Common Drug Review
Clinical Review Report

March 2017

Drug	Propranolol hydrochloride (Hemangiol)
Indication	Treatment of proliferating infantile hemangioma requiring systemic therapy: • Life- or function-threatening hemangioma • Ulcerated hemangioma with pain and/or lack of response to simple wound care measures Hemangioma with a risk of permanent scarring or disfigurement
Reimbursement request	As per indication
Dosage form(s)	3.75 mg/mL oral solution
NOC date	September 23, 2016
Manufacturer	Pierre Fabre Dermo-Cosmétique Canada Inc.

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ABBREVIATIONS

ADR	adverse drug reaction
CDR	CADTH Common Drug Review
CUP	compassionate use program
EMA	European Medicines Agency
FDA	Food and Drug Administration
IDMC	Independent Data Monitoring Committee
IH	infantile hemangioma
ITT	intention to treat
SAE	serious adverse event

EXECUTIVE SUMMARY

Introduction

Infantile hemangiomas (IHs) are the most common vascular tumours occurring in children. The incidence and prevalence of IH in Canada is uncertain; however, the manufacturer has estimated that the incidence of IH ranges from 4.5% to 10.0%. Hemangiol is an oral solution containing 3.75 mg/mL propranolol that is indicated for the treatment of proliferating IH requiring systemic therapy in the following circumstances: life- or function-threatening hemangioma; ulcerated hemangioma with pain and/or lack of response to simple wound care measures; or hemangioma with a risk of permanent scarring or disfigurement. The manufacturer has requested that propranolol oral solution receive a recommendation to reimburse in accordance with the Health Canada–approved indication.

Propranolol oral solution is the first treatment specifically indicated for the treatment of patients with IH in Canada. The product monograph states that treatment should be initiated in infants aged five weeks to five months and the age for treatment initiation should be corrected in cases of premature birth. The recommended therapeutic dosage of propranolol for the treatment of IH is 3 mg/kg/day (administered as 1.5 mg/kg twice daily). The product monograph recommends that the first dose and each dose escalation should be administered in a clinical setting where there are adequate facilities for handling adverse events, including events that require urgent measures.

The CADTH Common Drug Review (CDR) conducted a systematic review to evaluate the beneficial and harmful effects of propranolol oral solution for the treatment of proliferating IH requiring systemic therapy. The CDR review focused on the use of propranolol at the Health Canada–approved dosage regimen of 3 mg/kg/day for six months.

Results and Interpretation

Included Studies

The CDR systematic review included one adaptive, phase II/III, randomized, double-blind, placebo-controlled trial conducted to evaluate the efficacy and safety of propranolol oral solution in patients with IH requiring systemic therapy (N = 460). The inclusion criteria for Study 201 specified that patients were required to have proliferating IH requiring systemic therapy; those with the more severe forms of IH (i.e., life-threatening, function-threatening, and/or severely ulcerated) were excluded. The individual reasons for requiring systemic therapy were not collected by the manufacturer; therefore, there is uncertainty regarding how well the trial population aligns with the remaining subpopulation identified in the Health Canada–approved indication (i.e., those considered to be at risk for permanent scarring or disfigurement). Study 201 consisted of a 24-week active treatment phase followed by an open-label follow-up period of up to 72 weeks. Patients were randomized 1:2:2:2:2 to receive placebo or propranolol at one of the following dosages: 1 mg/kg/day for three months; 1 mg/kg/day for six months; 3 mg/kg/day for three months; or 3 mg/kg/day for six months. As noted above, the CDR review focused on the Health Canada–approved dosage regimen of 3 mg/kg/day for six months.

Study 201 was conducted with the following adaptive trial design:

- Stage I: To identify the dose and duration of propranolol treatment using an interim analysis conducted on the first 190 randomized patients.
- Stage II: To compare the selected dosage regimen(s) of propranolol against placebo at 24 weeks.

Based on the interim analysis, an Independent Data Monitoring Committee selected one dosage regimen for the final analysis (i.e., 3 mg/kg/day for six months).

Treatment success/failure was the primary end point of Study 201 and was defined as either: complete resolution (undefined in the protocol) or nearly complete resolution (defined as a minimal degree of telangiectasis, erythema, skin thickening, soft tissue swelling, and/or distortion of anatomical landmarks). The evaluation was based on centralized independent qualitative assessments of blinded photographs of the target IH compared with baseline. Treatment success was also evaluated by on-site study investigators, where the definition of nearly complete resolution was expanded beyond the visual assessment to include a minimal palpable component (i.e., to permit evaluation of the deep components of IH lesions), in addition to the visual components that were used by the centralized reviewers. Central reviewers, on-site study investigators, and the patient's parent(s) or guardian(s) separately evaluated the evolution of the target IH relative to the previous study visit using the following three-point scale: improvement, stabilization, or worsening. Criteria for concluding that the target IH had shown improvement, stabilization, or worsening were not provided in the study protocol and were assigned based on the judgment of the assessor (i.e., the central reviewer, on-site investigator, or parent/guardian). Additional end points in Study 201 included changes in the physical characteristics of the target hemangioma (i.e., colour and size).

The results from Study 201 are limited by the large and disproportionate number of early withdrawals from the study (65% in the placebo group versus 13% in the propranolol group). These early discontinuations from the placebo group may have biased efficacy results for the primary end point (i.e., complete or nearly complete resolution based on centralized evaluations) in favour of propranolol, as withdrawals from both groups were considered treatment failures. Conversely, the analyses for on-site evaluations conducted by the study investigators and parents/guardians may be biased against propranolol, as the withdrawals from both groups were excluded or censored and there were few placebo patients included in the week 24 evaluation (n = 19).

Efficacy

For the primary efficacy end point, a statistically significantly greater proportion of propranolol-treated patients demonstrated complete or nearly complete resolution compared with the placebo-treated patients (61/101 [60.4%] versus 2/55 [3.6%]; $P < 0.0001$). Results were similar in subgroup analyses based on age (35 to 90 days or more than 90 days) and IH location (i.e., facial or non-facial). When complete or nearly complete resolution was evaluated by the on-site study investigators, there was no statistically significant difference between the propranolol and placebo groups (24/90 [26.7%] versus 2/19 [10.5%]; $P = 0.4419$). Kaplan–Meier estimates for achieving the primary end point were 41.2% at 12 weeks and 66.8% at 24 weeks in the propranolol group and 8.3% at both time points in the placebo group ($P < 0.0001$).[1] When analyzed using the on-site assessments, there was no statistically significant difference in the Kaplan–Meier estimates for achieving complete or nearly complete resolution between the propranolol and placebo groups ($P = 0.5047$).

Treatment success or failure based on the on-site assessment of complete resolution of the target IH at week 48 was the key secondary efficacy end point of Study 201. There was no statistically significant difference between the propranolol and placebo groups with respect to the proportion of patients with complete resolution at week 48 (7.9% versus 1.8%; $P = 0.4876$).[1]

Time to first sustained improvement was defined as the interval between randomization and the time point at which the target IH demonstrated consistent improvement. At the initial week 5 assessment it

was estimated that 72.7% of propranolol-treated patients had demonstrated sustained improvement compared with 5.4% of the placebo group. At the final week 24 evaluation, the estimated proportion of patients with sustained improvement was 79.5% in the propranolol group and 9.0% in the placebo group.[1] The results from the on-site assessments were similar to the centralized assessment for propranolol (i.e., 70.9% at week 5 and 82.5% at week 24), but were considerably higher for the placebo group (i.e., 20.1% at week 5 and 32.4% at week 24). The difference between propranolol and placebo was statistically significant for both the centralized and on-site assessments (both $P < 0.0001$).[1]

Compared with the placebo-treated patients, the propranolol-treated patients demonstrated a statistically significant reduction in the surface area of the target IH at week 12 (−0.941 cm^2 versus 0.637 cm^2; $P = 0.0001$) and week 24 (−1.207 cm^2 versus 0.464 cm^2; $P = 0.0093$). The propranolol group also demonstrated statistically significant reductions in the colour density of the target IH compared with placebo at 12 and 24 weeks ($P < 0.0001$ in both cases). There were no statistically significant differences between the propranolol and placebo groups for changes in the maximum diameter of the target IH.[1]

Functional impairment, ulceration, and invasive procedures were rare in Study 201. There were no invasive procedures conducted on any target IH in either treatment group during the 24-week study period. Three placebo-treated patients experienced functional impairment that led to premature discontinuation from the study. There were no cases of functional impairment reported in the propranolol group. IH ulceration was reported for six patients in the propranolol group.

Harms

Mean exposure to the study treatments was much greater in the propranolol group compared with the placebo group (160.97 days versus 82.60 days). Due to this marked difference in exposure, any comparisons regarding the frequency of adverse events between the active and placebo groups should be interpreted with caution. The overall proportion of patients who experienced at least one adverse event was greater in the propranolol group compared with the placebo group at 24 weeks (96.0% versus 76.4%, respectively). Nasopharyngitis, diarrhea, pyrexia, teething, bronchitis, upper respiratory tract infection, cough, vomiting, and gastroenteritis were reported in at least 10% of propranolol-treated patients.

There were no deaths reported in Study 201. The proportion of patients who experienced at least one serious adverse event was similar in the propranolol and placebo groups (5.9% versus 5.5%, respectively). “Condition aggravated” (two placebo-treated patients) and “drug ineffective” (one patient in each group) were the only serious adverse events that were reported for more than one patient.

Withdrawals due to adverse events were more commonly reported in the placebo group (10.9%) compared with the propranolol group (3.0%). Similar to the evaluation of serious adverse events, “drug ineffective” was noted as a reason for discontinuation for one patient in both the propranolol and placebo groups; “condition aggravated” was cited as a reason for discontinuation for two placebo-treated patients.[1] There were no other events that resulted in the discontinuation of more than one patient. Bronchiolitis and bronchitis were cited as reasons for discontinuation for one patient in the propranolol group.

In consultation with a clinical expert, the CDR review included hypoglycemia, hypotension, bradycardia, and bronchospasm as adverse events of special interest for this review. Hypoglycemia was reported in one patient from the propranolol group (the event was not severe and did not result in discontinuation)

and no patients in the placebo group.[1] Hypotension was reported for one patient in the placebo group (1.8%) and no patients in the propranolol group. There were no events of bradycardia reported in either the propranolol or placebo groups. Three patients treated with propranolol experienced at least one event potentially linked with bronchospasm compared with one patient in the placebo group.

Place in Therapy[a]

IHs are the most common tumours occurring in early childhood, with rapid proliferation during early infancy. Slow involution follows over several years. Some IHs pose risks to young children (depending on size, location, and subtype). Complications including permanent disfigurement, ulceration and functional impairment are possible, and predicting which infant will experience those complications may be challenging.

Until recently, systemic corticosteroids were typically used for the treatment of IH with varied success and a variable safety profile. Evidence for the use of propranolol, a non-selective beta-blocker, as an effective treatment evolved over the last decade, and physicians in centres treating IH quickly adopted the drug. Before marketing authorization of propranolol for the treatment of IH, oral propranolol was available by compounding. While the use of compounded propranolol is common, a pre-formulated product may lead to a reduction in errors by having a common concentration of propranolol across pharmacies (avoiding potential changes in concentrations if a patient switches to a pharmacy that uses a different concentration), and reduce the potential for errors at the compounding step.

According to a clinical expert consulted for this review, it is likely that the approved indications cover the foreseeable reasons to treat a patient with IH. For patients for whom there may be a strong parental desire for treatment, for whom watchful waiting may be appropriate, it is possible that some physicians may offer treatment; however, this is unlikely to be a frequent occurrence. Most community physicians will not start patients on propranolol as they do not have the equipment to monitor blood pressure in infants. It is likely that most patients with IH who are eligible for treatment will attend care centres with physicians who have experience diagnosing, treating, and monitoring patients with IH.

The diagnosis, management, and follow-up of patients with IH is based on the judgment and expertise of the treating health care provider, and there is no specific test available to provide a more objective measure to indicate a patient's suitability for treatment. The initiation of treatment with propranolol is typically based on a physician's assessment of patient risk. Consequently, the management of a patient's IH would typically be driven by a reduction in the morbidity or risk of morbidity for which the treatment was initiated. There are multiple criteria that a physician uses to assess reduction of morbidity and improvement at each visit (for example, IH characteristics, photos of the hemangioma from previous visits, assessments from other physicians, and comments from parents).

Conclusions

The CDR systematic review included one adaptive phase II/III randomized, double-blind, placebo-controlled study conducted to evaluate the efficacy and safety of propranolol oral solution in patients with IH requiring systemic therapy (Study 201; N = 460). The pivotal clinical trial demonstrated that propranolol-treated patients were statistically significantly more likely to demonstrate complete or near complete resolution of the target hemangioma at 24 weeks when assessed by blinded centralized

[a] This information is based on information provided in draft form by the clinical experts consulted by CDR reviewers for the purpose of this review.

reviewers (61/101 [60.4%] versus 2/55 [3.6%]; *P* < 0.0001). However, there was no statistically significant difference when complete or nearly complete resolution was assessed by the on-site study investigators (24/90 [26.7%] versus 2/19 [10.5%]; *P* = 0.4419). The timing and rates of sustained improvement were similar when assessed by the central reviewers and the on-site investigators, with a statistically significant difference (*P* < 0.0001) between propranolol and placebo in both evaluations. The results from Study 201 are limited by the large and disproportionate number of early withdrawals from the study (65% in the placebo group versus 13% in the propranolol group). In the 72-week extension phase of Study 201, 11.5% of patients who had achieved treatment success at 24 weeks with propranolol experienced regrowth that required additional treatment. Overall, the treatment effects observed with oral propranolol were considered clinically relevant by the clinical experts consulted by CADTH and by major regulatory agencies. Nasopharyngitis, diarrhea, pyrexia, teething, bronchitis, upper respiratory tract infection, cough, vomiting, and gastroenteritis were reported in at least 10% of propranolol-treated patients. Events of hypoglycemia, bronchospasm, hypotension, and bradycardia were rare.

There were no controlled studies identified in the CDR systematic review that investigated the use of oral propranolol for patients with life-threatening, function-threatening, or ulcerated hemangiomas. Therefore, CADTH summarized observational data from the manufacturer's compassionate use program, which included patients with life-threatening, function-threatening, or ulcerated proliferating IH. The study was not designed to evaluate the efficacy of propranolol and the only effectiveness data were based on whether treatment success was cited as a reason for discontinuation. In a subset of patients for whom data were available, the manufacturer reported that 88.3% of the 697 patients discontinued from the compassionate use program as a result of efficacious treatment with Hemangiol.

TABLE 1: SUMMARY OF EFFICACY RESULTS

Outcome	Parameter	12 Weeks		24 weeks	
		Propranolol	Placebo	Propranolol	Placebo
Resolution of IH (ITT) (central assessment)	n/N (%)	NA		61/101 (60.4)	2/55 (3.6)
	RD (95% CI)			56.8% (43.7 to 66.1)	
	P value			< 0.0001	
Resolution of IH (on-site investigator)	n/N (%)	NA		24/90 (26.7)	2/19 (10.5)
	RD (95% CI)			16.1% (–6.2 to 28.7)	
	P value			0.4419	
IH surface area (cm^2)	Baseline	4.61 (4.88)	3.22 (2.56)	4.61 (4.88)	3.22 (2.56)
	Mean (SD)	−0.941 (1.557)	0.637 (2.224)	−1.207 (2.439)	0.464 (1.804)
	P value	0.0001		0.0093	
IH maximal diameter (cm)	Baseline	2.41 (1.22)	2.39 (1.09)	2.41 (1.22)	2.39 (1.09)
	Mean (SD)	−0.116 (0.661)	0.050 (0.635)	−0.179 (0.731)	−0.028 (0.743)
	P value	0.1084		0.4127	
IH colour (dE*2000)	Baseline	19.34 (7.87)	18.90 (6.71)	19.34 (7.87)	18.90 (6.71)
	Mean (SD)	–5.711 (5.975)	0.572 (5.972)	−7.369 (7.430)	−0.054 (4.824)
	P value	< 0.0001		< 0.0001	

CI = confidence interval; dE*2000 = Delta E*ab, year 2000 version; IH = infantile hemangioma; NA = not applicable; RD = risk difference; SD = standard deviation.
Source: Clinical Study Report.[1]

TABLE 2: SUMMARY OF ADVERSE EVENTS

Adverse events, n (%)	Placebo	Propranolol 3 mg/kg/day for 6 months
At least one TEAE	42 (76.4)	97 (96.0)
1 TEAE	14 (25.5)	14 (13.9)
2 TEAEs	8 (14.5)	13 (12.9)
≥ 2 TEAEs	20 (36.4)	70 (69.3)
Withdrawal due to adverse events	6 (10.9)	3 (3.0)
Serious adverse events	3 (5.5)	6 (5.9)
Notable harms		
Bronchospasm	1 (1.8)	3 (3.0)
Hypoglycemia	0 (0)	1 (1)
Hypotension[a]	1 (1.8)	0 (0)
Bradycardia[b]	0 (0)	0 (0)

TEAE = treatment-emergent adverse event.
[a] No events with propranolol 3 mg/kg/day for six months; however, one event occurred in the 1 mg/kg/day for six months group and one in the 3 mg/kg/day for three months group.
[b] No events with propranolol 3 mg/kg/day for six months; however, one event occurred in the 1 mg/kg/day for six months group and one in the 3 mg/kg/day for three months group.
Source: Clinical Study Report.[1]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Infantile hemangiomas (IHs) are the most common vascular tumours that occur in children. An IH is characterized by a proliferation phase during which the hemangioma undergoes rapid growth during the first several months of life, often reaching its maximum size within nine months.[2] This is followed by a spontaneous involution phase beginning in the later portion of the children's first year and often lasting until the child is five to 10 years of age.[2] The incidence and prevalence of IH in Canada is uncertain; however, the manufacturer has estimated that the incidence of IH ranges from 4.5% to 10.0%.[3]

The majority of infantile hemangiomas are benign; however, some can be life-threatening or have the potential to result in complications, including permanent disfigurement and damage to organ functions.[2] Table 3 provides examples of IHs for which systemic therapy would likely be initiated, based on whether the IH lesion(s) are considered to be life-threatening, functional-threatening, pose an aesthetic risk for the patient, or have become painful and ulcerated.[4]

TABLE 3: INFANTILE HEMANGIOMAS REQUIRING SYSTEMIC TREATMENT

Classification	Location or Type of IH
Life-threatening	Airways IH
	IH responsible for cardiac distress
	IH associated with severe hypothyroidism
	Compressive IH of the CNS
	Digestive IH
Functional-threatening	Orbital IH
	Ear IH
	Nasal IH
	Perineal IH
Aesthetic risk	Segmental facial IH
	Localized IH of the nose, lips or eyelids
	Breast IH in girls
Painful ulcerated IH	Multiple locations

CNS = central nervous system; IH = infantile hemangiomas.
Source: Adapted from Léauté-Labrèze et al. (2011).[4]

1.2 Standards of Therapy

Consensus statements and guidelines from experts engaged in the diagnosis and management of IH have indicated that oral propranolol is the preferred first-line treatment for IH requiring systemic therapy.[5-7] Oral corticosteroids (typically prednisolone oral solution)[5] are typically regarded as a second-line treatment option for patients who have a contraindication to propranolol or who fail to respond to treatment with propranolol.[5-7] Hemangiol is the first product with Health Canada's approval for use in the treatment of proliferating IH requiring systemic therapy. Prior to the approval and marketing of Hemangiol in Canada, oral propranolol solution was only available through compounding facilities. Neither corticosteroids nor compounded propranolol is specifically approved by Health Canada for the treatment of proliferating IH.

