CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205410Orig1s000

MEDICAL REVIEW(S)

Division Director Review

Date	2 March 2014
From	Norman Stockbridge
Subject	Division Director memo
NDA/BLA # **Supplement#**	205410 000
Applicant	Pierre Fabre Dermatologie
Date of Submission	17 May 2013
PDUFA Goal Date	17 March 2014
Proprietary Name / Established (USAN) names	Hemangeol Propranolol hydrochloride
Dosage forms / Strength	Solution; 3.75 mg/mL
Proposed Indication(s)	1. Treatment of proliferating infantile hemangiomas requiring systemic therapy, to be initiated in patients aged 5 weeks to 5 months.
Recommended:	Approval

Reference ID: 3464917

I refer to reviews of CMC (Shiromani; 31 December 2013), Biopharmaceutics (Riviere; 7 January 2014), pharmacology/toxicology (Yang; 7 August 2013), clinical pharmacology (Meno-Anderson; 18 January 2014), clinical (U; 20 December 2013), and statistics (Chen; 13 January 2014). There are also a CDTL memo (U; 7 February 2014), with which I am in agreement except as noted, and a memo by the Deputy Director for Safety (Southworth; 10 February 2014).

One CMC site inspection is incomplete. There are no other unresolved CMC issues.

Biopharmaceutics accepted the unusual bridging strategy, and I concur.

Rodents exposed throughout development show effects on neuromuscular development, kidneys, and lymphatics, at doses several-fold higher—and much longer—than the human exposure.

A 12-week study demonstrated pharmacokinetics in children similar, on a weight-adjusted basis, to what has been reported in adults.

Pharmacologically, there are no observed effects on blood pressure, heart rate, or blood glucose in children.

Study 201 had an adaptive design, with doses of 1 and 3 mg/kg/day for 3 and 6 months compared with placebo. After 188 subjects completed, only 3 mg for 6 months (and placebo) were continued into the second stage. During the first stage, 64% of subjects were discontinued from placebo, 33% from 3-month regimens, and 12% from 6-month regimens. In stage 2, 53% discontinued placebo and 5% discontinued propranolol. Discontinuations were largely for lack of effectiveness, as strong as the primary end point for supporting effectiveness.

The primary end point was complete or nearly complete resolution at 24 weeks, assessed by blinded assessment of photographs, with follow-up out to 96 weeks. At the end of stage 1, effects were seen with both 6-month regimens—$p=0.004$ for 1 mg/kg/day and $p<0.0001$ for 3 mg/kg/day. In stage 2 alone, the p-value was also <0.0001. Across both stages, the primary end point was met by 60% of subjects on 3 mg/kg/day and 4% of subjects on placebo.

There are no apparent effect differences by site of lesion, race, age at initiation, sex, or geographic region.

The literature and the sponsor's compassionate use program are also supportive of a high degree of effectiveness.

The entire review team supports approval, and, pending labeling negotiations, so do I.

Although not seen in the development program, there is a risk of hypoglycemia if infants receive propranolol when they are not feeding normally. Dr. U thinks a Med Guide will not help ensure caregivers heed this warning, but, while I harbor some concern that the message gets diluted in the boilerplate of a Med Guide, I and Dr. Southworth support using it here.

Dr. U recommends that the sponsor retain study subjects in a registry for 5-7 years to inform on effects on growth and development, neither I nor Dr. Southworth think those data will be interpretable without a control group.

Dr. U notes a small fraction of patients (on the order of 10%) require retreatment. He suggests that the sponsor be encouraged to conduct a study comparing 3 mg/kg/day for 6 months to 2

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mg/kg/day for a year. The latter would undoubtedly work and would reduce the number of cases requiring retreatment, but I question whether the recurrence rate and success treating recurrences warrant having everyone take propranolol for a year.

DMEPA initially agreed to the proprietary name (b) (4) but the sponsor and DMEPA seem to have agreed upon the proprietary name *Hemangeol*.

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/s/

NORMAN L STOCKBRIDGE
03/05/2014

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	205-410
Priority or Standard	Standard
Submit Date	17-May-2013
Received Date	17-May-2013
PDUFA Goal Date	17-Mar-2014
Division / Office	DCRP/ODE I/OND
Reviewer Name	Khin Maung U, M.D.
Review Completion Date	20-Dec-2013
Established Name	Propranolol Hydrochloride Oral Solution
(Proposed) Trade Name	(b) (4)
Therapeutic Class	Beta-adrenergic receptor antagonist
Applicant	Pierre Fabre Dermatologie
Formulation(s)	Oral solution: 3.75 mg/mL propranolol
Dosing Regimen	3 mg/kg/day for 6 months
Indication(s)	Treatment of proliferating infantile hemangioma requiring systemic therapy
Intended Population(s)	Infants age 5 weeks to 5 months

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

Background/Introduction

Infantile hemangiomas (IH) are the most common benign vascular tumors of childhood occurring in 3% to 10% of infants. IHs are usually not detectable at birth (nascent period) but appear during the first 4 to 6 weeks of life. Up to 24% of patients may experience complications which may be life-threatening (e.g., respiratory failure in airway IH, heart failure in liver IH with large circulation volume) or function-threatening (compression of eyeball causing anisometropia, astigmatism from periocular IH, feeding difficulties in lip IH) or, most commonly, ulceration, and may have sequelae such as skin discoloration, scars, telangiectasis or residual lesions.

Corticosteroids are the only treatment registered in two countries (France, Germany) for treatment of severe forms of angiomas in infants, but their efficacy in IH is variable. In 2008, treatment with propranolol in a 4-month-old infant was reported for the first time to provide an unexpected rapid improvement of a nasal IH that was enlarging despite corticosteroid therapy. This initial result was further confirmed in ten more children with severe or disfiguring IH and in 31 children with IH treated with propranolol in a prospective study. Numerous publications of the effectiveness of propranolol in the treatment of IH followed. Currently, propranolol is widely used off-label for this indication although it is not formulated for pediatric use.

Pierre Fabre, the applicant, developed a propranolol oral solution (3.75 mg/mL as propranolol base) to cover the expected weight range of infants to be treated (2 to 12 kg, i.e., 4.5 to 26.5 lbs.) at the selected dose (3 mg/kg/day) with an intake volume of less than 5 mL, and packaged in a (b) (4) glass bottle from which an accurate volume can be withdrawn with a graduated oral syringe to provide a patient-specific dose. This propranolol oral solution is proposed for the indication of treatment of proliferating IH requiring systemic therapy in infants aged 5 weeks to 5 months.

1.1 Recommendation on Regulatory Action

The overall efficacy analysis based on 1,333 patients (23 in Study 102, 456 in Study 201, 159 analyzed in the compassionate use program (CUP) and 695 in the key publications) shows that propranolol at 3 mg/kg/day dose for 6 months is an effective treatment for infants 5 weeks to 5 months old with IH requiring systemic therapy.

Safety data assessed on 2,451 patients treated with propranolol in the clinical trials (424 patients), the CUP (660 patients) and scientific publications (1,367 patients with IH treated with propranolol) showed no new unlabeled safety signals in infants with IH.

Based on review of the clinical data submitted in this NDA, the recommended regulatory action is **approval** (§21 CFR 314.110) pending the sponsor's response to agree to the suggested changes in the proposed labeling.

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1.2 Risk Benefit Assessment

The efficacy data for the primary endpoint is derived from a single randomized, placebo-controlled, multi-dose, 2-stage, seamless Phase II/III adaptive design study V00400 SB 2 01 (referred to as Study 201). Four hundred and sixty patients were randomized, and 456 were treated. Following an interim analysis that was conducted on 188 (of 190) intent-to-treat (ITT) Stage 1 patients who either completed the 24-Week study treatment period or prematurely withdrew from study, the Independent Data Monitoring Committee (IDMC) selected the 3 mg/kg/day 6 months arm, and recommended continuing the trial with this regimen and the placebo.

The results of the primary endpoint show efficacy of the selected regimen, 3 mg/kg/day 6 months vs. placebo on the primary efficacy analysis (ITT); the difference in the rate of complete/nearly complete resolution of IH at W24 (assessed by central reading of the photographs) was 60.4% with propranolol vs. 3.6% with placebo, which is statistically significant ($p<0.0001$) and also clinically meaningful. A sensitivity analysis using the per-protocol (PP) data set shows similar results.

There were no differences between the effects on facial and non-facial hemangioma, and between the two age strata (35 to 90 days, and 91 to 150 days).

Secondary endpoints based on centralized assessments of IH at paired consecutive visits show that improvement occurs early, with 72.7% of the patients showing sustained improvement at W5. A significant superiority of propranolol 3 mg/kg/day 6 months over placebo was also observed on two of the three centralized quantitative assessments: surface and color of hemangioma.

The pivotal study results were supported by those for the pharmacokinetic Study 102.

In the Compassionate Use Program (CUP), too, 60.3% (126 of 209) patients with high risk IH obtained good efficacy. Only 3% of patients who discontinued due to good efficacy required retreatment for regrowth of IH.

In 15 key publications and 3 meta-analyses in the medical literature reporting the effect of oral propranolol in children with IH, the beneficial response rate ranged from 50% to 100%; the regrowth rate ranged from 12% to 14%, and the patients who required retreatment with propranolol ranged from 6% to 8%.

The results observed in Study 201, in the CUP and the medical literature suggest that up to 10% of patients required re-introduction of treatment after discontinuing propranolol.

The efficacy analysis was based on 1,333 patients (23 in Study 102, 456 in Study 201, 159 analyzed in the CUP, and 695 in the key publications), and shows that propranolol at the 3 mg/kg/day dose for 6 months is an effective treatment for infants 5 weeks to 5 months old with IH requiring systemic therapy.

Safety was assessed on 2,451 patients treated with propranolol in the clinical trials (424 patients), the CUP (660 patients) and literature review of scientific publications (1,367

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patients with IH treated with propranolol). The propranolol HCl oral solution showed a comparable safety profile to marketed propranolol products with no new unlabeled safety signals reported in the pivotal study, the CUP and studies in children with IH in the scientific literature.

The important known risks of propranolol in infants (hypoglycemia, hypotension, bradycardia, and bronchospasm) were specifically reviewed. Patient monitoring after treatment initiation and after up-titrations in dose showed that heart rate was the most adequate parameter to follow and that a monitoring period of 2 hours post-treatment administration could be considered sufficient to detect bradycardia. Educating parents/ caregivers to provide frequent feeding to the infants and/or to feed the infant just before dosing with propranolol was shown to prevent hypoglycemia.

On the basis of the reviewed evidence, propranolol HCl oral solution at the dose of 3 mg/kg/day (in two divided doses), and used in accordance with the specific conditions described in the proposed Prescribing Information, can be considered an effective and safe treatment for infants 5 weeks to 5 months old with IH requiring systemic therapy.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The purpose of a REMS is to help the patient and/or the physician reduce the risks of a potentially fatal or serious adverse event.

Regarding the drug product (propranolol) itself, its safety profile has been extensively documented over several decades of clinical use in adult patients, and in infants with cardiology indications.

For use of propranolol in infants, the following risks were identified and evaluated: bradycardia, hypotension, hypoglycemia and exacerbation of bronchospasm/ bronchiolitis. The data in the submission in which patients were monitored during the clinical study and on the days of dose increments indicated that:

(i) the heart rate is the most adequate parameter to follow, and that a monitoring period of 2 hours post-treatment is sufficient to detect bradycardia; and

(ii) blood glucose monitoring on the days of uptitration did not reveal any signals of hypoglycemia that would be of concern, suggesting that hypoglycemia can be prevented with proper education of parents and guardians/caregivers on the importance of administrating propranolol oral solution during or right after a feeding.

In the case of oral propranolol solution to treat IH in infants, a Medication Guide will not be useful because (i) hypoglycemia, the most clinically important AE, is prevented by frequent feeding or feeding during and immediately after the oral administration, for which parental education is the effective measure, and (ii) reduction in heart rate and blood pressure observed are usually asymptomatic, with rapid development of tolerance to propranolol; only very rare instances have been reported in the literature.

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A Physician Communication Plan does not help the patient or the physician because the application-specific adverse events are very rare at the symptomatic level. None was reported in the pivotal clinical trial. Only three cases of symptomatic hypotension and one case of symptomatic bradycardia have been reported in the medical literature with use of oral propranolol solution for treatment of IH. The initial decrease in heart rate normalized over subsequent doses, suggesting rapid development of tolerance. Exacerbation of bronchospasm or bronchiolitis is easily recognized by parents and guardians from the audible wheeze the child develops.

Only eleven hypoglycemia (10 symptomatic) cases associated with propranolol therapy for IH have been reported in the medical literature. In eight cases, an additional stressor such as an acute infection, prolonged fasting or oral corticosteroids causing adrenal insufficiency have been present and assumed to have precipitated all but one of these cases, and two other cases were beyond the age group indicated (11 and 18 months old) at the time of starting treatment. There were no cases of hypoglycemia in the clinical trials in this NDA. In the CUP, there were four cases of hypoglycemia of which two had symptoms (hypoglycemic seizure); both resulted from failure to give feeds to the child before administering propranolol, and in both there was no documentation of blood glucose levels so the probable cause of seizure is determined by “clinical reasoning.” It is also noteworthy that propranolol was continued or re-administered to these infants without recurrence of hypoglycemia.

Therefore, I think the emphasis should be to educate parents and caregivers to give frequent feeding, and/or to give feeds with the drug, which will be more effective to prevent hypoglycemia than a Medication Guide which is not appropriate and may detract from the message to give feeds to prevent hypoglycemia.

Based on the clinical data in the application (both in the controlled clinical trial and in the CUP) and comprehensive safety data reported in the medical literature, my opinion is that neither a REMS nor a Medication Guide is necessary for approval.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

However, I recommend that the Division advise the sponsor in the approval letter to conduct the following studies:

(1) Keep a registry of all pediatric patients treated with propranolol in Studies 201 and 102 and the CUP, and follow these children over the next 5-7 years for any effect of propranolol on their growth and developmental milestones, such as:
- Anthropometric measurements to follow physical growth in pre-school age,
- Gross motor,
- Fine motor,
- Language,
- Cognitive development, and

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- Social and emotional development.

Justification: Studies in humans[1,2] indicates that prenatal beta blockade induces long-term neurological complications including impaired school performance, cognitive impairment, and psychiatric disorders; however, no studies to date have examined the long term neurological effects of acute or chronic beta blockade in one to two year old children. Extensive animal studies demonstrate that beta blockade in neonates induces long lasting neurological effects because of the inability of neonatal neural tissue to desensitize to beta adrenergic response,[3] and pre- and post natal modulation of beta adrenergic receptors with propranolol affects the long term levels of the noradrenaline metabolite 3-methoxy 4-hydroxyphenylglycol (MHPG) in the frontal cortex and striatum and serotonin signaling in the frontal cortex,[4] and induces a long term supersensitivity of the presynaptic alpha 2-adrenoceptor.[5]

While propranolol should definitely be used as a first line treatment in children suffering from disfiguring and/or life-threatening IHs, it should not be used in a widespread manner to treat merely cosmetic IHs. Appropriately controlled long term studies should be planned to evaluate the impact of use of propranolol in the neonatal and infantile period on their neurological, psychological and physical growth and development.

(2) Conduct a clinical trial of propranolol to show the effect of duration and dose of propranolol treatment:

(a) comparing 2 mg/kg/day x 12 months vs. 3 mg/kg/day x 6 months,

(b) in all types of IH, including patients with PHACES syndrome, life-threatening IH, function-threatening IH, IH with ulcers and severe IH, and

(c) using different clinical endpoints in addition to the number/ proportion of patients who achieved complete/near complete resolution and time to resolution (e.g., rate, time and extent (nature) of regrowth, need for systemic retreatment with propranolol, need for local (topical) retreatment with beta-blockers, need for systemic retreatment with corticosteroids).

Justification: There is a varying regrowth rate of 6 – 12% after treatment of IH with propranolol 3 mg/kg/day x 6 months. According to the pathophysiology and natural history of IH, the active proliferative phase lasts from 5 weeks to about 14 months of life.[6] It is possible that 6 months' treatment might not have covered the entire active proliferative phase in the patients who had regrowth. There is also the possibility of causing propranolol-resistant IH (PRIH) with an inadequate duration of treatment.[7] "Rebound growth" of focal hemangiomas have been reported after cessation of steroids as well as propranolol[8,9] whereas rebound growth after surgical resection is extremely unlikely.

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2 Introduction and Regulatory Background

Infantile hemangiomas (IHs) are the most common benign vascular soft-tissue tumors of childhood, occurring in 3% to 10% of the population[10,11,12,13]. They are composed of a complex mixture of clonal endothelial cells associated with pericytes, dendritic cells and mast cells[10], and characterized by endothelial cell proliferation. The lesions are usually not detectable at birth but appear during the first 4 to 6 weeks of life. Known risk factors for the development of IH are: female sex (female to male ratio of 2.4:1), Caucasian ethnicity, low birth weight (especially <1500 g), and products of multiple gestations[11,14,15]. Although most are not troublesome, around 12% of IHs can be complex, requiring referral to specialists for consideration of treatment[16].

The natural history of IH comprises three phases (Figure 1):

1) initial rapid growth (proliferation) phase: The proliferative phase occurs during the neonatal period, at which time the lesion growth rate is beyond that of the infant. In a prospective cohort of 526 IH cases in 433 patients[17], most IH growth occurred before 5 months (i.e. 150 days). During the growth phase, two major proangiogenic factors are involved: basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF)[10]; histologic studies have shown that both endothelial and interstitial cells are actively dividing in this phase.
2) stabilization phase: During the stabilization phase, which is of variable length, growth has stopped. It is followed by the involution phase.
3) involution phase: During the involution phase, apoptosis has been shown[10]; the lesion fades in color, becomes softer and more compressible, and reduces in volume, with sequelae in the majority of cases[18].

Most IH exhibit an uncomplicated clinical course. However, some may be associated with life-threatening complications (e.g., respiratory failure in airway IH, congestive heart failure in liver IH) or function-threatening (anisometropia, astigmatism, and amblyopia in periocular IH, feeding difficulties in lip IH, etc.). If left untreated, they leave permanent sequelae which may trigger psychological morbidity first in parents and later in affected children[10,19]. About 12% of IH cases require referral to specialists for consideration of treatment[16]. In a cohort of 1058 children with IH studied in 7 US pediatric dermatology clinics, 24% of patients experienced complications, most commonly ulceration, threat to vision, and airway obstruction[20]. Large IH, facial locations, and segmental IH have a higher risk of developing complications.

Moderate sequelae of IH include telangiectasias, atrophic scars, or yellowish skin discoloration. More severe consequences include the presence of excess skin with underlying fibroadipose tissue, destruction of underlying cartilage, or extensive scarring. Scarring is inevitable if ulceration (a complication of proliferation) has occurred. The final outcome of the involution phase depends mainly on the size reached by the IH during proliferation, its characteristics (superficial, deep, or mixed), and the presence of ulceration. A recent retrospective study[18] revealed that residual lesions were present in

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69% of untreated cases. Superficial nodular IH showed significantly more residual lesions (74%) than deep IH (25%), probably due to the irreparable damage to the skin of superficial IH. Untreated infection, ulceration, or bleeding produced a residual scar in 97% of cases[18].

Figure 1 Phases of Infantile Hemangioma

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(a) Growth and regression of IH. (b) Molecular markers characterizing individual phases of IH.
PCNA, proliferating cell nuclear antigen; VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor; TIMP, tissue inhibitor of metalloproteinases; GLUT-1, glucose transporter type 1.
(Source: Storch CH & Hoeger PH. *Brit J Dermatol* 2010;163: 269-74.)

In 2008, treatment with propranolol in a 4-month-old infant was reported for the first time to provide an unexpected rapid improvement of a nasal IH that was enlarging despite

corticosteroid therapy; the infant received propranolol because he developed an obstructive hypertrophic cardiomyopathy[21]. Ten more children with severe or disfiguring IH treated with propranolol also improved. This initial result was further confirmed in 31 patients with IH treated with propranolol in a prospective study[22]. This was followed by numerous publications of its effectiveness. Propranolol is now widely used off-label for this indication, despite the fact that it is not formulated for pediatric use.

Propranolol hydrochloride has monographs in the European and US Pharmacopoeia. It has well characterized pharmacological properties and has been in clinical use since the 1960s in several clinical situations. In children, specific dosing recommendations have been established and its clinical use is accepted in hypertension, arrhythmias, tetralogy of Fallot spells, hypertrophic myocardiopathy, and thyrotoxicosis. More recently, a propranolol oral solution (Syprol®) was registered in the UK for the use in children in the treatment of arrhythmia, phaeochromocytoma, thyrotoxicosis, migraine, and tetralogy of Fallot. An oral solution is also available in the US (Propranolol Hydrochloride, Roxane Lab.), but it is indicated in adults only.

Pierre Fabre developed a pediatric oral solution with a proposed strength of 3.75 mg/mL (expressed as propranolol base and coded propranolol) to cover the expected weight range of infants to be treated (2 to 12 kg, i.e., 4.5 to 26.5 lbs.) at the selected dose (3 mg/kg/day) with an intake volume of less than 5 mL, and packaged in a (b) (4) glass bottle from which an accurate volume can be withdrawn with a graduated oral syringe to provide a patient-specific dose. Pierre Fabre maintains that this complies with pediatric guidelines: Regulation (EC) No 1901/2006 and the latest International Conference on Harmonisation (ICH) recommendations for products for the pediatric population (EMEA/CHMP/PEG/194810/2005). Propranolol is pH-adapted and does not contain sugar, sweeteners, preservatives, alcohol, or propylene glycol, but instead contains water, aromas, and a selected sweetener, avoiding the use of sucrose, fructose, sorbitol, xylitol, and aspartame, complying with the guidelines to maximize safety and mask the bitter taste of the product.

2.1 Product Information

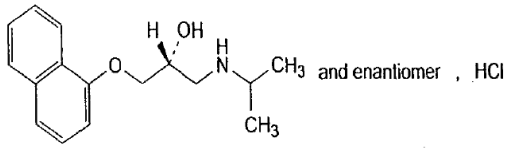
Proprietary Name: (b) (4)

Non-Proprietary Name: Propranolol Hydrochloride Oral Solution

Reference Listed Drug: NDA 16-418 INDERAL® (propranolol hydrochloride) tablets.

Chemical Name: (2RS)1-[(1-methylethyl)amino]-3-(naphthalene-1-yloxy)-propan-2-ol hydrochloride

Structural formula:



Molecular formula: $C_{16}H_{21}NO_2$-HCl

Mean Molecular Weight: 295.8 Dalton

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2.2 Tables of Currently Available Treatments for Proposed Indications

Corticosteroids, INF alpha and vincristine are recommended for use, as first, second and third line therapies, respectively, by the American Academy of Dermatology's Guidelines (1997)[23] since about 15 years ago. Recently, timolol maleate, a nonselective β-blocker used in ophthalmic solutions to treat glaucoma, has been evaluated as a topical 0.5% or 0.1% timolol maleate gel-forming solution to treat patients with IH.[24]

Table 1 summarizes the efficacy and safety information of currently available treatments for IH.

Table 1 Efficacy/safety profiles of currently available treatments for IH

	Corticosteroids (First line treatment)	**IFN alpha** (Second line treatment)	**Vincristine** (Third line treatment)	**Timolol** (recent topical treatment)
Efficacy and dose	**84% response rate[25]** (cessation of growth or reduction in size) Re-growth in 36% at 2.9 mg/kg/day, 1.8 months.[26] Inhibits growth rather than reducing IH size.	**40-50% complete response.[10]** First signs of regression are usually observed within 2-12 weeks.	**Shows a clear response in 7/9 (78%) infants.[27]** Successful in IH refractory to other therapies with vital structure involvement or associated with KMS. Dose: 1 mg/m2/day for 6 months	72 of 73 patients (median age 4.3 months) improved **(response rate = 99%)[24]** Dose: 62 were treated with 0.5% solution and 11 with 0.1% solution for 3.4 ± 2.7 months.
Safety and Tolerability	Mood changes, insomnia, GI symptoms. Cushingoid face frequent after 1-2 months tx, hypertension, adrenal suppression, immune-suppression, bone demineralization, hypertrophic cardio-myopathy[28], Pneumocystis carinii pneumonia in infants given high doses.	Transient neutropenia, fever, elevated liver enzymes and flu-like symptom. Neurotoxicity including spastic diplegia and motor developmental disturbances may occur in 10 to 30% of cases.[29] Motor developmental disturbances resolve in majority, diplegia is largely irreversible.[30]	AEs such as severe constipation and peripheral neuropathy are dose-related and dose-limiting.	Sleep disturbance noted in one patient. Predictors of better response: (i) superficial type of IH (p=0.01), (ii) 0.5% solution (p=0.01), and (iii) duration >3 months (p=0.04).

GI: gastrointestinal; IFN: interferon; IH: infantile hemangioma; KMS: Kasabach-Merrit syndrome; tx: treatment {Source: Sponsor's reference table}

2.3 Availability of Proposed Active Ingredient in the United States

Currently, Propranolol 3.75mg/mL oral solution (propranolol) has no marketing approval in any country.

An oral solution is available in the US (Propranolol Hydrochloride, Roxane Lab.), but it is indicated for use by adults only.

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2.4 Important Safety Issues with Consideration to Related Drugs

The following safety issues are known to be associated with propranolol and other β-blockers: bradycardia, hypotension, hypoglycemia and bronchospasm/bronchial asthma exacerbation.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Regulatory History

- 05-Sep-2008: orphan designation (08-2667) for proliferating IH requiring systemic therapy
- 31-Jan-2009: Parallel Scientific Advice Meeting with sponsor and EMA
- 01-Jul-2009: IND 104390 submitted
- 19-Aug-2009: clinical Special Protocol Assessment (SPA) submitted
- 02-Oct-2009: SPA *no agreement* letter sent to sponsor
- 10-Nov-2009: Type A meeting with sponsor re: SPA
- 21-May-2010: Type C teleconference with sponsor
- 01-Feb-2011: (b) (4)
- 26-Apr-2012: pre-NDA meeting
- 20-Aug-2012: Proposed Pediatric Study Request submitted: pending
- 15-Oct-2012: proprietary name "(b) (4) granted conditional approval.

The adaptive design method of the pivotal clinical study (V00400 SB 2 01) was finalized in accord with recommendations made by the FDA and the EMA after parallel scientific advice discussions, a Special Protocol Assessment (SPA) in the US, and a Pediatric Investigation Plan (PIP) in Europe. The adaptive design methodology was used to enable a minimal number of patients to be enrolled in the clinical development program and to adapt the sample size in the case of a wrong "hypothesis / estimation".

On 07-Dec-2012, the sponsor met with the Division, and the following review issues were discussed, with the sponsor agreeing to submit to FDA:

(i) A systematic selection of pre- and post-treatment photographs of treated patients,
(ii) SAS datasets of each subject's assessments of treatment outcome at every time point,
(iii) Efficacy and safety data for the "overrun" patients, including exploratory comparison of primary efficacy endpoints in these overrun patients to placebo-treated patients,
(iv) Time point at which patients discontinued prematurely
(v) Data related to persistent of treatment effect, recurrence (rebound of disease) and scarring
(vi) Efficacy data in infants with more severe hemangiomas – from literature reports and CUP
(vii) Safety data from 367 patients in CUP in France and Switzerland, and from case

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reports of >1,300 IH patients treated with propranolol solution published in the literature

(viii) Defining "inappropriate bradycardia" in infants.

The discussion also included the appropriateness of a REMS which the sponsor planned to submit, and the lack of drug-drug interaction studies (the sponsor will use the currently known interactions of propranolol adapted to the infant population as described in the PI).

2.6 Other Relevant Background Information

Pierre Fabre requested a Priority Review classification based on the following:

- IH requiring systemic therapy is an orphan disease, which can create serious and life-threatening medical complications in small children, including airway involvement, impediment of feeding, ophthalmologic complications often requiring surgery, associated structural anomalies such as cardiac defects, increased risk of visceral involvement, and hepatic lesions including congestive heart failure and hyperthyroidism;
- There is currently no FDA-approved treatment for IH;
- Patients who experience proliferating IH represent a clear unmet medical need;
- (b) (4) is specifically formulated and developed for pediatric use;
- Phase 2/3 study with (b) (4) demonstrated statistically significant and sustained clinical improvements in IH patients compared to placebo and a favorable safety profile, and
- The magnitude of the treatment effect is clinically relevant and significantly greater than that previously reported with historical treatments, suggesting that (b) (4) is a clear leader as a first-line treatment for IH requiring systemic therapy.

The Division classified this application as a Standard Review for the following reasons:

- For about 15 years the American Academy of Dermatology's Guidelines has recommended corticosteroids, INF alpha and vincristine (see Table 1). In addition, timolol maleate, as a topical 0.5% or 0.1% gel-forming solution, has recently been evaluated in the treatment patients with IH.
- The response rates obtained with the other available drugs (Table 1) appear to be as good as or better than those obtained with (b) (4) (60%) although the endpoints may not be exactly similar: corticosteroids produce a 84% response rate, INF alpha a 40-50% response rate (with regression starting at 2-12 weeks), Vincristine a 78% response rate (in 7 of 9 infants) and timolol a 99% response rate (72 of 73 patients improved).
- Although propranolol hydrochloride solution appears to be effective, its superiority over other available therapy has not been demonstrated in a direct head-to-head comparison.

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3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, the NDA is well-organized and appropriately cross-referenced with electronics hyper-links that work. The eCTD was easy to navigate and find information and data. The sponsor provided thorough information, including reports of the compassionate use program and case reports from the medical literature, and also complete data sets as discussed during the Pre-NDA and topline results meetings. The sponsor responded promptly to information requests from the Division before and during NDA submission.

The sponsor submitted documentation (audit certificates by (b) (4), Pierre Fabre QA and (b) (4)) that the clinical trial sites (#7105, #8101, #2702, #3201, #2302, #0508, #0506, #0601, #1101, #5002, #7102) which participated in the pivotal studies and the Imaging, Biometry and Randomization departments were audited.

3.2 Compliance with Good Clinical Practices

The clinical studies that were submitted in support of this NDA appeared to be compliant with GCP; there were informed consents that were reviewed and approved by the IEC/IRB before the study was initiated at the sites. The conduct of the phase II/III study was closely monitored by the sponsor, and the safety of patients these trials was monitored by an Independent Data Monitoring Committees (IDMC).

No particular site stands out for inspections. The Division requested OSI for GCP inspection of the conduct of the pivotal study 201 at two sites (0508 and 5001) which enrolled large numbers of patients, and showed relatively strong positive results (Table 2). At the third site (#7105) all subjects who received the intended marketing dose (3 mg/kg/day for 6 months) were adjudicated negative, which appeared unusual.

The EMA had also planned to inspect Site #0508 in France (similar to our selection), and a different site (#5002) in Lima, Peru for inspections. The reason for the difference in site selection between EMA and the Division is as follows:

Site #5001 randomized 16 subjects and completed 15 with 1 premature discontinuation; Site #5002 randomized 17, and treated 17 with 1 premature discontinuation. However, Site 5001 had 5 positive patients enrolled in the dose regimen intended for marketing (3 mg/kg/day for 6 months), and 4 who were positive with a different dose regimen i.e., 9 of 15 (56%) randomized were positive at Site #5001. In contrast, Site #5002 had 4 positive patients in the dose regimen intended for marketing, and 3 more who were positive with a different dose regimen, i.e., 7 of 17 (41%) randomized were positive at Site #5002. Thus, Site #5001 was selected for inspection because of a larger number and a larger proportion of positive patients compared to site 5002.

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Table 2 Sites selected for OSI – GCP Inspections

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects Randomized	Indication / Primary endpoint and other endpoints for verification
0508: Juliette Mazereeuw, MD Hopital des Enfants Département Cardio-Pédiatrique 330, avenue de grande bretagne **31100 Toulouse, FRANCE** Phone: +33 5 67 77 81 41 Fax: +33 5 67 77 81 42 e-mail: mazereeuw-hautier.j@chu-toulouse.fr	V00400 SB 201	28	Treatment of proliferating infantile hemangioma requiring systemic therapy
5001: Rosalia Ballona, MD Clinica Internacional Av. Garcilaso de la Vega #1420, **Lima 1, PERU** Phone(1): +51 161 96 161 ext 5004 Phone(2): +51 999 352 357 Fax: +51 14 31 96 77 e-mail: rballona@gmail.com	V00400 SB 201	16	Treatment of proliferating infantile hemangioma requiring systemic therapy
7105: Sheila Friedlander, MD Rady Children's Hospital San Diego Pediatric and Adolescent Dermatology 8010 Frost St., #602 **San Diego , CA 92123, USA** Phone: + 1 858-574-1700 ext 4219 Fax: + 1 858-966-4040 e-mail: Sfriedlander@rchsd.org	V00400 SB 201	16	Treatment of proliferating infantile hemangioma requiring systemic therapy

On 09-Dec-2013, OSI filed a clinical inspection summary which contained the results of an ORA/OSI conducted domestic inspection as well as the results of two EMA conducted foreign inspections in France and Peru, and an inspection conducted in France of the sponsor: Institut de Recherche Peirre Fabre (IRPF).

