date, seriousness, action taken, outcome, and causal relationship to propranolol, etc.) • Time course of IH Key survey items • Bradycardia, atrioventricular block, hypotension, hypoglycaemia-related or bronchial adverse events, hyperkalaemia

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the indication and dosage and administration statements as shown below, with the following conditions. As the product has been designated as an orphan drug, the re-examination period should be 10 years. The drug product is classified as a powerful drug. The product is not classified as a biological product or a specified biological product.

Indication

Infantile hemangioma

Dosage and Administration

The usual dosage is 1 to 3 mg/kg/day of propranolol, administered orally in 2 divided doses under non-fasting conditions. The starting dose is 1 mg/kg/day, and the dose is increased in increments of 1 mg/kg at intervals of ≥2 days until the maintenance dose of 3 mg/kg/day is reached. The dose may be adjusted according to the patient's condition.

Condition for approval

The applicant is required to develop and appropriately implement a risk management plan.