1.3 Drug

1.3.1 Indication and Requested Listing Criteria

Propranolol oral solution is indicated for the treatment of proliferating IH requiring systemic therapy:

- Life- or function-threatening hemangioma
- Ulcerated hemangioma with pain and/or lack of response to simple wound care measures
- Hemangioma with a risk of permanent scarring or disfigurement.

The product monograph states that treatment should be initiated in infants aged five weeks to five months and that the age for treatment initiation should be corrected in case of premature birth.[8]

Indication under review
Treatment of proliferating IH requiring systemic therapy: • Life- or function-threatening hemangioma. • Ulcerated hemangioma with pain and/or lack of response to simple wound care measures. • Hemangioma with a risk of permanent scarring or disfigurement
Reimbursement criteria requested by manufacturer
As per indication

1.3.2 Recommended Dosage

The product monograph states that therapy with propranolol oral solution should be initiated and monitored by health care professionals experienced in the use of beta-blockers in infants and in the management of IH.[8] The recommended therapeutic dose of propranolol for the treatment of IH is 3 mg/kg/day (administered as 1.5 mg/kg twice daily). The product monograph recommends a starting dosage of 1 mg/kg/day with the following up titration schedule:[8]

- Week 1: 0.5 mg/kg twice daily, taken morning and late afternoon (at least nine hours apart), during or immediately after meals
- Week 2: 1 mg/kg twice daily, taken morning and late afternoon (at least nine hours apart), during or immediately after meals
- Week 3: 1.5 mg/kg twice daily, taken morning and late afternoon (at least nine hours apart), during or immediately after meals.

The product monograph recommends that the first dose and each dose escalation should be administered in a clinical setting where there are adequate facilities for handling adverse events, including events that require urgent measures.[8]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of oral propranolol (3 mg/kg per day) for the treatment of proliferating IH requiring systemic therapy.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 4.

TABLE 4: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient population	Infants with proliferating IH requiring systemic therapy: • Life- or function-threatening hemangioma • Ulcerated hemangioma with pain and/or lack of response to simple wound care measures • Hemangioma with a risk of permanent scarring or disfigurement. **Subgroups** • Location of hemangioma • Type of hemangioma • Age of patient
Intervention	• Oral propranolol solution (3 mg/kg/day)
Comparators	• Placebo • Compounded oral propranolol solution

Outcomes	**Efficacy outcomes:**
	• Resolution[a]
	• Regrowth of hemangioma[a]
	• Complications
	• Need for surgical intervention[a]
	• Need for additional non-surgical treatments
	• Time to improvement
	• Ulceration
	• Quality of life for patient and/or caregiver[a]
	Harms outcomes:
	• Adverse events, serious adverse events, withdrawals due to adverse events
	• Mortality
	• Adverse events of special interest:
	  ○ Hypoglycemia
	  ○ Hypotension
	  ○ Bradycardia
	  ○ Bronchospasm

Study design	Published and unpublished randomized controlled trials

IH = infantile hemangioma.
[a] These outcomes were identified as being of particular importance to patients in the input received from patient groups.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records & daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Hemangiol (propranolol) and hemangioma.

Methodological filters were applied to limit retrieval to randomized controlled trials. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on September 22, 2016. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on January 18, 2017. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters): Advisories & Warnings, Background, Clinical Practice Guidelines, Databases (free), Health Economics, Health Technology Assessment Agencies, Internet Search, Open Access Journals, Regulatory Approvals. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 5.

3. RESULTS

3.1 Findings from the Literature

One study (V00400 SB 201; Study 201) was identified from the literature search and included in the CDR systematic review (Figure 1). Details of the included study are summarized in Table 5 and described in Section 3.2. A list of excluded studies is presented in Appendix 3.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

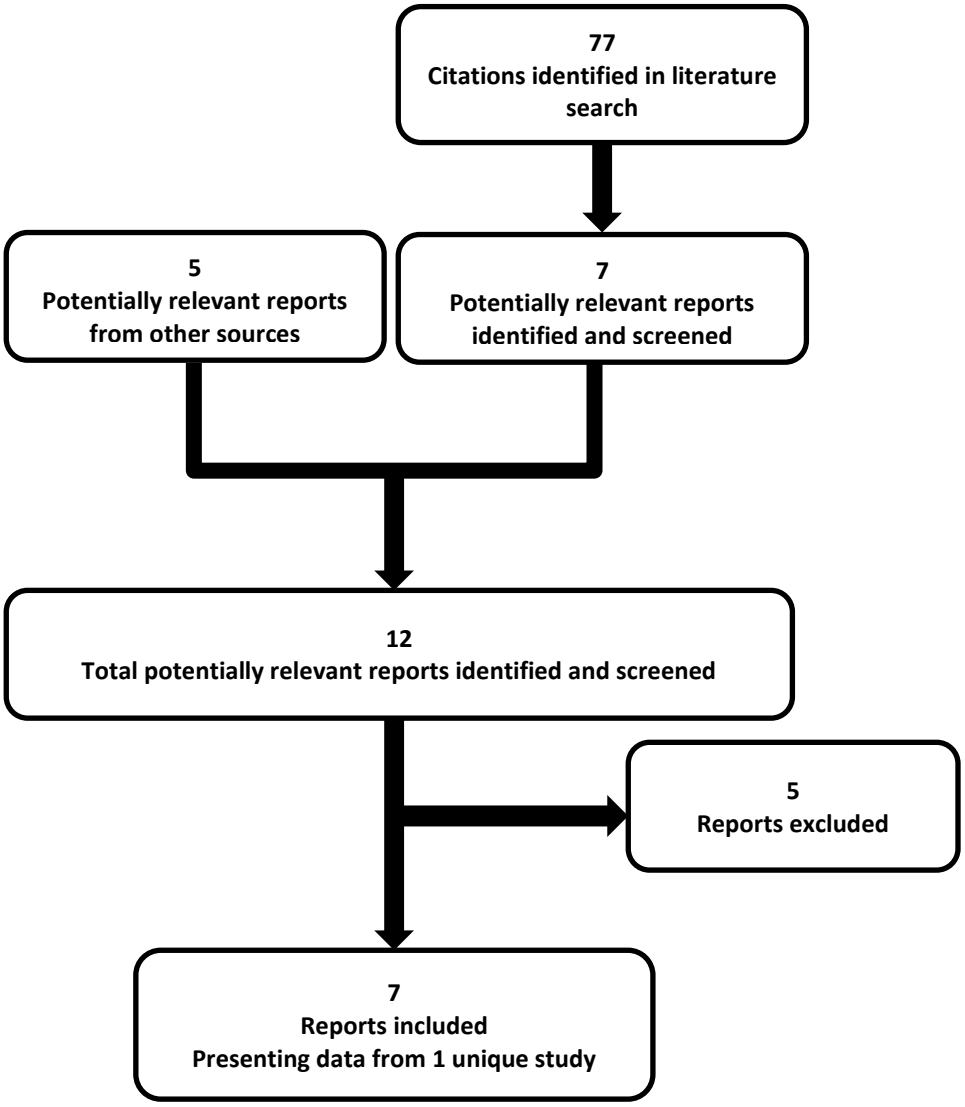


TABLE 5: DETAILS OF INCLUDED STUDIES

		Study 201	
DESIGNS AND POPULATIONS	**Study Design**	Multi-centre, adaptive phase II/III, double-blind, placebo-controlled RCT	
	Locations	16 countries (Australia, Canada, Czech Republic, France, Germany, Hungary, Italy, Lithuania, Mexico, New Zealand, Peru, Poland, Romania, Russia, Spain, US)	
	Randomized (N)	460	
	Inclusion Criteria	• 35 to 150 days old • Proliferating IH requiring systemic therapy was present anywhere except on the diaper area, with largest diameter of at least 1.5 cm	
	Exclusion Criteria	• One or more of the following types of IH were present: life-threatening IH, function-threatening IH; ulcerated IH with pain and lack of response to simple wound care measures. • One or more of the following: congenital hemangioma; Kasabach–Merritt syndrome; bronchial asthma; bronchospasm; hypoglycemia; pheochromocytoma; hypotension; second- or third-degree heart block; cardiogenic shock; metabolic acidosis; bradycardia (< 80 bpm); severe arterial circulatory disturbances; Raynaud's phenomenon; sick sinus syndrome; uncontrolled HF or Prinzmetal angina; PHACES with CNS involvement, LVEF ≤ 40%; cardiomyopathy; hereditary arrhythmia disorder. • Previous exposure to corticosteroids, imiquimod, vincristine, alfa-interferon, or beta-blockers. • Previous surgery or laser therapy for IH. • Patient and/or mother (if breastfeeding) had received ≥ 1 of the following agents within 14 days prior to randomization: anesthetic agents; anti-arrhythmics; calcium channel blockers; ACE inhibitors; inotropic agents; vasodilators; hypoglycemic agents; CYP2D6, CYP1A2, CYP2C19 inducers; anti-ulcer drugs, metoclopramide, NSAIDs at anti-inflammatory dose, sympathomimetic agents and parenteral adrenalin, benzodiazepines, neuroleptics.	
DRUGS	**Intervention**	**Interventions**	**Analysis**
		• Propranolol (1 mg/kg/day for 3 months)	Stage I
		• Propranolol (3 mg/kg/day for 3 months)	Stage I
		• Propranolol (1 mg/kg/day for 6 months)	Stage I
		• Propranolol (3 mg/kg/day for 6 months)	Stage I and II
	Comparator	• Placebo	
DURATION	**Phase**		
	Run-in	2 weeks	
	Double-blind	24 weeks	
	Follow-up	72 weeks	
OUTCOMES	**Primary End Point**	Complete/nearly complete resolution of the target IH at week 24 compared with baseline	

		Study 201
	Other End Points	• Success/failure (weeks 12, 36, 48, 72, and 96) • Time to first sustained complete/nearly complete resolution (24 and 96 weeks) • Time to first failure (up to week 96, from weeks 24 to 96) • Improvement, stabilization or worsening of target IH (each visit) • Global improvement (weeks 5 to 24) • Time to first sustained improvement (up to 24 weeks) • Change in size and colour of target IH at 12 and 24 weeks • Target IH complications: functional impairment/ulceration/hemorrhaging • Need for invasive procedures on the target IH • Need for IH treatment during the follow-up period
NOTES	**Publications**	• Léauté-Labrèze et al. (2014)[9,10] • Clinical Study Report[1] • FDA Medical Review[11] and Statistical Review[12] • European Public Assessment Report[13] and Australian Public Assessment Report[14] • Health Canada Pharmaceutical Safety and Efficacy Report[15] • Clinicaltrials.gov[16] • Product Monograph[8]

ACE = angiotensin converting enzyme; bpm = beats per minute; CNS = central nervous system; FDA = Food and Drug Administration; HF = heart failure; IH = infantile hemangioma; LVEF = left ventricle ejection fraction; NSAID = nonsteroidal anti-inflammatory drug; PHACES = posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects, eye abnormalities, sternal cleft and supraumbilical raphe syndrome; RCT = randomized controlled trial.

Source: Clinical Study Report.[1]

3.2 Included Studies

3.2.1 Description of Studies

Study 201 consisted of a 24-week active treatment followed by an open-label follow-up period of up to 72 weeks. Patients were randomized 1:2:2:2:2 to receive placebo or propranolol at one of the following doses: 1 mg/kg/day for three months; 1 mg/kg/day for six months; 3 mg/kg/day for three months; or 3 mg/kg/day for six months. Randomization was conducted using an interactive voice response system (IVRS) with stratification by age group (35 to 90 days and 91 to 150 days) and IH localization (facial and non-facial). Study 201 was conducted at 56 sites in 16 countries, with the majority of study participants enrolled at sites in Western Europe (51.5%). There were 18 patients enrolled at Canadian sites, including two in the placebo group (3.6%) and two in the propranolol 3 mg/kg/day for six months group (2.0%).[1]

Study 201 was conducted in the following two stages:[1]

- Stage I: To identify the dose and duration of propranolol treatment using an interim analysis conducted on the first 190 randomized patients.
- Stage II: To compare the selected dosage regimen(s) of propranolol against placebo at 24 weeks.

The stage I interim analysis was conducted based on 188 patients who received the study treatments. The results for this analysis are summarized in Table 6. A statistically significantly greater proportion of patients achieved complete or nearly complete resolution of their target IH in the 3 mg/kg/day for six months group (62.8%) and 1 mg/kg/day for six months group (37.5%) compared with the placebo group (8.0%). There were no statistically significant differences between either of the three-month treatment regimens and placebo. Based on the results of this interim analysis, the Independent Data Monitoring Committee (IDMC) recommended that the trial continue using only the 3 mg/kg/day for the six months group and the placebo group. The manufacturer noted that randomization of all patients to all five treatment groups was completed before the IDMC had selected the 3 mg/kg/day for six months

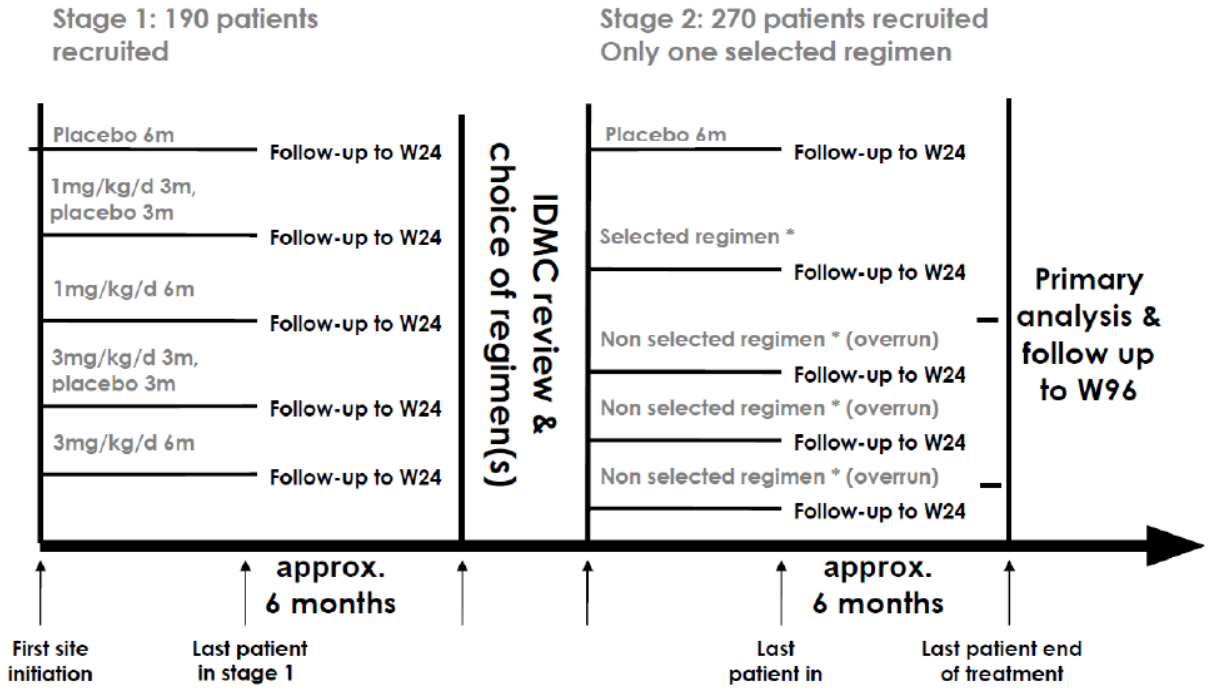
group as the regimen of choice; therefore, the sample sizes are similar across all of the treatment groups.[1]

TABLE 6: INTERIM ANALYSIS FOR DOSE SELECTION

PROPRANOLOL GROUP (N)	RESOLUTION OF TARGET IH, N (%)		*P* VALUE
	PROPRANOLOL	PLACEBO (N =25)	
1 mg/kg/day 3 months (N = 41)	4 (9.8%)	2 (8.0%)	0.4049
1 mg/kg/day 6 months (N = 40)	15 (37.5%)		0.0042
3 mg/kg/day 3 months (N = 39)	3 (7.7%)		0.5178
3 mg/kg/day 6 months (N = 43)	27 (62.8%)		< 0.0001

IH = infantile hemangioma.
Source: Clinical Study Report.[1]

FIGURE 2: SCHEMATIC SHOWING STAGE I AND STAGE II OF STUDY 201



d = day; IDMC = Independent Data Monitoring Committee; m = month; W = week.
Source: FDA Medical Review.[11]