The inspection of Dr. Friedlander's site was unremarkable. An important issue identified at the foreign sites and the sponsor was a failure to precisely identify in the protocol how the IH lesions should be measured. Since the majority of sites (48/54) used lesion size + induration, an overall effect on the study seems unlikely. There was a failure to classify some cases of Grade 4 neutropenia as "Clinically Significant" which could have resulted in missing AEs/SAEs, but the number appeared to be small (three subjects). OSI recommended that the data was considered adequate and could be used in support of the pending application.

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3.3 Financial Disclosures

Pierre Fabre submitted certification that the clinical investigators and sub-investigators who participated in studies 201 and 102 had no disclosable financial interest, that these investigators remained fully blinded throughout the study, and that no blinded or unblinded information was provided to these investigators during the study.

Pierre Fabre also submitted that Dr. Christine Labreze and Dr. Jean-Benoit Thambo, the inventors of the use of β-blockers in the treatment of IH, who participated in Studies 201 and 102, (b) (4) have no direct financial arrangement with these investigators).

Dr. Thambo is the cardiologist of the clinical center 0501. Dr. Labreze is the principal investigator and coordinating investigator for the pivotal Study 201, and was the signatory of the clinical study report for Study 201; therefore, the primary analysis at W24 were unblinded to Dr. Labreze. To avoid bias, Dr. Labreze committed in a written statement not to evaluate personally the patients from her investigational site during the visits planned between W24 and W96; the follow-up of these patients were transferred to another member of the clinical investigational staff.

Reviewer's comment: The actions taken by the sponsor and the coordinating investigator are acceptable.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

For the indication of treatment of proliferating Infantile Hemangioma requiring systemic therapy, NDA # 205-410 for Propranolol 3.75 mg/mL oral solution was submitted in accord with Section 505(b)(2) of the Federal Food, Drug & Cosmetic Act, making cross reference to the FDA's Summary Basis of Approval (SBA) for the original NDA approval of Inderal® (propranolol hydrochloride) tablets from 1967 (NDA #016-418).

Propranolol oral solution was granted an orphan designation by the Food and Drug Administration (FDA) on 5 Sep. 2008 (#08-667) for the same indication.

Bridging between Propranolol oral solution and Inderal® was established using a 2-step approach:

- An *in vivo* bioavailability comparison between the oral formulation of propranolol and a French approved propranolol tablet formulation (Avlocardyl®, the French brand name for Inderal®), which demonstrated in 12 healthy adults comparable bioavailability profiles between the 2 formulations, and
- An *in vitro* dissolution test which demonstrated equivalence of the dissolution profiles of Avlocardyl® and Propranolol HCl USP 40 mg tablets (Barr Laboratories, Inc, as Inderal® 40 mg tablet is no longer marketed).

4.2 Clinical Microbiology

Non-sterile aqueous drug products may potentially be contaminated with organisms in the *Burkholderia cepacia* complex (BCC) which have ability to ferment a wide variety of substrates and are known to survive and proliferate in the presence of many traditional preservative systems during storage.

The ONDQA reviewer issued an IR to the sponsor to (i) identify potential sources for introduction of BCC during the manufacturing process and describe the steps to minimize the risk of BCC organisms in the final drug product, (ii) provide test methods and acceptance criteria to demonstrate the drug product is free of BCC, and (iii) as there are currently no compendial methods for detection of BCC, to use a validated method capable of detecting BCC organisms, including description of the preconditioning step (time, temperature, and solution(s) used), the total number of inoculated organisms, and the detailed test method to include growth medium and incubation conditions.

The sponsor conducted studies which showed that (i) the residual risks for the propranolol 3.75 mg/mL oral solution to be contaminated by BCC during the

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manufacturing process are considered under control and in compliance with current regulations, (ii) a high antimicrobial activity of the drug product is demonstrated on 2 strains of BCC, and (iii) analysis performed on 6 industrial scale batches proved the absence of BCC in the drug product. The sponsor submitted that the microbiological quality of propranolol 3.75 mg/mL oral solution, including BCC, is under control.

4.3 Preclinical Pharmacology/Toxicology

The following is abstracted from the Pharm-Tox review.

To evaluate the potential toxic effects of propranolol on development, one nonclinical study using the oral route was performed in juvenile male and female SD pups (oral propranolol at 0, 10, 20, and 40 mg/kg from post-natal day 4 (PND 4) to PND 21).

Of the 5 deaths, two (one sacrificed male and one cannibalized female) in the 40 mg/kg/day groups cannot be excluded as being a test item-related.

Reversible lower body weight and/or lower body weight gain were observed in males and/or females at 20 and/or 40 mg/kg/day propranolol.

Higher incidence and degree of germinal centers in mandibular and mesenteric lymph nodes were noted in males and females at 40 mg/kg/day group (the only dose level checked) at the end of treatment in Subset I animals, dose-dependent increases (up to ~40%) in white blood cells, lymphocytes and large unstained cells, and basophils in both sexes (statistically significant mostly at 20 and 40 mg/kg/day) at 10 weeks post-treatment in Subset II animals. There were also reversible abnormalities (lower urine volume at 20 and 40 mg/kg/day associated with higher incidences of minimal renal cysts, dilation of kidney pelvis/tubule at 40 mg/kg/day, the only dose level checked) in both sexes. Thus, a No Observed Adverse Effect Level (NOAEL) for general toxicity was estimated to be 10 mg/kg/day (mean $AUC_{0\text{-}24\ h}$ = 50-237 ng.h/mL).

Regarding neurologic developmental toxicity, two out of 10 males at 40 mg/kg/day propranolol showed hypoactivity, and there was a dose-related increase in incidence of delayed air righting reflex ($p<0.05$ for males at 40 mg/kg/day). The NOAEL was estimated to be 20 mg/kg/day (mean $AUC_{0\text{-}24\ h}$ = 221-261 ng.h/mL).

There were no findings regarding reproductive parameters and reproductive development; the NOAEL was considered to be 40 mg/kg/day (mean $AUC_{0\text{-}24h}$ = 1051-2516 ng.h/mL).

Cardiovascular biomarkers were either negative or under detectable limits. However, these markers are not sensitive parameters for cardiovascular functional changes.

Thus, propranolol-affected organs/systems in juvenile rats were identified to be neuromuscular development, kidney, and lymphatic system.

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4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Figure 2 Molecular processes in IH that may be affected by propranolol

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The figure depicts the pathophysiological situation in IH in the absence of a β-adrenergic antagonist. (1) Control of vascular tone. β-adrenergic agonists lead to vasodilation via release of NO. Conversely, *β-adrenergic antagonists like propranolol lead to vasoconstriction (through inhibition of NO synthesis and NO release)*. (2) Angiogenesis. β-adrenergic agonists stimulate the synthesis of proangiogenic factors [growth factors (VEGF and bFGF) and matrix metalloproteinases (MMP-2 and MMP-9)] and activate proangiogenic cascades (ERK/MAPK cascade) thereby promoting angiogenesis. In contrast, *beta blockers like propranolol lead to a down regulation of these proangiogenic proteins and to an inhibition of the ERK/MAPK cascade thus repressing angiogenesis*. (3) Apoptosis. β-adrenergic agonists inhibit apoptosis via src/MAPK. In contrast, *beta blockers induce apoptosis*. Continuous arrows indicate activation; dashed arrows indicate inhibition; broad arrows indicate pharmacodynamic effects; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A (cAMP-dependent protein kinase); ERK, extracellular signal-related kinases; MAPK, mitogen activated protein kinases; VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor; MMP, matrix metalloproteinase; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; HIF-1, hypoxia-inducible factor 1. (Source: Storch CH & Hoeger PH. *Brit J Dermatol* 2010;163: 269-274.)

Potential mechanisms of action of propranolol in proliferating IH (Figure 2) include:

- A local hemodynamic effect (vasoconstriction, which is a classical consequence of β-adrenergic blockade and decrease of IH lesion perfusion); this is immediately visible as a change in color, associated with a palpable softening of the hemangioma
- An anti-angiogenic effect characterized by a decrease of the proliferation of vascular endothelial cells, a reduction of the neovascularization and formation of vascular tubules, and a reduction of the secretion of Matrix Metalloproteinase 9 which is crucial for endothelial cell migration. The hypotheses for the molecular mechanism

of action include decreased expression of the vascular endothelial growth factor (VGEF) and basic fibroblast growth factor (bFGF) genes through the down-regulation of the RAF–mitogen-activated protein kinase pathway[31] (which explains the progressive improvement of the hemangioma)

- An apoptosis-triggering effect on capillary endothelial cells[32]. β-2 adrenoceptors are expressed on the capillary endothelial cells, their activation promotes VGEF and bFGF signaling pathways and the resulting proangiogenesis/proliferation; their blockade by propranolol can inhibit capillary endothelial cell proliferation[33].

4.4.2 Pharmacodynamics

No pharmacodynamics studies were conducted.

4.4.3 Pharmacokinetics

The pharmacokinetic (PK) characteristics of propranolol have been extensively documented in adults, but PK data are sparse in children, especially in infants. In this NDA, the objectives of the PK program (reviewed by the clin-pharm reviewer) are:

- To assess in adults the PK profile and the relative bioavailability of the pediatric oral solution of propranolol (propranolol) in comparison with a current EU marketed propranolol tablet formulation (Study 101).

  Briefly, healthy adults were randomized in a single-center, open label, single dose, two period crossover study with a wash-out interval of ≥ 3 days to receive a single oral administration of either propranolol HCl oral solution (16 ml of the oral solution at 5 mg/ml) or propranolol HCl tablet (2 tablets of 40 mg). The study shows that the plasma concentration profiles are similar after administration of both formulations, and that the mean ratio of AUC of the solution vs. the tablet was 1.2 indicating that the absorption was 20% higher for the solution compared to the tablet formulation.
- To characterize the PK profile of propranolol when repeatedly administered in infants with IH (Study V00400 SB 1 02; Study 102).

  The steady-state PK of propranolol using the BID dosing regimen was evaluated on two groups of infants with IH: Group 1: 35~ 90 days-old; Group 2: 91~ 150 days old.
- To perform a population PK analysis using the data from Study 101.

  A population PK model using a body weight function on plasma clearance was established. This model adequately predicted the PK of propranolol in infants, and confirmed that the dose expressed as mg/kg should be used without further dose adaptation by range of age. This model also documented that the maximum concentration is marginally affected when comparing a 9- or 12-hour dosing interval.
- To compare the PK profile of propranolol when given as an oral solution in infants and adults. When corrected for weight, primary PK parameters such as clearance (CL/F) in infants were similar to those published in the literature for propranolol in adults (ranging from 2.1 to 5.2 L/h/kg), indicating that CL/F is a consistent parameter for propranolol across age.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The submission contains 4 clinical studies as listed in Table 3.

Table 3 Clinical Studies with propranolol Conducted by Pierre Fabre

Study No.	Phase	Study Title	Main Study Objective	Enrollment	Status
Studies conducted in healthy adult volunteers					
V00400 SB 1 01 2A (Study 101)	I	Evaluation of PK parameters of a new propranolol hydrochloride formulation (oral solution) compared to the reference propranolol formulation (tablet). A mono-centric, randomized, open-label, single dose, 2-way crossover study.	To evaluate the PK parameters of propranolol (solution) compared to the reference propranolol hydrochloride formulation (tablet) after a single oral dose in 12 healthy volunteers.	12 healthy volunteers	Completed
Studies conducted in infants with proliferating IH (target population)					
V00400 SB 1 02 (Study 102)	I	A multicenter, open-label, repeated dose, PK study of propranolol in infants treated for proliferating IH requiring systemic therapy.	To characterize the PK of propranolol at steady-state in infants during a treatment for proliferating IH requiring systemic therapy.	23 infants with IH	Completed
V00400 SB 2 01 (Study 201)	II/III	A randomized, double-blind, placebo-controlled, multiple-dose, multicenter, adaptive Phase II/III study in infants with proliferating IH requiring systemic therapy to compare 4 regimens of propranolol (1 or 3 mg/kg/day for 3 or 6 months) to placebo.	To identify the appropriate dose and duration of propranolol treatment and demonstrate its superiority over placebo based on the complete/nearly complete resolution of target IH at Week 24.	460 infants with IH	Week 24 (primary analysis) completed; follow-up on-going
Other					
V00400 SB 3 01 (Study 301)	III	Multicenter, open-label study of propranolol in infants with proliferating IH requiring systemic therapy.	To allow the use of propranolol with adequate conditions of administration and follow up in infants requiring this systemic treatment after participation in a previous trial. The safety profile (including long-term impact) and the effect on the resolution of target proliferating IH were	11 infants with IH (expected enrollment is about 100 infants)	On-going*

Source: Sponsor's Table 2 in clinical overview; *Only used for serious adverse event notification.

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5.2 Review Strategy

Strategy for efficacy review

The data in this NDA is based on a single Phase II/III pivotal clinical trial comparing the effect on a single "cosmetic" endpoint observed in 55 placebo-treated patients vs. 101 propranolol-treated patients.

However, there are many caveats in the clinical trial that needed to be evaluated.

The first issue is unblinding. Since the treatment effect becomes visually apparent within a few days of treatment, unblinding occurred to both the investigators and the children's parents. Also, unblinding could lead to many placebo-treated patients dropping out early for lack of effect, who would then seek open-label (prohibited concomitant) treatment with propranolol. These patients were classified according to the protocol as "failures" which could bias the results in favor of the propranolol-treated patients. To understand the impact of these "failures" and the noise associated with them, I plan to look at exploratory and sensitivity analyses using:

(i) completers (i.e., use 24-week as the cutoff for any patient who took concomitant medications),

(ii) a multiple imputation method, and

(iii) Avi's law (i.e., a stringently conservative analysis treating all dropouts in the propranolol-treatment arm as failures and all dropouts in the placebo-treated arm as censored).

Use of a randomization ratio of 1:2:2:2:2 caused a disproportionate number of placebo patients randomized to some countries. I grouped the countries into three regions: (i) USA, Canada and Other America, (ii) Western Europe, and (iii) Other Europe and Oceania. This allowed the placebo-treated patients to be almost evenly distributed by region; the primary endpoints are then analyzed by region to determine if the results by region conform to the overall findings.

With regard to the adaptive design, I found that randomization of all patients to all five initial treatment regimens had already been completed before the IDMC performed an interim analysis to determine the best treatment regimen. Therefore, I took the findings from ALL patients into consideration, and evaluated the data as coming from (i) a single trial of 5 treatment arms, and (ii) a group sequential trial.

According to the pathophysiology and natural history of IH, the active proliferative phase last from 5 weeks to about 14 months of life. In the pivotal trial, the propranolol treatment is for only 6 months. So, this regimen might not have covered the entire active proliferative phase, leading to regrowth or recurrence of IH which has been reported in about 6-12% of patients treated with propranolol in the literature. I evaluated the regrowth and retreatment with propranolol for IH in the pivotal study, the CUP and the medical literature to determine if the 6-month treatment regimen is adequate.

If the findings from the above analyses are in conformity with the primary efficacy analyses, they will support the robustness of the data and validity of efficacy findings.

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Strategy for safety review

While the safety database for an investigational drug that is generally accepted is approximately 1500 treated patients, ICH E1 allows several exceptions. A smaller number of patients may be accepted if there is already well-documented historical data available on a specific drug/drug class and if the population intended for treatment is small. Propranolol hydrochloride fulfills the former criterion (12% of 3 to 10% of births), and the target IH population fulfills the latter (0.36 to 1.2% of births).

The safety data in this NDA is derived from the pooled database of 424 patients with IH treated with propranolol for up to 24 weeks in Studies 201 and 102). Additional safety data are submitted from the following sources:

1. Cumulative safety analysis from the CUP in France (660 patients) including non-serious reported adverse drug reactions (ADRs)
2. All serious adverse events (SAEs) from Studies 201, 102, 301 and from the CUP, and
3. Literature review of scientific publications (involving 1,367 patients with IH treated with propranolol) of which individual case reports are extracted (involving 623 patients with IH treated with propranolol) and reported in a narrative form.

Thus, the total safety data comes from 2,451 patients with IH treated with propranolol. In each section my clinical safety review, I compiled data and information from (i) the pooled safety population, (ii) patients in the CUP, and (iii) patients described in the medical literature (case reports and meta-analyses), to provide a broad and objective presentation of safety issues in the context of infants with simple IH (in the pooled safety population of the clinical trials) and complicated (life-threatening, function-threatening or disfiguring) IH (in the CUP and medical literature).

For use of propranolol in the population of infants with IH, the submission specific safety concerns are hypoglycemia, bradycardia, hypotension and bronchospasm. These were monitored during the up-titration periods and throughout the clinical studies 201 and 102, and in the CUP. My opinion is that hypoglycemia is the most important safety parameter to evaluate in these young infants. I evaluated these four AEs of major safety concern by reviewing in detail (i) the narratives and case report forms of symptomatic cases in the clinical trials in this NDA, (ii) narratives of symptomatic patients reported in the CUP, and (iii) symptomatic cases reported in the medical literature pertaining to use of propranolol in the treatment of infants with IH, to get the fullest context of their seriousness and the circumstances associated with these four AEs.

5.3 Discussion of Individual Studies/Clinical Trials

The clinical development is based on 3 clinical studies: two are pharmacokinetic (PK) studies – one in healthy adults (Study V00400 SB 1 01 2A) and one in infants with IH (Study V00400 SB 1 02) – and the third is a seamless Phase II/III adaptive design study (Study V00400 SB 2 01, referred to as Study 201). Data from Study 201 is used as the

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pivotal clinical trial data in support of the indication: "treatment of proliferating Infantile Hemangioma requiring systemic therapy."

Study V00400 SB 2 01 (Study 201 – the pivotal trial)

Study 201 is a randomized, placebo-controlled, multi-dose, 2-stage, adaptive design study to select the best of four regimens of propranolol (1 and 3 mg/kg/day, each for 3 or 6 months, following up-titration) at the end of the first stage in a seamless phase II/III design[34], and, in the second stage, to demonstrate the efficacy of the selected dose regimen over placebo. Five treatment arms (placebo and 4 regimens of propranolol with different dose/duration combinations) were considered initially (Figure 3). Stratified block randomization (2 strata [age + IH localization] with 2 levels each) was applied during the first stage of the design in a 2:2:2:2:1 ratio (propranolol regimens : placebo).

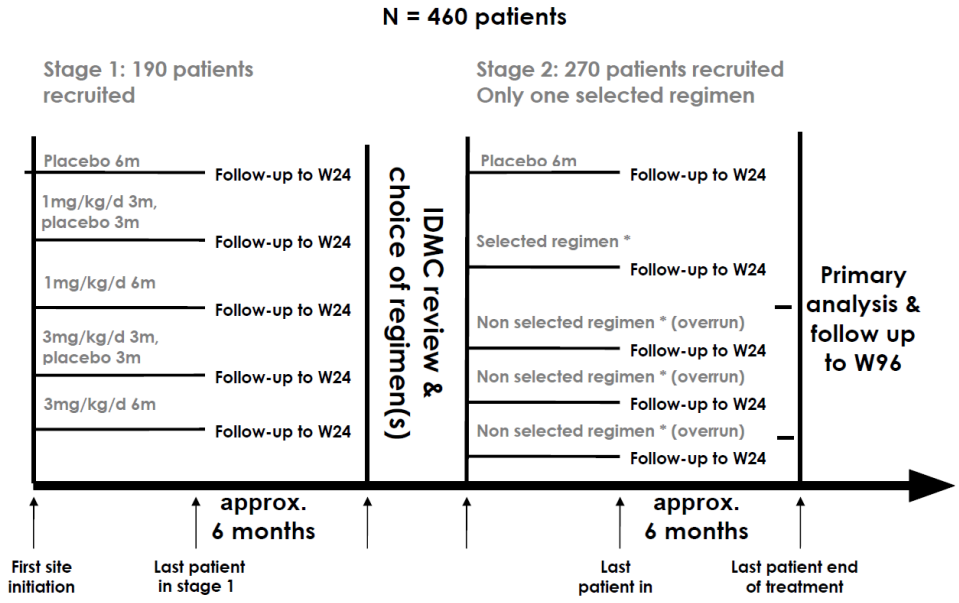
Figure 3 Treatment Flow Chart

	Visits	D0+	W1+	W2+	W3+	W5+	W8+	W12+	W16+	W20+	W24+
	Days	D0-D6	D7-D13	D14-D20	D21-D34	D35-D55	D56-D83	D84-D111	D112-D139	D140-D167	D168+
Therapy	Regimen										
Propranolol	1 mg/kg/day for 3 months	1	1	1	1	1	1	0	0	0	follow up
	1 mg/kg/day for 6 months	1	1	1	1	1	1	1	1	1	follow up
	3 mg/kg/day for 3 months	1	2	3	3	3	3	0	0	0	follow up
	3 mg/kg/day for 6 months	1	2	3	3	3	3	3	3	3	follow up
Placebo	NA				-	-	-	-	-	-	follow up

Note: If safety assessments at visit D7 or D14 suggest that there is a safety issue, the dose (dummy dose) will not be increased and the subject will be prematurely withdrawn from study treatment for intolerance.

Actual dose of study therapy administered to subject
Dummy titration

Figure 4 Actual Recruitment and Follow up



At the end of the first stage, after the first 190 patients had completed Week 24 or had been prematurely withdrawn from the study therapy, an interim analysis was conducted by an independent statistician, which was reviewed by the IDMC (Figure 4). Based on this review, the IDMC could decide either to stop the study for safety or futility, or to continue with the placebo arm and one or two 'best' regimens of propranolol, where the 'best' regimen was defined as the most efficacious of all regimens with a good safety profile. The IDMC made the decision to continue the study and select just *one* 'best' regimen for the primary efficacy analysis (which was 3 mg/kg/day for 6 months).

Patients already assigned to an unselected regimen of propranolol at the time of the interim analysis continued their treatment according to their randomization {called "overrun patients" (Figure 4)}. Their data were not included in the primary efficacy analysis, but were included in the safety analysis and exploratory efficacy analyses.

When all of the patients in both stages of the study had completed their W24 visit (or been prematurely withdrawn from study therapy), the treatments were unblinded to a limited list of study personnel (the sponsor, the (b) (4) biometry team), regulatory representatives, the independent statistician and the IDMC members. The blind was maintained for the monitoring teams and all investigational site staff until the end of the trial. (Review of the efficacy analyses of the primary, secondary and other exploratory endpoints are presented in Section 6.1.4 through 6.1.10.)

The 24-week active treatment comparative study period was followed by an open-label follow up period of up to 72 weeks, without any study drug administration. Including the screening period, the maximum total study duration per patient was approximately 98 weeks. This follow-up period is currently ongoing, and results will be available in Q2 2014. In response to a FDA request, the evolution of IH between the end of active treatment period (Week 24) and the 6 months of follow-up (to Week 48) was analyzed on available data to determine the sustainability of treatment effect. Safety data over this follow-up period, based on SAEs, are also submitted to FDA.

Reviewer's comments: (1) *Unblinding*: Since the treatment effect begins to be apparent within a few days to about 2 weeks, unblinding probably occurred, which I think can be considered a measure of the efficacy of propranolol in the treatment of IH. I found that patients in the US and non-EU countries stayed on placebo longer than in European countries: for example, the average time to end of study for Spain was 7 days, and for France 17.8 days, whereas for the US, it was 27 days. It is possible that the assignment of fewer placebo patients in the non-EU countries prevented unblinding in these non-EU countries so that most placebo patients in non-EU countries stayed longer in the trial.

(2) *Randomization*: The protocol amendment {Version 5 (dated 31-Aug-2010)} changed the randomization ratio from 1:1:1:1:1 to 1:2:2:2:2 in stage I, and from 1:1:(1) to 1:2:(2) in Stage II late in the clinical trial, i.e., over a year after Version 1 (25-Jun-2009). The original protocol mentions 30 centers, in Version 4 (02-Dec-2009), it was increased to 40 centers, and in Version 5 to 60 centers, with no more increase in centers thereafter.

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Every one of the total patients enrolled had been randomized to the 5 treatment arms by the time of the interim analysis at Stage I. There were very few placebo assignments throughout; 1:2:2:2:2 was the prevailing randomization ratio. From a review of the dates of randomization, and it appears that the change in randomization ratio from 1:1:1:1:1 to 1:2:2:2:2 took place in October 2010 (starting around patient #112), about 1-2 month after the date of the amendment (Version 5), which is reasonable.

At that point in time, the full planned sample size had already been recruited into all treatment arms ***before*** the IDMC meeting took place on 06-Jan-2012 for the interim analysis. I found no evidence of randomization of patients at a 1:2 ratio for placebo vs. treated group after the interim analysis.

(3) *Concomitant medications*: The protocol states that before enrollment patients were ineligible if they received at least one of the prohibited meds within 14 days for randomizations – anesthetics, CV treatments, hypoglycemic agents, NSAIDS, etc. Patients were also ineligible if they had received at least one of the following (systemic steroids, vincristine, propranolol and other beta-blockers), but a duration is not given so the patients were supposed have not received any of them at any point in time.

After discontinuation, the patient was not prohibited from taking IH drugs at any point in time. Patients on placebo had no obvious cosmetic response, so they dropped out early (decision by parents or their pediatricians) and then started open-label treatment – some enrolled in the open label Study 301 or in the compassionate use program (CUP) to get propranolol, and some received treatment outside the trial (since propranolol or prednisone or vincristine were available drugs for off-label use). The children with IH need to be treated at a young age (<3 months preferably) as soon as possible or permanent skin lesions could result. Therefore, doctors and parents started these placebo-treated children with IH immediately on some form of definitive IH therapy (propranolol or corticosteroids). Thus, the placebo-treated children with IH took propranolol right after they left the study.

Study V00400 SB 1 01 2A (Study 101 – PK study in healthy adults

Study 101 is a single-center, open label, randomized, single dose, two period crossover study in healthy adults with a wash-out interval of at least 3 days. On Day 1 of each period, subjects were randomized to receive a single oral administration of either propranolol hydrochloride oral solution (16 ml of the oral solution at 5 mg/ml) or propranolol hydrochloride tablet (2 tablets of 40 mg).

The duration of participation is at most 6 weeks, and the duration of treatment is 2 days (1 day for each period).

Blood samples for propranolol plasma level determination were drawn at specified time points.

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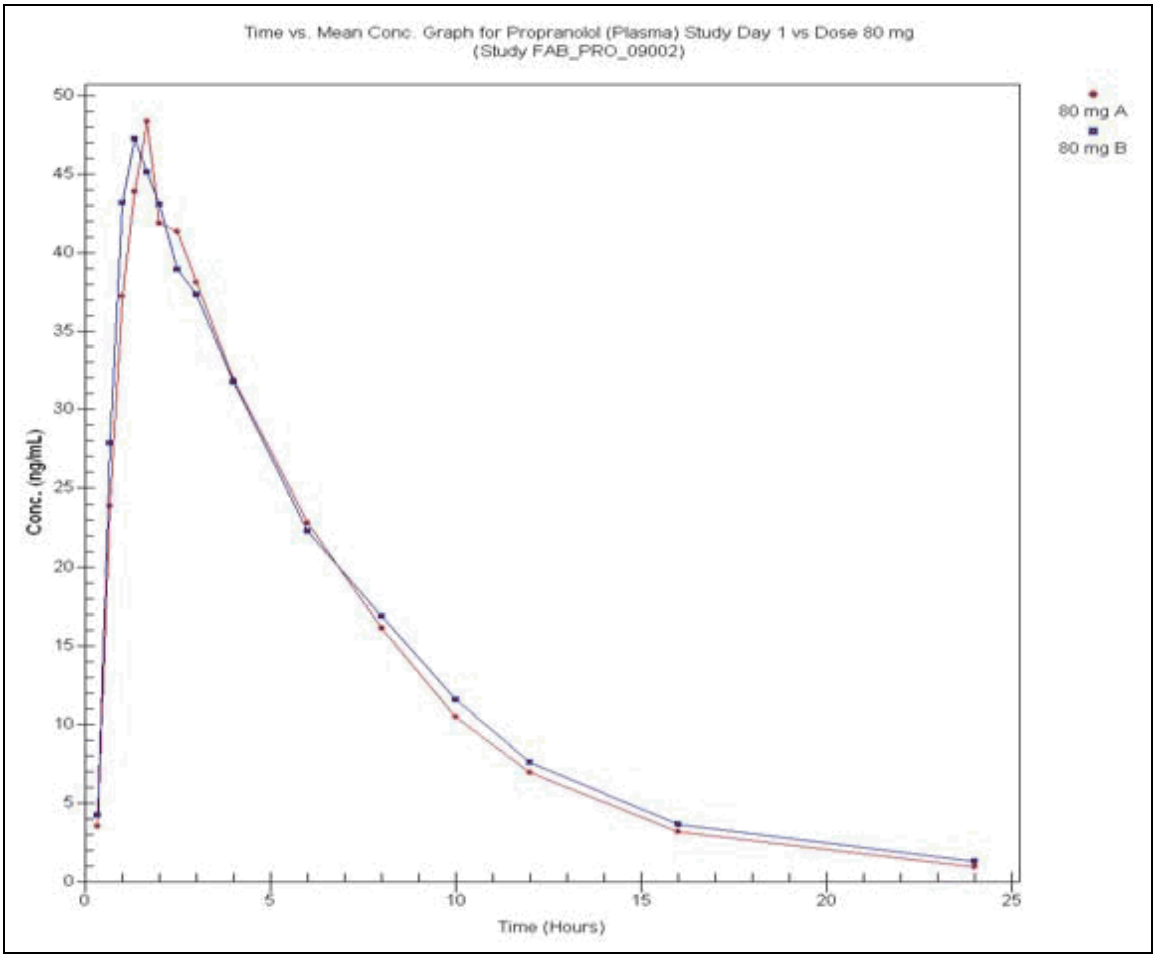
Figure 5 Plasma concentration – time profiles of propranolol (arithmetic means) following single oral doses of table and solution formulations (n=12 subjects)



This study shows that when comparing an equivalent oral dose of propranolol administered as a new propranolol hydrochloride solution and as a reference propranolol hydrochloride tablet:

- The plasma concentration profiles are similar after administration of both formulations (Figure 5).
- The mean ratio of AUC of the solution vs. the tablet was 1.2 indicating that the absorption was 20% higher for the solution compared to the tablet formulation.
- The individual ratio of test/reference AUC (at equivalent dose) obtained after administration of both the test solution and the reference tablet ranged from 0.5 to 3.28, with a high inter-individual variability. This variability is explained by the high variability associated with the extent of absorption observed with the tablet formulation (CV of 92%). The inter-individual variability of the pharmacokinetic parameters is lower for the solution formulation.

Study V00400 SB 1 02 (Study 102 – PK study in infants with IH)

Study 102 was an open-label, multicenter, repeated-dose study, in which 23 infants were stratified to 2 groups according to their age at inclusion, which defined the timing of their PK assessment at steady-state:

Group 1: age from 35 to 90 days inclusive at inclusion; PK assessment after 4 weeks of treatment

Group 2: age from 91 to 150 days inclusive at inclusion; PK assessment after 12 weeks of treatment.

Infants received propranolol solution for the treatment of IH (3 mg/kg/day given twice daily after a 2-week titration period). The target dose of 3 mg/kg/day was achieved after a 2-week titration period. During the 2-week titration period, 2 micro-blood samples were collected at D7 and D14.

Patients attended for 5 further visits at intervals of 1 to 4 weeks: D7±1 day, D14±1 day, D28±3 days and the end-of-treatment visit at D84±3 days. Six serial micro-blood samples were collected over a 9-hour period at steady-state (after 4 or 12 weeks of treatment for the lower (Group 1) and higher (Group 2) age groups, respectively) for propranolol and 4-OH-propranolol assay.

The PK results are summarized in Table 4. In both groups, the peak concentration was reached 2 hours after dosing, with a C_{max} of about 79 ng/mL (comparable to published literature for infants suffering from cardiovascular diseases). The corresponding plasma exposures (AUC_{0-12}) were 541 and 430 h*ng/mL in Groups 1 and 2, respectively. The total plasma clearance of propranolol was 2.7 and 3.3 L/h/kg in Groups 1 and 2, respectively. After correction by the body weight, the primary PK parameters for propranolol determined in infants were found to be similar to those reported in the literature for adults.

Table 4 PK parameters in infants with IH treated with oral propranolol solution

Grp		Tmax (h)	Cmax (ng/mL)	AUC□ (h*ng/mL)	CLtot/F (L/h)	CLtot/F/kg (L/h/kg)	M/P Cmax ratio	M/P AUC9h ratio
1	N	8	8	8	8	8	8	6
	Geom mean	2.00*	78.5	541	15.2	2.71	0.0785	0.0593
	Geom CV%	-	32.9	27.5	27.9	27.9	35.9	43.6
	Min	1.00	47.8	360	11.4	1.84	0.0524	0.0336
	Max	9.00	119	804	22.3	4.05	0.132	0.108
2	N	11	11	11	11	11	10	7
	Geom mean	2.00*	79.2	430	25.5	3.27	0.0503	0.0333
	Geom CV%	-	103	73.0	79.1	73.3	132	112
	Min	1.00	21.3	116	7.55	1.18	0.00712	0.00544
	Max	4.00	448	1193	94.5	12.3	0.202	0.0812

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Treatment of proliferating IH with propranolol for 12 weeks in 23 infants resulted in rapid improvement (within 7-14 days) in all patients. Resolution of the target IH was seen as early as D28 and by D84, 36.4% (8/22) patients (4 in each group) had resolution of their target IH. In addition, complications of IH disappeared over time, confirming the regression of the IH. Propranolol was well tolerated in the overall study population.

Study V00400 SB 3 01 (Study 301 – Open-label follow up study)

A fourth clinical study (Study 301) is the ongoing multicenter, open-label study of propranolol solution in infants with proliferating IH. This study was conducted at the request of the French Competent Authority (*Agence Nationale de Sécurité du Médicament et des Produits de Santé* [ANSM, formerly AFSSAPS]) to allow the use of propranolol with adequate conditions of administration and follow up in infants requiring this systemic treatment after participation in a previous trial Study 102 and Study 201). Only the study protocol is submitted with the NDA; no clinical data is submitted for this study. The number of infants with IH expected to be enrolled is around 100.

Compassionate Use Program (CUP)

A fifth study is the Compassionate Use Program (CUP), also named Early Expended Access in the US. It is on-going in France. The first nominative authorization (i.e., on a named patient basis) was approved on 13-Apr-2010 and was modified to a cohort authorization in July 2012. Within the remit of the CUP, propranolol is prescribed to infants with proliferating high risk IH who could not be included in one of the ongoing clinical studies. In addition a CUP has been ongoing in Switzerland since Feb 2011.

Among the 209 patients with high risk IH at the 2 CUP sites with the highest recruitment, 138 were discontinued from treatment. The reason for discontinuation was documented in 137 patients, of which 126 (92%) were discontinued due to good efficacy. The mean dose administered to these 126 patients (after titration) was 1.9 (SD ±0.7) mg/kg/day for 7.4 (SD ±3.1) months.

Post-treatment discontinuation results in these 126 patients showed that the need for re-introduction of systemic treatment with propranolol by the physician occurred infrequently (in 4 patients (3%)) at a time point more than 2 months after the first treatment discontinuation.

Please see section 9.4.1 – 9.4.6 for more details of the studies discussed above.

6 Review of Efficacy

Efficacy Summary

For the proposed indication: "Treatment of proliferating infantile hemangioma requiring systemic therapy, to be initiated in patients aged 5 weeks to 5 months," the efficacy data for the primary endpoint is derived from a single randomized, placebo-controlled, multi-dose, 2-stage, seamless Phase II/III adaptive design study V00400 SB 2 01 (referred to as Study 201).

The objective of Study 201 was to identify the appropriate dose and duration of propranolol treatment for children with IH, and to determine its superiority over placebo.

The primary efficacy endpoint was the complete/nearly complete resolution of target IH from baseline to Week 24 (or premature treatment discontinuation), based on blinded, centralized assessments of standardized photographs at Week 24 compared to those at baseline. The binary primary endpoint was success/failure. Treatment success was defined as a centralized assessment of complete/nearly complete resolution of the target IH at Week 24 compared to baseline.

The secondary endpoints were evaluations of target IH evolution based on (i) the investigator's on-site qualitative (success/failure) assessments of complete/nearly complete resolution with an additional category of 'minimal palpable component', target IH evolution at paired consecutive visits, and target IH complications, and (ii) parents'/ guardians' qualitative assessment of target IH evolution at paired consecutive visits.

Four hundred and sixty patients were randomized in Study 201, and 456 were treated. Patients were randomized in Stage 1 according to a 1:2:2:2:2 ratio, with the five randomization arms balanced within strata (age; IH location). Demographic patient characteristics and IH characteristics were similar among the five regimens.

An interim analysis was conducted on 188 (of 190) intent-to-treat (ITT) Stage 1 patients who either completed the 24-Week study treatment period or prematurely withdrew from study. Based on efficacy and safety findings at the interim analysis, the IDMC selected the 3 mg/kg/day 6 months arm and recommended continuing the trial with this regimen and the placebo, without sample size adjustment/re-estimation.

The results on the primary endpoint show efficacy of the selected regimen, 3 mg/kg/day 6 months, versus placebo on the primary efficacy analysis (ITT); the difference in rates of complete/nearly complete resolution of IH at W24 (assessed by central reading of the photographs) was 60.4% vs. 3.6% which is statistically significant ($p<0.0001$). The results were also consistent between the two stages: the success rate in the active treatment (3 mg/kg/day 6 months) arm was 62.8% for Stage 1 and 58.6% for Stage 2. A sensitivity analysis using the per-protocol (PP) data set shows similar results. An adjusted (placebo-subtracted) analysis of the primary endpoint for sub-populations (stratified by age and by location of IH) showed similar success rates between the two age groups and between the two localization groups. This statistically significant

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difference is also clinically meaningful.

Randomization of all patients to all five treatment groups had been completed before the IDMC interim analysis to select the best treatment regimen. Patients already assigned to an unselected regimen of propranolol at interim analysis continued their treatment according to their randomization (called “overrun patients”). Analysis of the primary efficacy endpoint on all treated patients including overrun showed that (i) all active arms had better success rates than the placebo arm, (ii) the two 6 months regimens were superior to the two 3 months regimens, (iii) and the 3 mg/kg/day regimens were superior to the 1 mg/kg/day regimens, with no treatment interaction by age or by IH localization.

A total of 137/456 patients prematurely discontinued their randomized treatment: nearly two-thirds of the patients in the placebo 6 months regimen 65.5% *vs.* 36.4% (1 mg/kg/day 3 months), 35.6% (3 mg/kg/day 3 months), 14.6% (1 mg/kg/day 6 months), and 13.7% (3 mg/kg/day 6 months) in the active regimens. Treatment inefficacy was the most frequent primary reason for treatment discontinuation in all regimens, and was highest in the placebo regimen (58.2%), intermediate in the two 3-month regimens (30.3% and 24.8%), and lowest in the two 6-month regimens (6.8% and 8.8%). Exploratory analysis of only patients who completed the 24-week period and exploratory analyses using multiple imputation method for those who dropped out support the primary efficacy analysis of the ITT and PP data sets.

Disproportionately fewer patients were randomized to placebo in non-European centers. Exploratory analyses of the primary efficacy endpoint (both ITT and PP data sets) by region (USA-Canada and Other America vs. Western Europe vs. Other Europe and Oceania) showed that in all 3 regions, the 3 mg/kg/day 6-month was consistently effective.

No differences between effects on facial and non-facial hemangioma were observed.

Treatment effect magnitude (placebo adjusted effect) was similar between the two age strata.

Secondary endpoints based on centralized assessments of IH at paired consecutive visits show that improvement occurs early, with 72.7% of the patients showing sustained improvement at W5. A significant superiority of propranolol 3 mg/kg/day 6 months over placebo was also observed on two of the three centralized quantitative assessments: surface and color of hemangioma (maximal diameter was also more improved in the active arm but the difference did not reach statistical significance).

On-site investigators’ assessments of complete/nearly complete resolution showed less striking results (26.7% in the 3 mg/kg/day 6 months arm); non-standardized assessment may have created statistical noise causing a smaller observed difference.

The pivotal study shows that propranolol at the 3 mg/kg/day dose for 6 months is an effective treatment for infants 5 weeks to 5 months old with IH requiring systemic therapy.

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6.1 Proposed Indication

Proposed indication: Treatment of proliferating infantile hemangioma requiring systemic therapy, to be initiated in patients aged 5 weeks to 5 months.

6.1.1 Methods

The **primary efficacy endpoint** was the complete/nearly complete resolution of target IH from baseline to Week 24 (or premature treatment discontinuation) to be based on standardized photographic capture and centralized, blinded assessments. The binary primary endpoint was success/failure.

Treatment success was defined as a centralized assessment of complete/nearly complete resolution of the target IH at Week 24 compared to baseline.

The primary efficacy assessment was made on digital photographs (one front and one side view of the target IH) taken by site investigators at each visit using standardized procedures. Intra-patient blinded centralized independent qualitative assessments were performed (Type 1)* of target IH resolution (complete/nearly complete).

Nearly complete resolution was defined as minimal degree of telangiectasis, erythema, skin thickening, soft tissue swelling, and/or distortion of anatomical landmarks (and for Study 102 only: 'and/or minimal palpable component).

[*Type 1: independent readers were presented with paired groups of photographs to compare Weeks 12, 24 (primary efficacy endpoint), 36, and 48 to baseline. The paired groups were placed side by side (with the baseline photographs to the left and the post-baseline photographs to the right) and the readers assessed whether or not the target IH had completely/nearly completely resolved in the photographs to the right.]

Interim analysis, protocol amendments and unplanned analyses:

For Study 201, the optimized Phase II/III adaptive design was based on a Seamless Phase II/III adaptive design statistical methodology to effectively identify one or two suitable propranolol regimens at an interim analysis (Stage 1, performed on the first 190 patients randomized followed until Week 24 or premature treatment discontinuation) and to investigate the efficacy of the chosen regimen(s) compared to placebo after all patients had completed Week 24 or had been prematurely withdrawn from study treatment (primary analysis).

The interim analysis was conducted by an independent statistician, after the first 190 patients had completed Week 24 or had been prematurely withdrawn from the study therapy. The interim analysis was reviewed by an independent data monitoring committee (IDMC) to avoid unblinding the study personnel and jeopardizing the integrity and the validity of the trial.

In order to optimize blinded conditions, the IDMC only informed Pierre Fabre that they recommended carrying forward one regimen of propranolol. The nature of this regimen

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was disclosed to Pierre Fabre after the primary analysis.

As a result, the full planned sample size had already been recruited into all five treatment regimens before the IDMC meeting had taken place and before the best treatment regimen had been selected, leading to more patients being treated in unselected regimens than planned (defined as 'overrun' patients). Therefore an analysis of the primary endpoint on all regimens including overrun patients was also performed.

Supplementary analyses were also performed in order to analyze time to treatment failure (up to Week 24 for maintenance of treatment effect analysis) and sustainability of treatment effect after treatment interruption.

Several amendments were made to the final protocol during the study to facilitate recruitment that was being hindered by the extensive off-label use of propranolol to treat IH. These amendments included:

- Reducing the number of patients to be randomized to placebo (by amending the randomization ratio from 1:1:1:1:1 to 2:2:2:2:1 [4 propranolol arms:placebo] in Stage 1, the regimen selection stage, and from 1:1 to 2:1 [selected propranolol arm: placebo] in Stage 2.
- Widening the inclusion criteria relative to the localization of IH – extended to non-facial IH (excluding diaper area) that present the same pathophysiological pattern as facial IH.
- Opening of new countries/centers for recruitment.

6.1.2 Demographics

The demographic and screening/baseline characteristics of the Integrated Efficacy Population by treatment group are displayed in Table 5 and Table 6. The demographic characteristics were well balanced between randomization arms.

Overall, 318 patients (69.7%) had a facial and 138 (30.3%) a non-facial target hemangioma. Frequency of facial IH varied between 64% (64 patients) in the 3 mg/kg/day 3 months arm and 72.7% (40 patients) in the placebo arm. Despite the secondary extension of the inclusion criteria to non-facial hemangiomas (protocol amendment 2) a majority (more than 2 thirds) of the included patients had facial hemangiomas, as planned in the initial version of the protocol.

A large majority of the IHs were localized (406 patients, 89.0% overall, varying between 87.3% and 90.8% between treatment arms). Twenty-five patients (5.5%) had a segmental IH (between 3.6% and 7.0%, Table 6) and 25 (5.5%) IHs were of indeterminate subtype (between 4.9% and 9.1%, Table 6).

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Table 5 Demography – enrollment by region and country

Characteristics	Placebo (N = 55)	1mg/kg/day 3mths (N = 98)	1mg/kg/day 6mths (N = 102)	3mg/kg/day 3mths (N = 100)	3mg/kg/day 6mths (N = 101)	Total (N = 456)
Continent						
USA-Canada	8 (14.5%)	18 (18.4%)	19 (18.6%)	14 (14.0%)	12 (11.9%)	71 (15.6%)
Other America	1 (1.8%)	7 (7.1%)	9 (8.8%)	11 (11.0%)	12 (11.9%)	40 (8.8%)
Western Europe	35 (63.6%)	51 (52.0%)	41 (40.2%)	56 (56.0%)	52 (51.5%)	235 (51.5%)
Other Europe	10 (18.2%)	17 (17.3%)	18 (17.6%)	13 (13.0%)	15 (14.9%)	73 (16.0%)
Oceania	1 (1.8%)	5 (5.1%)	15 (14.7%)	6 (6.0%)	10 (9.9%)	37 (8.1%)
Country						
France	21 (38.2%)	25 (25.5%)	18 (17.6%)	22 (22.0%)	28 (27.7%)	114 (25.0%)
Germany	8 (14.5%)	17 (17.3%)	9 (8.8%)	17 (17.0%)	9 (8.9%)	60 (13.2%)
Spain	5 (9.1%)	9 (9.2%)	14 (13.7%)	17 (17.0%)	14 (13.9%)	59 (12.9%)
USA	6 (10.9%)	13 (13.3%)	13 (12.7%)	11 (11.0%)	10 (9.9%)	53 (11.6%)
Peru	1 (1.8%)	5 (5.1%)	9 (8.8%)	8 (8.0%)	12 (11.9%)	35 (7.7%)
Australia	1 (1.8%)	5 (5.1%)	14 (13.7%)	5 (5.0%)	7 (6.9%)	32 (7.0%)
Poland	4 (7.3%)	4 (4.1%)	6 (5.9%)	8 (8.0%)	4 (4.0%)	26 (5.7%)
Canada	2 (3.6%)	5 (5.1%)	6 (5.9%)	3 (3.0%)	2 (2.0%)	18 (3.9%)
Lithuania	1 (1.8%)	7 (7.1%)	4 (3.9%)	1 (1.0%)	5 (5.0%)	18 (3.9%)
Hungary	1 (1.8%)	2 (2.0%)	4 (3.9%)	2 (2.0%)	2 (2.0%)	11 (2.4%)
Czech Republic	2 (3.6%)	1 (1.0%)	3 (2.9%)	1 (1.0%)	1 (1.0%)	8 (1.8%)
Romania	2 (3.6%)	2 (2.0%)	1 (1.0%)	0 (0.0%)	2 (2.0%)	7 (1.5%)
Mexico	0 (0.0%)	2 (2.0%)	0 (0.0%)	3 (3.0%)	0 (0.0%)	5 (1.1%)
New-Zealand	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (1.0%)	3 (3.0%)	5 (1.1%)
Russia	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (1.0%)	1 (1.0%)	3 (0.7%)
Italy	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	2 (0.4%)

Source: CSR Table 58

Reviewer's comments:: The data show a disproportionate number of patients randomized to placebo by country or region. Since the randomization ratio was 1:2:2:2:2, the placebo group should be around 11% for each region. It is rather unusual to see countries with ***zero*** placebo patients or regions with very few (only 1 or 2) placebo patients, whereas countries in Europe ("Western and Other") have disproportionately large numbers of placebo patients.

Randomization of patients to all 5 treatment regimens had been completed before the IDMC meeting took place on 06-Jan-2012 for the interim analysis, and before the best treatment regimen recommended by the IDMC was selected.

Therefore, it is doubtful that the interim analysis was necessary at all, or that a seamless Phase II and III adaptive design was required. The study could have proceeded as a single trial of 5 treatment arms with the current randomized number of patients, and analyzed as a traditional trial with five treatment arms, or as a group sequential design trial.

Table 6 Demographic and baseline characteristics – Safety data set

Characteristics	Placebo (N = 55)	1mg/kg/day 3mths (N = 98)	1mg/kg/day 6mths (N = 102)	3mg/kg/day 3mths (N = 100)	3mg/kg/day 6mths (N = 101)	Total (N = 456)
Male	17 (30.9%)	30 (30.6%)	32 (31.4%)	21 (21.0%)	31 (30.7%)	131 (28.7%)
Female	38 (69.1%)	68 (69.4%)	70 (68.6%)	79 (79.0%)	70 (69.3%)	325 (71.3%)
Age at baseline						
Mean (SD)	103.9 (31.0)	103.7 (33.2)	102.7 (30.2)	107.5 (30.1)	101.7 (31.0)	103.9 (31.1)
min max	37 151	37 154	42 156	49 150	35 152	35 156
Age group at baseline						
35 - 90 days	20 (36.4%)	36 (36.7%)	38 (37.3%)	36 (36.0%)	37 (36.6%)	167 (36.6%)
> 90 days	35 (63.6%)	62 (63.3%)	64 (62.7%)	64 (64.0%)	64 (63.4%)	289 (63.4%)
IH Site						
Facial	40 (72.7%)	71 (72.4%)	72 (70.6%)	64 (64.0%)	71 (70.3%)	318 (69.7%)
Non-Facial	15 (27.3%)	27 (27.6%)	30 (29.4%)	36 (36.0%)	30 (29.7%)	138 (30.3%)
Patient born prematurely N	55/0	97 (1 missing)	102/0	100/0	101/0	455 (1 missing)
> 2 mths premature	3 (5.5%)	1 (1.0%)	2 (2.0%)	2 (2.0%)	4 (4.0%)	12 (2.6%)
1-2 mths premature	6 (10.9%)	12 (12.4%)	9 (8.8%)	11 (11.0%)	9 (8.9%)	47 (10.3%)
0-1 mth premature	10 (18.2%)	8 (8.2%)	17 (16.7%)	17 (17.0%)	11 (10.9%)	63 (13.8%)
Not premature	36 (65.5%)	76 (78.4%)	74 (72.5%)	70 (70.0%)	77 (76.2%)	333 (73.2%)
Weight at birth (kg)						
Mean (SD)	2.9 (0.8)	3.0 (0.7)	3.0 (0.8)	3.0 (0.7)	3.1 (0.8)	3.0 (0.7)
Min max	0.9 4.4	0.7 4.3	0.8 4.7	0.8 4.6	0.7 5.4	0.7 5.4
Morphological subtype						
Segmental	2 (3.6%)	4 (4.1%)	7 (6.9%)	7 (7.0%)	5 (5.0%)	25 (5.5%)
Localized	48 (87.3%)	89 (90.8%)	90 (88.2%)	88 (88.0%)	91 (90.1%)	406 (89.0%)
Indeterminate	5 (9.1%)	5 (5.1%)	5 (4.9%)	5 (5.0%)	5 (5.0%)	25 (5.5%)
Primary anatomic location of the target IH						
Cheek	5 (9.1%)	16 (16.3%)	12 (11.8%)	18 (18.0%)	8 (7.9%)	59 (12.9%)
Forehead	9 (16.4%)	9 (9.2%)	15 (14.7%)	9 (9.0%)	7 (6.9%)	49 (10.7%)
Perioral, lower/upper lip	5 (9.1%)	7 (7.1%)	7 (6.9%)	9 (9.0%)	13 (12.9%)	41 (9.0%)
Scalp	5 (9.1%)	14 (14.3%)	11 (10.8%)	2 (2.0%)	7 (6.9%)	39 (8.6%)
Peri-ocular	4 (7.3%)	5 (5.1%)	9 (8.8%)	4 (4.0%)	11 (10.9%)	33 (7.2%)
Nasal tip	4 (7.3%)	3 (3.1%)	6 (5.9%)	7 (7.0%)	8 (7.9%)	28 (6.1%)
Chest	0 (0.0%)	5 (5.1%)	7 (6.9%)	6 (6.0%)	7 (6.9%)	25 (5.5%)
Other	1 (1.8%)	7 (7.1%)	2 (2.0%)	6 (6.0%)	6 (5.9%)	22 (4.8%)
Forearm	1 (1.8%)	6 (6.1%)	5 (4.9%)	6 (6.0%)	2 (2.0%)	20 (4.4%)
Neck	2 (3.6%)	4 (4.1%)	4 (3.9%)	4 (4.0%)	4 (4.0%)	18 (3.9%)
Abdomen	3 (5.5%)	2 (2.0%)	4 (3.9%)	5 (5.0%)	2 (2.0%)	16 (3.5%)
Back	2 (3.6%)	4 (4.1%)	4 (3.9%)	3 (3.0%)	2 (2.0%)	15 (3.3%)
Nasal sidewall	1 (1.8%)	1 (1.0%)	3 (2.9%)	3 (3.0%)	6 (5.9%)	14 (3.1%)
Ear	2 (3.6%)	2 (2.0%)	2 (2.0%)	3 (3.0%)	2 (2.0%)	11 (2.4%)
Glabella	1 (1.8%)	2 (2.0%)	2 (2.0%)	2 (2.0%)	4 (4.0%)	11 (2.4%)
Shoulder	1 (1.8%)	2 (2.0%)	1 (1.0%)	4 (4.0%)	1 (1.0%)	9 (2.0%)
Upper arm	1 (1.8%)	1 (1.0%)	1 (1.0%)	2 (2.0%)	3 (3.0%)	8 (1.8%)
Thigh	2 (3.6%)	1 (1.0%)	1 (1.0%)	2 (2.0%)	1 (1.0%)	7 (1.5%)
Hand	1 (1.8%)	2(2.0%)	2(2.0%)	0 (0.0%)	2 (2.0%)	7 (1.5%)
Peri-auricular parotid	0 (0.0%)	3 (3.1%)	1 (1.0%)	1 (1.0%)	2 (2.0%)	7 (1.5%)
Lower leg	2 (3.6%)	0 (0.0%)	0 (0.0%)	2(2.0%)	1 (1.0%)	5 (1.1%)
Chin	1 (1.8%)	0 (0.0%)	0 (0.0%)	2 (2.0%)	1 (1.0%)	4 (0.9%)
Foot	1 (1.8%)	0 (0.0%)	2 (2.0%)	0 (0.0%)	1 (1.0%)	4 (0.9%)
Nasal area	1 (1.8%)	2 (2.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	4 (0.9%)
IH Deep component						
None	20 (36.4%)	24 (24.5%)	36 (35.3%)	21 (21.0%)	29 (28.7%)	130 (28.5%)
Possible presence	10 (18.2%)	19 (19.4%)	22 (21.6%)	18 (18.0%)	16 (15.8%)	85 (18.6%)
Definite presence	25 (45.5%)	55 (56.1%)	44 (43.1%)	61 (61.0%)	56 (55.4%)	241 (52.9%)

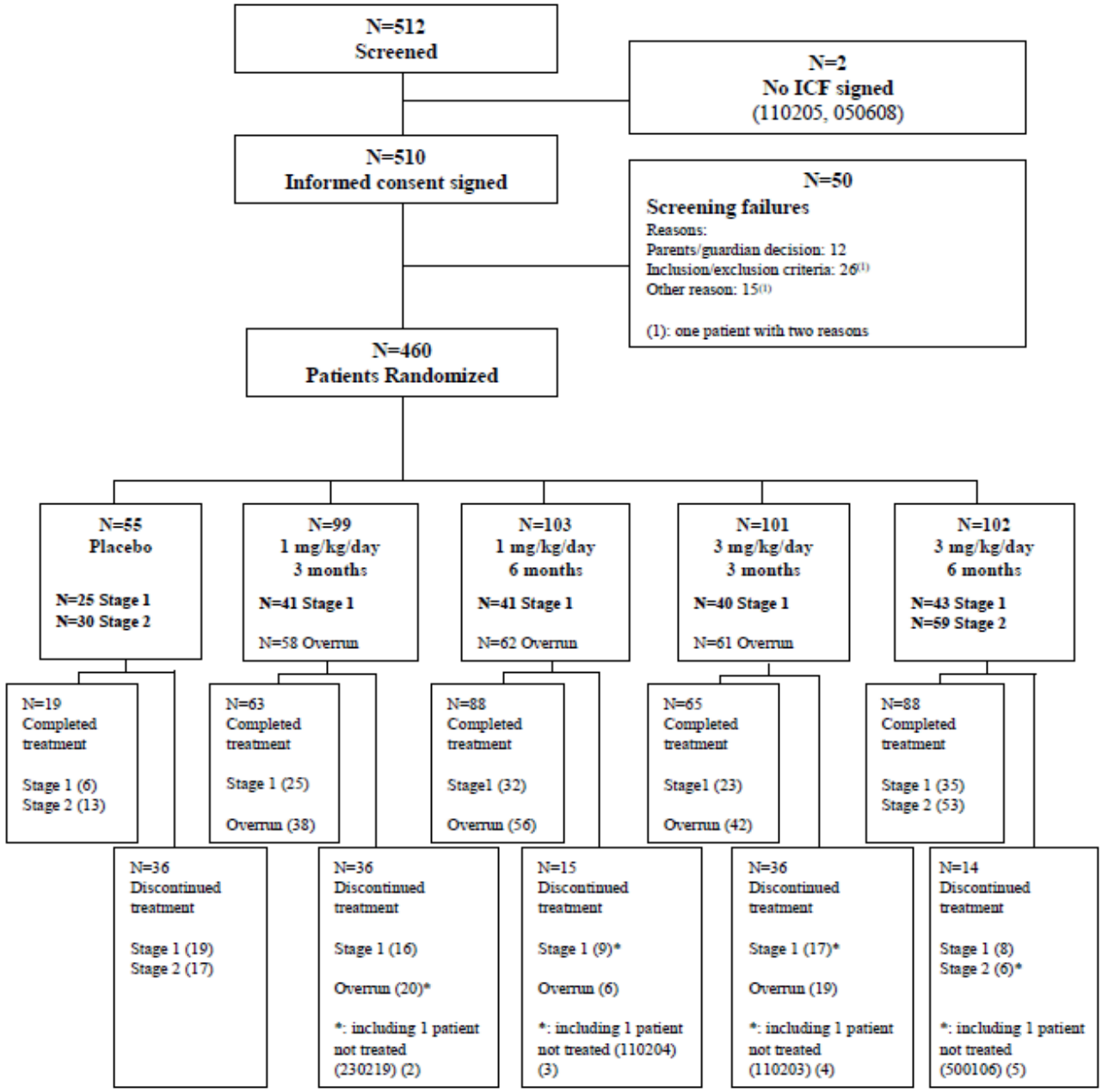
Source: CSR Table 58

Reference ID: 3426190

6.1.3 Subject Disposition

The patient disposition for the Efficacy Population is shown in Figure 6; the number of patients in each analysis data set, by stage and pooled over stages, is summarized in Table 7.

Figure 6 Disposition of patients



4 patients did not receive any medication: Reasons: (2) 230219 (1mg/d 3 m): no treatment available: Immediate treatment needed but bottles of study treatment leaking and no other treatment available at the pharmacy; (3) 110204 (1mg/d 6 m): parents decision (4) 110203 (3mg/d 3 m): parents decision (5) 500106 (3mg/d 6 m): no treatment available: Assigned treatment not available on site.

In Stage 1, 190 patients were randomized, of which two were not treated because parents changed their decision (one in 1mg/kg/day x 6 month arm, and one in 3 mg/kg/day x 3 month arm). Thus, the number of total ITT patients was 188 (Table 7).

Table 7 Number of patients in each dataset analyzed – Randomized data set

Stage / Population	Placebo (N=55)	Propranolol 1mg/kg/day x 3 mths (N=99)	Propranolol 1mg/kg/day x 3 mths (N=103)	Propranolol 3mg/kg/day x 3 mths (N=101)	Propranolol 3mg/kg/day x 6 mths (N=102)	TOTAL (N=460)
Stage1	25 (45.5%)	41 (41.4%)	41 (39.8%)	40 (39.6%)	43 (42.2%)	190 (41.3%)
Intention-to-treat	25 (45.5%)	41 (41.4%)	40 (38.8%)	39 (38.6%)	43 (42.2%)	188 (40.9%)
Per protocol	23 (41.8%)	38 (38.4%)	38 (36.9%)	37 (36.6%)	36 (35.3%)	172 (37.4%)
Safety	25 (45.5%)	41 (41.4%)	40 (38.8%)	39 (38.6%)	43 (42.2%)	188 (40.5%)
Stage2	30 (54.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	59 (57.8%)	89 (19.3%)
Intention-to-treat	30 (54.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	58 (56.9%)	88 (19.1%)
Per protocol	30 (54.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	57 (55.9%)	87 (18.9%)
Pooled (without overrun)	55 (100.0%)	41 (41.4%)	41 (39.8%)	40 (39.6%)	102 (100.0%)	279 (60.7%)
Intention-to-treat	55 (100.0%)	41 (41.4%)	40 (38.8%)	39 (38.6%)	101 (99.0%)	276 (60.0%)
Per protocol	53 (96.4%)	38 (38.4%)	38 (36.9%)	37 (36.6%)	93 (91.2%)	259 (56.3%)
Pooled (with overrun)	55 (100.0%)	99 (100.0%)	103 (100.0%)	101 (100.0%)	102 (100.0%)	460 (100.0%)
Safety	55 (100.0%)	98 (99.0%)	102 (99.0%)	100 (99.0%)	101 (99.0%)	456 (99.1%)

In Stage 2, 89 additional patients were randomized (30 in placebo arm and 59 in 3 mg/kg/day x 6 month arm), of which 1 patient (in 3 mg/kg/day x 6 month arm) was not treated because no units of the treatment assigned by the randomization code were available on site. Thus, the number of ITT patients enrolled in stage 2 was 88 (Table 7).

The ITT data set therefore totals 276 treated patients (188 patients in Stage 1 and 88 patients in Stage 2), and set was used for the primary efficacy analysis (of the primary and secondary endpoints). The ITT data set does not include the overrun patients.

In the “per protocol (PP)” data set, 17 patients with major protocol deviations are excluded thus counting 259 patients (i.e., 93.8% of the ITT data set). This PP data set was used for sensitivity analyses of the primary endpoint analysis.

Including the “overrun” patients, 460 patients were randomized, of which 4 were not treated (3 described above and one patient randomized to 1 mg/kg/day x 3 month arm who was not treated because the bottles of the assigned treatment were leaking. Thus, the safety analysis data set comprises 456 treated patients, which was used for the global safety analysis.

Reference ID: 3426190

6.1.4 Analysis of Primary Efficacy Endpoint(s)

Regimen selection at Interim Analysis: The interim analysis was conducted on the 188 Intent-to-Treat (ITT) Stage 1 patients: the first 190 patients having either completed the 24-week study treatment period or prematurely withdrawn from study treatment, 188 of whom were treated. The efficacy results clearly favored the **3 mg/kg/day 6 months regimen, with 62.8% (27 patients) presenting complete or nearly complete resolution** *vs.* 8.0% (2 patients) in the placebo 6 months regimen, 9.8% in the 1 mg/kg/day 3 months regimen, 37.5% in the 1 mg/kg/day 6 months regimen, and 7.7% in the 3 mg/kg/day 3 months regimen (Table 8).

Table 8 Interim analysis results: Complete or nearly complete resolution at week 24, central reading - ITT data set-Stage 1

	Placebo (N =25)	Propranolol 1 mg/kg/day 3mths (N = 41)		Propranolol 1 mg/kg/day 6mths (N = 40)		Propranolol 3 mg/kg/day 3mths (N = 39)		Propranolol 3 mg/kg/day 6mths (N = 43)	
Primary endpoint: Complete or nearly complete resolution of target IH at week 24									
			P-value		P-value		P-value		P-value
Yes	2 (8.0%)	4 (9.8%)	0.4049	15 (37.5%)	**0.0042**	3 (7.7%)	0.5178	27 (62.8%)	**<0.0001**
No	23 (92.0%)	37 (90.2%)		25 (62.5%)		36 (92.3%)		16 (37.2%)	

Source: CSR 201, Table 17. (P value is vs. placebo)

Based on the efficacy results and the favorable safety findings, the IDMC recommended **selecting the 3 mg/kg/day 6 months regimen for the primary efficacy analysis** and to continue the trial without sample size adjustment/re-estimation.

Table 9 Primary analysis results: complete or nearly complete resolution at Week 24, central reading – ITT data set

	Placebo N=55	Propranolol 3mg/kg/day 6mths N=101	*P value*
Primary endpoint: Complete or nearly complete resolution of target IH at week 24			
Stage 1			
Yes	2 (8.0%)	27 (62.8%)	<0.0001
No	23 (92.0%)	16 (37.2%)	
Stage 2			
Yes	0 (0.0%)	34 (58.6%)	<0.0001
No	30 (100.0%)	24 (41.4%)	
Overall/combined			
Yes	2 (3.6%)	61 (60.4%)	<0.0001
No	53 (96.4%)	40 (39.6%)	

Source: CSR Table 18

Reference ID: 3426190

The results of the primary analysis in Table 9 show that the difference in response was statistically significant between the placebo and 3mg/kg/day x 6 month treatment arms in both stages and overall. In the placebo group, two successes were seen in stage 1, with none in stage 2.