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Patients aged 35 to 150 days were eligible for Study 201 if they were diagnosed with proliferating IH requiring systemic therapy that was present anywhere except on the diaper area. The largest diameter of the target IH lesion had to be at least 1.5 cm. The study protocol did not specify criteria regarding why a particular lesion was considered to require systemic therapy; this was based on the opinion of the study investigators and the reasons were not captured or reported.[14] Patients with IH considered to be life-threatening or function-threatening were excluded from the trial, as were patients with an ulcerated IH demonstrating pain and a lack of response to simple wound care measures. The trial was restricted to

patients with IH while patients with congenital hemangioma were excluded. Study 201 had a number of important exclusion criteria related to medical conditions, including those related to cardiac function, respiratory function, circulation, and metabolic conditions (e.g., hypoglycemia or acidosis).[1]

b) Baseline Patient Characteristics

Key baseline and demographic characteristics are summarized in Table 7. There were more females than males enrolled in Study 201 (69% versus 31%). A majority of the study participants were white/non-Hispanic (72%). The mean age of participants was 103.9 days, mean weight at baseline was 5.9 kg, and 26.8% of patients were born prematurely. A greater proportion of patients in the placebo group were born prematurely compared with those in the propranolol group (34.5% versus 23.8%). The mean age of IH onset was approximately 15 days in the placebo group and 13 days in the propranolol group. The mean time since IH onset was approximately 89 days in both groups. There were no patients with PHACE syndrome[b] in either the propranolol 3 mg/kg/day for six months group or the placebo group.[1]

TABLE 7: SUMMARY OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Characteristics, n (%)		Placebo (N = 55)	Propranolol 3 mg/kg/day for 6 months (N = 101)
Sex	Male	17 (30.9)	31 (30.7)
	Female	38 (69.1)	70 (69.3)
Age at baseline	Mean (SD)	103.93 (31.0)	101.66 (31.0)
	35 to 90 days	20 (36.4)	37 (36.6)
	> 90 days	35 (63.6)	64 (63.4)
Age at IH onset	Mean (SD), days	14.93 (22.63)	12.92 (15.36)
	≤ 90 days	54 (98.2)	101 (100.0)
	> 90 days	1 (1.8)	0 (0.0)
Time from IH onset	Mean (SD), days	89.0 (35.76)	88.7 (33.85)
Patient born prematurely	Yes	19 (34.5)	24 (23.8)
	No	36 (65.5)	77 (76.2)
Birth weight (kg)	Mean (SD)	2.93 (0.79)	3.06 (0.77)

IH = infantile hemangioma; SD = standard deviation.
Source: Clinical Study Report.[1]

c) Baseline Hemangioma Characteristics

Key baseline characteristics with respect to the patients' hemangiomas are summarized in Table 8. Target hemangiomas were primarily located on the head of patients (70%). The majority of target hemangiomas were localized (89.0%), with a minority classified as being segmental or considered to be indeterminate (5.5% each). The placebo group had a greater proportion of patients with indeterminate hemangioma compared with the propranolol 3 mg/kg/day group (9.1% versus 5.5%, respectively).[1] Hemangiomas located on the perioral, lower or upper lip area were slightly more common in the propranolol group compared with the placebo group (12.9% versus 9.1%, respectively) and those

[b] PHACES syndrome refers to a relatively rare condition with the following clinical manifestations: posterior fossa anomalies, hemangioma, arterial anomalies, cardiac anomalies, eye anomalies, and sternal anomalies.[17] The product monograph states that propranolol may increase the risk of stroke some patients with PHACE syndrome (e.g., those with severe cerebrovascular anomalies) and recommends that specialist advice be sought for such patients.[8]

located on the forehead were less common in the propranolol group compared with the placebo group (16.4% versus 6.9%).[1] The proportion of patients with IH that had resulted in a slight distortion of local anatomical landmarks was greater in the propranolol group compared with the placebo group (33.7% versus 21.8%, respectively) and the proportion with no distortion was greater in the placebo group compared with the propranolol group (58.2% versus 45.5%, respectively).[1] With respect to the colour intensity of the target IH, the majority of IHs were classified as being bright red (54.5% in the propranolol group and 50.0% in the placebo group) or dull red (26.7% in the propranolol group and 29.6% in the placebo group).[1] A majority of the patients enrolled in Study 201 had IH lesions with definite or possible deep components.

TABLE 8: SUMMARY OF HEMANGIOMA CHARACTERISTICS AT BASELINE

Characteristics, n (%)		Placebo (N = 55)	Propranolol 3 mg/kg/day for 6 months (N = 101)
IH site	Facial	40 (72.7)	71 (70.3)
	Non-facial	15 (27.3)	30 (29.7)
Morphological subtype of the target IH	Segmental	2 (3.6)	5 (5.0)
	Localized	48 (87.3)	91 (90.1)
	Indeterminate	5 (9.1)	5 (5.0)
IH colour intensity	Barely perceptible	4 (7.4)	4 (4.0)
	Pale pink or mottled pink-red	3 (5.6)	4 (4.0)
	Red with central pallor	4 (7.4)	11 (10.9)
	Dull red	16 (29.6)	27 (26.7)
	Bright red	27 (50.0)	55 (54.5)
IH tenseness	Not appreciable	2 (3.6)	3 (3.0)
	Soft	22 (40.0)	48 (47.5)
	Firm	31 (56.4)	50 (49.5)
IH superficial component	Flat	4 (7.3)	9 (8.9)
	Slight elevation	19 (34.5)	22 (21.8)
	Moderate elevation	15 (27.3)	31 (30.7)
	Marked elevation	17 (30.9)	39 (38.6)
IH deep component	None	20 (36.4)	29 (28.7)
	Possible presence	10 (18.2)	16 (15.8)
	Definite presence	25 (45.5)	56 (55.4)
IH distortion of local anatomical landmarks	None	32 (58.2)	46 (45.5)
	Slight distortion	12 (21.8)	34 (33.7)
	Marked distortion	11 (20.0)	21 (20.8)
Primary anatomical location of the target IH	Forehead	9 (16.4)	7 (6.9)
	Glabella	1 (1.8)	4 (4.0)
	Nasal tip	4 (7.3)	8 (7.9)
	Nasal sidewall	1 (1.8)	6 (5.9)
	Perioral, lower/upper lip	5 (9.1)	13 (12.9)
	Cheek	5 (9.1)	8 (7.9)
	Ear	2 (3.6)	2 (2.0)
	Chin	1 (1.8)	1 (1.0)
	Neck	2 (3.6)	4 (4.0)

Characteristics, n (%)		Placebo (N = 55)	Propranolol 3 mg/kg/day for 6 months (N = 101)
	Scalp	5 (9.1)	7 (6.9)
	Chest	0 (0.0)	7 (6.9)
	Abdomen	3 (5.5)	2 (2.0)
	Back	2 (3.6)	2 (2.0)
	Shoulder	1 (1.8)	1 (1.0)
	Upper arm	1 (1.8)	3 (3.0)
	Forearm	1 (1.8)	2 (2.0)
	Hand	1 (1.8)	2 (2.0)
	Thigh	2 (3.6)	1 (1.0)
	Lower leg	2 (3.6)	1 (1.0)
	Foot	1 (1.8)	1 (1.0)
	Nasal area	1 (1.8)	0 (0.0)
	Periauricular, parotid	0 (0.0)	2 (2.0)
	Periocular	4 (7.3)	11 (10.9)
	Other	1 (1.8)	6 (5.9)

IH = infantile hemangioma.
Source: Clinical Study Report.[1]

3.2.3 Interventions

Patients were randomized to one of the following regimens: propranolol 1 mg/kg/day for three months; propranolol 1 mg/kg/day for six months; propranolol 3 mg/kg/day for three months; propranolol 3 mg/kg/day for six months; or placebo for six months. Patients who were randomized to one of the two 3 mg/kg/day regimens started with a dose of 1 mg/kg/day at day 1, which was increased to 2 mg/kg/day in the second week of the trial and 3 mg/kg/day in the third week of the trial (i.e., identical to the recommendations in the current product monograph).[1,8] To maintain blinding, patients in the 1 mg/kg/day groups and those in the placebo group underwent a dummy titration period during the first three weeks of the trial.[1] In addition, those in the three-month treatment regimens were administered placebo after three months of active treatment.[1]

3.2.4 Outcomes

a) Centralized Review of Treatment Success or Failure

Treatment success or failure was the primary end point of Study 201. Treatment success was defined as either: complete resolution (undefined in the protocol) or nearly complete resolution (defined as a minimal degree of telangiectasis, erythema, skin thickening, soft tissue swelling and/or distortion of anatomical landmarks).[1] The evaluation was based on centralized independent qualitative assessments of intra-patient blinded photographs of the target IH compared with baseline.[1] Any of the following were considered as treatment failures: early withdrawal from the study treatment; receipt of prohibited treatments; or missing the 24-week evaluation for patients who completed the 24-week study period.[1]

The study protocol states that at least two photographs of the target IH for each patient were taken by the on-site study investigators at each study visit (day 0 to week 96). At a minimum, the two photographs were to be taken as follows:

- Photograph 1: front-on view with the image plane parallel to the target IH

- Photograph 2: side-on view with the image plane at a different angle to allow the thickness of the lesion to be visualized.[1]

As shown in Table 9, two types of qualitative assessments were performed by the central reviewers: one comparing the most recent photographs with those obtained at baseline; and one comparing the most recent photographs with those obtained at the previous study visit.[1] The readers also evaluated the quality of the photographs as unevaluable, poor quality, or good quality (data were not reported). The manufacturer reported that the photographs could be retaken in case of unacceptable quality (while the patient was still on-site). After independent evaluation of the photographs, the two reviewers had a meeting to discuss any discrepant evaluations and reach consensus on a final evaluation.[1]

TABLE 9: CENTRALIZED ASSESSMENT OF TARGET IH PHOTOGRAPHS

Assessment	Description	Outcomes
Type I	Paired photographs were placed with the baseline to the left and the post-baseline to the right. Readers were to evaluate whether the target IH had completely or nearly completely resolved in the photographs to the right.	• Resolution at week 24[a] • Resolution at week 12, 36, 48, 72, 96 • Time to sustained resolution • Time to first failure
Type II	Paired groups of photographs were placed side-by-side, but in random order (i.e., photographs on the left did not necessarily correspond to the earlier visit). The readers evaluated whether the target IH was in a better, stable, or worse state in the photographs on the right compared with the photographs on the left.	• Time to sustained improvement • Improvement, stabilization, worsening of target IH • Time to worsening

IH = infantile hemangioma.
[a] Primary end point of Study 201.
Source: Clinical Study Report.[1]

b) On-site Review of Treatment Success or Failure

The key secondary efficacy end point of Study 201 was the treatment success or failure based on the on-site assessment of complete resolution of the target hemangioma at week 48.[1] Treatment success was defined as complete resolution of the target hemangioma with no sequelae or with minimal sequelae. For this evaluation, minimal sequelae were defined as minimal telangiectasis, macular discoloration, and/or textural change. Marked sequelae were defined as marked textural change with or without distortion of anatomical landmarks or skin contours.[1]

Similar to the central reviewers, the on-site study investigators also evaluated complete or nearly complete resolution relative to baseline.[1] The definition of nearly complete resolution was expanded beyond the visual assessment to include a minimal palpable component, in addition to the visual components of minimal degree of telangiectasis, erythema, skin thickening, soft tissue swelling or distortion of anatomical landmarks. The study protocol states that the investigators could use photographs to assist in their evaluations (i.e., suggesting that this was optional).[1]

c) Target IH Evolution

Central reviewers, on-site study investigators, and the patient's parent(s) or guardian(s) individually evaluated the evolution of the target hemangioma relative to the previous study visit using the following three-point scale: improvement, stabilization, or worsening.[1] Criteria for concluding that the target IH had shown improvement, stabilization, or worsening were not provided in the study protocol and were

assigned based on the judgment of the assessor (i.e., central reviewer, on-site investigator, or parent/guardian). These assessments were also used to evaluate time to first sustained improvement, which was defined as the interval between randomization and the time point at which the target IH demonstrated consistent improvement.

d) Size and Colour of the Target IH

Changes in the size and colour of the target hemangioma were assessed by the central reviewers. The photographs included a colour chart to enable calibration of the colour and size using the methods described by Vander Haeghen et al.[18] Front-on view photographs from baseline were compared with those obtained at week 12 and week 24 to quantitatively evaluate changes from baseline in the size and color of the target hemangioma.[1]

e) Target IH Complications and Need for Interventions

On-site investigators documented the following complications related to the target IH: functional impairment, ulceration, or hemorrhaging.[1] Categorical end points were also used to capture whether the patient underwent an invasive procedure for the target hemangioma during the study.[1]

3.2.5 Statistical Analysis

a) Primary End Point

Study 201 was conducted using a seamless adaptive design. The statistical analysis of the primary end point was conducted using the methodology described by Posch et al.[19] The statistical methodology controlled the type I error rate at the nominal level of 0.005. The following statistical tests were planned for the primary end point (i.e., complete or nearly complete resolution at 24 weeks):

- Stage I: the *P* values for the four propranolol dosage regimens versus placebo (i.e., 1 mg/kg/day for three months; 3 mg/kg/day for three months, 1 mg/kg/day for six months, and 3 mg/kg/day for six months) were calculated using a one-sided Z-test for proportions with pooled variance estimates.
- Stage II: the individual *P* value for the selected regimen (i.e., and 3 mg/kg/day for six months versus placebo) was calculated using one-sided Z-test for proportions with pooled variance estimates.

b) Secondary End Points

Complete or nearly complete resolution according to the on-site study investigators were evaluated using the same method as the primary end point (i.e., a one-sided Z-test for proportions).[1] Study 201 included several time-to-event measurements, including time to sustained complete or nearly complete resolution and time to sustained improvement.[1] For these analyses, any patients who discontinued the trial or received prohibited IH medications were right-censored.[1] The probability of patients demonstrating time to sustained complete or nearly complete resolution or sustained improvement up to week 24 were estimated using the Kaplan–Meier method on the pooled data across both stages of the trial. The propranolol and placebo groups were compared using a one-sided log-rank test. For the evaluation of IH evolution (i.e., improvement, stabilization, or worsening) the propranolol and placebo groups were compared using a combination test for ordinal regression based on a one-sided Z-test.[1]

c) Multiple Comparisons

All statistical tests for the week 24 efficacy analysis were conducted using an alpha level of 0.005. For the secondary end points, only the key secondary end point (i.e., on-site assessment of complete resolution) was analyzed using adjustment for multiplicity (i.e., alpha of 0.0025).[1] All other analyses of secondary end points were considered exploratory and were not adjusted for multiple comparisons.[1]

d) Sample Size Calculation

The manufacturer's sample size calculation was based on the following estimated success rates for complete or nearly complete resolution at 24 weeks: 55% in the 3 mg/kg/day for the six months group; 40% in the 3 mg/kg/day for the three months group; 30% in the 1 mg/kg/day for the six months group; 20% in the 1 mg/kg/day for the three months group; and 10% in the placebo group. At the time of the interim analysis for dose selection, the IDMC could also recommend that the sample size be increased if there was less than 80% power to demonstrate superiority of the selected propranolol dosage regimen(s) compared with placebo. The manufacturer reported that the required sample size would be 390 patients if one regimen was selected for use in stage II or 410 if two regimens were selected. The manufacturer reported that if only a single dosage regimen was selected for use in stage II, the sample size was calculated to achieve at least 98% power with an overall type I error rate of alpha = 0.005.[1]

e) Analysis Populations

The key data sets on which the efficacy analyses were performed are the following:[1]

- Intention-to-treat (ITT) data set: all randomized patients in stage I and all patients in stage II who were randomized to placebo or 3 mg/kg/day propranolol and who received at least one dose of the study drugs.
- Per-protocol set: a subset of the ITT data set composed of patients without any major protocol deviations.
- Safety data set: all randomized patients who received at least one dose of the study drugs.

3.3 Patient Disposition

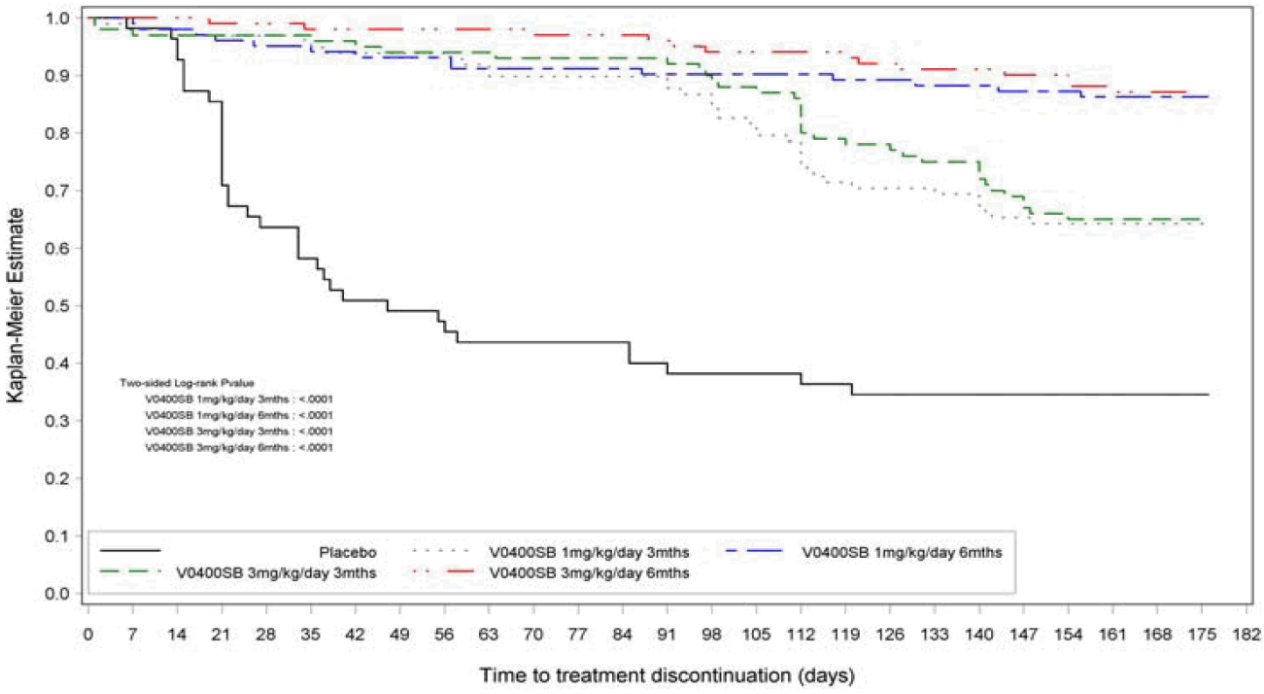
Patient disposition for Study 201 is summarized in Table 10. A total of 512 patients were screened for enrolment and 460 were randomized 1:2:2:2:2 to receive placebo (n = 55) or propranolol at one of the following doses: 1 mg/kg/day for three months (n = 99); 1 mg/kg/day for six months (n = 103); 3 mg/kg/day for three months (n = 101); or 3 mg/kg/day for six months (n = 102).[1] Eighty-six per cent of patients randomized to propranolol at the recommended dose and duration (i.e., 3 mg/kg/day for six months) completed the study. Of the 13% who discontinued treatment, inadequate response was the most commonly cited reason (nine of 13 patients).[1] The majority of patients (65%) in the placebo group discontinued the study, with inadequate response cited as a reason for nearly all discontinuations (32/36).[1] As shown in Figure 3, withdrawal from the placebo group occurred at a relatively rapid rate within the first six weeks of the trial.