A sensitivity analysis using the PP data set shows similar results with a statistically significant difference complete or nearly complete resolution of IH in favor of the 3 mg/kg/day 6 months group (60.2% *vs.* 1.9% in the placebo group, p<0.0001, Table 10).

Table 10 Primary analysis results using PP data set (sensitivity analysis)

	Placebo N=53	Propranolol 3mg/kg/day 6mths N=93	*P value*
Primary endpoint: Complete or nearly complete resolution of target IH at week 24			
Stage 1			
Yes	1 (4.3%)	23 (63.9%)	<0.0001
No	22 (95.7%)	13 (36.1%)	
Stage 2			
Yes	0 (0.0%)	33 (57.9%)	<0.0001
No	30 (100.0%)	24 (42.1%)	
Overall/combined			
Yes	1 (1.9%)	56 (60.2%)	<0.0001
No	52 (98.1%)	37 (39.8%)	

Source: CSR Table 19

Reviewer's comments: The results presented in Table 9 and Table 10 can be considered as coming from two trials: the Stage I trial comprising 59 patients, and the Stage 2 trial comprising 87 patients, with each trial exhibiting statistically significant (P<0.0001) resolution of IH in treated groups compared to placebo. These results demonstrate the efficacy of Propranolol HCl oral solution at a dose of 3 mg/kg/day for 6 months in producing complete or near complete resolution of target IH at week 24.

The interim (Stage I) results and Stage II results were consistently positive (Table 11). When the data from the two stages were pooled, and reviewed with the data from the overrun population, too, the results show a consistent benefit of the 3 mg/kg/day x 6 months dose group (Table 11).

The pooled data show the results as if statistical analysis had been done on a traditional trial with five treatment arms; using a two-sided Fisher's exact test with Bonferroni correction for multiplicity, only the 6 month regimens were statistically significant (Table 11). It appears that the 3-month dose regimens were not beneficial, whereas the 6-month dose regimens produced statistically significant benefit.

Table 11 Similar primary efficacy results for the treatment regimens between Stage 1 population (interim analysis) and Pooled with overrun population

	Placebo	Propranolol 1 mg/kg/day 3mths		Propranolol 1 mg/kg/day 6mths		Propranolol 3 mg/kg/day 3mths		Propranolol 3 mg/kg/day 6mths	
	n (%)	n (%)	P-value	n (%)	P-value	n (%)	P-value	n (%)	P-value
Stage I (interim analysis)									
N	25	42	0.4049	40	0.0042	39	0.5178	43	<0.0001
Primary endpoint	2 (8.0%)	4 (9.8%)		15 (37.5%)		3 (7.7%)		27 (62.8%)	
Stage II (ITT without overrun) Analysis									
N	30	56	0.0687	62	<0.0001	61	0.0133	58	<0.0001
Primary endpoint	0 (0%)	4 (7.0%)		35 (56.5%)		9 (14.8%)		34 (58.6%)	
Overall (Pooled ITT with overrun) Analysis									
N	55	98	0.138	102	<0.001	100	0.041	101	<0.0001
Primary endpoint	2 (3.6%)	8 (8.2%)		50 (49.0%)		12 (12.0%)		61 (60.4%)	
Two-sided Fisher's Exact test (after Bonferroni correction), P=			1.0000		<0.0001		0.561		<0.0001

Another post-hoc exploratory analysis was done for the pooled ITT with overrun population as a group sequential trial (Table 12), maintaining the parameters from the original analysis scheme, and selecting a conservative O'Brien-Fleming rule (the norminal level of significance was set to 0.00125 (0.005/4) according to Bonferroni correction for multiplicity).

Table 12 Primary efficacy endpoint results for pooled ITT with overrun population – sequential design analysis

Propranolol regimen	Look	Information Fraction	Nominal critical point		Test Statistics	Decision
			Reject H0	Accept H0		
1 mg/kg/day 3 months	Interim	0.448	4.684	0.420	0.211	Should have stopped for futility
	Final	1.022	3.023	3.023	1.059	Non Significant
1 mg/kg/day 6 months	Interim	0.434	4.760	0.325	2.395	Continue (NS)
	Final	1.046	3.023	3.023	**4.334**	**Significant**
3 mg/kg/day 3 months	Interim	0.428	4.799	0.277	-0.045	Should have stopped for futility
	Final	1.035	3.023	3.023	1.640	Non Significant
3 mg/kg/day 6 months	Interim	0.454	4.647	0.466	3.698	Continue (NS)
	Final	1.040	3.023	3.023	**4.942**	**Significant**

Reviewer's comments: The sequential design analyses (Table 12) show that the three-month regimens would have been stopped at the interim analysis for futility had the recruitment not been completed. Only the six month regimens showed statistically significant benefit.

Reference ID: 3426190

Discontinuations: 137 (29.8%) of the 460 patients randomized prematurely discontinued their randomized treatment: nearly two thirds of the patients in the placebo 6 months regimen 65.5% *vs.* 36.4% (1 mg/kg/day 3 months), 35.6% (3 mg/kg/day 3 months), 14.6% (1 mg/kg/day 6 months), and 13.7% (3 mg/kg/day 6 months) in the active regimens (Table 13). Treatment inefficacy was the most frequent primary reason for treatment discontinuation in all regimens, and was highest in the placebo 6 months regimen (58.2%), intermediate in the two 3-month regimens (30.3% and 24.8%), the majority after Week 12 (i.e. on placebo), and lowest in the two 6-month regimens (6.8% and 8.8%).

Table 13 Reasons for early treatment discontinuation – Randomized data set

Reasons for treatment discontinuation	Placebo (N=55)	Propranolol 1mg/kg/day x 3 mths (N=99)	Propranolol 1mg/kg/day x 6 mths (N=103)	Propranolol 3mg/kg/day x 3 mths (N=101)	Propranolol 3mg/kg/day x 6 mths (N=102)	TOTAL (N=460)
Treatment intolerance	0 (0.0%)	2 (2.0%)	0 (0.0%)	2 (2.0%)	0 (0.0%)	4 (0.9%)
Treatment inefficacy	32 (58.2%)	30 (30.3%)	7 (6.8%)	25 (24.8%)	9 (8.8%)	103 (22.4%)
Safety reason not linked to the protocol therapy	2 (3.6%)	1 (1.0%)	1 (1.0%)	3 (3.0%)	1 (1.0%)	8 (1.7%)
Parent(s)/guardian(s)	7 (12.7%)	9 (9.1%)	6 (5.8%)(1)	13 (12.9%)(2)	4 (3.9%)	39 (8.5%)
Other discontinuations	1 (1.8%)	5 (5.1%)(3)	2 (1.9%)	4 (4.0%)	2 (2.0%)(4)	14 (3.0%)
Overall discontinuations	36 (65.5%)	36 (36.4%)	15 (14.6%)	36 (35.6%)	14 (13.7%)	137 (29.8%)

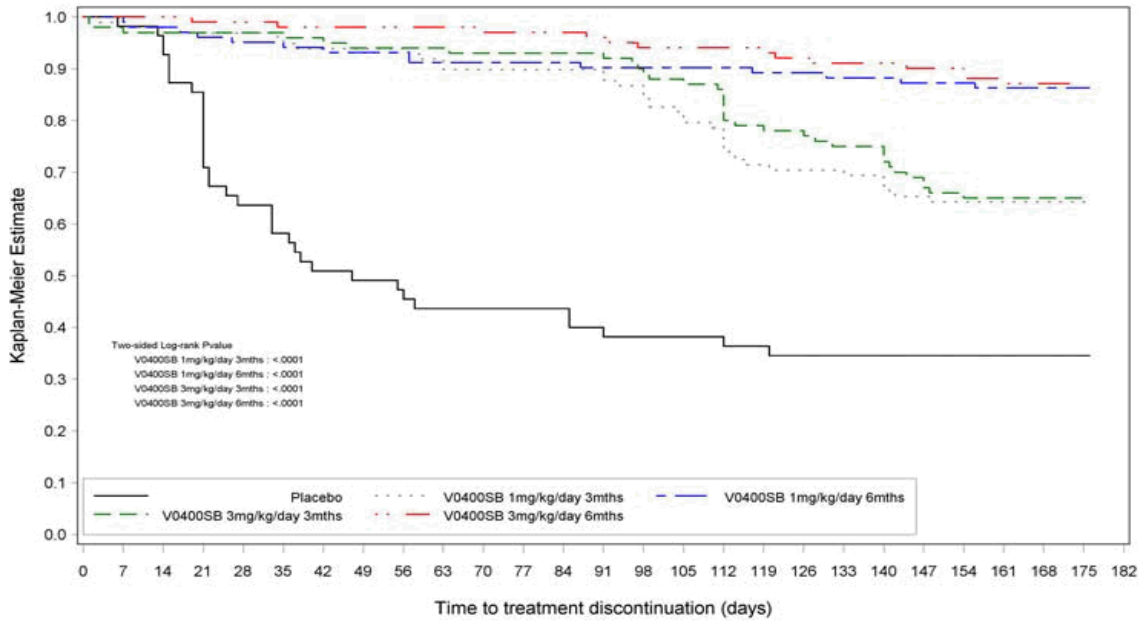
NOTE: Percentages are based on total subjects in each treatment arm. Subject can have more than one reason for treatment discontinuation.
(1) including patient 110203, not treated; (2) including patient 110204, not treated; (3) including patient 230216, not treated; (4) including patient 500106, not treated; Source: Table 9 in CSR

The pattern of treatment discontinuation differed between the treatment arms (Figure 7):

- In the placebo arm, treatment discontinuation started early (as soon as at W2), with a very steep decrease of the curve between W2 and W5, with 49.1% of the patients having discontinued treatment at W5. Treatment discontinuations continued at a lower rate thereafter, reaching 65.5% at W20;
- In the active treatment arms, the treatment discontinuation rates were much lower than in the placebo arm:
  - They presented a similar shape until W12, at which treatment discontinuation rates were slightly higher in the two 1 mg/kg/day arms than in the 3 mg/kg/day arms (11.1% in the 1 mg/kg/day 3 months arm, 10.7% in the 1 mg/kg/day 3 months arm, 7.9% in the 3 mg/kg/day 3 months arm and 4.9% in the 3 mg/kg/day 6 months arm),
  - After W12, treatment discontinuations increased in both 3 months arms while they were stable in both 6 months arms (36.4% in the 1 mg/kg/day 3 months arm, 31.7% in the 1 mg/kg/day 3 months arm, 12.6% in the 1 mg/kg/day 6 months arm and 11.8% in the 3 mg/kg/day 6 months arm).

Reference ID: 3426190

Figure 7 Kaplan Meier curve for Time to Treatment Discontinuation (Safety Data Set)



Source: CSR Study 201 Figure 5.

Table 14 Handling of discontinuations, prohibited treatment and missing data on the primary efficacy endpoint

	Analysis data set	
	ITT data set	**PP data set**
Early treatment withdrawal	*Failure*	*Failure*
Patients receiving, for any reason, prohibited treatments (after randomization and before the W24 evaluation) that may be used to treat IH (systemic [oral, intra-venous or intra-muscular], intra-lesional or topical corticosteroids, imiquimod, vincristine, alfa-interferon, beta-blockers other than the study treatment or laser therapy), *i.e.* in usual conditions for treating IH with appropriate formulation, dose and treatment duration	Failure	Failure
Patients receiving any other prohibited treatments before the W24 evaluation	Referred to efficacy assessment	Excluded from PP, according to Validation Committee*
Missing primary efficacy endpoint for a patient who completes the 24-week treatment period and Available investigator's on-site assessment of complete/nearly complete resolution at W24	Missing data replaced by the investigator's assessment	Excluded from PP
Missing primary efficacy endpoint for a patient who completes the 24-week treatment period and Missing investigator's on-site assessment of complete/nearly complete resolution at W24	Failure	Excluded from PP

Table 14 shows how the effect of discontinuations, prohibited treatment and missing

data on the primary efficacy endpoint are handled.

Reviewer's comments: One inherent problem with the above method of handling is that in the placebo group where no beneficial cosmetic improvement was noticed soon after randomization, more patients were likely to drop out early (for lack of effect) and also there were more patients who received prohibited concomitant medications. Both of these factors could have biased the study towards early treatment withdrawals and becoming classified as failures, thereby reducing the number of primary endpoint events in the placebo group, and causing the treated group more likely to win in the ITT analysis. Exploratory analyses would be useful to understand the impact of these "failures" on the primary efficacy endpoint. One possible analysis was (i) to use 168-day (24 W) as the cutoff for any patient who took concomitant medications (which could include some patients on placebo who had been discontinued before W24), and/or (ii) to consider those who dropped out before W24, not as failures but use some imputation method (such as multiple imputation method) to understand the noise associated with early discontinuation/failures from various causes.

Sensitivity analysis of patients who completed the 24-week treatment period: Any premature discontinuation of treatment was considered as a treatment failure; this could overestimate efficacy in groups with high withdrawal rates due to inefficacy, particularly in the placebo group in which patients are more likely to discontinue early because the lack of cosmetic benefit is obvious early to investigators and/or parents. A disproportionately large number of early discontinuations in the placebo group may create a bias favoring the propranolol regimens versus placebo. A *post-hoc* analysis of data on only the completers (i.e., patients who reached Week 24 and had photographs evaluated by central reading) is shown in Table 15.

Table 15 Primary endpoint in patients who completed the initial 24-week period

Centralized – complete or nearly complete resolution at Week 24	Placebo	Propranolol 1 mg/kg/day 3mths	Propranolol 1 mg/kg/day 6mths	Propranolol 3 mg/kg/day 3mths	Propranolol 3 mg/kg/day 6mths
N	19	63	88	65	88
No	17 (89.5%)	55 (87.3%)	38 (43.2%)	53 (81.5%)	27 (30.7%)
Yes	2 (10.5%)	8 (12.7%)	50 (56.8%)	12 (18.5%)	61 (69.3%)

Source: ISE Table 34

There was the same dose response finding in the results (Table 15) between treatment regimens (success rates of 69.3% and 56.8%, respectively, in the 3 mg/kg/day x 6 months and 1 mg/kg/day x 6 months regimens). Both of the 3 months regimens showed lower success rates close to that of placebo.

Reviewer's comment: This exploratory analysis overestimates the response rate in the group with the highest proportion of early withdrawals due to inefficacy (Placebo group). The analysis still shows results that are consistent with the primary efficacy analysis.

Reference ID: 3426190

In another exploratory sensitivity analysis, I treated ALL dropouts in treatment arms as failures and ALL dropouts in the placebo arms as censored (using a method I would call Avi's Law in memory of our late DCRP medical team leader Dr. Avi Karkowsky who insisted on this stringent analysis for most NDAs). Using this very conservative analysis, the success rates in the 3 month regimens did not differ from that of placebo (Table 16), but still support the primary efficacy analysis of the ITT and Per protocol data sets.

Table 16 Primary efficacy endpoint analysis using Avi's Law

Primary endpoint: Complete or nearly complete resolution of target IH at Week 24		Placebo	Propranolol 1 mg/kg/day 3mths	Propranolol 1 mg/kg/day 6mths	Propranolol 3 mg/kg/day 3mths	Propranolol 3 mg/kg/day 6mths
N		**55**	**98**	**102**	**100**	**101**
Overall						
Primary Endpoint	No	53 (96.4%)	90 (91.8%)	52 (51.0%)	88 (88.0%)	40 (39.6%)
	Yes	2 (3.6%)	8 (8.2%)	50 (49.0%)	12 (12.0%)	61 (60.4%)
Early discontinuations	n	36	35*	14*	35*	13*
Avi's Law – number of patients		**19**	**98**	**102**	**100**	**101**
Avi's Law – number of failures		17 (89.5%)	90 (91.8%)	52 (51.0%)	88 (88.0%)	40 (39.6%)
Number with primary endpoint		2 (10.5%)	8 (8.2%)	50 (49.0%)	12 (12.0%)	61 (60.4%)

*Does not include one patient in each treatment arm who did not receive treatment (Ref: Table 13 in this clinical review.)

Exploratory analyses using multiple imputation method for those who dropped out before W24: *Post-hoc* handling of early discontinuations was performed using multiple imputation method which consists of replacing any missing value by multiple plausible values instead of single imputation, assuming that data were "missing at random (MAR)", i.e., the missingness depends on the observed outcome values and is independent of the unobserved outcome values. The results of this exploratory analysis (Table 17) show a highly significant treatment effect (p=0.0006) for propranolol 3 mg/kg/day 6 months, and confirm the robustness of the primary endpoint.

Table 17 Primary endpoint: sensitivity analysis – multiple imputation (ITT with overrun)

	Placebo n=55	propranolol 1mg/kg/day 3mths n=98	propranolol 1mg/kg/day 6mths n=102	propranolol 3mg/kg/day 3mths n=100	propranolol 3mg/kg/day 6mths n=101
Logistic regression after multiple imputation					
Estimation of percentage of Success	13.8%	15.4%	55.0%	19.0%	67.9%
Treatment effect vs. Placebo (after Bonferroni Adjustment), p =		1.0000	0.0098	1.0000	0.0006

Summary: Overall, 2 patients (3.6%) in the placebo 6 months regimen and 61 patients (60.4%) in the 3 mg/kg/day 6 months regimen presented complete or nearly complete resolution of their IH at Week 24. The combined p-value (<0.0001) shows that the

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difference was statistically significant (at the 0.005 level). The results were consistent between the two stages, as were the absolute differences between the two regimens.

These results were supported by an analysis on the Per Protocol data set and a sensitivity analysis which used a wider definition of treatment failure.

Primary efficacy analyses by Region: To determine the effect of disproportionate placebo patients in some countries/regions (as stated in Section 6.1.2) I reviewed an exploratory analyses of the primary efficacy endpoint by region {(USA-Canada and Other America – 111 patients) vs. Western Europe (235 patients) vs. (Other Europe and Oceania) – 110 patients} for the pooled (with overrun) population of patients using (i) ITT data set and (ii) per protocol data set.

Table 18 Primary endpoint by Region (ITT data set with overrun population)

Primary Endpoint: Centralized Response at Week 24	Placebo n=55	propranolol 1mg/kg/day 3mths n=98	propranolol 1mg/kg/day 6mths n=102	propranolol 3mg/kg/day 3mths n=100	propranolol 3mg/kg/day 6mths n=101
USA-Canada and other America					
No	8 (88.9 %)	23 (92.0 %)	16 (57.1 %)	25 (100.0 %)	10 (41.7 %)
Yes	1 (11.1 %)	2 (8.0 %)	12 (42.9 %)		14 (58.3 %)
Western Europe					
No	34 (97.1 %)	46 (90.2 %)	22 (53.7 %)	48 (85.7 %)	25 (48.1 %)
Yes	1 (2.9 %)	5 (9.8 %)	19 (46.3 %)	8 (14.3 %)	27 (51.9 %)
Other Europe and Oceania					
No	11 (100.0 %)	21 (95.5 %)	14 (42.4 %)	15 (78.9 %)	5 (20.0 %)
Yes		1 (4.5 %)	19 (57.6 %)	4 (21.1 %)	20 (80.0 %)

Figure 8 Primary endpoint by Region (ITT data set with overrun population)

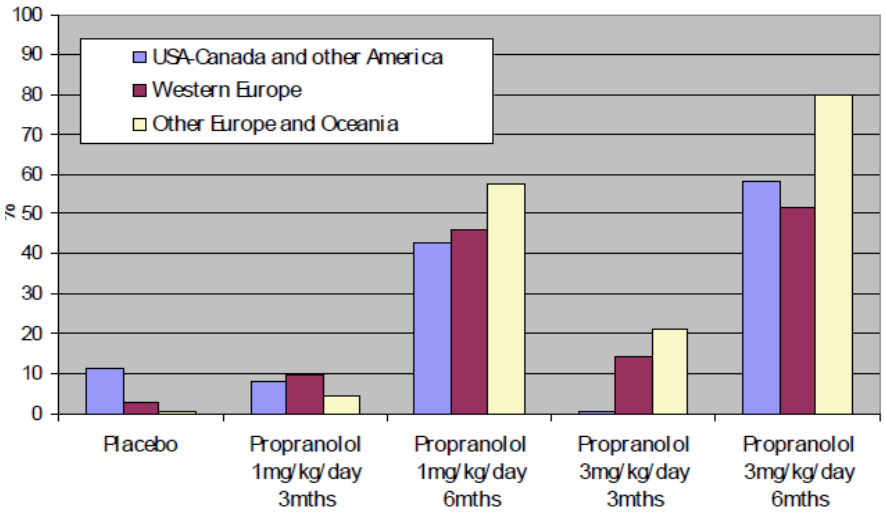

Table 18 and Figure 8 show that the 3 mg/kg/day 6-month regimen is consistently effective in all 3 regions. The small number of placebo patients in the data set does not allow comparison between regions. The PP data sets also show the same results.

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Reviewer's comments: No statistical bias was found as a result of the difference in the proportion of placebo patients between the 3 regions.

6.1.5 Analysis of Secondary Endpoints(s)

The key secondary efficacy endpoints are:

- Success/failure (binary endpoint) based on the investigator's on-site qualitative assessment of:
  1) complete/nearly complete resolution of the target IH compared to baseline (the definition of 'nearly complete resolution' for Study 102 was the same as for 201, but with the additional category of 'a minimal palpable component');
  2) target IH evolution, on a 3-point scale (improved, stabilized, worsened) at paired consecutive visits;
  3) target IH complications (according to defined grading assessments).
- The parents'/guardians' on-site qualitative assessment of target IH evolution (improved, stabilized, worsened) at paired consecutive visits and time to first sustained improvement (first improvement after which there was no worsening).

Other secondary efficacy endpoints included centralized assessments of:

1. target IH (complete/nearly complete resolution) at W 12, W36 and W48 compared to baseline
2. Time to first sustained complete/nearly complete resolution (W12, W24, W36 or W48 compared to baseline)
3. target IH evolution, on a 3-point scale (improved, stabilized, worsened) at paired consecutive visits
4. time to first sustained improvement (first improvement after which there was no worsening) of the target IH based on paired consecutive visits (Type 2), and
5. continuous and categorical endpoints (change in size and color of target IH) at W12 and W24 compared to baseline.

Investigator's on-site qualitative assessment of IH complete/nearly complete resolution at each visit: No patient was assessed with complete or nearly complete resolution by the investigators at D7, D14, D21, W5, and W8 in the placebo arm. One patient (4.2%) at W12, and 2 patients at W16, W20 and W24 (respectively 9.5%, 10.0% and 10.5% of the patients evaluated at the visit) were assessed with complete or nearly complete resolution in the placebo arm.

In the 3 mg/kg/day 6 months arm, 2 patients (2.0%) at W5, 4 patients (4.0%) at W8, 8 patients (8.2%) at W12, 10 patients (10.4%) at W16, 20 patients (21.5%) at W20 and 24 (26.7%) at W24 were assessed with complete/nearly complete resolution; the difference in complete/nearly complete resolution rate was not statistically significant for any visit.

Table 19 shows the investigators' on-site assessment for complete/nearly complete resolution of target IH at Week 24. The event rates and p-values were calculated using the number of patients who were randomized, not the number of patients who

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completed the study as the denominator. It is interesting to note that the placebo group even performed better than the 1 mg/kg/day 3mths dose group.

Table 19 LOCF analysis results for investigator on-site qualitative assessment

Investigator on-site qualitative assessment of complete/nearly complete resolution of the target IH	Placebo (N=55)	propranolol 1mg/kg/day 3mths (N=98)	propranolol 1mg/kg/day 6mths (N=102)	propranolol 3mg/kg/day 3mths (N=100)	propranolol 3mg/kg/day 6mths (N=101)
Response	2	2	20	6	24
Responder Rate	0.036	0.020	0.196	0.06	0.238
Two sided p-value		0.55	0.006	0.525	0.001

Source: analysis performed by statistical reviewer.

The investigators' findings contrast strikingly with the results of the primary endpoint (centralized assessment of complete/nearly complete resolution), which classified more IHs as completely/nearly completely resolved than the investigators on site (Table 20). Centralized assessment found 2 (3.6%) complete/nearly complete resolution *vs.* 0 found by investigators in the placebo arm; also centralized assessment found complete/near complete resolution for 61 ((i.e., 23 + 38) or 60.4%) *vs.* 24 ((i.e., 23 + 1) or 26.7%) found by investigators in the 3 mg/kg/day 6 months arm. In the propranolol 3 mg/kg/day 6 months arm, there is no agreement between centralized assessment and investigators assessment as complete/nearly complete resolution for 39 (i.e., 38 + 1) patients. In the placebo arm, there is no agreement between centralized assessment and investigators assessment as complete/nearly complete resolution for 2 patients. It is possible that the investigators' assessment of the same criterion is subject to greater heterogeneity (56 investigating sites *vs.* 2 expert readers), less reproducibility (no training for this parameter, no validation of intra/inter reader reproducibility) and also methodologically different (based on a direct visual examination of the patient at W24 with the W0 pictures and data available at the investigator site).

Table 20 Lack of consistency between centralized and investigator assessments of complete/nearly complete resolution at 24 weeks

Complete/nearly complete resolution		Placebo (n=55)	Propranolol 3 mg/kg/day 6mths (n=101)
Centralized assessment	Investigator assessment		
Yes	Yes	0	23
Yes	No	2	38
No	Yes	0	1
No	No	53	39

The parents'/guardians' on-site qualitative assessment of target IH evolution (improved, stabilized, worsened) at paired consecutive visits: Parents/guardians uniformly over-rated the response for both placebo and treated groups compared to centralized assessment (Table 21).

Table 21 Parent(s)/guardian(s) on-site assessment vs. centralized assessment (overall/combined) for time to first sustained improvement of target IH

	Placebo		Propranolol 3 mg/kg/d x 6 months	
	Parents	*Centralized*	*Parents*	*Centralized*
	N=55	N=55	N=101	N=101
	N n (KM rate)*	N n (KM rate)*	N n (KM rate)*	N n (KM rate)*
Day 0	55 0 (0.0%)	55 0 (0.0%)	101 0 (0.0%)	101 0 (0.0%)
Week 12	13 11 (24.4%)	24 2 (8.3%)	27 68 (71.9%)	97 40 (41.2%)
Week 24	5 14 (45.0%)	17 2 (0.3%)	8 76 (85.6%)	46 60 (66.8%)

Source: CSR Table 159; * N = number of patients at risk. n = cumulative number of events. KM rate = Kaplan-Meier cumulative incidence estimates.

There are many other secondary and exploratory efficacy endpoints based on (i) independent blinded Type 1 assessments[1] of complete/nearly complete resolution, (ii) independent blinded Type 2 assessments[2] of improvement, (iii) stabilization or worsening of the target IH, and (iv) centralized quantitative assessments (change in size, color of target IH). Some of the analyses are reviewed below.

Figure 9 Three-point evolution of IH over time – Proportion of improvement – ITT data set

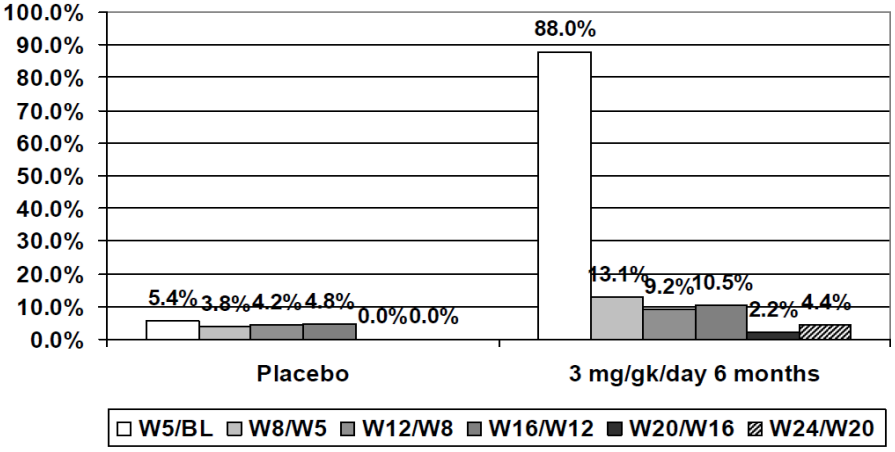


Figure 9 shows that improvement was seldom observed in the placebo arm (2 patients at the W5-baseline comparison and 1 at the three next comparisons) and about 11% worsening was observed at the two first comparisons (W5 versus baseline and W8

[1] Type 1: the independent readers assessed paired groups of photographs to compare W12, W24 (primary efficacy endpoint) to baseline. The paired groups were placed side by side (with the baseline photographs to the left and the post-baseline photographs to the right) and the readers were asked to assess whether or not the target IH had completely/nearly completely resolved in the photographs to the right. Nearly complete resolution was defined as a minimal degree of telangiectasis, erythema, skin thickening, soft tissue swelling and/or distortion of anatomical landmarks.

[2] Type 2: the independent readers reviewed paired groups of photographs to compare baseline, W5, W8, W12, W16 and W20 with W5, W8, W12, W16, W20 and W24, respectively. The paired groups of photographs were placed side by side in random order, so that the group of photographs to the left did not necessarily correspond to the earlier visit. The independent readers evaluated whether the target IH was in a better, stable or worse state in the photographs on the right compared to the photographs on the left.

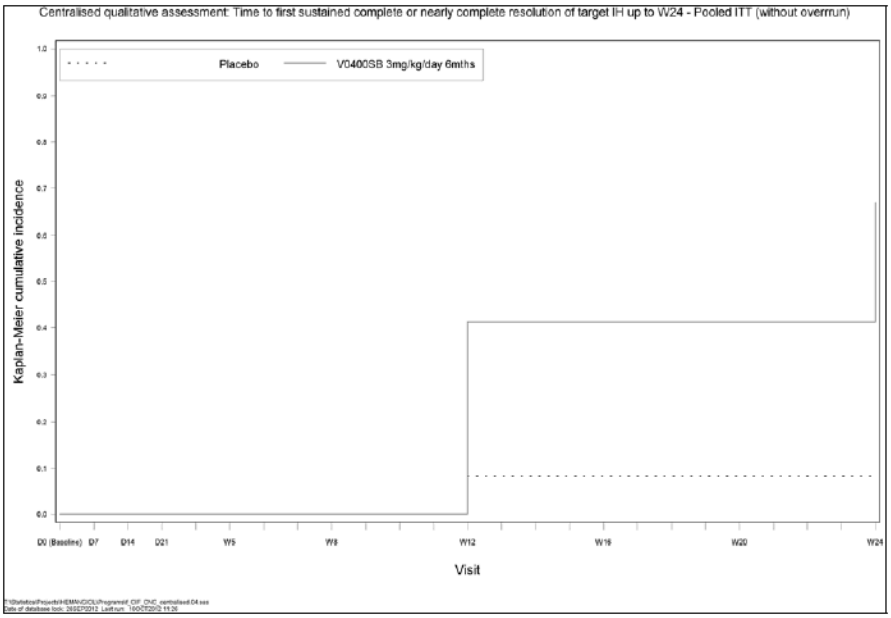
versus W5). The evolution was clearly different in the 3 mg/kg/day 6 months group, with early improvement in a vast majority of the patients. 88.0% of the patients are assessed as improved as soon as W5 *versus* baseline. Further improvement is observed afterwards in a few patients: 13.1% at W8 *versus* W5, 9.2% at W12 *versus* W8, 10.5% at W12 *versus* W16, 2.2% at W20 *versus* W16 and 4.4% at W24 *versus* W20.

Table 22 Time to first sustained complete/nearly complete resolution (ITT)

	Placebo N=55 N n (KM rate)*	Propranolol 3mg/kg/day 6mths N=101 N n (KM rate)*	*P value*
Stage 1			
Day 0 (Baseline)	25 0 (0.0%)	43 0 (0.0%)	
Week 12	8 2 (25%)	39 17 (43.6%)	
Week 24	4 2 (25%)	16 26 (75.3%)	0.0267
Stage 2			
Day 0 (Baseline)	30 0 (0.0%)	58 0 (0.0%)	
Week 12	16 0 (0.0%)	58 23 (39.7%)	
Week 24	13 0 (0.0%)	30 34 (61.8%)	<0.0001
Overall/combined			
Day 0 (Baseline)	55 0 (0.0%)	101 0 (0.0%)	
Week 12	24 2 (8.3%)	97 40 (41.2%)	
Week 24	17 2 (8.3%)	46 60 (66.8%)	<0.0001

* *N = number of patients at risk. n = cumulative number of events. KM rate = Kaplan-Meier cumulative incidence estimates.* Source: CSR Table 116

Figure 10 Time to first sustained complete or nearly complete resolution - ITT



Source: Figure 36 on page 559 of CSR.