TABLE 10: PATIENT DISPOSITION FROM STUDY 201

Disposition, n (%)	Placebo	Propranolol 3 mg/kg/day for 6 months
Randomized	55	102
Completed	19 (35)	88 (86)
Discontinued	36 (65)	13 (13)
Inadequate response	32 (58)	9 (9)
AE	0 (0)	0 (0)
AE not linked to treatment	2 (4)	1 (1)
Withdrawn consent	7 (13)	4 (4)
Other	1 (2)	1 (1)
Not treated	0 (0)	1 (1)

AE = adverse event.
Source: Léauté-Labrèze et al. (2014).[9]

FIGURE 3: TIME TO TREATMENT DISCONTINUATION IN STUDY 201



AE = adverse event; mths = months; V0400SB = oral propranolol solution.
Source: US Food and Drug Administration Medical Review.[11]

3.4 Exposure to Study Treatments

The exposure to propranolol and placebo in Study 201 are summarized in Table 11. Mean exposure to the study treatment was greater in the propranolol group (160.97 days) compared with the placebo group (82.60 days).

TABLE 11: EXPOSURE TO STUDY TREATMENTS

Exposure (days)	Placebo	Propranolol			
		1 mg/kg/day for 3 months	1 mg/kg/day for 6 months	3 mg/kg/day for 3 months	3 mg/kg/day for 6 months
Mean (SD)	82.60 (67.31)	142.74 (43.73)	156.92 (39.89)	146.61 (38.45)	160.97 (26.59)
Median	47.0	168.0	168.0	167.5	168.0
Min, Max	6,176	1,214	7,220	7,176	19,190

min = minimum; max = maximum; SD = standard deviation.
Source: Clinical Study Report.[1]

3.5 Critical Appraisal

3.5.1 Internal Validity

The adaptive trial design used for Study 201 was considered appropriate by Health Canada statisticians.[15] Randomization was conducted using appropriate methods with adequate measures to conceal treatment allocation (i.e., IVRS). The variables used to stratify randomization were relevant prognostic factors (e.g., IH location and age). Key baseline and demographic characteristics were well balanced across the propranolol and placebo treatment groups.[11,13] Reviewers for the US Food and Drug

Administration (FDA) noted that there were no apparent differences in the effect of propranolol by site of lesion, race, age, sex, or geographic region.[11]

It is possible that randomization was compromised due to the large and disproportionate number of early withdrawals from the study (i.e., 65% in the placebo group versus 13% in the propranolol group).[14] The early discontinuations from the placebo group may have biased efficacy results for the primary end point in favour of propranolol, as withdrawals from both groups were considered to be treatment failures, which may have underestimated the proportion of patients who would have demonstrated spontaneous resolution of their IH over the 24-week study.[14] However, lack of efficacy was cited as the reason for withdrawal for 32 of 36 patients in the placebo group, suggesting that categorizing these early withdrawals as treatment failures is a reasonable reflection of their clinical situation (as judged by the study investigator). In addition, the clinical expert consulted by CADTH suggested that IH lesions do not typically enter a regression phase until at least the latter part of the first year; therefore, the expected rate of spontaneous regression would be low at 24 weeks. The FDA also conducted a series of exploratory sensitivity analyses to examine the potential impact of these early withdrawals (e.g., completer analysis with multiple imputation) and reported that results were supportive of the primary efficacy analysis.[11] The analyses for on-site evaluations conducted by the study investigators and parents/guardians may be biased against propranolol, as the withdrawals from both groups were excluded or censored. The limited number of placebo-treated patients (n = 19) included in the week 24 on-site evaluations likely represents an enriched study population and may have overestimated the proportion of patients with a response in the absence of active treatment.

Given that the inclusion criteria of Study 201 were restricted to patients with IH requiring systemic therapy, watchful waiting and subsequent collection of data regarding spontaneous resolution may not have been feasible or ethical for this patient population. Reviewers for the FDA noted that the early discontinuation of patients from the placebo group was not surprising and that children with IH require treatment as soon as possible or permanent skin lesions could result.[11] Overall, the Canadian indication for oral propranolol is restricted to situations where the IH requires systemic therapy. Therefore, it is likely that all patients who fall within the approved indication would receive some form of intervention in clinical practice (i.e., watchful waiting for spontaneous resolution is unlikely to be applied for the indicated patient population).

The proportion of patients with complete resolution and the proportion of patients with nearly complete resolution were not reported separately for the centralized assessment of the primary end point; however, these proportions were reported separately for the on-site investigator assessments. Health Canada requested these data during their review, but the manufacturer indicated that the end point was binary and that a breakdown of response type was not captured or reported in the study.[15] There was no analysis conducted to evaluate whether patients who achieved "nearly complete resolution" eventually achieved "complete resolution" of the target hemangioma. In addition, it is unclear if nearly complete resolution would be considered treatment success in clinical practice or if patients would continue to be treated until the target IH had resolved completely.

The European Medicines Agency (EMA) noted that the primary outcome (i.e., complete or nearly complete resolution) of Study 201 was established following discussions with regulatory agencies.[13] Study 201 included standardized procedures for acquiring and ensuring the quality of the photographs for IH evaluation,[1,13] and Health Canada noted the use of photography to evaluate the efficacy of IH treatment was a validated approach.[15] The definition of nearly complete resolution included a minimal degree of skin thickening and soft tissue swelling.[1] The study protocol required study investigators to

obtain side-view photographs to capture changes in thickening and swelling. However, some regulatory reviewers expressed doubts regarding how accurately these characteristics could be evaluated using two-dimensional photographs.[14] The criteria used to evaluate resolution was the same for the central reviewers and the on-site investigators, with the exception that the on-site evaluation could also evaluate the deep component of lesions.[1,14] A majority of the patients enrolled in Study 201 had IH lesions that had definite or possible deep components (Table 8); therefore, changes in the deep component of the lesions could have influenced the results reported by the on-site investigators.

For the primary efficacy analysis, resolution was assessed using intra-patient blinded central review.[1] The centralized review process was conducted by two reviewers, which would likely increase consistency in the interpretation of the results compared with the interpretation of the investigators located at the 56 different study sites in 16 countries. However, a comparison of the results demonstrates a substantial difference in the interpretation and application of the response criteria by the central reviewers and the study investigators, particularly for the propranolol-treated patients, for whom response rates varied from 60.4% (61/101) based on centralized review to 26.7% (24/90) based on investigator review.[14] This was primarily due to 38 patients who were considered to have complete or nearly complete resolution by the central reviewers and not by the study investigators.[14] The manufacturer conducted an analysis to examine the divergent results between the centralized and on-site assessments of complete or nearly complete resolution. The manufacturer reported that the differences were primarily due to the application of a more stringent threshold for success by on-site investigators.[20] Both the timing and rates of sustained improvement were similar when assessed by the central reviewers and the on-site investigators,[21] suggesting that these criteria may have been easier to apply consistently in the two different evaluation contexts (i.e., clinic versus photographs alone).

Overall, the clinical examination of the target IH that was conducted by the on-site study investigators is a more accurate reflection of how patient response to propranolol treatment would be evaluated in Canadian clinical practice (i.e., it has greater external validity). However, Health Canada and the clinical expert consulted by CADTH for this review indicated that the evaluation conducted by centralized assessors of photographs likely represents a more objective measurement of the treatment effect (i.e., it has greater internal validity).[15] The clinical expert consulted by CADTH also indicated that photographs from previous visits are often used to evaluate responses at subsequent visits in major pediatric dermatology clinics in Canada.

The number of patients who withdrew from the trial exceeded the number that was anticipated in the statistical analysis plan for Study 201.[14] Due to the high rate of withdrawal in the placebo group, the overall mean exposure to the study treatments was nearly double in the propranolol group compared with the placebo group (161 days versus 83 days).[1] This may bias the adverse event data from Study 201 against propranolol, as it was not adjusted for differences in exposure to the study treatments. As noted previously, early discontinuation from the placebo may have biased efficacy results for the primary end point in favour of propranolol, as withdrawals from both groups were considered to be treatment failures.

Propranolol and placebo were administered in a double-blind manner. Dummy titration periods were used to ensure the dosage regimens were similar across each of the active treatment groups (i.e., 1 mg/kg/day and 3 mg/kg/day) as well as the placebo group. Patients in the three-month propranolol treatment groups were administered placebo treatments in months 3 to 6 to maintain blinding following discontinuation of the active treatment. The placebo solution used in Study 201 contained the same excipients as the propranolol solution, including the flavouring. The interim analysis (stage I) was

completed by an independent statistician and was reviewed by an IDMC; hence, the study personnel were not unblinded.[1,11] The adverse event profile for propranolol was unlikely to compromise blinding of the study; however, the FDA noted that the relatively rapid onset of action for propranolol treatment would have been visually noticeable to investigators and caregivers.[11] This may have influenced the decision to withdraw some patients in the placebo group for perceived lack of efficacy.

The use of prohibited concomitant medication for IH was more commonly reported in the propranolol group (14.7%) compared with the placebo group (3.6%).[1] The manufacturer stated the observed imbalance could be partially explained by the shorter treatment duration for patients in the placebo group. The manufacturer considered the major use of prohibited IH medication to be a major protocol violation and these patients were considered to be treatment failures in the per-protocol analysis.[1] Health Canada reviewers questioned the manufacturer regarding this discrepancy in protocol violations and accepted the manufacturer's explanation of the violations and conclusion that these were unlikely to significantly affect the results (details were not reported).[15]

3.5.2 External Validity

Oral propranolol is indicated for the treatment of proliferating IH requiring systemic therapy, in one or more of the following clinical circumstances: life- or function-threatening hemangioma; ulcerated hemangioma with pain and/or lack of response to simple wound care measures; and/or hemangioma with a risk of permanent scarring or disfigurement.[8] The inclusion criteria for Study 201 specified that patients were required to have proliferating IH requiring systemic therapy; those with the more severe forms of IH (i.e., life-threatening, function-threatening, and/or severely ulcerated) were excluded. The individual reasons for requiring systemic therapy were not collected by the manufacturer;[14] therefore, there is uncertainty regarding how well the trial population aligns with the remaining subpopulation identified in the Health Canada–approved indication (i.e., those considered to be at risk for permanent scarring or disfigurement). Based on an examination of the patient characteristics, a clinical expert consulted by CADTH indicated that the study population appeared to be a reasonable reflection of the target population in Canada for patients with less-severe forms of IH. In addition, 71% of the study population had IHs that were classified as "facial" and patient groups have indicated that hemangiomas located on or near a child's face are particularly concerning for parents/guardians (Appendix 1). Patient groups noted facial IH can have a significant negative impact on the psychosocial development of a child, suggesting that these patients would likely receive systemic therapy in Canada.

The primary end point was a composite outcome of "complete resolution" and "nearly complete resolution" (referred to as "treatment success" by the manufacturer). A clinical expert consulted by CADTH indicated that complete or nearly complete resolution may be overly rigid end points and may not be reflective of how treatment success is evaluated in clinical practice. The expert noted that treatment success in clinical practice is typically based on whether the treatment has addressed the risks posed by the hemangioma (e.g., the function-threatening problem). Therefore, the expert noted that the treatment can be considered successful even if there is some residual lesion remaining.

The dosage and duration of treatment in Study 201 is reflective of the recommendations in the product monograph (i.e., 3 mg/kg/day for six months).[8] The clinical expert consulted by CADTH indicated that oral propranolol is likely to be prescribed and administered in a manner consistent with Study 201; however, dose adjustment due to changes in body weight could occur less frequently in routine clinical practice and would be determined based on the frequency of clinic visits. The length of follow-up for the core phase of the trial (i.e., six months) was appropriate to evaluate the efficacy end points that were specified in the trial (e.g., resolution, improvement, and changes in IH appearance). Although the study

included an 18-month open-label extension period, early discontinuations (i.e., 27.5% of propranolol-treated patients) could underestimate the proportion of patients who would experience IH regrowth.

The pivotal study for oral propranolol was a placebo-controlled trial. Although oral propranolol solution is the only treatment approved in Canada for use in the treatment of IH, a number of systemic treatments have been used off-label for this condition. Compounded oral propranolol solution[c] is typically used as the first-line treatment option. The manufacturer has stated that the FDA indicated that placebo was the appropriate comparator and that it was not considered acceptable by regulators to use an active comparator group (e.g., a corticosteroid) as it did not have regulatory approval for the treatment of IH in the US and in the majority of European countries (Germany and France being the exceptions).[11,13] This statement is supported by the reports from the FDA and the EMA in which they noted that the study treatments were in compliance with FDA and EMA advice.[13] Nevertheless, systemic treatments are currently being used in Canada for the treatment of IH, and the absence of an active comparator in Study 201 is a limitation of the trial.

The proportion of patients who experienced IH-related complications during the trial was low in both the active and placebo groups. As noted above, the pivotal trial excluded patients with high-risk IH; therefore, the trial population may have been at a lower risk of experiencing IH-related complications. In addition, the rate of complications could be underestimated due to the high proportion of early withdrawals for lack of efficacy.

Study 201 had a number of important exclusion criteria related to medical conditions, including those related to cardiac function, respiratory function, circulation, and metabolic conditions (e.g., hypoglycemia or acidosis).[1] The majority of these conditions are currently listed as contraindications for use of oral propranolol,[8] and the exclusion of these patients should not significantly compromise the generalizability of the study results to the Canadian population.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol (Section 2.2, Table 4) are reported.

3.6.1 Resolution of Hemangioma

The results for resolution of the target hemangioma at 24 weeks are summarized in Table 12. For the primary efficacy end point, a statistically significantly greater proportion of propranolol-treated patients demonstrated complete or nearly complete resolution compared with the placebo-treated patients (61/101 [60.4%] versus 2/55 [3.6%]; $P < 0.0001$).[1] Results were similar in the per-protocol analysis, with response rates of 60.6% in the propranolol group and 1.9% in the placebo group ($P < 0.0001$).[1] Subgroup analyses based on age (35 to 90 days or more than 90 days) and IH location (i.e., facial or non-facial) demonstrated results similar to the primary analysis.

[c] Health Canada's *Policy on Manufacturing and Compounding Drug Products in Canada* defines compounding as follows: The combining or mixing together of two or more ingredients (of which at least one is a drug or pharmacologically active component) to create a final product in an appropriate form for dosing. It can involve raw materials or the alteration of the form and strength of commercially available products. It can include reformulation to allow for a novel drug delivery. Compounding does not include mixing, reconstituting, or any other manipulation that is performed in accordance with the directions for use on an approved drug's labelling material.[22]

When complete or nearly complete resolutions were analyzed using the assessment conducted by the study investigators, there was no statistically significant difference between the propranolol and placebo groups (24/90 [26.7%] versus 2/19 [10.5%]; *P* = 0.4419).[1] The manufacturer conducted an analysis to examine the divergent results between the centralized and on-site assessments of complete or nearly complete resolution (Table 22 on page 43).[10] This analysis demonstrated a difference of 38 propranolol-treated patients that were considered to have complete or nearly complete resolution by the central reviewers and not by the study investigators.[14]

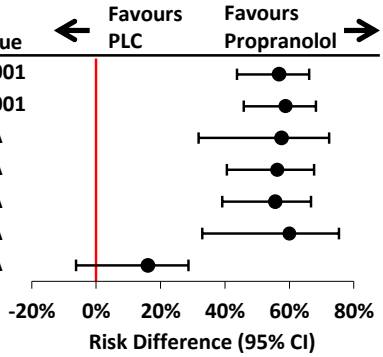
TABLE 12: COMPLETE OR NEARLY COMPLETE RESOLUTION OF HEMANGIOMA

Analysis	Resolution	Propranolol	Placebo	*P* value
ITT	n	101	55	< 0.0001
	Yes	61 (60.4%)	2 (3.6%)	
	No	40 (39.6%)	53 (96.4%)	
Per-Protocol	n	94	53	< 0.0001
	Yes	57 (60.6%)	1 (1.9%)	
	No	37 (39.4%)	52 (98.1%)	
Age 35 to 90 days	n	37	20	NA
	Yes	25 (67.6%)	2 (10.0%)	
	No	12 (32.4%)	18 (90.0%)	
Age > 90 days	n	64	35	NA
	Yes	36 (56.3%)	0 (0.0%)	
	No	28 (43.8%)	35 (100%)	
Facial IH	n	71	40	NA
	Yes	43 (60.6%)	2 (5.0%)	
	No	28 (39.4%)	38 (95.0%)	
Non-facial IH	n	30	15	NA
	Yes	18 (60.0%)	0 (0.0%)	
	No	12 (40.0%)	15 (100%)	
On-site investigator	n	90	19	0.4419
	Yes	24 (26.7%)	2 (10.5%)	
	No	66 (73.3%)	17 (89.5%)	

IH = infantile hemangioma; NA = not applicable.
Source: Clinical Study Report.[1]

FIGURE 4: RISK DIFFERENCE FOR COMPLETE OR NEARLY COMPLETE RESOLUTION OF HEMANGIOMA

Analysis	Achieved endpoint; n/N (%) Propranolol	PLC	Propranolol vs. PLC RD (95% CI)	P value
ITT	61/101 (60.4)	2/55 (3.6)	56.8% (43.7 to 66.1)	<0.0001
Per-protocol	57/94 (60.6)	1/53 (1.9)	58.8% (45.8 to 68.2)	<0.0001
Age 35 to 90 days	25/37 (67.6)	2/20 (10.0)	57.6% (31.8 to 72.3)	NA
Age > 90 days	36/64 (56.3)	0/35 (0.0)	56.3% (40.6 to 67.7)	NA
Facial IH	43/71 (60.6)	2/40 (5.0)	55.6% (39.2 to 66.7)	NA
Non-facial IH	18/30 (60.0)	0/15 (0.0)	60.0% (33.0 to 75.4)	NA
On-site investigator	24/90 (26.7)	2/19 (10.5)	16.1% (−6.2 to 28.7)	NA



CI = confidence interval; IH = infantile hemangioma; ITT = intention-to-treat analysis; n = number of patients with event; N = number of patients in the analysis; PLC = placebo; RD = risk difference.
Note: Unadjusted risk differences and 95% confidence intervals were calculated by CADTH.
Source: Data from Clinical Study Report[1] (with the exception of risk differences).