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Table 22 and Figure 10 show that the Kaplan Meier estimates for rate of sustained complete or nearly complete resolution (first improvement after which there is no worsening) of the target IH based on Type 2 centralized qualitative assessments of paired patient-visits) was 41.2% of the patients in the 3 mg/kg/day 6 months arm and 8.3% (2 patients) in the placebo arm. At W24 the estimate rose to 66.8% in the 3 mg/kg/day 6 months arm but did not change in the placebo arm. The two Kaplan-Meier curves differ significantly (p<0.0001).

Continuous and categorical endpoints (change in size and color of target IH) at W12 and W24 compared to baseline. {Note: the size of IH were calculated in two ways: surface area (cm²) and maximal diameter (cm)}

IH surface area: Results of analyses of change in IH surface area are shown in Table 23. At week 24 for all patients combined, there was a decrease of 1.21 cm² (SD: 2.44) in the 3 mg/kg/day 6 months arm *vs.* an *increase* of 0.46 (SD: 1.80) in the placebo arm (p=0.009). The between arms difference was higher in patients from stage 1 (active arm: -1.84 cm² vs. +0.65 cm² in the placebo arm) than in patients from stage 2 (active arm -0.79 cm² vs. placebo: +0.38 cm²).

Table 23 Change in IH surface area between baseline and Week 24 – ITT data set

	Placebo N=55	Propranolol 3mg/kg/day 6mths N=101	*P value*
Stage 1			
n/missing	19 / 6	35 / 8	0.0250
Mean (SD)	0.65 (2.04)	-1.84 (2.98)	
Min, max	-1.08, 4.22	-13.08, 3.38	
Stage 2			
n/missing	17 / 13	53 / 5	0.0233
Mean (SD)	0.38 (1.77)	-0.79 (1.92)	
Min, max	-4.35, 2.69	-8.66, 4.70	
Overall/combined			
n/missing	36 / 19	88 / 13	0.0093
Mean (SD)	0.46 (1.80)	-1.21 (2.44)	
Min, max	-4.35, 4.22	-13.08, 4.70	

Source: CSR Table 110

IH maximal diameter: Table 24 presents the results of the analysis at W24 when the maximal diameter decreased in the two treatment arms, with a larger mean change in the active arm (0.18 cm, SD: 0.73) than in the placebo arm (0.03 cm, SD: 0.74), a difference not statistically significant (p=0.41).

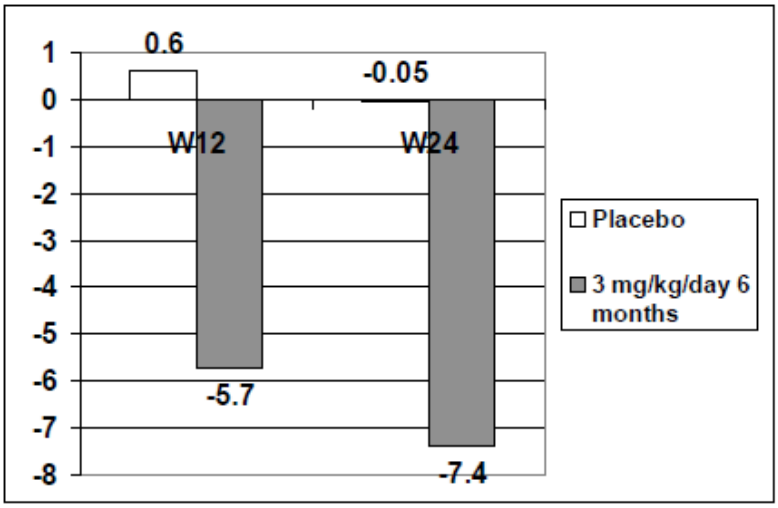
Table 24 Change in IH maximal diameter between baseline and Week 24

	Placebo N=55	Propranolol 3mg/kg/day 6mths N=101	*P value*
Stage 1			
n/missing	19 / 6	35 / 8	0.1843
Mean (SD)	0.12 (0.84)	-0.24 (0.92)	
Min, max	-1.01, 1.33	-2.15, 2.28	
Stage 2			
n/missing	17 / 13	53 / 5	0.4083
Mean (SD)	-0.10 (0.72)	-0.14 (0.59)	
Min, max	-1.51, 0.69	-1.56, 1.64	
Overall/combined			
n/missing	36 / 19	88 / 13	0.4127
Mean (SD)	-0.03 (0.74)	-0.18 (0.73)	
Min, max	-1.51, 1.33	-2.15, 2.28	

Source: CSR Table 112

Change in IH color: Results of the analysis of the change in IH color assessment between baseline and W12 and W24 are summarized in Figure 11. At W12, a significant difference (p<0.0001) was observed between the two groups, with a mean decrease of 5.7 units (SD: 6.0) in the active arm compared to an *increase* of 0.6 units (SD 6.0) in the placebo arm. Results at W24 show a statistically significant difference (p<0.0001) between the two treatment arms, with a mean decrease in color of 7.4 units (SD: 7.4) in the active arm vs. a slight decrease in color of 0.05 units (SD: 4.8) in the placebo arm. Between arms differences were similar for the two stages.

Figure 11 Change in IH color (dE*2000)



The overall findings of the secondary endpoint analyses are shown in Table 25.

Table 25 Secondary efficacy endpoints – ITT data set

Secondary Efficacy Endpoints	Placebo N=55	Propranolol 3mg/kg/day 6mths N=101	P value
Centralized quantitative assessments			
Change in surface area at W24 vs baseline (cm^2) Mean (SD)	0.46 (1.804)	-1.21 (2.439)	0.0093
Change in max diameter at W24 vs baseline (cm) Mean (SD)	-0.03 (0.743)	-0.18 (0.731)	0.4127
Change in color at W24 vs baseline (dE2000) Mean (SD)	-0.05 (4.824)	-7.4 (7.430)	<0.0001
Centralized qualitative assessment			
Sustained improvement at W5 (KM rate*)	5.4%	72.7%	<0.0001†
Sustained improvement at W24 (KM rate*)	9.0%	79.5%	
Investigator's on-site assessment			
Complete/nearly complete resolution of IH at W24 vs baseline	10.5%	26.7%	0.4419
Sustained improvement at W5 (KM rate*)	20.1%	70.9%	<0.0001‡
Sustained improvement at W24 (KM rate*)	32.4%	82.5%	
Parents' on-site assessment			
Sustained improvement at W5 (KM rate*)	19.9%	67.4%	<0.0001‡
Sustained improvement at W24 (KM rate*)	45.0%	85.6%	

†Calculated on time to first sustained improvement assessed at D0, W5, W8, W12, W16, W20, W24. *KM rate = Kaplan-Meier cumulative incidence estimate.
‡Calculated on time to first sustained improvement assessed at D0, D7, D14, D21, W5, W8, W12, W16, W20, W24. Source: Section 5.3.5.1, Study 201.

Table 26 Complete or nearly complete resolution at W12 – ITT data set

	Placebo N=55	Propranolol 3mg/kg/day 6mths N=101	*P value*
Primary endpoint: Complete or nearly complete resolution of target IH at week 12			
Stage 1			
N / missing	25 / 0	42 / 1	
Yes	2 (8.0%)	19 (45.2%)	<0.0007
No	23 (92.0%)	23 (54.8%)	
Stage 2			
N / missing	30 / 0	58 / 0	
Yes	0 (0.0%)	25 (43.1%)	<0.0001
No	30 (100.0%)	33 (56.9%)	
Overall/combined			
N / missing	55 / 0	100 / 1	
Yes	2 (3.6%)	44 (44.0%)	<0.0001
No	53 (96.4%)	56 (56.0%)	

Source: CSR Table 115

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6.1.6 Other Endpoints

Table 27 shows the time to first sustained improvement (as assessed by parent(s)/ guardian(s) on a 3-point scale of pairwise consecutive visits) and the corresponding Kaplan Meier analysis. Sustained improvement was achieved early in the 3 mg/kg/day 6 month group, with Kaplan Meier estimates of 55.8% on D7, 64.2% on D14, 65.3% on D21, 67.4% at W5 and progressed slower to reach 85.6% at W24 (76 patients of the group having achieved sustained improvement). In the placebo arm, sustained improvement started also on D7 with a lower estimate (12.7%) and had a slower progression, reaching a maximum of 45.0% on W16 (14 patients having achieved sustained improvement). The difference between the two Kaplan Meier curves was statistically significant (p<0.0001).

Table 27 Parent(s) or guardian(s) on-site assessment: time to first sustained improvement of target IH – ITT data set

		Propranolol Hydrochloride solution							
	Placebo	1 mg/kg/d		1 mg/kg/d		3 mg/kg/d		6 mg/kg/d	
		3 mths		6 mths		3 mths		6 mths	
	N=55	N=41		N=40		N=39		N=101	
	N n (KM rate)*	N n (KM rate)*		N n (KM rate)*		N n (KM	P value	N n (KM rate)*	P value
Day 0	55 0 (0.0%)	41 0 (0.0%)		40 0 (0.0%)		39 0 (0.0%)		10 1 0	
Day 7	55 7 (12.7%)	40 12 (30.0%)		36 18 (50.0%)		39 9 (23.1%)		95 53 (55.8%)	
Day 14	47 7 (12.7%)	27 12 (30.0%)		15 19 (53.3%)		29 10 (25.7%)		42 61 (64.2%)	
Day 21	41 9 (17.0%)	26 12 (30.0%)		13 20 (56.9%)		28 10 (25.7%)		34 62 (65.3%)	
Week 5	28 10 (19.9%)	26 12 (30.0%)		11 20 (56.9%)		28 10 (25.7%)		32 64 (67.4%)	
Week 8	18 11 (24.4%)	24 12 (30.0%)		11 21 (60.8%)		28 11 (28.4%)		29 66 (69.7%)	
Week 12	13 11 (24.4%)	24 12 (30.0%)		8 21 (60.8%)		25 11 (28.4%)		27 68 (71.9%)	
Week 16	11 14 (45.0%)	23 12 (30.0%)		8 21 (60.8%)		25 11 (28.4%)		23 70 (74.4%)	
Week 20	6 14 (45.0%)	15 12 (30.0%)		8 21 (60.8%)		17 13 (36.8%)		16 74 (80.8%)	
Week 24	5 14 (45.0%)	12 12 (30.0%)	**0.4755**	7 22 (66.4%)	**0.0007**	11 13 (36.8%)	**0.5185**	8 76 (85.6%)	**<0.0001**

Source: CSR Table 159; * N = number of patients at risk. n = cumulative number of events. KM rate = Kaplan-Meier cumulative incidence estimates.

Ulceration: Table 28 shows maximal ulceration after baseline. 31 patients presented with ulceration of IH, 2 in placebo arm and the rest in the propranolol treatment arms. In 18 patients with pre-existing ulcerations (all on propranolol), 17 resolved and 1 patient discontinued treatment; for 1 patient there was no information. In 13 patients who had treatment-emergent ulcerations two patients on placebo prematurely discontinued; the ulceration in 11 patients on propranolol secondarily resolved on propranolol in all but 2 patients.

Bleeding/Hemorrhaging: Table 29 shows maximal bleeding/hemorrhaging post baseline. Seven patients presented with bleeding/hemorrhaging of their IH: one in the placebo arm and 6 in the propranolol treatment arms. The bleeding was mild and resolved at W5 at the latest. None required transfusion. In all but one case, the bleeding/hemorrhage was associated with an IH ulceration.

Table 28 Maximal ulceration of IH post baseline – ITT data set with overrun

	Placebo (N=55)	Propranolol 1 mg/kg/d 3 m (N=98)	Propranolol 1 mg/kg/d 6 m (N=102)	Propranolol 3 mg/kg/d 3 m (N=100)	Propranolol 3 mg/kg/d 6 m (N=101)
Other investigator's on-site assessment: Maximal ulceration of hemangioma					
Stage 1 Maximal ulceration of hemangioma post- baseline					
n/missing	25 / 0	41 / 0	40 / 0	39 / 0	43 / 0
Grade 0	24 (96.0%)	36 (87.8%)	38 (95.0%)	36 (92.3%)	41 (95.3%)
Grade 1	1 (4.0%)	4 (9.8%)	2 (5.0%)	0 (0.0%)	1 (2.3%)
Grade 2	0 (0.0%)	1 (2.4%)	0 (0.0%)	1 (2.6%)	1 (2.3%)
Grade 3+	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.1%)	0 (0.0%)
Stage 2 (with overrun) Maximal ulceration of hemangioma post- baseline					
n/missing	30 / 0	56 / 1	62 / 0	59 / 2	58 / 0
Grade 0	29 (96.7%)	53 (94.6%)	59 (95.2%)	55 (93.2%)	54 (93.1%)
Grade 1	1 (3.3%)	2 (3.6%)	1 (1.6%)	2 (3.4%)	2 (3.4%)
Grade 2	0 (0.0%)	1 (1.8%)	1 (1.6%)	1 (1.7%)	0 (0.0%)
Grade 3+	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (1.7%)	2 (3.4%)
Pooled (with overrun) Maximal ulceration of hemangioma post- baseline					
n/missing	55 / 0	97 / 1	102 / 0	98 / 2	101 / 0
Grade 0	53 (96.4%)	89 (91.8%)	97 (95.1%)	91 (92.9%)	95 (94.1%)
Grade 1	2 (3.6%)	6 (6.2%)	3 (2.9%)	2 (2.0%)	3 (3.0%)
Grade 2	0 (0.0%)	2 (2.1%)	1 (1.0%)	2 (2.0%)	1 (1.0%)
Grade 3+	0 (0.0%)	0 (0.0%)	1 (1.0%)	3 (3.1%)	2 (2.0%)

Source: CSR Table 163

Table 29 Maximal hemorrhaging/bleeding of IH post-baseline – ITT dataset with overrun

	Placebo (N=55)	Propranolol 1 mg/kg/d 3 m (N=98)	Propranolol 1 mg/kg/d 6 m (N=102)	Propranolol 3 mg/kg/d 3 m (N=100)	Propranolol 3 mg/kg/d 6 m (N=101)
Other investigator's on-site assessment: Maximal hemorrhaging/bleeding from hemangioma					
Stage 1 Maximal hemorrhaging/bleeding from hemangioma post- baseline					
n/missing	25 / 0	41 / 0	40 / 0	39 / 0	43 / 0
Grade 0	24 (96.0%)	41 (100.0%)	38 (95.0%)	38 (97.4%)	43 (100.0%)
Grade 1	1 (4.0%)	0 (0.0%)	2 (5.0%)	1 (2.6%)	0 (0.0%)
Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Grade 3+	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Stage 2 (with overrun) Maximal hemorrhaging/bleeding from hemangioma post- baseline					
n/missing	30 / 0	56 / 1	62 / 0	59 / 2	58 / 0
Grade 0	30 (100.0%)	55 (98.2%)	61 (98.4%)	59 (100.0%)	57 (98.3%)
Grade 1	0 (0.0%)	1 (1.8%)	1 (1.6%)	0 (0.0%)	1 (1.7%)
Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Grade 3+	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pooled (with overrun) Maximal hemorrhaging/bleeding from hemangioma post- baseline					
n/missing	55 / 0	97 / 1	102 / 0	98 / 2	101 / 0
Grade 0	54 (98.2%)	96 (99.0%)	99 (97.1%)	97 (99.0%)	100 (99.0%)
Grade 1	1 (1.8%)	1 (1.0%)	3 (2.9%)	1 (1.0%)	1 (1.0%)
Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Grade 3+	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: CSR Table 165

6.1.7 Analysis of Subpopulations

An adjusted analysis of the primary endpoint in sub-populations was conducted, using an extension of the combination test for logistic regression and adjusting for the stratification factors and randomization ratio (Table 30).

Table 30 Subpopulation analyses for the primary efficacy criterion – ITT data set

Primary efficacy endpoint: Complete or nearly complete resolution of target IH at week 24	Placebo N=55	Propranolol 3mg/kg/day 6mths N=101
Age 35 – 90 days		
n/missing	20 / 0	37 / 0
Yes	2 (10.0%)	25 (67.6%)
No	18 (90.0%)	12 (32.4%)
Age > 90 days		
n/missing	35 / 0	64 / 0
Yes	0 (0.0%	36 (56.3%)
No	35 (100%)	28 (43.8%)
Facial IH		
n/missing	40 / 0	71 / 0
Yes	2 (5.0%)	43 (60.6%)
No	38 (95.0%)	28 (39.4%)
Non Facial IH		
n/missing	15 / 0	30 / 0
Yes	0 (0.0%)	18 (60.0%)
No	10 (83.3%)	12 (40.0%)
Randomization ratio 1:1		
n/missing	12 / 0	13 / 0
Yes	2 (16.7%)	10 (76.9%)
No	38 (95.0%)	3 (13.1%)
Randomization ratio 2:1		
n/missing	43 / 0	88 / 0
Yes	0 (0.0%)	51 (58.0%)
No	43 (100%)	37 (42.0%)
Overall / combined		
n/missing	55 / 0	101 / 0
Yes	2 (3.6%)	61 (60.4%)
No	53 (96.4%)	40 (39.6%)
Logistic regression analysis	P<0.0001	

Source: ISE Table 34; CSR Table 20

The observed success rates were higher in the younger (35 – 90 days) age group compared to the older (>90 day) age group; however, the placebo-corrected effect was similar for the two age strata (57.6% for younger patients and 56.3% for older patients) with no evidence of any treatment-by-age interaction.

There is no evidence of any IH localization effect, the success rate being similar between the two localization groups.

The success rate was slightly higher with the initial randomization ratio (1:1) with 76.9% showing complete or nearly complete resolution at Week 24 than with the 2:1 ratio (58.0%). There is no explanation for this difference, which could be attributed to the small number of patients randomized with the 1:1 scheme (with only 12 and 13 patients in the placebo and propranolol HCl treatment groups).

Table 31 presents the results of the analysis of the primary efficacy endpoint on all treated patients of the 5 arms (including overrun). All active arms showed better success rate than the placebo arm, the two 6 months regimens superior to the 3 months regimens, and the 3 mg/kg/day regimens were superior to the 1 mg/kg/day regimens.

Table 31 Primary efficacy criterion – ITT data set with overrun

Primary endpoint: Complete or nearly complete resolution of target IH at Week 24	Placebo	Propranolol 1 mg/kg/day 3mths	Propranolol 1 mg/kg/day 6mths	Propranolol 3 mg/kg/day 3mths	Propranolol 3 mg/kg/day 6mths
N	**55**	**98**	**102**	**100**	**101**
Overall					
Primary Endpoint :	2 (3.6%)	8 (8.2%)	50 (49.0%)	12 (12.0%)	61 (60.4%)
No	53 (96.4%)	90 (91.8%)	52 (51.0%)	88 (88.0%)	40 (39.6%)
Age at baseline 35 - 90					
Primary Endpoint :	2 (10.0%)	2 (5.6%)	21 (55.3%)	3 (8.3%)	25 (67.6%)
No	18 (90.0%)	34 (94.4%)	17 (44.7%)	33 (91.7%)	12 (32.4%)
Age at baseline > 90 days					
Primary Endpoint :	0 (0.0%)	6 (9.7%)	29 (45.3%)	9 (14.1%)	36 (56.3%)
No	35	56 (90.3%)	35 (54.7%)	55 (85.9%)	28 (43.8%)
Facial IH					
Primary Endpoint :	2 (5.0%)	5 (7.0%)	34 (47.2%)	4 (6.3%)	43 (60.6%)
No	38 (95.0%)	66 (93.0%)	38 (52.8%)	60 (93.8%)	28 (39.4%)
Non-Facial IH					
Primary Endpoint :	0 (0.0%)	3 (11.1%)	16 (53.3%)	8 (22.2%)	18 (60.0%)
No	15	24 (88.9%)	14 (46.7%)	28 (77.8%)	12 (40.0%)

Source: CSR Table 21

No treatment by age stratum interaction was observed. In each of the two 6 months regimen, showing the highest response rates, the placebo corrected effect is similar for the two age strata.

There was no effect of IH by site (facial or non-facial) except in the 3 mg/kg/day 3 months arm where more successes were observed for the non facial IH: 22.2% vs. 6.3% for the facial IH.

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6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

In Table 32, both the 1 mg/kg/day 6 month and the 3 mg/kg/day 6 month regimens produced statistically significant resolution of IH. The success rates in the 1 mg/kg/day 6 months regimen and the 3 mg/kg/day 6 months were, respectively 37.5% and 62.8% in Stage 1, and 49.0% and 60.4% in the overall pooled analysis including data from the overrun patients. Thus, there appears to be a form of dose response (though not sought for in a prospectively-specified manner) for the 1 mg/kg/day 6 month and 3 mg/kg/day 6 month regimens in the Stage I and Overall (pooled) results (Table 11).

Table 32 Primary efficacy endpoint results for the treatment regimens in Stage 1 population (interim analysis) and Pooled with overrun population

	Placebo	Propranolol 1 mg/kg/day 3mths		Propranolol 1 mg/kg/day 6mths		Propranolol 3 mg/kg/day 3mths		Propranolol 3 mg/kg/day 6mths	
Stage I (interim analysis)									
			P-value		P-value		P-value		P-value
N	25	42		40		39		43	
Primary endpoint	2 (8.0%)	4 (9.8%)	0.4049	15 (37.5%)	0.0042	3 (7.7%)	0.5178	27 (62.8%)	<0.0001
Stage II (ITT without overrun) Analysis									
			P-value		P-value		P-value		P-value
N	30	56		62		61		58	
Primary endpoint	0 (0%)	4 (7.0%)	0.0687	35 (56.5%)	<0.0001	9 (14.8%)	0.0133	34 (58.6%)	<0.0001
Overall (Pooled ITT with overrun) Analysis									
			P-value		P-value		P-value		P-value
N	55	98		102		100		101	
Primary endpoint	2 (3.6%)	8 (8.2%)	0.138	50 (49.0%)	<0.001	12 (12.0%)	0.041	61 (60.4%)	<0.0001

However, in an exploratory analysis of the response rates during Stage II (again, not prospectively specified) in the children who received the 1 mg/kg/day x 6 months and 3 mg/kg/day x 6 months regimens, the response rates were nearly the same (56.5% and 58.6%, respectively, Table 32). From this finding, the 3 mg/kg/day x 6 months regimen did not appear to have produced a proportionately larger response rate compared to the 1 mg/kg/day x 6 months regimen in a consistent manner.

The sponsor attributed the difference in response rates between Stage I and Stage II for the propranolol 1 mg/kg/day 6 month regimen to random variations, because: (i) Jeffreys 95% CI of dose response rates for the two six-months regimens showed overlap between stages of the propranolol 1 mg/kg/day 6 month regimen (Figure 12), and (ii) test of the interaction of dose by stage for the two six-months regimens using a logistic regression model showed a p-value of 0.1065 suggesting that it is not possible to conclude to a difference between doses varying between the stages.

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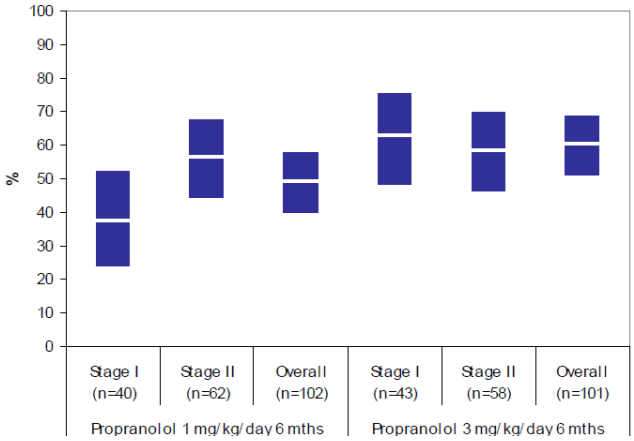
Figure 12 Primary efficacy endpoint results – Jeffreys 95% CI of response rates for 6 months regimens



The sponsor chose the 3 mg/kg/day 6 months regimen as their marketing dose based on the findings that patients treated with this dose:

(i) had a higher success (complete or near complete resolution) rate than the 1 mg/kg/d 6 months group at the time of the interim analysis and also at the overall primary efficacy analysis

(ii) showed a more rapid response than the 1 mg/kg/day 6 month regimen (87.1% of patients with improvement at Week 5 vs. 69.6%),

(iii) had a higher proportion of those with sustained improvement post-treatment at Week 5 (71.3% vs. 61.8%), and

(iv) did not appear to have any increased adverse events.

Reviewer's comments:

(1) From the above efficacy results (Table 32), I do not think that the 3 mg/kg/day x 6 months regimen produced a proportionately larger response rate compared to the 1 mg/kg/day x 6 months regimen in a consistent manner. I found that for a three-fold (one log) increase in dose, the benefit obtained is about:

- 11% more responders at 24 weeks,
- 17% more responders at 5 weeks, and
- 10% more patients obtaining a sustained improvement post treatment at week 5.

(2) In Figure 14, the 1 mg/kg/day x 6 months regimen and the 3 mg/kg/day x 6 months regimen displayed almost similar survival rates at the end of treatment (Week 24) compared to the placebo and 3 month regimens.

(3) In the Compassionate Use Program (CUP) in which 922 patients with high risk IH were treated (CUP Report #6, 12-Apr-2013), 313 patients had a documented treatment discontinuation, of which 262 (83.7%) patients achieved good efficacy

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(Table 33). In the CUP, the recommended dose was 2 mg/kg/day. 202 patients had at least one dose of propranolol 3 mg/kg/day, of which 79 discontinued treatment, with 68 (86.1%) for good efficacy. Although the photograph evaluations in the CUP were not standardized rigorously as in the pivotal Study 201, and the denominators may be biased from a statistical perspective, the findings in CUP suggest that it is not necessary to use a dose of 3 mg/kg/day to accrue a response rate of 60%.

(4) In the medical literature, the beneficial response rates range from 50% to 70% in infants treated with 2 mg/kg/day to 87% to 100% in infants treated with 3 mg/kg/day (Table 33).

Therefore, even patients with high risk IH or more severe IH achieved a response rate comparable to that observed in patients in the pivotal clinical trial when treated with propranolol at doses ***less than*** 3mg/kg/day (about 2 mg/kg/day). This finding supports that notion that it is not necessary to use the higher dose of 3mg/kg/day for 6 months to obtain the 60% response rate.

Table 33 Effect size (% patients who reached primary endpoint)

Study	1 mg/kg/day	2 mg/kg/day*	3 mg/kg/day
Clinical Study 201	49% (37.5% - 56.5%)	--	60.4% (58.6% - 62.8%)
CUP		83.7%	86.1%
Studies in medical literature†		50% - 75%	87% - 100%

*2 mg Propranolol HCl contains 1.75 mg Propranolol base; †primary endpoints are variable

It is not known whether a dose ***higher*** than 3 mg/kg/day for 6 months would provide greater efficacy because the sponsor did not test higher doses than 3 mg/kg/day.

Reviewer's comments regarding the duration of treatment, in Study 201, about 10% of patients in the 3 mg/kg/day 6 months regimen required the re-introduction of a systemic treatment. In the CUP, too, the mean dose of propranolol after titration in these patients with high risk IH was 1.9 (SD ±0.7) mg/kg/day for 7.4 (SD ±3.1) months, i.e., longer than 6 months in a large number of patients. In the case reports in scientific publications, although exact percentages were not always presented, approximately 5% to 25% of patients showed signs of IH regrowth after discontinuing treatment, but **less than 10%** of patients required re-introduction of therapy. A recent publication[38], in which a retrospective cohort of IH patients was consecutively treated in one center (by propranolol 1, 2 or 3 mg/kg/day), also showed that 40 of 158 infants treated with propranolol (25.3%) showed IH regrowth, of which 19/158 (12%) patients had major regrowth requiring reintroduction of propranolol. Overall, the results in Study 201, the CUP and the medical literature suggest that about 10% of patients require re-introduction of treatment after discontinuing propranolol treatment. It is likely that these patients could have required longer duration of treatment because the proliferative phase of IH may persist for about one year (Figure 1) suggesting that one year (not just 6 months) of continuous treatment may be necessary.

Sponsor's argument: The sponsor explained that the 6-month treatment duration was chosen based on the limited clinical experience and published information available at the time of writing the protocol in 2009, although both longer and shorter treatment durations had also been reported.[22] The sponsor agreed that the proliferative phase of IH offers an important therapeutic window to halt progression of the IH and to induce early involution. In a prospective cohort of 526 IH cases in 433 patients,[17] most IH growth occurred before 5 months (i.e. 150 days) and it is generally accepted that proliferation can last up to one year of age. In Study 201, the upper age limit at inclusion (5 months) and the maximum duration of treatment (6 months) aimed at ensuring exposure to treatment during (but no later than) the proliferative phase, when efficacy is most likely to occur.

The sponsor also alluded to the fact that the design of Study 201, including treatment duration and timing of the primary efficacy assessment was discussed with the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) and was specified and agreed in the Special Protocol Assessment (SPA) and Pediatric Investigation Plan (PIP) (for the US and the EU respectively). The dose and duration pre-specified in the SPA produced good overall treatment success rates in the final efficacy analysis (60.4% versus 3.6% with placebo), with a relatively low rate (11%) of patients needing re-treatment during the post-W24 off-treatment follow-up period. Thus, the sponsor submitted that the efficacy results from study 201 support the efficacy of the 6-month treatment duration.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

At Week 5, for the ITT with overrun data set, the percentages of patients with an improvement in IH (Type 2 assessment) were 87.1% and 69.6% in the 3 mg/kg/day and 1 mg/kg/day 6 months regimens, respectively; 82.0% and 65.3% in the 3 mg/kg/day and 1 mg/kg/day 3 months regimens, respectively; and 3.6% in the placebo 6 months regimen (Figure 13).

From Week 5 onwards, the percentages of patients with *sustained* improvement were 71.3% and 61.8% in the 3 mg/kg/day and 1 mg/kg/day 6 months regimens, respectively; 34.0% and 32.7% in the 3 mg/kg/day and 1 mg/kg/day 3 months regimens, respectively; and 3.6% in the placebo 6 months regimen. The reasons for lack of sustained improvement from Week 5 for the 3-month regimens were largely a worsening Type 2 assessment or premature discontinuation of treatment. These results for sustained improvement supported the conclusion that the treatment of IH with propranolol for 3 months (followed by 3 months placebo) was not sufficient to maintain the positive effect of treatment after its cessation.

The results indicated also that for patients treated with propranolol for 6 months, there is little evidence of tachyphylaxis, as the majority of those with improvement at Week 5 displayed sustained improvement from Week 5 onwards.

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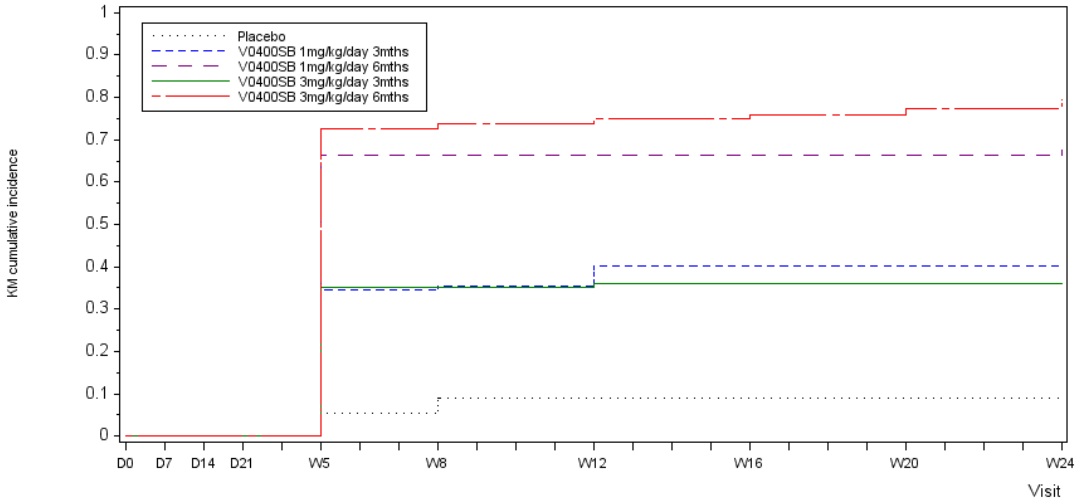
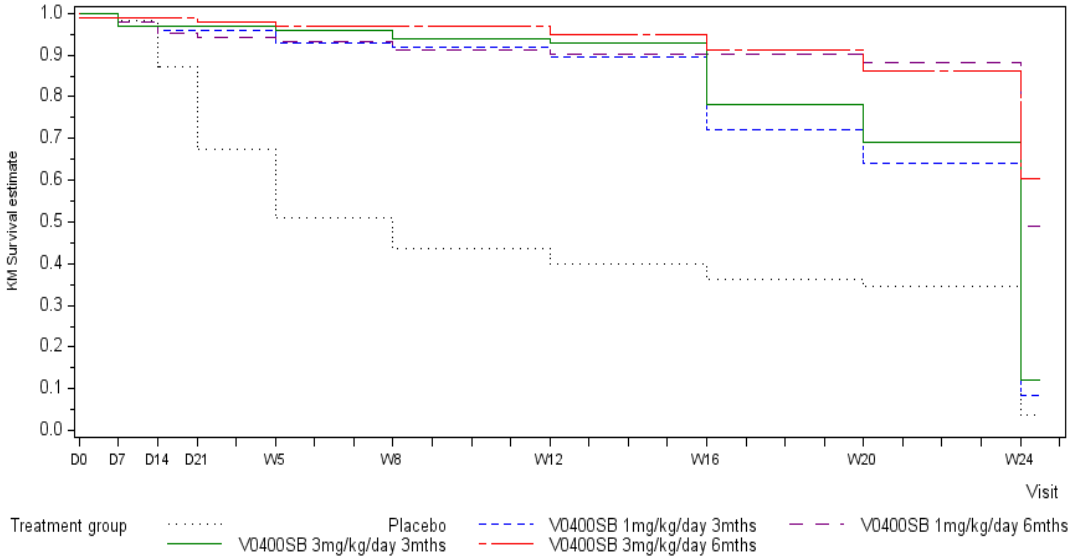
Figure 13 Cumulative incidence curves for the first sustained improvement (ITT with overrun)



Source: ISE Figure 17. No assessment of improvement was performed before Week 5

Figure 14 Survival curves for time to treatment failure (ITT with overrun)



Source: CSR 201 – additional information.