3.6.2 Time to Complete or Nearly Complete Resolution

Kaplan–Meier estimates for achieving complete or nearly complete resolution were 41.2% at 12 weeks and 66.8% at 24 weeks in the propranolol group and 8.3% at both time points in the placebo group ($P < 0.0001$).[1] As noted in section 0, there was considerable variability in the assessments of the centralized assessors and the on-site assessors regarding whether a patient had achieved complete or nearly complete resolution of the target hemangioma. When analyzed using the on-site assessment, there was no statistically significant difference in the Kaplan–Meier estimates for achieving complete or nearly complete resolution between the propranolol and placebo groups ($P = 0.5047$).

TABLE 13: TIME TO COMPLETE OR NEARLY COMPLETE RESOLUTION

Analysis	Time point	Propranolol (N = 101)		Placebo (N = 55)		*P* value
		At risk	n (%)	At risk	n (%)	
Centralized Assessment	Week 12	97	40 (41.2)	24	2 (8.3)	< 0.0001
	Week 24	46	60 (66.8)	17	2 (8.3)	
On-site Assessment	Day 7	100	0 (0.0)	55	0 (0.0)	0.5047
	Day 14	100	0 (0.0)	54	0 (0.0)	
	Day 21	100	0 (0.0)	48	0 (0.0)	
	Week 5	99	1 (1.0)	37	0 (0.0)	
	Week 8	97	3 (3.1)	28	0 (0.0)	
	Week 12	95	6 (6.1)	24	1 (4.2)	
	Week 16	90	9 (9.2)	21	2 (8.7)	
	Week 20	82	18 (19.2)	18	2 (8.7)	
	Week 24	69	23 (25.1)	17	2 (8.7)	

Source: Clinical Study Report.[1]

3.6.3 Complete Resolution

Treatment success or failure based on the on-site assessment of complete resolution of the target IH at week 48 was the key secondary efficacy end point of Study 201.[1] As shown in Table 14, there was no statistically significant difference between the propranolol and placebo groups with respect to the

proportion of patients with a complete response at week 48 (7.9% versus 1.8%; *P* = 0.4876) in the ITT or any of the subgroup analyses.[1] However, there was a numerical increase in the proportion of patients with complete resolution in the propranolol group relative to the placebo group.

TABLE 14: COMPLETE RESOLUTION AT WEEK 48 ASSESSED BY ON-SITE INVESTIGATOR

Analysis	Resolution	Propranolol	Placebo	*P* value
ITT	n	101	55	0.4876
	Yes (%)	8 (7.9)	1 (1.8)	
	No (%)	93 (92.1)	54 (98.2)	
Age 35 to 90 days	n	37	20	NA
	Yes (%)	3 (8.1)	1 (5.0)	
	No (%)	34 (91.9)	19 (95.0)	
Age > 90 days	n	64	35	NA
	Yes (%)	5 (7.8)	0 (0.0)	
	No (%)	59 (92.2)	35 (100.0)	
Facial IH	n	71	40	NA
	Yes (%)	5 (7.0)	1 (2.5)	
	No (%)	66 (93.0)	39 (97.5)	
Non-facial IH	n	30	15	NA
	Yes (%)	3 (10.0)	0 (0.0)	
	No (%)	27 (90.0)	15 (100.0)	

IH = infantile hemangioma; ITT = intention-to-treat; NA = not applicable.
Source: Clinical Study Report.[1]

3.6.4 Time to Sustained Improvement

Time to first sustained improvement was defined as the interval between the initiation of treatment with the study drugs (i.e., randomization) and the point at which the target IH demonstrated consistent improvement. Results for time to first sustained improvement are summarized in Table 15 for both the centralized assessment and the assessment conducted on-site by the study investigators. The time to first sustained improvement was evaluated using a Kaplan–Meier analysis beginning at week 5. As shown in Table 15, at the initial week 5 assessment it was estimated that 72.7% of propranolol-treated patients had demonstrated sustained improvement compared with 5.4% of patients in the placebo group.[1] At the final week 24 evaluation, the estimated proportion of patients with sustained improvement was 79.5% in the propranolol group and 9.0% in the placebo group.[1]

The results from the on-site assessments by the investigators were similar to the centralized assessment for propranolol (i.e., 70.9% at week 5 and 82.5% at week 24), but were considerably higher for the placebo group (i.e., 20.1% at week 5 and 32.4% at week 24). Results for the on-site assessments by the parents and guardians were similar, with sustained improvement demonstrated in an estimated 85.6% (n = 76) of propranolol-treated patients and 45.0% (n = 14) of placebo-treated patients. The difference between propranolol and placebo was statistically significant for the centralized assessment and the on-site assessments performed by both the study investigators and the parents/guardians (both *P* < 0.0001).[1] Due to the high rate of discontinuation, the number of placebo-treated patients included in these analyses was low (n = 19).

TABLE 15: TIME TO SUSTAINED IMPROVEMENT

Analysis	Time point	Propranolol (N = 101)		Placebo (N = 55)		*P* value
		At risk	n (%)	At risk	n (%)	
Centralized Assessment	Week 5	99	72 (72.7)	37	2 (5.4)	< 0.0001
	Week 8	26	73 (73.8)	26	3 (9.0)	
	Week 12	25	74 (74.8)	21	3 (9.0)	
	Week 16	22	75 (76.0)	19	3 (9.0)	
	Week 20	16	76 (77.5)	17	3 (9.0)	
	Week 24	11	77 (79.5)	16	3 (9.0)	
On-site Assessment (Investigator)	Day 7	96	50 (52.1)	54	6 (11.1)	< 0.0001
	Day 14	46	62 (64.6)	47	8 (14.9)	
	Day 21	34	66 (68.8)	39	9 (17.1)	
	Week 5	29	68 (70.9)	27	10 (20.1)	
	Week 8	26	70 (73.1)	17	11 (24.8)	
	Week 12	24	72 (75.4)	12	11 (24.8)	
	Week 16	20	73 (76.6)	10	12 (32.4)	
	Week 20	14	75 (80.0)	7	12 (32.4)	
	Week 24	8	76 (82.5)	6	12 (32.4)	
On-site Assessment (Parent/ Guardian)	Day 7	95	53 (55.8)	55	7 (12.7)	< 0.0001
	Day 14	42	61 (64.2)	47	7 (12.7)	
	Day 21	34	62 (65.3)	41	9 (17.0)	
	Week 5	32	64 (67.4)	28	10 (19.9)	
	Week 8	29	66 (69.7)	18	11 (24.4)	
	Week 12	27	68 (71.9)	13	11 (24.4)	
	Week 16	23	70 (74.4)	11	14 (45.0)	
	Week 20	16	74 (80.8)	6	14 (45.0)	
	Week 24	8	76 (85.6)	5	14 (45.0)	

Source: Clinical Study Report.[1]

3.6.6 Changes in Size and Colour of Hemangioma

Table 16 summarizes the results for change from baseline in size and colour of the target hemangiomas as evaluated by the blinded centralized assessors. Compared with the placebo-treated patients, the propranolol-treated patients demonstrated a statistically significant reduction in the surface area of the target IH at week 12 (−0.941 cm^2 versus 0.637 cm^2; $P = 0.0001$) and week 24 (−1.207 cm^2 versus 0.464 cm^2; $P = 0.0093$).[1] The propranolol group also demonstrated statistically significant reductions in the colour density of the target IH compared with placebo at both 12 and 24 weeks ($P < 0.0001$ in each case).[1] There were no statistically significant differences between propranolol and placebo for changes in the maximum diameter of the target IH.[1]

TABLE 16: CHANGE FROM BASELINE IN SIZE AND COLOUR OF HEMANGIOMA

End Point	Time Point	Propranolol (N = 101)		Placebo (N = 55)		*P* value
		n/missing	Mean (SD)	n/missing	Mean (SD)	
IH surface area (cm^2)	Baseline	99 / 2	4.61 (4.88)	24 / 31	3.22 (2.56)	NA
	Week 12	98 / 3	−0.941 (1.557)	24 / 31	0.637 (2.224)	0.0001
	Week 24	88 / 13	−1.207 (2.439)	19 / 36	0.464 (1.804)	0.0093
IH maximal diameter (cm)	Baseline	99 / 2	2.41 (1.22)	24 / 31	2.39 (1.09)	NA
	Week 12	98 / 3	−0.116 (0.661)	24 / 31	0.050 (0.635)	0.1084
	Week 24	88 / 13	−0.179 (0.731)	19 / 36	−0.028 (0.743)	0.4127
IH colour (dE*2000)	Baseline	99 / 2	19.34 (7.87)	24 / 31	18.90 (6.71)	NA
	Week 12	98 / 3	−5.711 (5.975)	24 / 31	0.572 (5.972)	< 0.0001
	Week 24	88 / 13	−7.369 (7.430)	19 / 36	−0.054 (4.824)	< 0.0001

dE*2000 = Delta E*ab, year 2000 version; IH = infantile hemangioma; NA = not applicable; SD = standard deviation.
Source: Clinical Study Report.[1]

3.6.7 Complications

a) Functional Impairment

The manufacturer reported that functional impairment as a result of IH was rare across all treatment groups. Three placebo-treated patients experienced eye-related functional impairment during the study that led to premature discontinuation. These events were listed treatment-emergent for two patients and pre-existing for one patient. Given the exclusion criteria of Study 201, it is unclear why the patient with pre-existing functional impairment was randomized. In the group that received propranolol 3 mg/kg/day for six months, there were no cases of functional impairment reported (pre-existing or treatment-emergent).[1]

b) Ulceration

IH ulceration was reported for six patients in the group that received propranolol 3 mg/kg/day for six months and two patients in the placebo group. Of the cases in the propranolol group, two patients had pre-existing IH ulceration and both resolved while on the study treatment. The remaining four patients experienced treatment-emergent IH ulceration (two led to discontinuation of treatment and two resolved while on the study treatment).[1]

c) Need for Invasive Procedures

The manufacturer reported that there were no invasive procedures conducted on any target IH in either treatment group during the 24-week study period. However, the data appeared to be limited to patients who remained on the study treatments and a considerable number of observations were missing for patients in the placebo group (e.g., 36 of 55 patients have no data related to invasive procedures for the week 20 to week 24 period).[1]

3.6.8 Need for Additional IH Treatment

In the subgroup of patients who achieved treatment success in the 24-week double-blind treatment period, seven (11.5%) re-initiated IH treatment during the 72-week follow-up period. Of those, six (9.8%) received a systemic treatment.[1] The manufacturer reported that five of the seven patients who required retreatment achieved complete or near complete resolution by week 96.[20] Complete details regarding the extension phase are provided in Appendix 4.

3.7 Harms

Only those harms identified in the review protocol are reported (see: 2. OBJECTIVES AND METHODS). As noted previously, the CDR systematic review is focused only on the Health Canada–approved dosage of propranolol oral solution; therefore, data for the other dosage regimens are not summarized. A summary of adverse events from Study 201 is provided in Table 17. The overall proportion of patients who experienced at least one adverse event was greater in the propranolol group compared with the placebo group (96.0% versus 76.4%, respectively). The proportion of patients who experienced at least one serious adverse event (SAE) was similar in the propranolol and placebo groups (5.9% versus 5.5%).[1] Withdrawals due to adverse events were commonly reported in the placebo group (10.9%) compared with the propranolol group (3.0%). There were no deaths reported in Study 201.[1]

As reported in section 3.4 Exposure to Study Treatments (Table 11), mean exposure to the study treatment was much greater in the propranolol group compared with the placebo group (160.97 days versus 82.60 days). Due to this marked difference in exposure, any comparisons regarding the frequency of adverse events between the active and placebo groups should be interpreted with caution.

TABLE 17: SUMMARY OF ADVERSE EVENTS AT 24 WEEKS

Adverse events, n (%)	Placebo (N = 55)	Propranolol 3 mg/kg/day for 6 months (N = 101)
At least one TEAE	43 (78.2)	97 (96.0)
1 TEAE	14 (25.5)	14 (13.9)
2 TEAEs	8 (14.5)	13 (12.9)
≥ 2 TEAEs	20 (36.4)	70 (69.3)
Withdrawal due to adverse events	6 (10.9)	3 (3.0)
Serious adverse events	3 (5.5)	6 (5.9)

TEAE = treatment-emergent adverse event.
Source: Clinical Study Report.[1]

3.7.1 Adverse Events

As shown in Table 18, a greater proportion of propranolol-treated patients experienced at least one treatment-emergent adverse event compared with placebo-treated patients (96.0% versus 76.4%). Nasopharyngitis, diarrhea, pyrexia, teething, bronchitis, upper respiratory tract infection, cough, vomiting, and gastroenteritis were reported in at least 10% of propranolol-treated patients.

TABLE 18: ADVERSE EVENTS IN ≥ 5% OF PATIENTS IN THE PROPRANOLOL GROUP AT 24 WEEKS

Adverse events, n (%)	Placebo (N = 55)	Propranolol 3 mg/kg/day for 6 months (N = 101)
At least one adverse event	42 (76.4)	97 (96.0)
Nasopharyngitis	10 (18.2)	34 (33.7)
Diarrhea	4 (7.3)	28 (27.7)
Pyrexia	6 (10.9)	28 (27.7)
Teething	6 (10.9)	22 (21.8)
Bronchitis	1 (1.8)	17 (16.8)
URTI	4 (7.3)	16 (15.8)
Cough	4 (7.3)	14 (13.9)
Vomiting	3 (5.5)	13 (12.9)
Gastroenteritis	2 (3.6)	11 (10.9)
Bronchiolitis	3 (5.5)	10 (9.9)
Peripheral coldness	1 (1.8)	10 (9.9)
Toothache	2 (3.6)	10 (9.9)
Dermatitis diaper	2 (3.6)	9 (8.9)
Conjunctivitis	2 (3.6)	8 (7.9)
Vaccination complication	2 (3.6)	8 (7.9)
Sleep disorder	1 (1.8)	7 (6.9)
Middle insomnia	3 (5.5)	6 (5.9)
Nightmare	1 (1.8)	5 (5.0)
Rhinitis	5 (9.1)	5 (5.0)

URTI = Upper respiratory tract infection.
Source: Léauté-Labrèze et al. (2014).[10]

3.7.2 Serious Adverse Events

Table 19 provides a summary of SAEs in Study 201. The proportion of patients who experienced at least one SAE was similar in the propranolol (5.9%) and placebo (5.5%) groups. “Condition aggravated” (two placebo-treated patients) and “drug ineffective” (one patient in each group) were the only SAEs reported for more than one patient. A large proportion of placebo-treated patients withdrew due to lack of efficacy; the difference between “lack of efficacy” and “drug ineffective” is unclear.