The primary efficacy results were confirmed by the short time to treatment failure (Figure 14) in the placebo 6 months regimen (treatment failure in approximately 50% of patients by Week 5) and the rapid increase in treatment failures in the 3-month regimens from Week 12 onwards (after switching to placebo for 3 months at Week 12), compared with the low rate of treatment failures in the 6-month regimens up to Week

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24, with the 3 mg/kg/day regimen displaying the highest survival rate at the end of treatment (60.4%).

Treatment failure was defined as follows:

- Withdrawn prematurely for lack of efficacy or any other reasons; the time of withdrawal was used as time to failure.
- Having received prohibited treatments that may have been used to treat IH; the first time of intake of prohibited treatment was used as time to failure.
- Considered as not complete/nearly complete resolution on Type 1 centralized qualitative assessments at Week 24; the time of photograph acquisition was used as time to failure.

Reviewer's comments: Additional data for the sustainability of the initial treatment effect after discontinuation of treatment showed consistent results between Study 201, the compassionate use program (CUP) and the medical literature. I have compiled the number of patients who experienced regrowth of IH requiring re-treatment with propranolol in Table 34.

Table 34 Regrowth and retreatment with propranolol for IH

Study	Number treated/ Number responded	Number (%) regrowth	Number (%) retreated
Study 201 (3 mg/kg/d arm)	101 / 61	3*	6 (10%)
CUP (2-3 mg/kg/d)	209 / 126	NA	4 (3%)
Ahogo et al[38] (1 – 3 mg/kg/day, 117 pts got 2 mg/kg/d)	158 / 158	40 (25%)	19 (12%)
Meta-analysis 35 studies[54]	1,282	174 (14%)	102 (8%)
13 publications (2 – 3 mg/kg/d)	573	70 (12%)	35 (6%)

*3 patients had IH regrowth after W24, of which 2 received off-label timolol ophthalmic drops on the IH; NA = not available

In Study 201 (patients treated with propranolol 3 mg/kg/day for 6 months), some changes (*e.g.* re-coloration of the hemangioma) were observed that lead to the loss of complete/nearly complete response status: about 10% of patients of the 3 mg/kg/day 6 months regimen required the re-introduction of a systemic treatment (Table 34).

In the CUP, among the 209 patients included at the 2 sites with the highest recruitment (Bordeaux, Hôpital Pellegrin, and Paris Hôpital Necker Enfants Malades, data updated to 31-Dec-2012), 138 discontinued from treatment. The reason for discontinuation was documented in 137 patients: 126 (92%) discontinued due to efficacy. In this population of 126 patients who were discontinued for efficacy, 4 (3%) of patients required reintroduction of systemic propranolol treatment (Table 34); this second course of oral propranolol was stopped for efficiency for 3 patients, and is still on-going for one patient.

In a meta-analysis of 35 publications, 174 patients (14% of the 1,282 patients treated with propranolol) experienced regrowth of IH (Table 34). Of these 174 patients who

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experienced regrowth, 102 required re-treatment (58% of those experiencing regrowth and 8% of the 1,282 patients overall). The regrowth rate reported in the medical literature ranged from 12% to 14%, and the proportion of patients who required retreatment with propranolol ranged from 6% to 8% (Table 34). When re-treatment was required, 61/62 patients (98%) showed a good response, with no further recurrence.

Table 35 IH Regrowth after end of propranolol treatment in key publications

Publication, Year	No. treated with propranolol	Average (range) age at initiation	IH type	Average dose of propranolol	Average (range) duration of treatment	No. experiencing regrowth/No. of responders (%)†	Positive response after reintroduction of propranolol
[35]**Bernabeu-Wittel,** 2011	28	<12 m: 3.86 m >12 m: 20.1 m	Various	2 mg/kg/day	8.7 m (2 – 16 m)	5/28 (13%) after complete cessation	No requirement for re-treatment
[36]**Bertrand,** 2012	35	3.5 m (1 m – 10 yr)	Various	2.6 mg/kg/day	8.9 m (1 – 13 m)	5/35 (14%) after stopping propranolol	NS
[51]**Buckmiller,** 2010	32	7.1 m (1.5 – 30 m)	Various	Planned: 2 mg/kg/day	NS	1	NS
[40]**Haider,** 2010	17	3 weeks – 12 m	Peri-ocular	Planned: 2 mg/kg/day	Until CR/ regression or 9-11 m old	0 (after initial cessation)	NA
[46]**Hermans,** 2011	20	3.5 m	Ulcerated	Planned: 2 – 2.5 mg/kg/day	9.1 m	4/19 (21%)	Re-treat for 1 patient; response NS
[37]**Holmes,** 2011	31	3.9 m (1.2 – 9.7 m)	Various	Planned: 3 mg/kg/day	12.5 wk (1 – 58 wk)	6	6/6
[48]**Leboulanger,** 2010	14	5.2 m (0.7-16 m)	Airway	2.5 mg/kg/day	6 m	2/14 (14%)	1/2
[39]**Phillips,** 2012	188	4 m (5 days-7 yr)	Various	2 mg/kg/day	8 m (10 days-30	30/136 (22%)	NS/17
[47]**Price,** 2011	68	4.9 m	Various	Planned: 2 mg/kg/day	7.9 m (3.5-14 m)	2	2/2
[49]**Saint-Jean,** 2011	33	NS	Ulcerated	2 mg/kg/day	5.9 m	4	4/4
[22]**Sans,** 2009	32	Early interventions 4.2 m Late interventions: 31 m	Various	Planned: 2-3 mg/kg/day	6.1 m	7	NS/2
[44]**Schiestl,** 2011	25	3.6 m (1.5-9.1 m)	Various	Planned: 2 mg/kg/day	10.5 m (7.5-16 m)	2	2/2
[41]**Talaat**, 2012	50	Early tx: 5.3 m (1-12 m) Late tx: 15.8 m (13-33 m)	Various	Planned: 2 mg/kg/day	6.5 m (5 - 8 m)	2	NS
TOTAL	**573**					**70**	**35-reintroduced; 15/16 positive response**

Source: ISE Table 41. CR: complete response; IH: infantile hemangioma; NA: not applicable; NS: not specified. m: month; wk: week; yr: year
†Number of responders and % is only for publications where the total number of responders who completed treatment could be determined.

Table 35 shows the post-treatment evaluation of IH which was measured in 13 articles on 573 patients treated with propranolol. The cases of regrowth were largely observational, but the analysis of post-treatment persistence of efficacy was pre-planned in 4 publications[41,43,47,37]. Seventy (12%) of 573 patients treated with propranolol in these 13 studies experienced IH regrowth. Where an exact percentage of patients experiencing regrowth was reported, this ranged from 13% to 22%. The average propranolol dose varied from 2 to 3 mg/kg/day, and average duration of treatment ranged from 12.5 weeks to 12 months. It was not always specified whether propranolol was reintroduced or whether re-introduction was successful. However, in the publications with such details available, 35 patients received re-treatment (50% of those experiencing regrowth and 6% of the 573 patients overall, which I have complied in Table 34).

Overall, the results observed in the Study 201, and observed also in the CUP and the medical literature, suggest that up to about 10% of patients require re-introduction of treatment after discontinuing propranolol treatment.

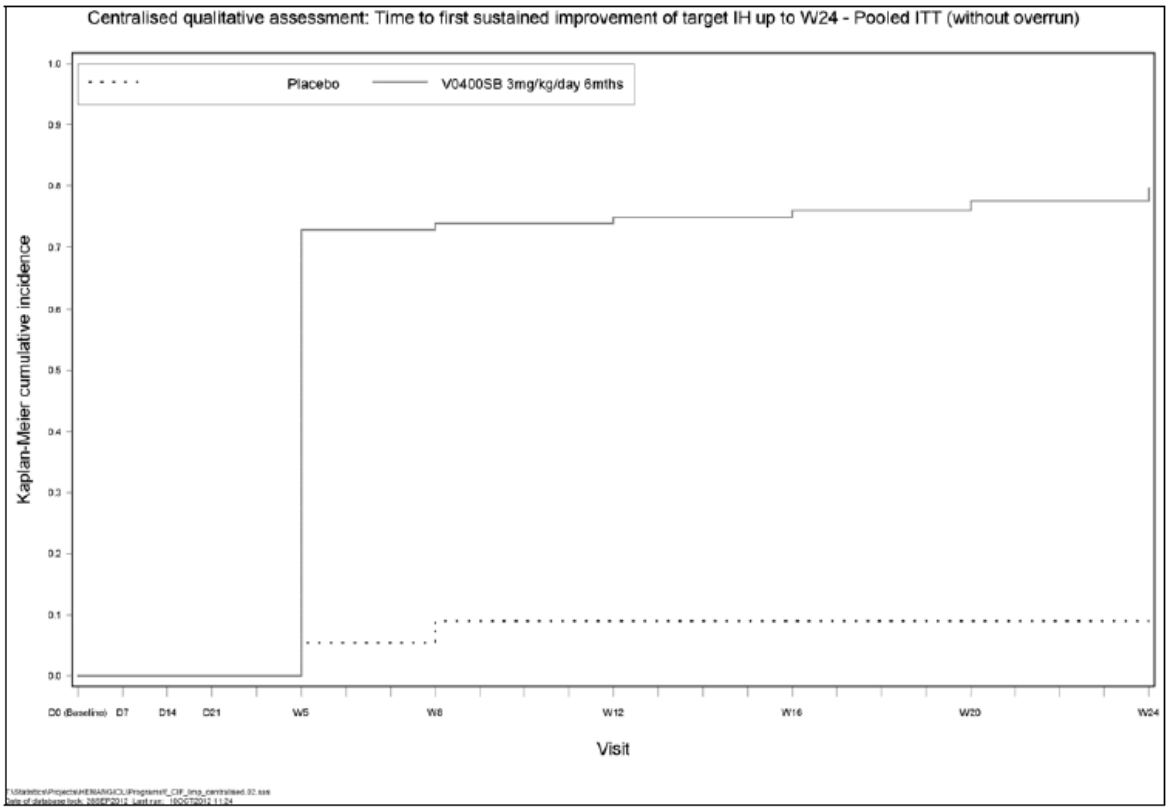
A recent publication[38], in which a retrospective cohort of IH patients was consecutively treated in one center (by propranolol 1, 2 or 3 mg/kg/day), showed the overall response of patients treated with propranolol and the persistence of effect after treatment interruption: of 158 infants treated (all responders, at least partially), 118 did not show signs of IH regrowth and 40 (25.3%) patients showed IH regrowth. Most regrowth was limited to re-coloration of the IH; of these, 19/158 patients had major regrowth requiring reintroduction of propranolol (12%) (Table 34).The analysis identified two independent factors associated with regrowth: segmental distribution (10-fold risk) and the presence of a deep component. Neither dose of propranolol nor age at initiation of treatment affected the risk of IH regrowth.

This regrowth and retreatment rate observed with propranolol (about 10%) is much less than a 36% regrowth rate observed with corticosteroid treatment.[26]

6.1.10 Additional Efficacy Issues/Analyses

Time to first sustained improvement: Figure 15 presents the Kaplan Meier analysis of time to first sustained improvement. In the 3 mg/kg/day 6 months arm sustained improvement was observed early, as soon as W5 in 72.7% of patients, and continued to increase slightly, up to 79.5% at W24. In the placebo arm, sustained improvement was rare (5.4%; 2 patients) at W5 and 9.0% (1 additional patient at W8) from W8 to W24.

Figure 15 Time to first sustained improvement – ITT data set



Source: CSR for Study 201, Figure 12.

Key publications: In Table 36, I have abstracted the information from key publications (15 studies and 3 meta-analyses) which are selected based on their robust study designs and analysis of quantitative data for the treatment of patients with IH requiring systemic therapy.

Findings in 15 key studies: There are some limitations associated with these studies, including their largely retrospective non-controlled designs, small sample sizes (12-71 patients, one exception being 188 patients studied at Royal Children's Hospital in Melbourne, Australia)[39], with the majority studying less than 35 patients, and the lack of standardization of the primary efficacy assessment (improvement/resolution of IH). The planned dose of propranolol varied from 2 to 3 mg/kg/day, and two individual patients received a maximum dose of 4 mg/kg/day. Planned duration of treatment, when provided, ranged from 3 months to an unspecified time when the patient was over 12 months of age, or until satisfactory resolution of the IH. All of these studies included some patients with high risk IH. Twelve studies either did not specify the IH phase included, or actively included patients with IH beyond the proliferative phase. Inclusion age, where specified, varied between 3 weeks and 5 years. Despite these limitations, review of the 15 publications and 3 meta-analyses provide some information about the efficacy of off-label propranolol treatment in patients with high risk IH.

Table 36 Findings in key publications of propranolol treatment of infants with IH

Study	Disease	Number treated	Propranolol Dose (mg/kg/d)	Response Reported
[45] Hogeling M, Adams S, Wargon O. *Pediatr* 2011; 128: 259-270	**Facial** IH **(Australia)**	40 (Propranolol =20 vs. placebo =20)	**2 mg** x 6 m	-60% in vol of IH at W24 in Propranolol group (vs -14% in placebo group); P=0.01
[39] Phillips RJ, Penington A, Bekhor P et al. *J Pediatr Chld Hlth* 2012; 48:902-6	**Facial** IH **(Australia);** outpatient study	188 infants (80% IH on face)	**2 mg** x duration not specified	50% excellent response 76% - 100% regression), 30% good response (51% - 75% regression), 20% poor response (26% to 50% regression) at 4 month
[42] Bertrand J, McCuaig C, Dubois J et al. *Pediatr Dermatol* 2011; 28: 649-54	**Facial** IH **(Canada)**	24 (12 Propranolol vs. 12 Prednisone)	Mean: **2.7 mg** x 10.6 m	Visual Analog Scale 78.33 Propranolol vs 44.82 Prednisone; P<0.001
[41] Talaat AA, Elbasiouny MS, Elgendy DS et al. *J Pediatr Surg* 2012;47:707-14.	IH **(Egypt)**	50 infants (44 early and 6 late treatment-for non-involuting IH)	**2 mg** x ≥12 Wk	75% patients had excellent regression, 19% had good and 6% had fair regression of IH
[50] Bagazgoitia L, Torrelo A, Gutierrez JCL et al. *Pediatr Dermatol* 2011;28: 108-114.	Eyelid, **airway** (5), large or **ulcerated** IH (8) **(Spain, Argentina)**	71 infants	**2 mg** x ≥12 Wk	Reduction in severity scores by 60% at Wk 20 (reduction in size by 60%, P<0.01)
[49] Saint-Jean M, Leaute-Labreze C, Mazereeuw-Hautier J, et al. *J Am Acad Dermatol* 2011; 64: 827-32.	Ulcerated IH **(France)**	33 infants (retrospective, uncontrolled study)	**2 to 3 mg** (Mean = **2 mg** x 5.9 m)	Mean time to complete ulcer healing = 5.7 Wk, mean time to complete pain control = 14.5 days.
[48] Leboulanger N, Fayoux P, Teissier N et al. *Int J Pedia Otorhinol* 2010;74:1254-7.	Infantile **laryngo-tracheal (subglottis)** hemangioma **(France)**	14 infants	Mean: **2.5 mg** (4 pt = stopped after 5.2 m)	Stenosis (mean 68%) was reduced to 22% in 2 Wk, and 12% in 4 wks. (? Need to treat up to 18 months)
[43] Snir M, Reich U, Seigel R et al. *Eye* 2011; 25: 1627-34.	Infants with infantile **periocular** capillary hemangioma **(Israel)**	30 infants	**2 mg** x 6 m (reduced to 1 mg in 3 infants)	Sig. (P<0.0001) mean reduction in involved extraocular area, and sig. reduction in cylindrical power in involved eyes (P<0.02)
[44] Schiestl C, Neuhaus K, Zoller S, et al. *Eur J Pediatr* 2011; 170: 493-501.	Complicated IH **(Switzerland)**	25 (infraorbital, ear, nose, eyelid, parotid, lip, head, perianal, genital, and ulcers)	**2 mg** x median 10.5 m (range 7.5 to16 m)	All except 2 responded; 2 patients required re-treatment with propranolol. All 5 ulcers healed within 2 wk, visual obstruction improved in weeks to 2 mo.
[46] Hermans JJ, van Beynum IM, van der Vijver RJ et al. *J Pediatr Hematol Oncol* 2011; 33:e171-3. (case report)	Kasabach-Merritt syndr (Kaposiform hemangio-endothelioma with consumptive coagulopathy	**(The Netherlands)** One 6 wk old boy with abdominal wall vascular abnormality	**2 mg** x (from age Wk 6 to 15 mo). Vincristine in first 4 wks	Lesion has disappeared after 4 weeks (dual propranolol and vincristine). No growth or hematologic abnormalities at 17 months
[47] Price CJ, Lattouf C, Baum B, et al. *Arch Dermatol* 2011; 147: 1371-6. (Multicenter retrospective chart rev)	IH **(Florida, US)**	110 patients (68 treated with propranolol and 42 with corticosteroids)	Corticosteroids 4 mg/kg/d x5.2m, Propranolol **2mg** x 7.9 m	89% of patients on corticosteroid vs. 81% of patients on propranolol achieved lesion clearance of ≥75%. (Not sig.) 12% patients treated with propranolol required surgery vs 29% of patients treated with corticosteroids.
[51] Buckmiller LA, Munson PS, Dyamenahalli U, et al. *Laryngoscope* 2010; 120: 676-681	Problematic (face, ear, parotid, orbit, airway) IH **(Arkansas, US)**	41 children enrolled, 32 had data and photos	**2 mg** x till child reaches age of 12 m	97% patients showed improvement in IH (excellent responders = 50%, partial = 47%, nonresponders = 3%)
[38] Ahogo CK, Ezzedine K, Prey S et al. *Brit J Dermatol* 2013; 1-29 (In Press)	Relapsed IH **(France)** – retrospective observational study	158 children (40 who relapsed, 118 who had not relapsed)	**1 to 3 mg** (Dr. Leaute-Labreze's center)	Only deep IH with a subcutaneous component and IHs with segmental distribution were associated with relapse.
[37] Holmes WJM, Mishra A, Gorst C et al. *J Plast Reconstr Aesthet Surg* 2011; 64: 445-51.	Problematic IH {with rapid growth (51%), ulcer (26%), functional impaired (23%)}	31 patients **(UK)**	**3 mg**	Rapid halt of IH progression in 100%, sig. regression in 87%
[40] Haider KM, Plager DA, Neely DE et al. *J Am Assoc Ped Ophthalmo Strabismus* 2010; 14: 251-6.	Vision-threatening IH **(Indiana, US)**	17 children	**2 mg** (outpatient treatment) till full regression	10 excellent response (>50% reduction in size), 6 good response (<50 reduction), 1 fair response (no more growth) at 4 month
		META-ANALYSES		
[52] Peridis S, Pilgrim G, Athanasopoulos I et al. *Int J Pediatr Otorhinolaryngol* 2011; 75:455-460 .	Infants with **airway hemangiomas**	Of 37 studies, 13 reports selected (36 patients) and presented in article	Mean**: 2 mg** x 6 m	Resolution of infantile airway hemangiomas In a meta-analysis of 13 studies.
[53] Izadpanah A, Izadpanah A, Kanevsky J et al, *Plas Reconstr Surg* 2012;1-36 – pre-publication.	16 studies of 2,629 corticosteroid-treated IH patients vs. 25 studies of 795 propranolol-treated IH patients	2,629 corticosteroid-treated patients and 795 propranolol-treated patients	Corticosteroids 2-3 mg/kg/d x 4-8 Wk, Propranolol **2mg** x 4Wk to 12 m	16 corticosteroid studies have pooled response rate of 69% vs. 25 propranolol studies' response rate of 97% (P<0.001).
[54] Marqueling AL, Oza V, Frieden IJ, et al. *Pediatr Dermatol* 2013; 1-10 (in press)	IH (**Periorbital** 115; **face** 24; **head & neck** 74; **airway** 14; **parotid** 9)	41 studies of 1,264 patients	Mean: **2 mg** x 6.6 m	Response rate: 98% (range 82% - 100%)

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Overall, the efficacy of oral propranolol presented in each publication is positive and independent of IH localization. When the percentage of patients with improvement in IH was measured, the majority showed a positive response with 49% to 75% of patients in each study falling within the best response category (49% with excellent response in Australia[39], and 75% excellent response in Cairo, Egypt[41]). A study in Montreal, Canada, showed 100% of patients with a response in the top two categories (good/excellent) at 6 months[42]. A similar pattern was seen for studies that presented average response data, measured as change in IH presentation through a variety of scales ranging from an improvement of 52% (diseased area improvement in 30 children at Schneider Children's Medical Center of Israel in Petah Tiqwa, Israel[43]) to 90% (color visual analogue scale score in 25 children at University Children of Zurich in Zurich, Switzerland[44]). When average IH response was presented for several time points during treatment, IH improvement increased over time (with a maximum overall improvement up to Month 5 to Month 8).

In a randomized placebo-controlled study investigating oral propranolol for the treatment of IH in Sydney, Australia[45], patients received propranolol 2 mg/kg/day (n=19) or placebo (n=20) for 6 months. All propranolol-treated patients experienced an abrupt stop in growth of the IH within 4 weeks with a significant difference to placebo at all time points, the largest difference being at week 12, -48.5% for propranolol and 17.9% for placebo (p = 0.03); at week 24 the percent change in IH volume was -60.0% for propranolol and -14.1% for placebo (p = 0.01).

In three studies comparing oral propranolol to corticosteroids[42,46,47], propranolol therapy was found to be superior.

A study in Canadian children[42] showed that the clinical improvement rating (on a 0-4 scale) in the propranolol-treated patients was superior to the prednisone-treated patients after 1, 2, and 6 months of continuous treatment (2.2 *vs.* 1.1, p =0.007; 2.3 *vs*. 1.3, p = 0.002; and 3.7 *vs*. 1.8, p <0.001, respectively), with corresponding visual observations in matched serial photographs. The mean visual analogue scale response to treatment score after 6 months of treatment was 78.73 for propranolol-treated patients compared to 44.82 for prednisone-treated patients (p <0.001).

Airway IH studied in France[48] showed a significant improvement from a mean baseline obstruction of 62.5% to 22% after 2 weeks and 12% after 4 weeks of treatment.

Time to complete healing of ulceration, studied specifically in a case report in the Netherlands[46] and in 39 infants in France[49] was 8.7 and 5.7 weeks, respectively.

Propranolol was considered ineffective in 4 patients presented in 3 of the 18 key publications: one unspecified case each in (i) Spain[50] and in (ii) Little Rock, Arkansas[51], (iii) a case of eyebrow IH, and (iv) a case of large focal IH with ulceration in Sydney, Australia[45]. Regrowth of IH after treatment cessation was reported in some publications.

<u>Findings in 3 meta-analyses:</u> Three meta-analyses reviewing the literature for treatment of IH requiring systemic therapy with oral propranolol are summarized in Table 36.

The first meta-analysis of 13 studies published between 2009 and 2010 in a total of 36 patients with airway IH[52] showed that propranolol was an effective treatment for the resolution of airway IH (p <0.00001, odds ratio 0.03, confidence interval 0.01-0.12). Compared with other treatments (steroids, CO_2 laser, and vincristine), propranolol was significantly more effective in all comparisons. After 1 week of propranolol treatment, the mean degree of airway stenosis was reduced from 77.6% % at baseline (range, 55-95%) to 38.3% (range, 25–50%), and after 4 weeks it was reduced to 24.6% (range, 9.17–50%). Clinical improvement in signs and symptoms of patients treated with propranolol was observed within a range of 24 hours to 3 weeks (mean 3.8 days).

The second meta-analysis of 41 studies published between 1965 and 2012 in 3,424 patients (comprising 16 studies in 2,629 patients treated with corticosteroids and 25 studies in 795 patients treated with propranolol)[53] showed that the most common corticosteroid dose was 2-3 mg/kg/day for 4-8 weeks, and the most common propranolol dose was 2 mg/kg/day for a duration of 4 weeks to 12 months. Overall, there was a significant difference (p <0.001) in the pooled response rate between patients treated with propranolol (97%) and those treated with corticosteroids (69%).

In the third meta-analysis of 41 studies published between Jun 2008 and Jun 2012 in 1,264 patients with IH[54], the mean age at initiation of treatment was 6.6 months (3 days to 10 years), at a mean dose of 2.1 mg/kg/day (range 1-4 mg/kg/day) for a mean treatment duration of 6.4 months (one week to 15 months). Primary indications for treatment were risk of disfigurement, functional impairment, and ulceration. Other specified indications were rapid growth, potentially life-threatening complications, segmental distribution, psychosocial stress, failure of systemic corticosteroids, and avoidance of aggressive and potentially scarring procedures. The response rate (any improvement with propranolol) was 98% (range 82%–100%).

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EFFICACY CONCLUSION

Statistically significant clinical efficacy of propranolol in the treatment of proliferating IH requiring systemic therapy was demonstrated in the pivotal Study 201:

- propranolol 3 mg/kg/day 6 months was the best regimen selected at interim analysis in Study 201, which was confirmed by the full primary analysis. For this regimen, compared to the placebo 6 months regimen:
  - There was a statistically significant difference in complete/nearly complete resolution rates at Week 24 (60.4% *vs*. 3.6%; p <0.0001). The results were supported by an analysis on all patients treated.
  - Improvement occurred early, the majority by Week 5 (88.0%) and was sustained in most patients (72.7%).
- There was a sustained effect of treatment after cessation of treatment in the propranolol 3 mg/kg/day 6 month regimen. Only 6 (10%) of 61 infants who initially responded required retreatment with propranolol for regrowth of IH.

In the CUP, too, 60.3% (126 of 209) patients with high risk IH obtained good efficacy. Only 3% of patients who discontinued due to good efficacy required retreatment for regrowth of IH.

In 15 key publications and 3 meta-analyses in the medical literature reporting the effect of oral propranolol in children with IH, the beneficial response rate ranged from 50% to 100%; the regrowth rate ranged from 12% to 14%, and the patients who required retreatment with propranolol ranged from 6% to 8%.

The pivotal study results were supported by those for the pharmacokinetic Study 102.

The results observed in Study 201, in the CUP and the medical literature suggest that up to about 10% of patients require re-introduction of treatment after discontinuing propranolol treatment for resolution of IH.

With respect to IH complications reported during the course of Study 201:

- IH functional impairments were reported in 3 placebo patients who all prematurely withdrew for treatment inefficacy; no IH functional impairments were reported in the propranolol regimen.
- IH ulcerations were reported in 2 placebo-treated infants both of whom prematurely withdrew for treatment inefficacy, and in 6 propranolol-treated infants of whom 2 prematurely withdrew for treatment inefficacy and 4 recovered on study treatment.

On the basis of the above findings in the NDA, oral propranolol at the 3 mg/kg/day dose for 6 months can be considered an effective treatment in infants with IH requiring systemic therapy.

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7 Review of Safety

Safety Summary

The safety analysis comprises data from more than 2,451 patients treated with propranolol in the clinical trials (424 patients), CUP (660 patients) and literature review of scientific publications (1,367 patients with IH treated with propranolol).

In the clinical trials, the demographics for the pooled safety population were generally similar across treatment regimens, with 26.2% of patients born prematurely. The mean duration of exposure for the pooled safety population was shorter for the placebo regimen (82.6 days) compared to the propranolol regimens (156.9 days to 161.0 days), reflecting the high rate of discontinuation on placebo due to lack of efficacy. In the CUP, the mean exposure was 246.1 days (8.1 months), and in the scientific publications, the majority of patients were treated up to 30 months.

No death was reported in the pooled safety population. One death was reported in the CUP (associated with AV block followed by cardiac arrest after lauromacrogol injection to sclerose esophageal varices) and one death in the scientific publication (infant had PHACE syndrome with extensive IH of face, chest, back, neck, arm, hand, airway and the gastrointestinal tract, and died from worsening of peripheral arteriopathy). The deaths do not appear attributable to propranolol.

Thirty-six SAEs were reported in 26 patients in the pooled safety population, with roughly comparable incidences in each treatment regimen. The most common SAEs were: condition aggravated, drug ineffective, and bronchiolitis (each reported in 3 patients), and bronchitis (2 patients). All other TE SAEs were reported in a single patient each. In general, the SAEs reported in the pooled safety population corresponded to the known safety profile of propranolol. In the CUP, there were 3 SAEs (poor weight gain and decreased appetite, purpura and fall and loss of consciousness); all resolved and were continued on propranolol treatment. In the scientific publications, the analysis of safety in terms of SAEs is limited by the lack of information on vital status, hospitalization or prolongation of hospitalization, and permanent sequelae.

In the pooled safety population, 26 TEAEs leading to permanent discontinuation of the study drug were reported for 22 patients, with slightly higher incidence in the pooled placebo group (4.7%) than in the pooled propranolol groups (2.0% - 3.1%).

TEAEs were experienced by 65.3% of patients in the pooled placebo group and 86.8% of patients in the pooled all propranolol group, with no difference between the propranolol dose groups. The most common TEAEs were diarrhea, peripheral coldness, sleep disorder, and nightmare, all of which are known AEs of propranolol. In the CUP, 46 cases (19 serious) including 81 ADRs (36 serious) were reported. The most frequent ADRs were bronchiolitis (11 ADRs, 5 serious), sleep disorder (5 ADRs, 0 serious), and diarrhea, bronchitis, and agitation (3 ADRs each, 0 serious). Most of the scientific publications had incomplete individual safety data on propranolol use for IH treatment.

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Information on 132 ADRs (0 serious) involving 114/623 treated patients was documented in 39 publications. The most frequent ADRs were sleep disorder (20 events), hypotension (18 events; 4 symptomatic, 14 asymptomatic), diarrhea (13 events), and cold extremities (8 events); the majority resolved.

The submission specific safety risks associated with propranolol (hypoglycemia, bradycardia, hypotension, and bronchospasm) were monitored during uptitration and throughout the clinical studies (102 and 201), and in the CUP.

Bronchospasm was reported in four patients in the pooled safety population (2 on placebo and 2 on propranolol), 9 patients in the CUP (as bronchiolitis, presumed associated with a viral respiratory infection in 7 patients) and 10 patients in the scientific publications. None required hospitalization, all resolved and were able to re-administer propranolol in most. Bronchospasm is a known AE associated with propranolol.

There were no instances of clinically significant hypoglycemia in the pooled safety population; blood glucose level monitoring did not reveal differences from pre-dose levels to the +2h and +4 h periods, and between the treatment groups. In the CUP, there were 2 cases of asymptomatic hypoglycemia and 2 cases of presumed hypoglycemic seizures (blood glucose levels were not measured to confirm that the seizures were attributable to hypoglycemia). In the scientific publications, 11 events of hypoglycemia were reported (10 symptomatic, of which 7 had an additional stressor such as an acute infection, prolonged fasting or oral corticosteroids, 2 were beyond the age group indicated (11 months and 18 months old) and the last child had a positive nasopharyngeal swab for respiratory syncytial virus and symptoms of cough 1 day prior). There is no new safety signal for hypoglycemia with propranolol treatment; all of these patients resumed propranolol treatment without recurrence of hypoglycemia. I think hypoglycemia can be prevented with proper education of parents and care givers on the importance of administering propranolol during or right after a feeding.

Blood pressure (BP) was monitored as an indicator of hypotension in the clinical studies. There were no large falls in systolic or diastolic BP in the 1, 2, 3 and 4 hour periods following drug administration during the uptitration period. There were 6 TEAEs of hypotension (3 patients during the uptitration period and 3 patients after uptitration). All were asymptomatic, were not serious or severe in intensity, and did not lead to temporary or permanent drug discontinuation, or dose modification for any patient. In the CUP, 2 serious adverse reactions of hypotension were reported associated with too fast an increase in up titration; both continued on propranolol. In the scientific publications 4 events of hypotension were reported of which one was symptomatic (drowsiness, cold extremities); however, the BP values were not reported, and the symptoms resolved after treatment discontinuation.

Heart rate was monitored as an indicator of bradycardia. One patient in the pooled safety population had a SAE of bradycardia (while having an event of enterocolitis) during uptitration and 1 patient had a TEAE of bradycardia after uptitration. In the CUP, 3 SAEs of bradycardia (one case with cardiac sinus pause, another with hypotonia and malaise, and the third associated with hypoglycemia) were reported. In the Scientific

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Publications, 9 events of bradycardia were reported; none was symptomatic, all were transient and resolved after dose decrease or temporary discontinuation.

In ECGs of infants in the pooled safety population, the PR interval increased from the pre-dose values at +2h and +4h on each day of dose increase, with a greater increase observed with propranolol than with placebo (maximum increase: 11.42 ms on propranolol at 1 mg/kg/day). After the uptitration period, increases from baseline in PR interval were greater with propranolol than with placebo (maximum increase: 9.89 ms on propranolol at 1 mg/kg/day at Week 24).

The safety data reviewed showed no new or unexpected safety signals.

7.1 Methods

The Safety Population is defined as all patients who received at least 1 study treatment. Patients were aged between 35 and 150 days at inclusion, had proliferating IH requiring systemic therapy and for Study 201 excluded life-threatening, function-threatening and ulcerated IH and for Study 102 excluded life-threatening IH.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

In compliance with the FDA request during the pre-NDA meeting on 26-Apr-2012, the sponsor submitted safety data composed of data from > 2,451 patients treated with propranolol in the following studies:

(1) Frequency of adverse events (AEs) from the pooled database {Study 201 (401 propranolol/55 placebo) and Study 102 (23 infants)} totaling 424 patients with IH treated with propranolol HCl solution for up to 24 weeks,

(2) Cumulative safety analysis from the CUP in France (660 patients) including non-serious reported adverse drug reactions (ADRs),

(3) Literature review of 60 scientific publications (involving 1,367 patients with IH treated with propranolol) of which individual case reports were extracted from 39 publications (involving 623 patients with IH treated with propranolol) and reported in a narrative form, and

(4) Presentation of all serious adverse events (SAEs) from Studies 201, 102, 301 (ongoing, with 11 enrolled as of 31-Dec-2012, and 1 SAE) and from the CUP.

7.1.2 Categorization of Adverse Events

AEs and SAEs are reported using MedDRA Preferred Terms and patient-reported Verbatim Terms.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

The following two clinical studies performed in infant patients were pooled in the propranolol oral solution safety database for the purpose of this submission:

- Study 201, a pivotal, adaptive Phase II/III, randomized clinical trial to compare four regimens of propranolol (1 and 3 mg/kg/day, each for 3 or 6 months) to placebo in infants with proliferating IH.
- Study 102, which was designed primarily to assess the PK of propranolol (at a dose of 3 mg/kg/day) in infants with proliferating IH.

Demographics for the pooled safety population were generally similar across treatment regimens. Overall, the mean age at randomization was 103.8 days, with 63.0% of patients aged 91-150 days at randomization and 37.0% aged 35-90 days at randomization. Mean weight at birth was 3.0 kg and most patients were female (71.4%). The target IH was more commonly facial (71.2%) than non-facial (28.8%). Most patients were from Europe (Western and Other) or the USA-Canada and the most common race/ethnicity combinations were Non-Hispanic-White (72.1%), Hispanic-White (7.2%) and Hispanic-Other (7.2%). In total, 26.2% of patients were born prematurely, with a slightly higher incidence of prematurity in the placebo regimen (34.5%) compared to the propranolol regimens (21.6-27.5% across the propranolol regimens).

Results were similar when data were pooled by dose of propranolol, all propranolol or all placebo.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Minimum Requirements for Safety Analysis: According to ICH E1, a smaller number of patients may be accepted rather than the generally accepted size of the safety database for an investigational drug (approximately 1,500 treated patients) if there is already well-documented historical data available on a specific drug/drug class and if the population intended for treatment is small. Propranolol hydrochloride fulfills the former criterion, and the target IH population fulfills the latter (12% of 3 to 10% of births, i.e., 0.36% to 1.2% of births).

During the pre-NDA meeting on 26-Apr-2012, the Division emphasized that the adequacy of sample size for safety was contingent upon the quality and adequacy of safety data from (i) the 460 infants followed for 18 months after the end of treatment in the pivotal trial, (ii) the children who exited clinical studies 102 and 201 and were enrolled into clinical study 301 and continued open-label oral propranolol solution treatment, (iii) the patients who were included in a compassionate use program (CUP) in France and Switzerland, and (iv) the cases of infantile hemangiomas treated with oral

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propranolol solution reported in the literature to date.

Thus, the safety analysis submitted is composed of data from more than 2,451 patients treated with propranolol as outline above in section 7.1.1.

The sponsor agreed also to provide full safety data for the infants followed for 18 months after the end of treatment in the pivotal study when the full follow-up period has been completed and analyzed.

Pooled Safety Population: The duration of exposure for the pooled safety population (Table 37) was shorter for the placebo 6 months regimen (82.6 days) compared to the 1 mg/kg/day 6 months regimen (156.9 days) and the 3 mg/kg/day 6 months regimen (161.0 days). This pattern was repeated in the 2 regimens of 3 months propranolol HCl followed by 3 months placebo: 1 mg/kg/day 3 months regimen (81.1 and 68.6 days in the propranolol and placebo phases, respectively) and in the 3 mg/kg/day 3 months regimen (84.1 days and 70.3 days, respectively). This pattern of shorter duration of exposure with placebo probably reflects the high rate of discontinuation on placebo treatment due to lack of efficacy, and the increased rate of associated treatment-emergent adverse event (TEAE) “condition aggravated” with placebo: 3.4% of patients in the pooled placebo group vs. 1.2% in the pooled all propranolol group.

Table 37 Extent of exposure: Safety population – pooled (with overrun)

Extent of exposure (days)*	Placebo	Propranolol 1 mg/kg/day 3mths	Propranolol 1 mg/kg/day 6mths	Propranolol 3 mg/kg/day 3mths	Propranolol 3 mg/kg/day 6mths	Propranolol Total
N/missing	55/0	98/0	102/0	100/0	101/0	456/0
Mean (SD)	82.6 (67.3)	142.7 (43.7)	156.9 (39.9)	146.6 (38.5)	161.0 (26.6)	143.6 (48.3)
Q1 Q2 Q3	21.0 47.0 168.0	113.0 168.0 169.0	168.0 168.0 169	135.5 167.5 169.0	167.0 168.0 169.0	141.0 168.0 169.0
Min, max	6, 176	1, 214	7, 220	7, 176	19, 190	1, 220

**Estimated day of end of treatment (EOT) - day of first treatment administration +1; Source: Table 18 in Study 20-1 Protocol Amendments*

Exposure to propranolol was lower with placebo than with propranolol (562.3, 841.5 and 758.8 patient-months in the pooled placebo, pooled 1 mg/kg/day, and pooled 3 mg/kg/day groups, including up-titration, respectively), due to t lower number of patients treated with placebo (as per randomization) and also the higher rate of discontinuations in the placebo regimen and the placebo phases of the 3 month- regimens. Due to the lower exposure in the pooled placebo group (number of patients and duration of exposure), there was less opportunity for TEAEs to emerge. Therefore data are biased.

Compassionate Use Program: Up to 12 Oct 2012, 660 patients have been treated in France under this CUP. Mean (and median) propranolol dose was 2 mg/kg/day. Mean treatment duration for the CUP population was 246.1 days (8.1 months) and median treatment duration was 215 days (7.1 months) ranging from 8 to 673 days.

Scientific Publications: A total of 1,367 IH patients presented in the 60 scientific publications contained in this review were treated with oral propranolol. Information on ADRs could be documented in 39 publications (involving a total of 623 IH patients

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treated with oral propranolol). The majority of patients were treated with 2 mg/kg/day. The maximum exposure duration was up to 30 months (in the 60 publications) and up to 16 months (in the 39 publications). The safety review of these publications did not lead to any additional safety concern for patients treated for this extent of time.

7.2.2 Explorations for Dose Response

TEAEs leading to dose adjustment, temporary dose interruption or permanent discontinuation of study drug did not show a dose-related effect except for diarrhea and bronchitis:

- 4 patients had dose reduction (QT prolongation, enteritis, diarrhea and URTI);
- 63 patients had temporary dose interruptions (all recovered from their TEAEs);
- 26 TEAEs lead to definitive study drug discontinuation in 22 patients (11 (4.7%) in placebo, 4 (2.0%) in pooled 1 mg/kg/day group and 7 (3.1%) in pooled 3 mg/kg/day group)

Important identified risks associated with propranolol also did not show a dose-related effect:

(i) *Hypoglycemia*: two patients: one patient in 1 mg/kg/day regimen and one patient in 3 mg/kg/day regimen (Note: mild, both recovered without requiring dose reduction)

(ii) *Bradycardia*: two patients: one pre-mature baby during up-titration from 1 mg/kg/day to 3 mg/kg/day (also had enterocolitis), and one patient on 1 mg/kg/day regimen 20-24 weeks after starting treatment (mild, detected by ECG as 99bpm, recovered without treatment)

(iii) *Bronchospasm*: four patients, two on placebo (mild bronchospasm) and 2 on 3 mg/kg/day regimen (both required corrective treatment, with one not requiring change to dose, and the other requiring temporary discontinuation of dose)

(iv) *Hypotension*: 6 patients: three in 1 mg/kg/day regimen, 2 in 3 mg/kg/day regimen (both on day of up-titration to 2 mg/kg/day), and 1 in placebo group

Reviewer's comments: I think it is noteworthy that the majority of the above events occurred in children in the 3 mg/kg/day dose. These events occurred *during* the conduct of clinical trial which is closely monitored and therefore permitted early detection and prompt intervention for these events, including dose reduction, dose interruption or corrective treatment as required. While no child in the clinical trial experienced severe TEAEs, it is a concern that when the drug is approved for use in the general pediatric population, parents or caregivers may not be able to detect the symptoms and/or signs of the above events which often are subtle in these small babies, especially if the babies are premature or small-for-date. The babies with the above events may simply be observed as some form of crying, listlessness, poor feeding or suckling, sleepiness, peripheral coldness, fatigue, etc., which may not be easily detected or their importance not fully realized by the baby's parents or caregivers or babysitters.

7.3 Major Safety Results

7.3.1 Deaths

Pooled Safety Population: There were no deaths in the pooled safety population.

Compassionate Use Program: There was one death in the CUP (FR-2011-1487): A 5-month infant, with biliary atresia and severe pulmonary arterial hypertension, had received propranolol for 13 days with good cardiovascular tolerance. She received five injections of lauromacrogol for sclerosis of esophageal varices under general anesthesia. Fifteen minutes after the last injection, she experienced an atrioventricular block grade 3, refractory to treatment, followed by cardiac arrest and death of the infant in the following hours despite intensive resuscitations measures.

Reviewer's comment: Propranolol is not likely to be the causal drug because the child had tolerated it well; the death was probably the result of a reaction to lauromacrogol (which has also been reported with other sclerosants injected into esophageal varices).

Scientific Publications: One death was reported in the medical literature which presented response to propranolol in 32 infants with PHACE syndrome with cervical and intracranial arterial anomalies.[55] This patient with PHACE syndrome had IH of the face, chest, back, neck, arm, hand, airway, and the gastro-intestinal tracts, and was treated with oral propranolol 1 mg/kg/day in combination with corticosteroids 2 mg/kg/day. The IHs responded, but after being on propranolol treatment for 16 months the patient experienced severe sleeping disturbances and worsening of peripheral arteriopathy with digital infarction leading to death.

Reviewer's comment: This is a very sick infant with multiple vascular abnormalities that contributed to death.

7.3.2 Nonfatal Serious Adverse Events

Pooled Safety Population*:* 36 treatment-emergent (TE) SAEs were reported for 26 patients, with roughly comparable incidences in each regimen (Table 38):

- 3 TE SAEs were reported in 3 patients (5.5%) in the placebo regimen
- 5 TE SAEs were reported in 5 patients (5.1%) in the 1 mg/kg/day 3 months regimen
- 5 TE SAEs were reported in 3 patients (2.9%) in the 1 mg/kg/day 6 months regimen
- 16 TE SAEs were reported in 10* patients (8.1%) in the 3 mg/kg/day 3 months regimen (*note: 1 patient [050101] was from study 102 and was only treated for 3 months, and 1 patient [060403] had a TE SAE in both the propranolol and placebo phases of the study)
- 7 TE SAEs were reported in 6 patients (5.9%) in the 3 mg/kg/day 6 months regimen.

Table 38 Treatment Emergent SAEs by Regimen (Pooled Safety Population)

Patient-Study Sex -Age (days)	Preferred Term	Actual treat. taken	Onset time /1st study drug admin. - Duration	Intensity	Action taken with Study drug	Outcome Recovered	Suspected to be related to study drug
Placebo for 6 months							
060305- SB201-F-39	Condition aggravated	Placebo	14 D-15 D	Severe	Withdrawn	Yes (with sequelae)	Yes
110304- SB201-M-139	Drug ineffective	Placebo	21 D-2 D	Mild	Withdrawn	Yes	No
540601- SB201-F-87	Condition aggravated	Placebo	113 D + 19:57 -	Severe	Withdrawn	Recovering	No
Propranolol 1 mg/kg/day for 3 months followed by placebo for 3 months							
050311- SB201-M-55	Bronchiolitis	Propranolol	22 D-9 D	Moderate	Interrupted	Yes	No
060109- SB201-M-87	Cataract operation	Propranolol	42 D + 21:30-1 D	Mild	None	Yes	No
110305- SB201-M-140	Drug ineffective	Placebo	31 D-1 D	Mild	Withdrawn	Yes	No
270203- SB201-F-123	Cystitis	Propranolol	24 D-7 D	Moderate	None	Yes	No
500211- SB201-M-112	Atrioventricular block second degree	Propranolol	3:56 -1 D	Mild	Withdrawn	Yes	Yes
Propranolol 1 mg/kg/day for 6 months							
110215- SB201-M-85	Ileostomy closure	Propranolol	109 D-15 D	Moderate	Interrupted	Yes	No
	Inguinal hernia repair	Propranolol	109 D-15 D	Moderate	Interrupted	Yes	No
230208- SB201-F-57	Epilepsy	Propranolol	150 D-7 D	Severe	Withdrawn	Yes (with sequelae)	No
320114- SB201-M-95	Bronchopneumonia	Propranolol	80 D-18 D	Severe	Interrupted	Yes	No
	Gastroenteritis	Propranolol	80 D18 D-	Severe	Interrupted	Yes	No
Propranolol 3 mg/kg/day for 3 months followed by placebo for 3 months							
050106- SB201-F-55	Pyelonephritis	Propranolol	35 D-18 D	Severe	None	Yes	No
060201- SB201-F-52	Apathy	Propranolol	27 D + 23:15-1 D	Moderate	Interrupted	Yes	No
	Cyanosis	Propranolol	27 D + 23:15 -1 D	Moderate	Interrupted	Yes	No
060402- SB201-M-89	Gastroesophageal reflux disease	Propranolol	5 D-4 D	Mild	None	Yes	No
060403- SB201-F-88	Bronchitis	Propranolol	39 D-9 D	Severe	Interrupted	Yes	No
	Rotavirus infection	Propranolol	35 D-3 D	Severe	None	Yes	No
110120- SB201-F-51	Condition aggravated	V0400SB	23 D-47 D	Severe	Withdrawn	Yes	Yes
110206- SB201-F-114	Bronchiolitis	Placebo	46 D-4 D	Mild	Interrupted	Yes	No
110604- SB201-F-73	Gastroesophageal reflux disease	Propranolol	65 D-7 D	Severe	None	Yes	No
160209- SB201-F-102	Dehydration	Propranolol	62 D-3 D	Severe	Interrupted	Yes	No
	Viral infection	Propranolol	62 D-3 D	Severe	Interrupted	Yes	No
550401- SB201-M-90	Bradycardia	Propranolol	6 D + 9:15 -3 D	Moderate	Withdrawn	Yes	Yes
	Enterocolitis	Propranolol	6 D + 9:15 -9 D	Moderate	Withdrawn	Yes	No
050101- SB102-F-118	Crying	Propranolol	0 D-8 D	Mild	None	Yes	No
	Otitis media acute	Propranolol	21 D-10 D	Moderate	None	Yes	No
	Pallor	Propranolol	0 D-8 D	Mild	None	Yes	No
Propranolol 3 mg/kg/day for 6 months							
050619- SB201-F-136	Inflammation*	Propranolol	154 D-12 D	Moderate	None	Yes	No
	Pyrexia *	Propranolol	154 D-12 D	Moderate	None	Yes	No
060119- SB201-F-148	Head injury	Propranolol	28 D + 22:00 -3 D	Mild	None	Yes	No
110211- SB201-F-150	Apathy	Propranolol	36 D-2 D	Mild	None	Yes	No
110302- SB201-F-96	Drug ineffective	Propranolol	20 D-2 D	Mild	Withdrawn	Yes	No
450101- SB201-M-92	Bronchiolitis	Propranolol	61 D + 1:40 -7 D	Severe	Interrupted	Yes	No
520313-M-76	Bronchitis	Propranolol	120 D-19 D	Moderate	None	Yes	No

*D = day(s) ; (e) = Estimated date or duration; *This was not treatment emergent;* Source: Table 22 ISS.

The most common TE SAEs were: condition aggravated, drug ineffective, and bronchiolitis (each reported in 3 patients), and bronchitis (2 patients). All other TE SAEs were reported in a single patient each. The TE SAEs corresponded to the known safety

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profile of propranolol, with no new safety signals.

Five patients (all on propranolol) had TE SAEs that can be considered treatment-related: bradycardia in a patient with enterocolitis, second degree AV block in a patient with a pre-existing cardiac disease, and aggravated condition (in 2 patients), and one TE SAE of severe bronchitis. All related TE SAEs resolved with corrective treatment, except for AV block which spontaneously resolved.

Study 201 post-Week 24: At the cutoff of 31 Dec 2012, 319 patients had entered the follow-up period. In total, 20 patients had a total of 30 SAEs in the period after Week 24/end of treatment, of which 11 occurred in patients previously treated with propranolol and 2 occurred in patients previously treated with placebo; the blind was maintained for the remaining 17 SAEs. All of these SAEs were unlisted, and led to hospitalization; none were considered life-threatening. All had an outcome of recovered/resolved.

SAEs reported in the CUP: These were poor weight gain and decreased appetite, purpura; fall and loss of consciousness. Narratives follow:

- FR-2011-0991: A 6-month old female patient with hyperalgic ulcerated tuberous IH started propranolol 1 mg/kg/day, later up-titrated to 3 mg/kg/day. After 2 months, she was admitted to hospital for progressive decrease appetite and poor weight gain. She had experienced several episodes of respiratory disorders, the first ones started before treatment (asthma diagnosed) and GERD. Investigations, including coeliac disease test, malabsorption, and oropharyngeal obstruction, were unremarkable; the results of allergic tests for allergy in proteins of cow's milk and/or in wheat were negative. A lack of nutritional intake was considered and the patient received enriched milk. Propranolol was continued. The patient's condition improved with greater food intake.
- FR-2011-0662: A 3 month-old female patient was treated with propranolol 2 mg/kg/day for IH of the right upper and lower eyelid and right temporal area (risk of visual impairment), with punctiform IH on the neck and scalp. Nine days later, she was hospitalized due to the occurrence of non-painful purpuric spots on his left leg and foot. The baby had not been wearing socks which can affect venous constriction. Propranolol treatment was temporarily discontinued. Concomitantly, the patient had been experiencing dyspnea and feeding difficulties, caused by rhinitis. The origin of the purpura could not be found, since all the blood samples were coagulated, and the platelet count could not be performed (urine tests were negative). The event spontaneously regressed and propranolol was reintroduced.
- FR-2011-2410: A 14 month-old female patient was treated with propranolol 2 mg/kg/day for ulcerated IH of lip, more than 1.6 cm diameter with risk of functional impairment. Nine months later, she took her morning treatment as usually in her bottle-feed. At 9:45AM, while she was at the day-nursery, she fell forward against a door, and hit her left eye against a doll. She quickly got up crying, fell again on the back of the head and lost consciousness (hypotonia and eyeball movements) for 10-15 sec. There were no abnormal movements and no vomiting. On admission to hospital, BP was 73/55 mmHg and consciousness was 15 on the Glasgow scale. Cardio-pulmonary work-up was normal. There was no bruise of the scalp, just a small scratch on the left eyelid. The fall and loss of consciousness were attributed to a probable vaso-vagal event. Propranolol was continued.

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Reviewer's comments: There were other probable causes of the SAEs reported in the CUP. In all 3 instances, propranolol was continued.

Study 301*:* 1 SAE was reported in the open-label extension Study 301. The patient (#0501001) was hospitalized with bronchiolitis about 6 months after last administration of propranolol; patient had a medical history of bronchiolitis; patient recovered)

Scientific publications: The analysis of safety in terms of seriousness is limited by the lack of information in most cases on vital risk, hospitalization or prolongation of hospitalization, and permanent sequelae.

7.3.3 Dropouts and/or Discontinuations

Pooled Safety Population: 26 TEAEs leading to permanent study drug discontinuation were reported for 22 patients (Table 39), with slightly higher incidence in the pooled placebo group (4.7%) than in the pooled propranolol 1 mg/kg/day group (2.0%) and the pooled propranolol 3 mg/kg/day group (3.1%).

Table 39 TEAEs leading to study drug discontinuation (Pooled Safety Population)

Preferred Term	All Placebo n=236	All Propranolol 1mg/kg/day n=200	All Propranolol 3mg/kg/day n=224	All Propranolol n=424
Patients with at least one TEAE leading to definitive study drug discontinuation	11 (4.7%)	4 (2.0%)	7 (3.1%)	11 (2.6%)
CONDITION AGGRAVATED	3 (1.3%)	-	1 (0.4%)	1 (0.2%)
DRUG INEFFECTIVE	2 (0.8%)	-	1 (0.4%)	1 (0.2%)
BRONCHIOLITIS	2 (0.8%)	-	1 (0.4%)	1 (0.2%)
FATIGUE	-	-	1 (0.4%)	1 (0.2%)
APNOEA	-	-	1 (0.4%)	1 (0.2%)
ASTHMA	-	-	1 (0.4%)	1 (0.2%)
BRONCHITIS	-	-	1 (0.4%)	1 (0.2%)
BRADYCARDIA	-	-	1 (0.4%)	1 (0.2%)
ENTEROCOLITIS	-	-	1 (0.4%)	1 (0.2%)
OLIGURIA	-	-	1 (0.4%)	1 (0.2%)
OBSTRUCTIVE AIRWAYS DISORDER	-	1 (0.5%)	-	1 (0.2%)
BRONCHIAL OBSTRUCTION	1 (0.4%)	-	-	-
NASAL OBSTRUCTION	1 (0.4%)	-	-	-
GASTROENTERITIS	1 (0.4%)	-	-	-
ATRIOVENTRICULAR BLOCK SECOND DEGREE	-	1 (0.5%)	-	1 (0.2%)
ECG - QT PROLONGED	-	1 (0.5%)	-	1 (0.2%)
EPILEPSY	-	1 (0.5%)	-	1 (0.2%)
RASH	1 (0.4%)	-	-	-
VASCULAR SKIN DISORDER	1 (0.4%)	-	-	-

Source: Table 24 ISE. Note: Patients could have had more than 1 TEAE leading to discontinuation, therefore the sum of each column can be different to the total number of patients with at least 1 TEAE leading to discontinuation

TEAEs leading to permanent study drug discontinuation that occurred in more than 1 patient were: condition aggravated (4 patients:- 3 in placebo group and 1 in 3 mg/kg/day group), drug ineffective (3 patients:- 2 in placebo group and 1 in 3 mg/kg/day group), and bronchiolitis (3 patients:- 2 in placebo group and 1 in 3 mg/kg/day group).

Nine patients had related TEAEs leading to permanent study drug discontinuation:

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- 3 with placebo (patient 201-051205 had bronchiolitis, patients 201-160209 and 201-060305 had condition aggravated)
- 3 patients with 1 mg/kg/day (patient 201-060135 had prolonged QT, patient 201-500211 had second degree AV block, patient 201-060104 had obstructive airways disorder)
- 3 patients with 3 mg/kg/day (patient 201-060134 had fatigue, patient 201-110120 had condition aggravated, and patient 201-550401 had bradycardia).

Nine patients had 10 TEAEs leading to permanent study drug discontinuation that were also reported as TE SAEs:

- 4 patients in the pooled placebo group had 4 TE SAEs leading to permanent study drug discontinuation, all associated with non-improvement/ worsening of IH. Patient 201-110305 (in the placebo phase of the propranolol 1 mg/kg/day regimen) had drug ineffective on D31. In the placebo 6 months regimen, patient 201-110304 had drug ineffective on D21 and patients 201-060305 and 201-540601 had condition aggravated on D14 and D113, respectively.
- 2 patients in the pooled propranolol 1 mg/kg/day group had 2 TE SAEs leading to definitive study drug discontinuation: patient 201-500211 had AV block second degree and patient 201-230208 had epilepsy
- 3 patients in the pooled propranolol 3 mg/kg/day group had 4 TE SAEs leading to definitive study drug discontinuation: patient 201-110120 had condition aggravated, patient 201-550401 had bradycardia and enterocolitis, and patient 201-110302 had drug ineffective.

The numbers of patients with TEAEs leading to permanent study drug discontinuation were too low to see any meaningful trends when data were pooled by regimen, and by dose of propranolol or placebo within regimen.

7.3.4 Other Significant Adverse Events

Four patients had TEAEs leading to dose reduction:

- patient 102-050102 had ECG QT prolonged,
- patient 201-320105 had enteritis,
- patient 201-500115 had diarrhea and
- patient 201-711407 had URTI.

None of the events were severe and all patients recovered, except one (URTI: outcome unknown).

Sixty-three patients had dose interruptions; all of them recovered from their TEAE.

7.3.5 Submission Specific Primary Safety Concerns

Hypoglycemia, bradycardia, hypotension, and bronchospasm were monitored during uptitration and throughout the clinical studies (102 and 201), and during the CUP. Parents/guardians were advised by the investigator of the potential risk of hypoglycemia and were educated on evocative signs. To avoid risks of hypoglycemia, propranolol treatment was to be given with feeding and to be temporarily discontinued in the case of predisposing events such as vomiting or a prolonged fasting period. If there were any hypoglycemia alerts, parents/guardians were instructed to administer oral liquids containing sugar and seek medical support in the case of persistence of these signs. In the case of severe symptomatic hypoglycemia, the infants were to be managed appropriately and the study treatment was to be permanently discontinued for intolerance.

Pooled Safety Population***:*** Important identified risks of propranolol that occurred in the pooled safety population were: hypoglycemia (total 2 patients; both during uptitration), bradycardia (total 2 patients; 1 during uptitration), hypotension (total 6 patients including 1 on placebo; 3 during uptitration), bronchospasm (total 4 patients including 2 on placebo; 1 during uptitration).

Apart from one treatment-emergent serious adverse event (TE SAE) of bradycardia (in a child with enterocolitis), none of these events were serious or severe in intensity, and all patients recovered, sometimes with corrective treatment and mostly without change to study drug dose.

Other identified risks of propranolol that occurred in the pooled safety population were: bundle branch right block: (1 patient on propranolol), QT prolonged (4 patients: 1 on placebo, 3 on propranolol), decreased appetite (14 patients, 1 on placebo, 13 on propranolol), neurodevelopment disorder (1 patient on propranolol). TEAEs of hepatobiliary events, routinely monitored as possible indicators of drug-induced liver damage were: cytolytic hepatitis (1 patient on propranolol), increased AST (6 patients: 2 on placebo, 4 on propranolol), increased alanine aminotransferase (ALT; 2 patients, both on propranolol), increased transaminases (1 patient on placebo). TEAEs possibly indicating allergic reactions to study drug were lip swelling (1 patient on propranolol) and pharyngeal edema (1 patient on propranolol). Other TEAEs judged medically relevant were: petit mal epilepsy (1 patient on propranolol), epilepsy (1 patient on propranolol), and intestinal obstruction (1 patient on propranolol).

Compassionate Use Program***:*** Important identified risks of propranolol that occurred in the CUP were: bradycardia (2 serious cases), hypotension (2 serious cases), respiratory disorders (7 serious cases, including bronchospasm and bronchiolitis), hypoglycemia (2 serious cases) and hypoglycemic seizure (2 cases).

Other significant serious adverse drug reactions (SADRs) in the CUP were one case each of atrioventricular (AV) block, poor weight gain and decreased appetite, purpura, fall and loss of consciousness. Other significant non-serious ADRs that were experienced by more than one patient largely involved sleep disorders such as

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somnolence, nightmares, sleep disorder, insomnia, and nocturnal awakening, as well diarrhea; one case of asymptomatic overdose was reported.

Scientific Publications***:*** 13 events were detailed as leading to definitive treatment discontinuation; the majority of these events were those associated with identified risks with propranolol treatment in infants: bradycardia, hypotension, respiratory disorders, and hypoglycemia. The same was true for the 30 events that were detailed as leading to a dose reduction or a temporary discontinuation of propranolol treatment, with the addition of non-serious known risks such as sleep disorders, fatigue, restlessness, and gastrointestinal disorders.

Two cases of hyperkalemia, one of which was related to tumor lysis syndrome of a large, ulcerated IH, were also reported.

Of the four submission specific safety concerns (namely, hypoglycemia, bradycardia, hypotension, and bronchospasm), bronchospasm is reviewed below, and the other three safety concerns are reviewed under Section 7.4.2 Laboratory Findings.

Bronchospasm*:*

Bronchospasm in Pooled Safety Population: 4 patients (2 on placebo and 2 on propranolol, 1 patient during the uptitration period and for 3 patients after uptitration) reported bronchospasm. Narratives are as follows:

- Patient 201-500111 in the 3 mg/kg/day 6 months propranolol regimen experienced bronchospasm in the interval Weeks 1- 2 (i.e., on 2 mg/kg/day); it was moderate in intensity and the patient recovered without change of dose, but with corrective treatment.
- Patient 201-080103 in the placebo for 6 months group had bronchospasm on D21 21:20 minutes after drug administration. The event was graded as mild and lasted 10 days. The drug was temporarily discontinued; following corrective treatment, the patient recovered.
- Patient 201-500112 in the propranolol phase of the 3 mg/kg/day for 3 months group had mild bronchospasm on D79 6:50 minutes after drug administration. The event was graded as mild and lasted 12 days. Propranolol was temporarily discontinued; and following corrective treatment, the patient recovered.
- Patient 201-110604 in the placebo phase of the propranolol 3 mg/kg/day for 3 months group experienced bronchospasm. The event was mild and the patient recovered with corrective treatment and without change to the dose of study drug.

Bronchospasm in the Compassionate Use Program**:** There were 9 reports of bronchiolitis, one reported as serious and 8 as non-serious. Seven cases occurred during winter time when infants are at increased risk of viral infections. Respiratory syncytial virus was not investigated in any of these cases. Case narratives follow:

- **FR-2013-1066:** A 4-month-old female infant experienced an episode of bronchiolitis one month after the initiation of Propranolol, 2 mg/kg/day, for IH. The treatment was discontinued and the patient received only respiratory physiotherapy. Three weeks later, bronchiolitis worsened, with respiratory discomfort, rhinorrhea, cough and fever at 38.5° C, leading to hospitalization for 4 days. After 2 weeks of treatment with salbutamol, the patient was recovered and propranolol treatment was readministered. Events did not recur again.