TABLE 19: SUMMARY OF SERIOUS ADVERSE EVENTS AT 24 WEEKS

Serious adverse events, n (%)	Placebo (N = 55)	Propranolol 3 mg/kg/day for 6 months (N = 101)
Any serious adverse event	3 (5.5)	6 (5.9)
General disorders and admin. site	3 (5.5)	2 (2.0)
Drug ineffective	1 (1.8)	1 (1.0)
Inflammation	0 (0.0)	1 (1.0)
Pyrexia	0 (0.0)	1 (1.0)
Condition aggravated	2 (3.6)	0 (0.0)
Infections and infestations	0 (0.0)	2 (2.0)
Bronchiolitis	0 (0.0)	1 (1.0)
Bronchitis	0 (0.0)	1 (1.0)
Injury, poisoning, procedural complications	0 (0.0)	1 (1.0)
Traumatic brain injury	0 (0.0)	1 (1.0)
Psychiatric disorders	0 (0.0)	1 (1.0)
Apathy	0 (0.0)	1 (1.0)

Source: Clinical Study Report.[1]

3.7.3 Withdrawals Due to Adverse Events

Table 20 provides a summary of patients who discontinued Study 201 as a result of adverse events (multiple reasons could be cited for each patient). Withdrawals due to adverse events were more commonly reported in the placebo group compared with the propranolol group (10.9% versus 3.0%).[1] Similar to the evaluation of SAEs, "drug ineffective" was noted as a reason for discontinuation for one patient in both the propranolol and placebo groups, while "condition aggravated" was cited as a reason for two placebo-treated patients.[1] There were no other events that resulted in the discontinuation of more than one patient. Bronchiolitis and bronchitis were cited as reasons for discontinuation for one patient.[1]

TABLE 20: SUMMARY OF WITHDRAWALS DUE TO ADVERSE EVENTS

WDAEs, n (%)	Placebo (N = 55)	Propranolol 3 mg/kg/day for 6 months (N = 101)
Any WDAEs	6 (10.9)	3 (3.0)
Infections and infestations	1 (1.8)	2 (2.0)
Bronchiolitis	0 (0.0)	1 (1.0)
Bronchitis	0 (0.0)	1 (1.0)
Gastroenteritis	1 (1.8)	0 (0.0)
General disorders and admin. site	3 (5.5)	1 (1.0)
Drug ineffective	1 (1.8)	1 (1.0)
Condition aggravated	2 (3.6)	0 (0.0)
RTM disorders	1 (1.8)	0 (0.0)
Bronchial obstruction	1 (1.8)	0 (0.0)
Upper airway obstruction	1 (1.8)	0 (0.0)
Skin/subcutaneous disorders	1 (1.8)	0 (0.0)
Vascular skin disorder	1 (1.8)	0 (0.0)

RTM = respiratory, thoracic and mediastinal; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report.[1]

3.7.4 Mortality

No deaths were reported during the study.[1]

3.7.5 Notable Harms

In consultation with a clinical expert, the CDR review included hypoglycemia, hypotension, bradycardia, and bronchospasm as adverse events of special interest for this review. Table 21 provides a summary of the proportion of patients who reported one or more these adverse events.

a) Hypoglycemia

Hypoglycemia was reported in one patient from the propranolol 3 mg/kg/day for six months group and no patients in the placebo group.[1] The event was not considered to be severe or serious.[1]

b) Hypotension

Hypotension was reported for one patient in the placebo group (1.8%) and no patients in the propranolol 3 mg/kg/day for six months group. Events of hypotension were reported in the other propranolol treatment groups: 1 mg/kg/day for 3 months (2.0%), 1 mg/kg/day for six months (1.0%), 3 mg/kg/day for three months (3.0%).[d1] No events were considered to be severe or serious and no patients discontinued as a result of these events.[1]

c) Bradycardia

There were no events of bradycardia reported in either the propranolol (3 mg/kg/day for six months) or placebo groups. The manufacturer did report that two propranolol-treated patients (one in the

[d] The CDR review is focused on the recommended dosage of 3 mg/kg/day for six months; however, these additional safety data are included to provide additional context for adverse events that were considered particularly important by the clinical expert consulted by CADTH.

1 mg/kg/day for six months group and one in the 3 mg/kg/day for three months group) experienced bradycardia. The event in the 3 mg/kg/day for three months group was classified as an SAE and led to discontinuation from the study treatment.[1]

d) Bronchospasm

As part of the manufacturer's safety evaluation plan, a specialized Medical Dictionary for Regulatory Activities (MedDRA) search was conducted to identify events that were potentially linked to a bronchospasm and/or bronchiolitis.[1] Events linked to bronchospasm were identified using the following approach:[1]

- High-level term: bronchospasm and obstruction
- Low-level terms: apnea, asthma, asthma bronchial, bronchial hyperactivity, bronchitis asthmatic, bronchospasm, shortness of breath, wheeze, and wheeze worsened.

As shown in Table 21, three patients treated with propranolol (3 mg/kg/day for six months) experienced at least one event potentially linked with bronchospasm compared with one patient in the placebo group.[1]

TABLE 21: SUMMARY OF NOTABLE ADVERSE EVENTS

Events, n (%)	Placebo (N = 55)	Propranolol 3 mg/kg/day for 6 months (N = 101)
Bronchospasm	1 (1.8)	3 (3.0)
Hypoglycemia	0 (0)	1 (1)
Hypotension[a]	1 (1.8)	0 (0)
Bradycardia[b]	0 (0)	0 (0)

Source: Clinical Study Report.[1]

[a] No events with propranolol 3 mg/kg/day for six months; however, one event occurred in the 1 mg/kg/day for six months group and one in the 3 mg/kg/day for three months group.

[b] No events with propranolol 3 mg/kg/day for six months; however, one event occurred in the 1 mg/kg/day for six months group and one in the 3 mg/kg/day for three months group.

4. DISCUSSION

4.1 Summary of Available Evidence

The evidence for this review was derived primarily from one adaptive phase II/III randomized, double-blind, placebo-controlled study conducted to evaluate the efficacy and safety of propranolol oral solution in patients with IH requiring systemic therapy (Study 201; N = 460).[1] The CDR review focused on the use of propranolol at the Health Canada–approved dose and duration (i.e., 3 mg/kg/day for six months). Study 201 also included treatment groups that used a lower dose of propranolol (i.e., 1 mg/kg/day) and a shorter treatment period (i.e., three months). These were excluded from the CDR review as they are not currently recommended in the product monograph and were not fully evaluated in the confirmatory phase (stage II) of Study 201. The data from the core phase of the study is limited to 24 weeks of double-blind treatment; the CDR review also considered the results of the 72-week open-label follow-up phase.

4.2 Interpretation of Results

4.2.1 Efficacy

In the pivotal clinical trial, treatment with oral propranolol was associated with a statistically significant improvement in the proportion of patients with complete or nearly complete resolution of IH compared with placebo (61/101 [60.4%] versus 2/55 [3.6%]). CADTH calculated a risk difference for propranolol versus placebo of 56.8% (95% CI, 43.7% to 66.1%), suggesting that approximately one in every two patients would demonstrate complete or nearly complete resolution following six months of treatment with propranolol. The efficacy results were similar when stratified by age group (i.e., 35 to 90 days or more than 90 days) and hemangioma location (i.e., facial and non-facial). The treatment effect observed with oral propranolol was considered clinically relevant by a clinical expert consulted by CADTH and by a number of international regulatory agencies (e.g., Health Canada, the FDA, the EMA, and the Australian Therapeutic Goods Administration)[11,13-15] and health technology assessment agencies (e.g., Institute for Quality and Efficiency in Health Care and Haute Autorité de Santé).[23,24]

There was a substantial discrepancy in the rates of complete and nearly complete resolution as assessed by the central reviewers (i.e., statistically significant differences between groups) and the on-site study investigators (i.e., no statistically significant differences between groups). This difference was primarily due to differences in the response rates within the propranolol group, where the central reviewers concluded that 60% of patients had complete or nearly complete resolution and the study investigators concluded that 27% of patients had achieved resolution.[14] The criteria used to evaluate resolution were the same for the central reviewers and the on-site investigators, with the exception that the on-site evaluation could also evaluate the depth of IH lesions.[1] The manufacturer reported that the differences were primarily due to the application of a more stringent threshold for nearly complete resolution by on-site investigators, particularly with respect to the presence of residual telangiectasis.[20]

As opposed to an independent central review of photographs, a visual and palpable examination of the IH in a clinical setting is likely a more accurate reflection of how the response to propranolol treatment would be evaluated in Canadian clinical practice (although photographs from previous visits would be used to inform clinical decision-making). Given that the on-site investigators were less likely to conclude that a patient had achieved resolution after six months, it is possible that the duration of treatment would continue for a longer period in routine clinical practice. Similarly, it is unclear if nearly complete resolution would be considered as treatment success in clinical practice or if patients would continue to be treated until the target IH had resolved completely.

Although the on-site investigators were less likely to conclude that patients had achieved complete or nearly complete resolution of their IH, both the timing and rates of sustained improvement were similar when assessed by the central reviewers and the on-site investigators.[21] A clinical expert consulted by CADTH indicated that, although many IH lesions do demonstrate complete or nearly complete resolution, these are not the only accepted measurements of treatment success that are used by physicians. The expert noted that treatment success in clinical practice is typically based on whether the treatment has addressed the risks that necessitated the need for treatment of the IH. The expert noted that the rate of improvement of an IH lesion during treatment can slow down, in which case the physician may reconsider the benefits and risks of continued treatment before resolution has been achieved. The clinical expert suggested that the decision to continue treatment in clinical practice is based on the observation of measurable, significant improvement in the IH lesion(s) between clinical evaluations.

It is challenging to interpret the differences between the results of the centralized assessments and the results of the on-site assessments because the two assessments differed with respect to how patients were classified if they withdrew from the trial. Specifically, those cases in which treatment was discontinued were considered treatment failures for the purposes of centralized assessments, which may have underestimated the rate of spontaneous resolution in the placebo group and potentially biased the efficacy results in favour of propranolol. Conversely, patients who discontinued treatment were excluded or censored from the analyses for the purposes of the on-site evaluations, which may have overestimated the rate of spontaneous resolution in the placebo group and therefore biased the efficacy results against propranolol.

The Canadian product monograph states that the duration of treatment with propranolol is six months,[8] with no distinction in dosage made based on location or severity. This reflects the duration of treatment in Study 201, but may not necessarily reflect the duration of a treatment that is applied in routine clinical practice. In the manufacturer's compassionate use program, which included patients with more severe forms of IH, the average duration of propranolol treatment was reported to be 8.6 months.[25] Similarly, in a survey conducted by the American Society of Pediatric Otolaryngology (ASPO), the majority (67%) of the pediatric otolaryngologists who were surveyed indicated that the typical treatment duration with propranolol was eight to 12 months.[26] However, in both the manufacturer's compassionate use program (CUP) and the ASPO survey, the median dosage used was reported to be 2.0 mg/kg/day,[25,26] which is below the recommended dosage for the treatment of IH and may have contributed to the duration of treatment exceeding the six-month period currently recommended in Canada.

The product monograph recommends that propranolol should be discontinued if there is an absence of any improvement within the first two months of treatment.[8] However, discontinuations occurred much earlier in Study 201 (e.g., less than half of the placebo group remained after two months). The clinical expert consulted by CADTH indicated that this discontinuation criterion is reasonable and likely reflective of Canadian clinical practice, provided the patients and caregivers were compliant with the treatment. The FDA reviewers noted that the relatively rapid onset of action for propranolol treatment would have been visually noticeable to investigators and caregivers, which may have influenced the decision to withdraw some patients from the placebo group for perceived lack of efficacy.[11]

In the open-label extension phase of Study 201, 11.5% of patients who had achieved treatment success at 24 weeks with propranolol experienced regrowth that required additional treatment (five of seven of these patients achieved complete or nearly complete resolution by week 96).[20] This is consistent with

meta-analyses that have investigated the use of propranolol in the treatment of IH in which the proportion of patients experiencing regrowth ranged from 12% to 14% and the proportion requiring retreatment ranged from 6% to 12%.[11] The risk factors associated with the regrowth of IH have not been fully elucidated. The clinical expert consulted by CADTH indicated that IH patients who experience regrowth following treatment with propranolol would typically reinitiate treatment with propranolol. The product monograph for propranolol states that patients showing a relapse of symptoms after treatment discontinuation may be retreated with propranolol. However, the re-initiation of treatment should be performed using the conditions and clinical monitoring scheme that is recommended during the initial administration of propranolol.[8] A clinical expert consulted by CADTH indicated that regrowth of IHs would not necessarily indicate failure of propranolol treatment and may be related to the natural history of a subset of hemangiomas. The expert indicated that retreatment would be initiated if the regrowth was perceived to be associated with risks for the patient, while in other cases watchful waiting until spontaneous regression begins could be used to treat regrowth in the absence of risk.

Study 201 was a placebo-controlled trial and there were no active-controlled trials that met the inclusion criteria for the CDR review. Oral propranolol is generally considered to be the preferred first-line treatment for IH requiring systemic therapy in Canada.[5-7] Prior to the approval and marketing of Hemangiol in Canada, oral propranolol solution was only available through compounding facilities. Although compounded oral propranolol is not specifically approved by Health Canada for the treatment of proliferating IH, it is currently reimbursed by the majority of CDR-participating drug plans. The absence of evidence comparing oral propranolol to standard therapy (i.e., compounded propranolol) limits CADTH's ability to comment objectively on the therapeutic value of propranolol treatment compared with standard care. Health Canada reviewers, in their review of Hemangiol, noted that there is currently a need for treatment options that are safe, effective, and of consistent and high quality for IHs requiring systemic therapy.[14] A clinical expert consulted by CADTH for this review indicated that concentrations of oral propranolol suspensions may vary among different compounding pharmacists. The manufacturer also noted that Hemangiol is specifically formulated for pediatric use in compliance with the International Conference on Harmonization (ICH) recommendations (e.g., volume of administration less than 5 mL and the use of a selected sweetener).[14]

Oral propranolol is indicated for the treatment of proliferating IH requiring systemic therapy, in one or more of the following clinical circumstances: life- or function-threatening hemangioma; ulcerated hemangioma with pain and/or lack of response to simple wound care measures; and/or hemangioma with a risk of permanent scarring or disfigurement.[8] In accordance with ethical principles regarding the use of placebo, patients with life-threatening, function-threatening, and/or severely ulcerated hemangiomas were excluded from the pivotal study.[1] Therefore, there is an absence of controlled clinical studies investigating the efficacy of oral propranolol in the treatment of more serious IH. In the absence of controlled studies, CADTH summarized observational data regarding the use of propranolol in these patients from the manufacturer's CUP.[25] The CUP included 1,661 patients with proliferating IHs that were considered to be life-threatening, function-threatening, or ulcerated and not responding to simple treatment. The study was not designed to evaluate the efficacy of propranolol for the treatment of IH and there are substantial limitations with the available data (e.g., uncontrolled, unblinded, unplanned analyses, and incomplete). The only effectiveness data reported for this study were based on whether treatment success (i.e., good efficacy) was cited as a reason for discontinuation in a subset of patients for whom data were available. Overall, the manufacturer reported that 88.3% of the 697 patients with data available discontinued from the CUP as a result of efficacious treatment with Hemangiol. Health Canada noted that the CUP and additional literature involving off-label usage support oral propranolol as an effective treatment for the types of IH that were not included in Study 201.[27]

Patient groups expressed an interest in an orally administered treatment for IH that could reduce the need for invasive procedures such as surgery or laser treatment (Appendix 1). The pivotal clinical trial for propranolol was not designed to evaluate differences in the need for invasive follow-up treatments for IH; therefore, the potential benefits of treatment with propranolol for reducing the need for invasive procedures cannot be evaluated. However, several retrospective cohort studies have suggested that treatment with propranolol has reduced the need for invasive IH treatments in clinical practice compared with alternative treatments.[28,29]

4.2.2 Harms

Nasopharyngitis, diarrhea, pyrexia, teething, bronchitis, upper respiratory tract infection, cough, vomiting, and gastroenteritis were the most commonly reported adverse events in propranolol-treated patients. Regulatory authorities noted that the risks associated with the treatment of IH with propranolol are consistent with the established adverse event profile of propranolol that has been observed in adults.[14] The Canadian product monograph contains a black-box warning regarding the risk of hypoglycemia with related coma or seizure, bronchospasm and bronchial hyperreactivity reactions, bradycardia, hypotension, and heart block. These events were rare in propranolol-treated patients in Study 201, with one event of hypoglycemia, three events of bronchospasm, and no events of hypotension or bradycardia.

The list of medical conditions where the use of propranolol is contraindicated[8] is largely reflective of the exclusion criteria that were used in the selection of patients for Study 201 (e.g., conditions related to cardiac function, respiratory function, circulation, and metabolism). Therefore, the exclusion of these patients should not substantially compromise the generalizability of the study results to the Canadian population.

The Canadian product monograph has a black-box warning stating that therapy with propranolol should be initiated and monitored by health care professionals experienced in the use of beta-blockers in infants and in the management of IH, and that the first dose and each dose escalation should be administered in a controlled clinical setting where adequate facilities for handling of adverse events, including those requiring urgent measures, are available.[8] A clinical expert consulted for this review indicated that many centres do not follow such a rigorous monitoring program and that the first dosage of propranolol is often given at the patient's home.

4.3 Potential Place in Therapy[e]

IHs are the most common tumours occurring in early childhood, with rapid proliferation during early infancy. Slow involution follows over several years. Some IHs pose risks to young children (depending on size, location, and subtype). Complications including permanent disfigurement, ulceration, and functional impairment are possible, and predicting which infant will experience those complications may be challenging.[4]

Until recently, systemic corticosteroids were typically used for the treatment of IH with varied success and with a variable safety profile.[4] Evidence for the use of propranolol, a non-selective beta-blocker, as an effective treatment evolved over the last decade,[4,30,31] and physicians in centres treating IH quickly adopted the drug.[4,30] Prior to marketing authorization of propranolol for the treatment of IH, oral

[e] This information is based on information provided in draft form by the clinical experts consulted by CDR reviewers for this review.

propranolol was available by compounding. While the use of compounded propranolol is common, a pre-formulated product may lead to a reduction in errors by means of having a common concentration of propranolol across pharmacies (for example, avoiding potential differences in concentrations if a patient switches to a pharmacy that uses a different concentration), and reduce the potential for errors at the compounding step.

According to a clinical expert consulted for this review, it is likely that the approved indications cover the foreseeable reasons to treat a patient with IH. For patients for whom there may be a strong parental desire for treatment, and for whom watchful waiting may be appropriate, it is possible that some physicians may offer treatment; however, this is unlikely to be a frequent occurrence. Most community physicians will not start patients on propranolol as they do not have the equipment to monitor blood pressure in infants. It is likely that most patients with IH who are eligible for treatment will attend care centres with physicians who have experience diagnosing, treating, and monitoring patients with IH.

The diagnosis, management and follow-up of patients with IH is based on the judgment and expertise of the treating health care provider, and there is no specific test available to provide a more objective measure to indicate a patient's suitability for treatment. The initiation of treatment with propranolol is typically based on a physician's assessment of patient risk. Consequently, the management of a patient's IH would typically be driven by a reduction in the morbidity or risk of morbidity for which the treatment was initiated. There are multiple criteria that a physician uses to assess reduction of morbidity and improvement at each visit (for example, IH characteristics, photos of the hemangioma from previous visits, assessments from other physicians, and comments from parents).

5. CONCLUSIONS

The CDR systematic review included one adaptive phase II/III randomized, double-blind, placebo-controlled study conducted to evaluate the efficacy and safety of propranolol oral solution in patients with IH requiring systemic therapy (Study 201; N = 460). The pivotal clinical trial demonstrated that propranolol-treated patients were statistically significantly more likely to demonstrate complete or nearly complete resolution of the target hemangioma at 24 weeks when assessed by blinded centralized reviewers (61/101 [60.4%] versus 2/55 [3.6%]; $P < 0.0001$). However, there was no statistically significant difference when complete or nearly complete resolution was assessed by the on-site study investigators (24/90 [26.7%] versus 2/19 [10.5%]; $P = 0.4419$). The timing and rates of sustained improvement were similar when assessed by the central reviewers and the on-site investigators, with the difference between propranolol and placebo being statistically significant in both evaluations ($P < 0.0001$). The results from Study 201 are limited by the large and disproportionate number of early withdrawals from the study (65% in the placebo group versus 13% in the propranolol group). In the 72-week extension phase of the study, 11.5% of patients who had achieved treatment success at 24 weeks with propranolol experienced regrowth that required additional treatment. Overall, the treatment effects observed with oral propranolol were considered clinically relevant by the clinical experts consulted by CADTH and by major regulatory agencies. Nasopharyngitis, diarrhea, pyrexia, teething, bronchitis, upper respiratory tract infection, coughing, vomiting, and gastroenteritis were reported in at least 10% of propranolol-treated patients. Events of hypoglycemia, bronchospasm, hypotension, and bradycardia were rare.

There were no controlled studies identified in the CDR systematic review that investigated the use of oral propranolol for patients with life-threatening, function-threatening, or ulcerated hemangiomas. Therefore, CADTH summarized observational data from the manufacturer's CUP, which included patients with life-threatening, function-threatening, or ulcerated proliferating IH. The study was not designed to evaluate the efficacy of propranolol and the only effectiveness data were based on whether treatment success was cited as a reason for discontinuation. In a subset of patients for whom data were available, the manufacturer reported that 88.3% of the 697 patients discontinued from the CUP as a result of efficacious treatment with Hemangiol.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group Supplying Input

AboutFace is a national charity that aims to empower individuals with facial differences and their families by helping them develop confidence, skills, and self-esteem. In addition, AboutFace also seeks to promote the positive mental and emotional well-being of all affected individuals and promote a culture of empowerment and diversity within communities through the provision of social and peer support, information, educational programs, and public awareness. Nothing was provided regarding funding and no conflicts of interest were declared.

2. Condition-Related Information

Information for this submission was gathered in the summer and fall of 2014 (the date of the original CADTH Common Drug Review submission) through social media (including Facebook), email and one-on-one telephone discussions, and using their database.

Individuals with hemangiomas can be affected both physically (especially with regard to where they occur) and psychologically (by way of mental, emotional, or psychological distress). Hemangiomas physically affect individuals in many ways. Patients may have to deal with painful treatments, including laser treatment and invasive surgery, which may subsequently lead to scarring. Patients may also experience deformity from the hemangioma itself in addition to how it may affect or interact with other anatomical structures. In certain areas, hemangiomas can harm the affected individual, particularly through significant bleeding, as one patient stated, *"For example when I was in my late teens I was eating a toasted tomato sandwich and a piece of the toast nicked the corner of my mouth and boy did I ever bleed. It took over two hours for the bleeding to stop and that was when I was at rest, not participating in sports with my cheek puffed up full of blood and under pressure."*

Even more damaging to individuals with hemangiomas (some of which can be particularly striking and un-concealable) are the negative psychosocial effects associated with having these facial differences. Societal reactions such as staring, whispering, double-takes, name-calling, and even verbal, physical, and attitudinal violence lead to isolation and long-term damage to patients' self-confidence, self-esteem, and socialization. Many patients experience bullying and discrimination, both of which result in further avoidance of social situations, increase isolation, and damage one's sense of self-worth. As one affected patient stated, *"There are "normal" kids that are bullied so much that they commit suicide. What must it be like for someone with a facial difference to get by?"* While children can be mean to each other, caregivers of young children with hemangiomas often find that the attention (while it can still lead to isolation) from other younger children is mostly out of curiosity and the failure to comprehend the situation; hence, although direct and blunt language is used, it is not of malicious intent. This, however, does not reflect the practice of adults, and patients often find that more hurtful and damaging interactions come from other adults. This is usually due to the more direct and intrusive questions, comments, and stares. In a society that idolizes physical perfection, adolescents and adults often face ridicule, humiliation, discrimination, and suffering in public, school, or workplace situations. In turn, these patients increasingly avoid social situations and are also more prone to social problems, anxiety disorders, depression, and substance abuse.

Caregivers of individuals with hemangiomas often face daily difficulties, guilt, isolation, stress, and anxiety. Parents are faced with major decisions regarding treatment; in particular, whether to pursue treatments that are painful and may not be successful (accompanied by risks, benefits, and limitations) or opt out of treatment and face subsequent long-term consequences. Anxiety and stress often are associated with not only the decisions they face regarding their child's care but also the anticipated psychosocial impacts of living with a child with hemangiomas. This often negatively affects their social network, self-esteem, aspirations for both themselves and their children, and mental health. Parents are often the sole social network and friend of a child that may not have many (or any) friends (either perceived or real) due to these facial differences, thus leading to increased stress and isolation. Potential guilt and stress is associated with the aging child as their awareness of their situation increases, especially in situations where the parent opts out of treatment or decides to not prolong treatment (particularly if a treatment such as surgery was not successful and the hemangiomas grew back). In addition, some of the treatments are expensive and some parents worry about whether they will be able to afford treatment. As one parent stated, *"The only thought I can imagine to be any more terrifying than this is knowing that the effective treatment is out there and available but for whatever reason, I couldn't afford it because of my financial situation. Because I couldn't afford to pay for a treatment for my child, they could be severely affected for the rest of their lives."*

3. Current Therapy-Related Information

Current therapies available to individuals with hemangiomas include oral systemic corticosteroids, laser therapy, and surgical removal. Adults with hemangiomas often had minimal success with treatments received as children as the hemangiomas often grew back or there was little to no difference upon treatment. This was evidenced by one adult patient, *"I spent a good deal of my childhood having surgeries to stop the advancement of my hemangioma with limited success at best. I have averaged a surgery almost every two years of my life using a wide range of treatments. None of these have proven particularly successful. These surgeries have been painful both physically and emotionally, not to mention extremely expensive for the medical system."* Patients feel that there is a need and a place for additional treatments, especially non-surgical alternatives, in the current realm of therapies.

4. Expectations About the Drug Being Reviewed

There is hope from both individuals and their caregivers that Hemangiol will give children born with (or who develop) hemangiomas a treatment option that will prove effective in reducing or getting rid of the hemangiomas and enabling patients to live full lives, free of discrimination and isolation. Patients and caregivers indicated that an orally administered treatment for IH would be beneficial, particularly if it can reduce the need for invasive procedures such as surgery or laser treatment.

Most of the feedback regarding patients with Hemangiol experience came from patients outside of Canada, particularly from Australia and the US. Caregivers of these patients have been very satisfied with the treatment outcomes, noting that there have been distinct changes in both the size and colours of the hemangiomas. In some cases, parents have observed that hemangiomas have disappeared. Caregivers have noted that there are no major side effects; however, some parents have noted that side effects such as restlessness and insomnia have occurred in the first few weeks of treatment (although it was regarded as manageable). A few parents noted that some patients who were weaned off treatment experienced a recurrence of their hemangioma(s): *"My daughter started propranolol at three months and I weaned her off it at about 18 months as it was completely flat and all colour had gone. She is now 2.5 years old and over the last month or so it's raised by only about a millimetre or two and some light red colouring has come back."*

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase Ovid MEDLINE Ovid MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	September 22, 2016
Alerts:	Monthly search updates began September 22, 2016 and ran until January 2017.
Study Types:	Randomized controlled trials; controlled clinical trials; multi-centre studies; cohort studies; cross-over studies; case control studies; comparative studies; epidemiologic studies; also costs and cost analysis studies, quality of life studies, and economic literature.
Limits:	Humans

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	CAS registry number

MULTI-DATABASE STRATEGY	
1	Propranolol/
2	(Hemangiol* or Acifol* or Anaprilin* or Anapriline* or Angilol* or Apsolol* or Arcablock* or Artensol* or Avlocardyl* or Beprane* or Berkolol* or beta Neg* or Beta-Tablinen* or Beta-Timelets* or Biocard* or Blocaryl* or Cardinol* or Caridolol* or Cinlol* or Ciplar* or Corbeta* or Deralin* or Detensol* or Dibudinate* or DL-Anapriline* or DL-Propranolol hydrochloride* or Dociton* or Dumopranol* or Duranol* or Duraprox* or Efectolol or Elbrol* or Emforal* or Farprolol* or Frekven* or Half-Inderal* or Hemangeol* or Hemipralon* or Herzbase* or Herzul* or Ikopal* or Inderal* or Inderalici* or Inderex* or Indermigran* or Indobloc* or Innopran* or KEMI or Kidoral* or Naprilin* or Nedis* or Nelderal* or Noloten* or Novopranol* or Obsidan* or Oposim* or Panolol* or Prandol* or Pranix* or Prano-Puren* or Proberta LA* or Procor* or Pronovan* or Propabloc* or Propadex* or Propalong* or Propayerst* or Prophylux* or Propra or Proprahexal* or Propral* or Propranolol chloride* or Propranolol HCl* or Propranolol hydrochloride* or Propranovitan* or Propranur* or Propraratiopharm* or Prosin* or Pur-Bloka* or Pylapron* or R+C5989educor* or Rapynogen* or Sagittol* or Sawatol* or Scandrug* or Sinal* or Sloprolol* or Sudenol* or Tensiflex* or Tesnol* or Tiperal* or Tonum or CCRIS 1105 or HSDB 3176 or I 2065 or ICI 45520 or NSC 91523 or NSC-91523 or EINECS 222-501-5 or EINECS 206-268-7 or AY 64043).ti,ab,kf,ot,hw,rn,nm.
3	(F8A3652H1V or 9Y8NXQ24VQ).rn,nm.
4	or/1-3
5	4 use ppez
6	exp Hemangioma/
7	(hemangioma* or Angioma* or Chorioangioma* or Chorangioma*).ti,ab,kf.
8	6 or 7
9	8 use ppez
10	5 and 9
11	*propranolol/
12	(Hemangiol* or Acifol* or Anaprilin* or Anapriline* or Angilol* or Apsolol* or Arcablock* or Artensol* or Avlocardyl* or Beprane* or Berkolol* or beta Neg* or Beta-Tablinen* or Beta-Timelets* or Biocard* or Blocaryl* or Cardinol* or Caridolol* or Cinlol* or Ciplar* or Corbeta* or Deralin* or Detensol* or Dibudinate* or DL-Anapriline* or DL-Propranolol hydrochloride* or Dociton* or Dumopranol* or Duranol* or Duraprox* or Efectolol or Elbrol* or Emforal* or Farprolol* or Frekven* or Half-Inderal* or Hemangeol* or Hemipralon* or Herzbase* or Herzul* or Ikopal* or Inderal* or Inderalici* or Inderex* or Indermigran* or Indobloc* or Innopran* or KEMI or Kidoral* or Naprilin* or Nedis* or Nelderal* or Noloten* or Novopranol* or Obsidan* or Oposim* or Panolol* or Prandol* or Pranix* or Prano-Puren* or Proberta LA* or Procor* or Pronovan* or Propabloc* or Propadex* or Propalong* or Propayerst* or Prophylux* or Propra or Proprahexal* or Propral* or Propranolol chloride* or Propranolol HCl* or Propranolol hydrochloride* or Propranovitan* or Propranur* or Propraratiopharm* or Prosin* or Pur-Bloka* or Pylapron* or R+C5989educor* or Rapynogen* or Sagittol* or Sawatol* or Scandrug* or Sinal* or Sloprolol* or Sudenol* or Tensiflex* or Tesnol* or Tiperal* or Tonum or CCRIS 1105 or HSDB 3176 or I 2065 or ICI 45520 or NSC 91523 or NSC-91523 or EINECS 222-501-5 or EINECS 206-268-7 or AY 64043).ti,ab,hw,kw.
13	11 or 12
14	exp hemangioma/
15	(hemangioma* or Angioma* or Chorioangioma* or Chorangioma*).ti,ab,kw.
16	14 or 15
17	13 and 16
18	17 use oemezd
19	conference abstract.pt.
20	18 not 19
21	10 or 20

MULTI-DATABASE STRATEGY	
22	remove duplicates from 21
23	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial).pt.
24	Randomized Controlled Trial/
25	exp Randomized Controlled Trials as Topic/
26	"Randomized Controlled Trial (topic)"/
27	Controlled Clinical Trial/
28	exp Controlled Clinical Trials as Topic/
29	"Controlled Clinical Trial (topic)"/
30	Randomization/
31	Random Allocation/
32	Double-Blind Method/
33	Double Blind Procedure/
34	Double-Blind Studies/
35	Single-Blind Method/
36	Single Blind Procedure/
37	Single-Blind Studies/
38	Placebos/
39	Placebo/
40	Control Groups/
41	Control Group/
42	(random* or sham or placebo*).ti,ab,hw,kf,kw.
43	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
44	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
45	(control* adj3 (study or studies or trial*)).ti,ab,kf,kw.
46	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.
47	allocated.ti,ab,hw.
48	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.
49	or/23-48
50	22 and 49

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.

Grey Literature

Dates for Search:	September 2016
Keywords:	Hemangiol (propranolol) and hemangioma
Limits:	None

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Advisories & Warnings
- Background
- Clinical Practice Guidelines
- Databases (free)
- Health Economics
- Health Technology Assessment Agencies
- Internet Search
- Open Access Journals
- Regulatory Approvals

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Bauman et al. 2014. Propranolol vs prednisolone for symptomatic proliferating infantile hemangiomas: a randomized clinical trial. JAMA Otolaryngol Head Neck Surg. 2014 Apr;140(4):323-30.[32]	This study was a phase II study that used an unapproved dosage regimen for propranolol.
Malik et al., 2013. Effect of propranolol vs prednisolone vs propranolol with prednisolone in the management of infantile hemangioma: a randomized controlled study. J Pediatr Surg. 2013 Dec;48(12):2453-9.[33]	This study used an unapproved dosage regimen for propranolol. Patients were outside of the age range approved by Health Canada.
Léauté-Labrèze C, Dumas de la Roque E, Nacka F, Abouelfath A, Grenier N, Rebola M, et al. Double-blind randomized pilot trial evaluating the efficacy of oral propranolol on infantile haemangiomas in infants < 4 months of age. Br J Dermatol. 2013 Jul;169(1):181-3.[34]	This study used an unapproved dosage regimen for propranolol.
Menezes MD, McCarter R, Greene EA, Bauman NM. Status of propranolol for treatment of infantile hemangioma and description of a randomized clinical trial. Ann Otol Rhinol Laryngol. 2011 Oct;120(10):686-95.[35]	This publication reports the results of the literature review.
Hogeling M, Adams S, Wargon O. A randomized controlled trial of propranolol for infantile hemangiomas. Pediatrics. 2011 Aug;128(2):e259-e266.[36]	This study used an unapproved dosage regimen for propranolol.

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 22: CONSISTENCY BETWEEN CENTRALIZED AND ON-SITE RESPONSES FOR COMPLETE OR NEARLY COMPLETE RESOLUTION AT 24 WEEKS

Complete or nearly complete resolution at 24 weeks	Placebo (N = 55)	Propranolol 3 mg/kg/day for 6 months (N = 101)
Centralized review assessment (Yes)	2 (3.6%)	61 (60.4%)
On-site (No)	-	38 (37.6%)
On-site (Yes)	2 (3.6%)	23 (22.8%)
Centralized review assessment (No)	53 (96.4%)	40 (39.6%)
On-site (No)	53 (96.4%)	40 (39.6%)
On-site (Yes)	-	-

Notes: Centralized review: Minimal degree of telangiectasis, erythema, skin thickening, soft tissue swelling, and/or distortion of anatomical landmarks. On-site review: Minimal degree of telangiectasis, erythema, skin thickening, soft tissue swelling, distortion of anatomical landmarks, and/or a minimal palpable component.
Source: Adapted from Léauté-Labrèze et al. (2015).[10]

APPENDIX 5: SUMMARY OF STUDY 201 EXTENSION PHASE

Objective

This section of the report provides a summary of the efficacy results from the 72-week, open-label, follow-up phase of Study 201.

Study Design

Patients who completed the 24-week double-blind phase of the study were eligible to enrol in a 72-week follow-up period. The extension phase of the study consisted of four additional study visits (weeks 36, 48, 72, and 96).

Patient Disposition

Patient disposition for the extension phase are summarized in Table 23. The proportion of patients who completed the core phase of Study 201 and subsequently enrolled in the extension phase of the study was much greater in the propranolol group (85.3%) compared with the placebo group (34.5%). A majority of those who enrolled in the extension phase completed the 72-week study period (16/19 [84.2%] in the placebo group and 74/87 [85.1%] in the propranolol group). The most commonly cited reasons for discontinuation were decisions made by the guardian or parent, loss to follow-up, and decision by the investigator.

TABLE 23: PATIENT DISPOSITION FROM STUDY 201 EXTENSION PHASE

Disposition, n (%)	Placebo (N = 55)	Propranolol 3 mg/kg/day 6 months (N = 102)
Treated patients	55 (100.0)	101 (99.0)
Completed 24-week period	19 (34.5)	88 (86.3)
Entered follow-up period	19 (34.5)	87 (85.3)
Completed follow-up period	16 (29.1)	74 (72.5)
Discontinued follow-up period	3 (5.5)	13 (12.7)
Discontinued 24-week period	36 (65.5)	14 (13.7)
Entered follow-up period	14 (25.5)	8 (7.8)
Completed follow-up period	12 (21.8)	6 (5.9)
Discontinued follow-up period	2 (3.6)	2 (2.0)

Source: Common Technical Document section 2.7.3[3] and Clinical Study Report.[1]

Complete Resolution of Target Infantile Hemangioma

Treatment success or failure based on the on-site assessment of complete resolution of the target IH at week 48 was the key secondary efficacy end point of the core phase of Study 201 (summarized in section 3.6.4). Table 24 provides a summary of investigator-assessed complete resolution at weeks 36, 72, and 96. Few patients demonstrated complete resolution throughout the 72-week follow-up period. There was a numerical increase in the proportion of patients with a complete response in the propranolol 3 mg/kg/day for six months group at each of the time points (range: 8.3% to 13.5%) compared with the placebo group (range: 1.9% to 3.7%).

TABLE 24: COMPLETE RESOLUTION OF TARGET IH IN THE EXTENSION PHASE

TIME POINT	COMPLETE RESOLUTION	PLACEBO (N = 55)	PROPRANOLOL 3 MG/KG/DAY 6 MONTHS (N = 101)
Week 36	n/missing	54/1	96/5
	Yes, n (%)	1 (1.9)	8 (8.3)
	No, n (%)	53 (98.1)	88 (91.7)
Week 72	n/missing	54/1	93/8
	Yes, n (%)	2 (3.7)	10 (10.8)
	No, n (%)	52 (96.3)	83 (89.2)
Week 96	n/missing	52/3	89/12
	Yes, n (%)	1 (1.9)	12 (13.5)
	No, n (%)	51 (98.1)	77 (86.5)

IH = infantile hemangioma.
Note: Patients who prematurely discontinued study treatment were considered to have failed treatment. In addition, patients who received prohibited IH treatments between the day of the end of study treatment (included) and the assessment day (excluded) were also considered to have failed treatment.
Source: Clinical Study Report.[1]

Complete or Nearly Complete Resolution

Similar to the core phase of Study 201, complete or nearly complete resolution (the primary efficacy outcome) in the extension phase was more commonly reported by the centralized evaluators compared with the on-site study investigators. Table 25 summarizes the results for complete or nearly complete resolution of target infantile hemangioma (IH) at weeks 36, 48, 72, and 96 for both the centralized and on-site evaluations. At all of the time points, there was a greater proportion of propranolol-treated patients (range: 40.6% to 46.9%) who demonstrated complete or nearly complete resolution compared with those who received placebo (range: 10.9% to 20.4%), based on the centralized assessments.

TABLE 25: COMPLETE OR NEARLY COMPLETE RESOLUTION OF TARGET IH IN THE EXTENSION PHASE

Time Point	Complete or Nearly Complete Resolution	Placebo (N = 55)		Propranolol 3 mg/kg/day 6 months (N = 101)	
		On-site Investigator Analysis	Centralized Assessment	On-site Investigator Analysis	Centralized Assessment
Week 36	n/missing	54/1	54/1	96/5	96/5
	Yes, n (%)	2 (3.7)	6 (11.1)	16 (16.7)	39 (40.6)
	No, n (%)	52 (96.3)	48 (88.9)	80 (83.3)	57 (59.4)
Week 48	n/missing	55/0	55/0	96/5	96/5
	Yes, n (%)	2 (3.6)	6 (10.9)	14 (14.6)	45 (46.9)
	No, n (%)	53 (96.4)	49 (89.1)	82 (85.4)	51 (53.1)
Week 72	n/missing	54/1	54/1	93/8	94/7
	Yes, n (%)	4 (7.4)	11 (20.4)	16 (17.2)	40 (42.6)
	No, n (%)	50 (92.6)	43 (79.6)	77 (82.8)	54 (57.4)
Week 96	n/missing	52/3	53/2	89/12	90/11
	Yes, n (%)	4 (7.7)	9 (17.0)	19 (21.3)	42 (46.7)

Time Point	Complete or Nearly Complete Resolution	Placebo (N = 55)		Propranolol 3 mg/kg/day 6 months (N = 101)	
		On-site Investigator Analysis	Centralized Assessment	On-site Investigator Analysis	Centralized Assessment
	No, n (%)	48 (92.3)	44 (83.0)	70 (78.7)	48 (53.3)

IH = infantile hemangioma.
Note: Patients who prematurely discontinued study treatment were considered to have failed treatment. In addition, patients who received prohibited IH treatments between the day of the end of study treatment (included) and the assessment day (excluded) were also considered to have failed treatment.
Source: Clinical Study Report.[1]

Need for Additional Treatment

Many of the patients who enrolled in the 72-week extension phase received additional treatment for their IH(s). Beta-blockers were reported to be the most commonly prescribed therapeutic class. A larger proportion of patients in the placebo group (48.5%) received treatment with beta-blockers compared with the 3 mg/kg/day for six months group (22.1%) based on the safety evaluation data set (i.e., including both responders and non-responders from the 24-week core phase of the study).

In the subgroup of patients who achieved treatment success in the 24-week double-blind treatment period in the propranolol arm, seven patients (11.5%) re-initiated IH treatment during the 72-week follow-up period. Of those, six patients (9.8%) received a systemic treatment.[1] The manufacturer reported that five of the seven patients who required retreatment achieved complete or nearly complete resolution by week 96.[20] In the subgroup of patients who failed to achieve treatment success in the 24-week double-blind treatment period, four patients (15.4%) re-initiated treatment during the 72-week follow-up period, with all four receiving systemic treatment. Detailed results are presented in Table 26.

TABLE 26: SUMMARY OF ADDITIONAL IH TREATMENTS

IH Treatment	Category	Success at 24-weeks, n (%)		Failure at 24-weeks, n (%)	
		Placebo (N = 2)	Propranolol (N = 61)	Placebo (N = 17)	Propranolol (N = 26)
Any IH treatment	Extension of duration[a]	0 (0.0)	2 (3.3)	1 (5.9)	1 (3.8)
	Re-initiation[b]	0 (0.0)	7 (11.5)	1 (5.9)	4 (15.4)
Systemic IH treatment	Extension of duration[a]	0 (0.0)	1 (5.9)	1 (1.6)	0 (0.0)
	Re-initiation[b]	0 (0.0)	6 (9.8)	1 (5.9)	4 (15.4)

IH = infantile hemangioma.
[a] The manufacturer defined extension of extension of IH treatment duration as receipt of beta-blockers, corticosteroids, and/or lasers ≤ 7 days after the day of the end of study treatment.
[b] The manufacturer defined re-initiation of IH treatment as receipt of beta-blockers, corticosteroids, and/or lasers > 7 days after the day of the end of study treatment.
Source: Clinical Study Report.[1]

Limitations

The primary limitations of the data from the extension phase of Study 201 were the observational nature of the study design, the enrichment of the patient population, and the relatively small number of patients who completed both the 24-week core phase and the 72-week extension phase of the study.

The decision to enter the follow-up period was likely influenced by the fact that patients with more favourable treatment results (e.g., those who received active treatment who were successfully treated in the 24-week double-blind period) were more likely to enter the 72-week follow-up period, thereby enriching the patient population. In addition, there was a notably smaller sample size in the placebo group who entered and successfully completed the extension phase. Inconsistencies between the centralized assessment and the on-site investigator's assessment of complete or nearly complete resolution potentially decrease the confidence in the results and decrease the internal validity of the extension phase.

Summary

The extension phase of Study 201 demonstrated that 11.5% of patients who had achieved complete or nearly complete resolution of the target IH following a full course of oral propranolol (i.e., 3 mg/kg/day for six months) required re-initiation of IH treatment during the 72-week follow-up period.

APPENDIX 6: SUMMARY OF COMPASSIONATE USE PROGRAM

Objective

No controlled clinical studies investigating the efficacy and safety of oral propranolol for the treatment of patients with more serious IH were available for this review. In the absence of controlled studies, CADTH Common Drug Review summarized observational data from the manufacturer's compassionate use program (CUP), which included the use of propranolol in patients from France who were considered to have more severe forms of IH.[25]

Study Design

The manufacturer initiated a CUP for the treatment of proliferating IH considered to be life-threatening, function-threatening, or ulcerated and not responding to simple treatment. The CUP included patients who, as result of the above noted criteria, were unable to be included in a clinical trial (e.g., Study 201). A total of 1,661 patients were enrolled in the CUP from April 2010 to July 2014.[25]

Patient Characteristics

Table 27 provides a summary of key characteristics for patients who were enrolled in the CUP. A majority of the study participants were female (75.4%) and 22.9% were born prematurely. The average age of patients was 5.6 months (median 3.8 months). Hemangiomas were primarily located on the face (62.7%), followed by the body (42.1%), and a smaller minority were located internally (9.3%). The majority of patients (72.4%) had one or more hemangiomas that were considered a risk factor for functional impairment. Severe ulceration of the hemangiomas were reported for 39.3% of patients, and 15.8% of patients were considered to have hemangiomas that posed a vital risk (i.e., were potentially life-threatening).[25]

TABLE 27: PATIENT CHARACTERISTICS IN THE CUP

Characteristic		Propranolol n/N (%)
Sex	Female	1,227/1,628 (75.4)
	Male	401/1,628 (24.6)
Age	Mean	5.6 months
	Median	3.8 months
Birth weight	Mean	2.98 kg
Medical history	Cardiac diseases	44/1,642 (2.7)
	Anaphylactic reaction	2/1,641 (0.1)
	Asthma	7/1,624 (0.4)
	Bronchitis/bronchiolitis	68/1,418 (4.8)
	Atopic state	306/1,599 (19.1)
	Other pathology	78/1,369 (5.7)
Location	On face	1031/1,645 (62.7)
	On body	692/1,645 (42.1)
	Internal	151/1,619 (9.3)
	Multiple hemangiomas (≤ 3)	142/1,645 (8.6)
Severity	Functional impairment	166/1,610 (72.4)
	Severe ulceration	624/1,587 (39.3)
	Vital risk	249/1,579 (15.8)

Source: Compassionate Use Program Final Bridging Report.[25]

Exposure to Propranolol in the CUP

Table 28 summarizes the exposure to propranolol in the CUP. The recommended dosage of propranolol in the CUP was 2 mg/kg/day; however, the dosage could be increased to 3 mg/kg/day at the discretion of the physician depending on patient response to treatment and tolerability.[24] The manufacturer reported that 2 mg/kg/day was the mean and median dosage of propranolol that was administered in the CUP. The estimated mean treatment duration was 8.6 months and the maximum was 36.8 months.[25]

TABLE 28: EXPOSURE TO PROPRANOLOL

Exposure		Propranolol (N = 1,645)
Dosage of propranolol	Mean	2.0 mg/kg/day
	Median	2.0 mg/kg/day
Duration of treatment	Mean	8.6 months
	Median	7.3 months
	Maximum	36.8 months

Source: Compassionate Use Program Final Bridging Report.[25]

Efficacy and Discontinuation from the CUP

The reasons for treatment discontinuation are summarized in Table 29. The manufacturer's CUP was not designed to evaluate the efficacy of propranolol for the treatment of IH. However, the manufacturer extracted data from the case report forms regarding the reasons for discontinuation due to treatment success (i.e., good efficacy) or treatment failure (i.e., insufficient efficacy). Of the 1,645 patients enrolled in the CUP, data regarding discontinuation for reasons related to treatment efficacy were limited to 697 patients.[25]

TABLE 29: SUMMARY OF DISCONTINUATION FROM THE CUP

Reason for Discontinuation	Propranolol (N = 697)
Number of available data	697
Adverse event	29 (4.2%)
Sufficient efficacy	584 (83.8%)
Insufficiently efficacy	28 (4.0%)
Onset of an unspecified contraindication	20 (2.9%)
Unknown	45 (6.5%)

Source: Compassionate Use Program Final Bridging Report.[25]

Regrowth and Retreatment

The manufacturer's final bridging report for the CUP did not report on the proportion of patients who required retreatment for IH after being successfully treated. However, the US Food and Drug Administration (FDA) reported that 3% of patients who discontinued from the CUP as a result of good efficacy experienced regrowth that required retreatment.[11] The analysis reported by the FDA was based on a small subset of patients (i.e., 126 responders from a total of 209 patients evaluated).[11]

Harms Data from the CUP

Adverse drug reactions (ADR) and serious ADRs reported in the CUP are summarized in Table 30. A total of 161 patients reported a total of 259 ADRs; 61 of which were considered to be serious. The manufacturer reported that the most frequently reported ADRs in the CUP were: bronchiolitis (38; 12 serious), sleep disorders (39; initial insomnia, middle insomnia, nightmare, and sleep disorder), agitation (eight), decreased appetite (eight; one serious); and hypoglycemia (eight; five serious).[25]

TABLE 30: SUMMARY OF ADVERSE DRUG REACTIONS IN THE CUP

SOC	Adverse Drug Reaction	Events	
		ADRs	Serious ADRs
Cardiac disorders	Atrioventricular block complete	1	1
	Bradycardia	3	3
	Cardiac failure acute	1	1
	Cyanosis	1	0
	Sinus arrest	1	1
Ear, Labyrinth disorders	Hypoacusis	1	0
Eye disorders	Fixed pupil	1	0
	Eye movement disorder	1	1
Gastrointestinal disorders	Abdominal pain	2	0
	Constipation	1	0
	Diarrhea	5	0
	Flatulence	1	0
	Frequent bowel movements	1	0
	Nausea	1	0
	Regurgitation	2	0
	Vomiting	4	0
General disorders and administration site conditions	Unspecified adverse event	1	0
	Asthenia	1	0
	Chills	1	0
	Condition aggravated	2	1
	Crying	3	0
	Decreased activity	1	1
	Drug ineffective	2	1
	Malaise	5	4
	Edema peripheral	1	0
	Pyrexia	2	0
Infections and infestations	Bronchiolitis	38	12
	Bronchitis	7	0
	Ear infection	2	0
	Gastroenteritis	2	1
	Nasopharyngitis	1	0
	Otitis media	1	0
	Respiratory syncytial virus bronchiolitis	1	1
	Rhinitis	2	0
	Urinary tract infection	1	1

SOC	Adverse Drug Reaction	Events	
		ADRs	Serious ADRs
Injury, poisoning and procedural complications	Accidental overdose	1	0
	Expired drug administered	2	0
	Fall	1	1
	Inappropriate schedule of drug admin	2	0
	Incorrect dose administered	1	0
	Medication error	3	0
	Overdose	1	0
	Wrong technique in drug usage process	1	0
Investigations	Body height below normal	2	0
	ECG repolarization abnormality	1	0
Metabolism and nutrition disorders	Abnormal weight gain	1	0
	Decreased appetite	8	1
	Failure thrive	2	0
	Hypoglycemia	7	4
	Hypophagia	1	0
	Weight gain poor	4	1
Nervous system disorders	Altered state of consciousness	1	1
	Hypersomnia	1	0
	Hypoglycemic seizure	2	2
	Hypotonia	5	1
	Loss of consciousness	2	2
	Somnolence	3	0
Psychiatric disorders	Abnormal behaviour	2	0
	Agitation	8	0
	Apathy	1	0
	Eating disorders	1	0
	Initial insomnia	1	0
	Middle insomnia	6	0
	Nightmare	19	0
	Sleep disorder	13	0
Respiratory, thoracic and mediastinal disorders	Asthma	3	1
	Bronchospasm	6	6
	Cough	6	0
	Lung disorders	1	1
	Respiratory arrest	2	2
	Respiratory disorder	1	0
	Respiratory distress	2	2
Skin and subcutaneous tissue disorders	Cold sweat	1	0
	Hyperhydrosis	1	0
	Erythema	1	0
	Purpura	2	1
Social circumstances	Contraindication to medical treatment	1	0
Surgical and medical	Analgesic therapy	1	0

SOC	Adverse Drug Reaction	Events	
		ADRs	Serious ADRs
procedures	Intentional drug misuse	2	2
	Off-label use	2	1
Vascular disorders	Hypotension	4	2
	Pallor	5	1
	Peripheral coldness	6	0
	Peripheral vascular disorder	1	0
	Raynaud's syndrome	3	0
	Shock	1	0
	Vasoconstriction	3	0

ADR = adverse drug reaction; CUP = Compassionate Use Program; ECG = electrocardiogram; SOC = system, organ, class
Source: Compassionate Use Program Final Bridging Report.[25]

Critical Appraisal

All data from the CUP are uncontrolled and propranolol was administered in an open-label manner. The CUP was not designed to evaluate the effectiveness of treatment with propranolol. The only efficacy data available were obtained from a post hoc decision to capture whether efficacy (either adequate or inadequate) was cited as a reason for withdrawal. There were no statistical analyses conducted for these data. In addition, these data were only available for a fraction of the patients who were enrolled in the CUP (i.e., 647 of 1,645). There were no definitions provided or reported regarding how adequate efficacy was established in the CUP. There was also a considerable amount of data missing with respect to patient characteristics (see Table 27).

The average dose of propranolol that was administered to patients enrolled in the CUP was 2.0 mg/kg/day, which is below the 3.0 mg/kg/day dosage that is recommended in Canada. The use of a lower dose could potentially bias the limited available efficacy data against propranolol and potentially underestimate the harms associated with this treatment. In addition, the average and median duration of treatment with propranolol was 8.6 and 7.3 months, respectively. This indicates that the majority of patients in the CUP received treatment with propranolol for a period that was greater than the six-month treatment duration that is recommended in the Canadian product monograph (at least one patient was treated for a little more than three years [i.e., 36.8 months]).

The Canadian product monograph states that treatment with propranolol should be initiated in infants who are aged five weeks to five months.[8] However, the average age of patients in the CUP was 5.6 months, indicating that a number of patients enrolled in the CUP exceeded the five-month threshold recommended by Health Canada.

Conclusion

Uncontrolled and unblinded data obtained from a subset set of patients treated in the manufacturer's CUP suggested that 83.8% of propranolol-treated patients discontinued treatment as a result of experiencing adequate efficacy with the treatment. These data are limited by the absence of a control group, open-label administration of propranolol, use of an approved dosage (i.e., 2.0 mg/kg/day), use of extended treatment durations (i.e., exceeded six months for the majority of patients), large amounts of missing data, and the absence of any pre-specified efficacy evaluations.

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