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- **FR-2013-0031:** A 1-year-old female patient experienced an episode of bronchiolitis 8 months after initiation of treatment with Propranolol for facial IH. Treatment was discontinued during 3 weeks when the patient received as corrective betaméthasone and fluticasone, leading to complete recovery. Propranolol was permanently discontinued due to resolution of IH.
- **FR-2012-4019:** A 6-month-old infant experienced bronchial obstruction with sibilants one month after Propranolol initiation at 2 mg/kg/day for orbital IH. The treatment was discontinued and the patient received salbutamol for asthma. At the time of report, the patient was recovering. No additional investigations were performed, but a viral etiology was suspected.
- **FR-2012-4027:** A 4-month-old female infant experienced an episode of bronchiolitis 3 months after Propranolol initiation for facial IH. The treatment was discontinued and the patient received respiratory physiotherapy. After a week, the infant recovered completely and propranolol was readministered.
- **FR-2012-4138:** A 17-month-old female patient experienced bronchiolitis 15 months after Propranolol initiation for suborbital IH. Propranolol was completely stopped and the patient received beclometasone for 10 days and betametasone for 3 days, after which the patient completely recovered. However, propranolol treatment was not readministered.
- **FR-2013-0458:** A 7-month-old female infant experienced bronchiolitis 5 months after treatment with Propranolol at a dose of 5 mg/kg/day for lower palpebral IH. Pulmonary examination disclosed bilateral sibilant rales. The treatment was temporary discontinued, but the events did not resolve. Propranolol was readministered while the child was still suffering from pulmonary symptoms. At the time of report, the patient was reported as recovering.
- **FR-2013-0516:** A 7-month-old child experienced bronchiolitis after 5 months of treatment with Propranolol at a dose of 3 mg/kg/day for segmental IH. Corrective treatment included salbutamol and discontinuation of propranolol.
- **FR-2013-1081:** A 10-month-old female infant experienced 2 episodes of asthmatoid bronchitis, 4 months after treatment initiation with Propranolol 2 mg/kg/day for ulcerated IH of the left arm. The first episode occurred following the dose increase from 2 to 2.5 mg/kg/day. The treatment was temporary discontinued and the patient received fluticasone. After resolution the treatment was readministered and asthmatoid bronchitis reoccurred 6 days later. Causal relationship was assessed as probable based on positive dechallenge and rechallenge. The bronchoconstrictive effect of propranolol may have worsened a bronchitis of probable infectious origin.
- **FR-2013-0204:** A 9-month-old female infant experienced bronchiolitis with cough and sibilants rales while she was receiving propranolol initiated 5 months before for IH of nasal tip. Propranolol was temporary discontinued and corrective treatment included salbutamol and beclomethasone. After resolution of bronchiolitis, propranolol was readministered and the events did not reoccur.

Bronchospasm in the Scientific Publications: In the medical literature of infants treated with propranolol for IH, 10 cases of respiratory disorders (asthma, bronchospasm, bronchial hyper reactivity or wheezing) were reported. These included one 9-month old infant with life-threatening IH, one 2-month old infant with complicated IH of nose, lip and mouth, one 3-month old female patient with IH of nasal tip, five patients with cavernous or mixed IH, and two patients with problem IH with risk of serious

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disfigurement or ulceration or interference with normal function. In all instances, the dose of oral propranolol was 2 mg/kg/day. The time to onset after treatment with propranolol was not documented (one patient had pre-existing asthma). None was reported as requiring hospitalization. Propranolol was discontinued permanently in 7 cases; and in 3 cases it was temporarily discontinued.

Reviewer's comment: The cases narrated above consist of children who experienced bronchospasm or bronchiolitis, the latter probably associated with a viral infection. Bronchospasm is a known adverse effect of propranolol. There is no new safety signal.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Pooled Safety Population*:* Overall, TEAEs (and related TEAEs) were experienced by 65.3% of patients (14.8% related) in the pooled placebo group and 86.8% of patients (36.3% related) in the pooled all propranolol group, with no difference between propranolol dose groups. TEAEs in the pooled safety population are shown in Table 40.

Table 40 Summary of TEAEs by pooled dose (Pooled Safety Population)

	All Placebo N = 236	All Propranolol 1mg/kg/d N = 200	All Propranolol 3 mg/kg/day N=224	All Propranolol N=424
Patients with at least one TEAE	154 (65.3%)	169 (84.5%)	199 (88.8%)	368 (86.8%)
Patients with one TEAE	60 (25.4%)	35 (17.5%)	39 (17.4%)	74 (17.5%)
Patients with two TEAEs	47 (19.9%)	24 (12.0%)	36 (16.1%)	60 (14.2%)
Patients with at least 3 TEAEs	47 (19.9%)	110 (55.0%)	124 (55.4%)	234 (55.2%)
Patients with at least one TEAE leading to definitive study drug discontinuation	11 (4.7%)	4 (2.0%)	7 (3.1%)	11 (2.6%)
Patients with at least one related TEAE	35 (14.8%)	75 (37.5%)	79 (35.3%)	154 (36.3%)
Patients with at least one Serious TEAE	6 (2.5%)	7 (3.5%)	14 (6.3%)	21 (5.0%)
Total number of TEAEs	357	679	759	1438
Total number of TEAEs leading to definitive discontinuation of study drug	12	4	10	14
Total number of Related TEAEs	56	160	132	292
Total number of Serious TEAEs	6	9	19	28

AEs in the 3mg/kg/day arm include those that occurred during the uptitration period; * Related = events with a relationship to the study drug other than 'Not Suspected'; ** Each patient was counted only once by Preferred Term; Source: Table 19 in ISS.

TEAEs that occurred in ≥2% of patients in any pooled propranolol group, and with ≥3-fold higher incidence in the pooled all propranolol group than in the pooled placebo group were known non-serious AEs of propranolol (diarrhea, vomiting, peripheral coldness, sleep disorder, middle insomnia, somnolence, restlessness, hypersomnia, and agitation) or non-specific events frequently occurring in young infants (constipation, vaccination complication, conjunctivitis, gastroenteritis, dermatitis of diaper, infantile colic, flatulence, influenza, gastro-esophageal reflux disease, viral infection, erythema,

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viral upper respiratory tract infection, and abdominal pain).

The most common TEAEs were diarrhea, peripheral coldness, sleep disorder, and nightmare, all of which are known AEs of propranolol.

Compassionate Use Program*:* Of 660 patients included since 13-Apr-2010 in France, 46 cases (19 serious) including 81 ADRs (36 serious) were reported to the sponsor.

The system organ classes in which ADRs were reported most frequently were infections and infestations (18 ADRs, 6 serious) and psychiatric disorders (14 ADRs, 0 serious).

The most frequent ADRs were bronchiolitis (11 ADRs, 5 serious), sleep disorder (5 ADRs, 0 serious), and diarrhea, bronchitis, and agitation (3 ADRs each, 0 serious).

Scientific Publications***:*** Most of the scientific publications in the field had incomplete individual safety data on propranolol use for IH treatment. Despite these limitations, information on 132 ADRs involving 114/623 treated patients could be documented in 39 publications. No unknown serious ADR was reported.

The most frequently reported events per system organ class were cardiovascular disorders (40 events); nervous system or psychiatric disorders (26 events); gastro-intestinal disorders (26 events); and respiratory system disorders (24 events).

The most frequent ADRs were sleep disorder (20 events), hypotension (18 events; 4 symptomatic, 14 asymptomatic), diarrhea (13 events), and cold extremities (8 events).

Where ADR outcome was known/provided, the majority resolved (all except one ADR of mild wheezing that did not change and one ADR of dental caries that was ongoing).

Neither a new unexpected safety signal, nor predisposing factors for any ADR arose from this analysis.

7.4.2 Laboratory Findings

Biochemistry parameters (other than glucose) and hematology parameters in blood samples did not show any results that are of concern or generate a new safety signal.

While “clinically significant (CS) values” in the investigators’ opinions occurred occasionally, there were no trends over time noted for any parameter to indicate a new safety signal. The most common TEAE associated with biochemistry abnormalities was increased aspartate aminotransferase (AST) and the most common TEAE associated with hematological abnormalities was the grouped term “anemia.” None of the TEAEs associated with biochemistry or hematology abnormalities were serious, led to study drug discontinuation (temporary or definitive), or dose modification.

Hypoglycemia:

Hypoglycemia in Pooled Safety Population: there were no instances of potentially clinically significant (PCS) blood glucose values (<2.22 mmol/L) as measured by pinprick at +2h and +4h post dose on the days of dose increase.

Table 41 shows the change in blood glucose from pre-dose values on days of uptitration of study drug. Monitoring of blood glucose levels did not reveal any difference between groups or between the +2h and +4h time point.

Table 41 Change in blood glucose levels from pre-dose values on days of dose increase, by pooled dose of propranolol or placebo (pooled safety population)

		Blood Glucose (mmol/L)			
Predose value Change from predose		**All Placebo n=55**	**All propranolol 1 mg/kg/day n=200**	**All propranolol 3 mg/kg/day n=224**	**All propranolol n=424**
		Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Day 0 Predose value		5.406 (0.786)	5.444 (0.900)	5.429 (0.814)	5.436 (0.854)
			1mg/kg/day	**1mg/kg/day**	**1mg/kg/day**
Change from predose	D0 +2H D0 +4H	0.206 (0.972) 0.128 (0.954)	-0.069 (0.964) -0.023 (0.973)	0.009 (0.974) 0.017 (0.921)	-0.027 (0.969) -0.001 (0.944)
Day 7 Predose value		5.309 (0.662)	5.302 (0.791)	5.306 (0.846)	5.304 (0.819)
			1mg/kg/day	**2mg/kg/day**	
Change from predose	D7 +2H D7 +4H	0.120 (0.844) 0.267 (0.746)	0.108 (0.839) 0.135 (0.867)	0.154 (0.913) 0.225 (1.072)	0.133 (0.878) 0.183 (0.982)
Day 14 Predose value		5.252 (0.959)	5.346 (0.929)	5.256 (0.858)	5.298 (0.892)
			1mg/kg/day	**3mg/kg/day**	
Change from predose	D14 +2H D14 +4H	0.081 (1.046) 0.221 (1.041)	0.122 (1.029) 0.140 (0.868)	0.105 (0.883) 0.186 (0.871)	0.113 (0.953) 0.165 (0.869)

Source: ISS Table 28

Routine blood biochemistry during the study revealed 3 patients with isolated low blood glucose values (<2.6 mmol/L) during uptitration and 2 patients with isolated low values at Week 24. Two patients had mild TEAEs of hypoglycemia, both of which occurred during uptitration and one of which occurred during an episode of gastroenteritis (vomiting and diarrhea) and poor feeding. However, this should be interpreted with caution due to the high degree of variability in the data and physiological biological changes with age in infants (more important in the 6 months groups due to longer exposure), and the very low number of symptomatic changes.

Reviewer's comment: Infants have lower glycogen stores (leading to a reduced fasting ability) and their glucose utilization rates are higher in the fasting state (by as much as 3-fold in the case of infants) partly due to their great brain mass relative to their body weight.[56] Propranolol may impair glucose homeostasis through inhibition of β-adrenergic mediated glycogenolysis, gluconeogenesis and lipolysis, and, therefore, propranolol can put the infants at risk of hypoglycemia.

However, the blood glucose results in the clinical trials show no cause for concern.

Hypoglycemia in the Compassionate Use Program: Four ADRs of hypoglycemia were reported: two events of hypoglycemia and two events of hypoglycemic seizure. The narratives follow:

- **FR-2010-1786:** A 5-month male patient, with gastroesophageal reflux and asthma, taking concomitant sodium alginate and esomeprazole; patient experienced one serious event of hypoglycemia (1.1 mmol/L, 0.20 mg/L) after the first propranolol intake (1 mg/kg/day). The event was without clinical signs and was discovered during initial monitoring by capillary glucose measurement (T=2 hours). The patient recovered after feeding and glucose perfusion. The patient was kept under close monitoring. At the 4th or 5th day after treatment initiation, the dose was increase to 2 mg/kg/d. This dose was well tolerated. It was not reported if he treatment was given at the time of meal.
- **FR-2011-3402**: A 15-month old female patient experienced several episodes of asthenia and somnolence during the first week of propranolol treatment (1 mg/kg/day). Asymptomatic hypoglycemia were suspected by the physician because fasting blood glucose level was at 0.4g/L at D7. The patient did not have an infectious episode or concomitant disease and there had been no reduction in food intake. She had no particular past history except allergy to milk protein. Propranolol treatment was permanently discontinued.
- **FR-2012-0275**: An 8-month old patient experience one serious event of a hypoglycemic seizure which was related to a period of fasting and vomiting during an acute Norovirus gastroenteritis and viral infection of ENT. The propranolol treatment was not temporarily discontinued, as recommended during the fasting and feeding difficulties. The blood glucose level was not reported.
- **FR-2012-2819**: A 9-month-old male patient, experienced hypoglycemic seizure while he was receiving propranolol at a dose of 2 mg/kg/ day, 6 months after the beginning of the treatment. The patient had not eaten his full evening ration of milk and his parents still administered 1 mg/kg propranolol. The following morning the patient's nanny administered a further 1 mg/kg dose of propranolol on an empty stomach believing the parents to have already fed the patient at home. He experienced tonic-clonic generalized convulsions and was kept to hospital by the emergency team. The blood glucose was not determined and the patient's state deteriorated despite treatment with clonazepam, until severe bradycardia occurred, requiring resuscitation measures. It was only, when the parents were questioned on current treatment that blood glucose was measured leading to the correct diagnosis and treatment of hypoglycemic seizure. Propranolol treatment was permanently discontinued.

Reviewer's comments: The first two cases of hypoglycemia were asymptomatic and were not associated with an intercurrent illness or feeding interruption.

In the two infants who experienced "hypoglycemic seizure," lack of feeding at the time of administration of propranolol probably contributed to the AE. These events could have been avoided had feeding been continued. I note that blood glucose levels were not available to confirm that the seizure was due to hypoglycemia; the probable cause of seizure was attributed to hypoglycemia by "clinical reasoning."

Hypoglycemia in the Scientific Publications: The sponsor reported from the medical literature 11 events of hypoglycemia (10 symptomatic, including 5 seizures and 5 unresponsiveness) associated with propranolol dose of 2mg/kg/day. The time of onset

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ranged from 2 weeks to 9 months of treatment. Two occurred during fasting period, 4 during an infection, one as the patient received concomitant corticosteroids and one who received an overdose of propranolol.

For example, 4 patients with problematic IH (functional or disfigurement risk) receiving propranolol 0.5 mg/kg/day (first day), 1 mg/kg/day (second day) or 2 mg/kg/day (from third day) had hypoglycemia within the first week of treatment, which disappeared after stopping propranolol, and did not recur after rechallenge and encouragement to feed frequently. One patient with head and neck IH (with significant functional impairment or risk of permanent disfigurement) receiving propranolol 2 mg/kg/day had a seizure episode several months into treatment in association with an upper respiratory infection and reduced feeding for several days. Blood glucose levels were not done to document hypoglycemia. The seizure responded to glucose therapy. Parents continued propranolol at full dose (because of apparent clinical improvement in IH) with food till complete resolution of the IH.

Reviewer's comment: In 7 of these 10 cases of symptomatic hypoglycemia associated with propranolol treatment of IH reported in the medical literature, an additional stressor such as an acute infection, prolonged fasting or oral corticosteroids causing adrenal insufficiency were present and could have precipitated all but one of them.[57,58,59,60,61]

Three symptomatic hypoglycemia patients treated with propranolol for IH (off-label use, given 2 mg/kg/day in 3 divided doses) were reported in a recent US study.[69] Hypoglycemia was documented by blood glucose levels.

Reviewer's comment: I found that 2 of these 3 patients in the US study were beyond the age group indicated at the time of starting treatment (one was 11 months old, and the other 18 months old – both should not have been treated with propranolol as they have aged beyond the actively proliferating phase of IH which is from 5 weeks age to about 5-6 months of age). The third patient, a 5-week old girl, had been on propranolol 2 mg/kg/day for 8.5 months without AEs and with marked improvement of her IH. At the age of 10 months, she was found limp and pale 2½ hours after having a normal breakfast and receiving her morning dose of propranolol, with a serum glucose level of 20mg/dL. This child had had symptoms of cough and runny nose 1 day prior, and a positive nasopharyngeal swab for respiratory syncytial virus. The child was discharged from hospital the next day, and resumed propranolol treatment (2 mg/kg/day in 3 divided doses) for IH.

I do not think there is a new safety signal for hypoglycemia with propranolol treatment. I think that hypoglycemia can be prevented with proper education of parents and guardians on the importance of administering propranolol during or right after a feeding.

7.4.3 Vital Signs

Hypotension:

Hypotension in the Pooled Safety Population: Blood pressure (BP) was monitored as an

indicator of hypotension in the clinical studies. There were no large falls in systolic or diastolic BP in the 1, 2, 3 and 4 hour periods following drug administration during the uptitration period (Table 42) that caused symptoms.

Table 42 Systolic and diastolic BP, change from predose values on days of dose increase, by pooled dose of propranolol or placebo (Pooled Safety Population)

Predose Value Change from predose		Diastolic Blood Pressure (mmHg)				Systolic Blood Pressure (mmHg)			
		All Placebo n=55	All Propranolol 1 mg/kg/day n=200	All Propranolol 3 mg/kg/day n=224	All Propranolol n=424	All Placebo n=55	All Propranolol 1 mg/kg/day n=200	All Propranolol 3 mg/kg/day n=224	All Propranolol n=424
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Day 0 Predose value		55.2 (12.7)	**1mg/kg/day** 55.7 (11.6)	**1mg/kg/day** 53.7 (12.0)	**1mg/kg/day** 54.6 (11.8)	92.2 (14.9)	**1mg/kg/day** 92.8 (14.7)	**1mg/kg/day** 92.4 (13.8)	**1mg/kg/day** 92.6 (14.2)
Change from predose	D0 +1H	-3.1 (14.7)	-3.6 (15.8)	-0.9 (16.1)	-2.2 (16.0)	4.1 (19.9)	-2.4 (15.9)	-0.7 (14.9)	-1.5 (15.4)
	D0 +2H	-1.5 (16.7)	-3.9 (14.9)	-1.0 (15.7)	-2.4 (15.4)	2.8 (22.3)	-3.3 (17.1)	-0.5 (17.2)	-1.8 (17.2)
	D0 +3H	-2.2 (14.4)	-3.8 (15.1)	-2.2 (15.2)	-3.0 (15.2)	2.9 (18.0)	-4.1 (16.8)	-2.1 (15.7)	-3.0 (16.2)
	D0 +4H	2.5 (15.5)	-2.8 (13.0)	-1.7 (16.0)	-2.2 (14.7)	6.2 (19.1)	-3.3 (16.4)	-1.9 (16.5)	-2.5 (16.5)
			1mg/kg/day	**2mg/kg/day**			**1mg/kg/day**	**2mg/kg/day**	
Day 7 Predose value		52.0 (10.7)	53.6 (12.6)	51.8 (12.3)	52.7 (12.4)	91.8 (14.4)	90.9 (14.3)	90.1 (13.2)	90.5 (13.7)
Change from predose	D7 +1H	0.6 (10.3)	-1.4 (14.1)	-2.3 (14.4)	-1.8 (14.3)	0.0 (14.9)	-2.5 (14.7)	-1.4 (14.4)	-1.9 (14.5)
	D7 +2H	-1.3 (12.1)	-2.1 (12.4)	-1.7 (14.1)	-1.9 (13.3)	0.9 (19.8)	-2.5 (14.5)	-1.6 (16.3)	-2.1 (15.5)
	D7 +3H	-1.7 (13.4)	-3.8 (13.1)	-1.2 (13.8)	-2.4 (13.5)	-0.3 (18.6)	-3.2 (15.0)	-2.3 (15.5)	-2.7 (15.2)
	D7 +4H	5.0 (13.5)	-1.4 (13.5)	-1.1 (13.6)	-1.2 (13.5)	2.8 (16.4)	-1.9 (15.2)	-1.6 (14.5)	-1.7 (14.8)
			1mg/kg/day	**3mg/kg/day**			**1mg/kg/day**	**3mg/kg/day**	
Day 14 Predose value		56.0 (11.3)	53.4 (11.4)	52.5 (11.8)	53.0 (11.6)	93.4 (14.3)	91.1 (13.1)	91.8 (13.5)	91.5 (13.3)
Change from predose	D14 +1H	-5.1 (15.6)	-3.8 (14.2)	-3.9 (13.6)	-3.9 (13.9)	0.3 (14.2)	-3.5 (16.6)	-3.7 (15.5)	-3.6 (16.0)
	D14 +2H D14	-3.0 (13.0)	-2.2 (13.9)	-1.6 (14.7)	-1.9 (14.3)	-0.3 (14.9)	-2.4 (17.6)	-1.4 (17.0)	-1.9 (17.2)
	+3H D14 +4H	-3.5 (15.3)	-4.0 (13.6)	-3.0 (14.1)	-3.4 (13.9)	-2.5 (13.1)	-2.9 (16.3)	-3.7 (15.9)	-3.3 (16.1)
		-0.1 (13.9)	-2.4 (13.6)	-2.8 (14.4)	-2.6 (14.0)	1.3 (14.6)	-2.4 (15.0)	-3.6 (16.4)	-3.1 (15.8)

Source: Table 35 in ISS

Overall, the proportion of patients with age-adjusted low BP was small throughout the uptitration period and the rest of the study (maximum: 6.5% in the pooled placebo group at Day 14+3h), with patient numbers too low to observe any trends over time or between groups.

There were 6 TEAEs of hypotension in this study (3 patients during the uptitration period and 3 patients after uptitration). All were asymptomatic, were not serious or severe in intensity, and did not lead to temporary or permanent drug discontinuation, or dose modification for any patient. These results suggest that the propranolol dosage regimen did not induce symptomatic hypotension in the studied population.

Hypotension (BP<80mmHg) in the Compassionate Use Program: Two (2) serious adverse reactions of *hypotension* were reported:

- **FR-2011-0698**: A 3-month-old female patient started Propranolol 3.75 mg/ml treatment at dose of 0.5 mg/kg/d, increased to1 mg/kg/day the following day and then to 2 mg/kg/day. At this dose, the patient (two days after treatment introduction) experienced one episode of hypotension (systolic BP 70 mmHg) without symptoms. The treatment was discontinued 2

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days later due to persistence of hypotension. She fully recovered the day after discontinuation. Five months later, Propranolol 3.75 mg/ml treatment was readministered at 2 mg/kg/day (in two divided doses), and 4-hour monitoring was unremarkable.

- **FR-2012-1339**: An 8-month-old male patient started Propranolol 3.75 mg/ml treatment at a dose of 1 mg/kg/d (5 mg bid). A week later, the dose was increased to 2 mg/kg/day (10mg bid). During monitoring, the patient had decreased BP to 73/45mmHg with stable pulse (around 105 bpm), and without symptoms. There was no change in the ECG. He was kept under monitoring in the hospital and received 7.5 mg of propranolol in the evening. Blood pressure was low (no data). The following day, in the morning, the infant received 10mg of Propranolol and experienced hypotension (79/45mmHg). The patient was discharged with 1 mg/kg/d (5 mg bid) and later, propranolol was slowly increased to 3 mg/kg/day.

Reviewer's comment: In the first case, hypotension occurred probably because the dose increase was too fast. In the second case, dose reduction and slow uptitration allowed an increase in dose up to 3 mg/kg/day. Both cases continued on propranolol.

Hypotension in the Scientific Publications: Four events of hypotension were reported, of which one was symptomatic (drowsiness and cold extremities). Narratives follow:

An extremely premature infant (30 weeks' gestation) with a periorbital IH was treated with propranolol at 1 mg/kg/day in 3 divided doses. The therapy had to be discontinued early due to hypotension, drowsiness and cold extremities. IH treatment was continued with corticosteroids.

Two patients with problematic IH (functional or disfigurement risk) receiving propranolol 0.5 (first day), 1 (second day) or 2 mg/kg/day (from third day) had mild hypotension without symptoms within the first week of treatment that disappeared after cessation of propranolol and did not recur after re-challenge at lower doses.

A 7-month-old male patient with superficial eyelid infantile capillary hemangioma was treated with propranolol at 2 mg/kg/day. Treatment was discontinued after 2 months because of hypotension. The patient improved 1 hour after discontinuation of treatment.

Reviewer's Comments: In these publications, the BP values were not available for these cases. The time to onset was within the first week to 2 months of propranolol treatment. The dose of propranolol was between 1 and 2 mg/kg/day (0.5 mg/kg/day in one case). The events resolved after treatment cessation (3 cases documented) and did not recur after rechallenge (2 cases documented). The event led to definite discontinuation in 2 cases (the symptomatic case and the case that occurred at 2 months of treatment).

Bradycardia:

Bradycardia in the Pooled Safety Population: Heart rate was closely monitored as an indicator of bradycardia. Heart rate results indicating bradycardia (both heart rate decreases from pre-dose of ≥30 bpm and absolute heart rate values <80 bpm) appeared to be more common with the higher dose of propranolol (Table 43), but

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overall numbers were too small (1-4 patients) to make meaningful comparisons between pooled dose groups or to distinguish trends over time.

Table 43 Heart rate change from predose values on days of dose increase, by pooled dose of propranolol or placebo (Pooled Safety Population)

Predose Value Change from predose		Heart Rate (Beats/min)			
		All Placebo n=55	All Propranolol 1 mg/kg/day n=200	All Propranolol 3 mg/kg/day n=224	All Propranolol n=424
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
			1mg/kg/day	2mg/kg/day	
Day 0 Predose value		136.2 (17.4)	136.2 (16.1)	137.4 (17.8)	136.8 (17.0)
Change from predose	D0 +1H	-4.6 (21.6)	-9.5 (17.3)	-10.4 (19.0)	-10.0 (18.2)
	D0 +2H	3.4 (20.8)	-9.7 (17.5)	-10.0 (18.7)	-9.8 (18.1)
	D0 +3H	-0.6 (21.7)	-10.9 (18.2)	-10.1 (18.5)	-10.5 (18.3)
	D0 +4H	4.6 (25.5)	-9.9 (18.7)	-10.4 (20.8)	-10.1 (19.8)
			1mg/kg/day	2mg/kg/day	
Day 7 Predose value		136.4 (19.2)	128.4 (15.5)	130.0 (16.7)	129.2 (16.2)
Change from predose	D7 +1H	-1.9 (19.0)	-4.7 (16.2)	-7.4 (16.6)	-6.1 (16.5)
	D7 +2H	1.8 (17.4)	-5.8 (16.4)	-7.4 (17.0)	-6.6 (16.7)
	D7 +3H	-0.5 (18.0)	-6.3 (16.6)	-7.0 (17.0)	-6.6 (16.8)
	D7 +4H	0.4 (20.0)	-5.9 (17.6)	-7.0 (15.8)	-6.5 (16.7)
			1mg/kg/day	3mg/kg/day	
Day 14 Predose value		138.4 (16.6)	128.7 (14.6)	126.7 (17.3)	127.6 (16.1)
Change from predose	D14 +1H	-4.9 (14.5)	-5.4 (15.4)	-5.4 (16.5)	-5.4 (16.0)
	D14 +2H	-5.6 (17.4)	-5.5 (15.0)	-5.1 (16.9)	-5.3 (16.0)
	D14 +3H	-5.9 (18.0)	-6.7 (16.6)	-6.0 (17.3)	-6.3 (16.9)
	D14 +4H	-3.6 (16.7)	-4.3 (17.7)	-6.0 (17.9)	-5.2 (17.8)

Source: Table 41 in ISS

One patient had a TE SAE of bradycardia (while having an event of enterocolitis) during uptitration and 1 patient had a TEAE of bradycardia after uptitration. Of note, the decrease in heart rate observed with propranolol was observed in the first hour after dosing which continued at the same level of decrease during the 4-hour post-dose monitoring period.

Reviewer's Comments: The decrease in heart rate observed with propranolol is consistent with the known effects of propranolol. These results do not suggest that the propranolol regimen induced symptomatic bradycardia in the studied population.

Bradycardia in the Compassionate Use Program: Three SAEs of bradycardia, associated in one case with cardiac sinus pause, in another with hypotonia and malaise, and in the third associated with hypoglycemia were reported:

- **FR-2011-0464**: A 4-month-old female infant experienced bradycardia and cardiac sinus

pause while she was receiving Propranolol. At increased to 2 mg/kg/day, a 24h Holter monitoring was performed and revealed bradycardia with cardiac sinusal break. The patient was symptom-free during this period. Propranolol was discontinued and the patient did not receive any corrective treatment. The control Holter monitoring was normal.

- **FR-2012-3688**: A one-month-old female infant experienced bradycardia (<60 bpm), with symptoms of hypotonia and transient loss of consciousness the day after initiation of treatment with Propranolol. The dose reported at the time of the event was 2 mg/kg/day.
- **FR-2012-2819**: A 9-month-old male infant, experienced hypoglycemic seizure and severe bradycardia (30 bpm) related to a lack of treatment of the severe hypoglycemia. (described also under hypoglycemia).

There was an additional case of complete AV block and acute cardiac failure (fatal).

- **FR-2011-1487**: A 5-month-old female infant with 3 cm painful ulcerated IH on back started propranolol 3 mg bid, titrated to 6 mg bid after one week. Five days later, the infant developed complete AV block and heart failure during hospitalization for sclerotherapy, and died. No further details were submitted.

Bradycardia in the Scientific Publications: Nine events of bradycardia were reported as follows:

- A patient (aged between 8 weeks and 17 months at start of treatment), with IH at risk (ocular involvement, airway compromise, ulceration, and/or function impairment) was initiated with 1 mg/kg/day of propranolol (in 3 divided doses). This child also had underlying congenital hypothyroidism and was on thyroxine replacement therapy. The patient experienced bradycardia on starting propranolol, and had dose halved to 0.5 mg/kg/day from Day 1. A week later, the treatment tolerated without bradycardia, the dose was titrated to 1mg/ kg/day and was continued without problems.
- Six (6) patients with problematic IH started with propranolol at 2 mg·/kg/day in 3 divided doses (with no dose escalation performed) had a total of 6 episodes of transient asymptomatic bradycardia (defined as an HR below the fifth percentile for age) within the first day of treatment. Of these 6 episodes, the largest decrease to asymptomatic bradycardia was by 36 bpm, followed by 22 bpm; the other four episodes resulted in decreases of less than 16 bpm.
- A patient with problematic IH (functional or disfigurement risk) receiving propranolol 0.5 (first day), 1 (second day) or 2 mg/kg/day (from third day) had mild bradycardia within the first week of treatment; it resolved after cessation of propranolol and did not recur after rechallenge at lower doses.
- A ~4.5-month-old female infant with a hepatic IH and a skin IH, on oral levothyroxine, and previously unsuccessfully treated for the IH with oral prednisone, then vincristine followed by cyclophosphamide, was started with oral propranolol at a dose of 1 mg/kg/day. During the 48 hours of hospitalization, transient and asymptomatic bradycardia was observed. Treatment with propranolol was discontinued when the patient was 14 months old.

The administered dose of propranolol was between 1 and 2 mg/kg/day (possibly 0.5 mg/kg/day in one case). Value of heart rate was not available for any case, but in 6 cases the HR was reported as below the fifth percentile for age. No symptoms were reported in all cases. Time to onset was noted to be within the first two days of treatment. All events were transient, resolved after dose decrease or temporary

discontinuation, and did not recur with dose re-increase or re-challenge (2 documented cases) or with propranolol continuation.

7.4.4 Electrocardiograms (ECGs)

PR interval in the Pooled Safety Population: Propranolol is known to be associated with AV block intensification and PR interval prolongation. Electrocardiograms (ECGs) were monitored on the days of dose increase (Table 44) and throughout the study.

Table 44 PR interval change from predose values on days of dose increase, by pooled dose of propranolol or placebo (Pooled Safety Population)

Predose Value Change from predose		PR Interval (milliseconds)			
		All Placebo n=55	All Propranolol 1 mg/kg/day n=200	All Propranolol 3 mg/kg/day n=224	All Propranolol n=424
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Day 0 Predose value		101.51 (15.41)	100.03 (15.22)	103.29 (15.67)	101.75 (15.52)
			1mg/kg/day	**1mg/kg/day**	**1mg/kg/day**
Change from predose	D0 +2H D0 +4H	1.85 (14.76) 2.31 (13.61)	11.42 (14.38) 11.36 (15.13)	10.28 (15.86) 10.12 (14.88)	10.82 (15.17) 10.69 (14.99)
Day 7 Predose value		99.09 (17.16)	104.31 (15.76)	105.63 (15.24)	105.01 (15.48)
			1mg/kg/day	**2mg/kg/day**	
Change from predose	D7 +2H D7 +4H	1.40 (17.55) 2.13 (16.95)	4.43 (12.66) 4.78 (13.38)	5.30 (13.40) 6.68 (14.25)	4.90 (13.05) 5.79 (13.87)
Day 14 Predose value		98.38 (15.49)	106.28 (16.84)	109.16 (17.67)	107.82 (17.33)
			1mg/kg/day	**3mg/kg/day**	
Change from predose	D14 +2H D14 +4H	2.00 (7.44) 0.51 (10.00)	2.38 (13.80) 4.22 (13.70)	4.77 (14.57) 5.43 (25.15)	3.67 (14.25) 4.86 (20.59)

Source: Table 47 in ISS

The PR interval increased from the predose values at +2h and +4h on each day of dose increase, with a greater increase observed with propranolol than with placebo (maximum increase: 11.42 ms on propranolol at 1 mg/kg/day). After the uptitration period, increases from baseline in PR interval were greater with propranolol than with placebo (maximum increase: 9.89 ms on propranolol at 1 mg/kg/day at Week 24).

Reviewer's comment: The PR interval prolongation observed with propranolol is consistent with the known effects of propranolol and its physiological increase with age.

QT interval in the Pooled Safety Population: Mean QT_c calculated with the Bazett formula was 409.4 ms (SD: 27.9). Mean QT_c calculated with the Fridericia formula was 354.7 (SD: 23.9) and mean QT_c calculated using the formula for pediatric population was 369.2 (SD: 24.7). One patient had a Bazett QT_c above 480 ms in the 3 mg/kg/day 3 months arm (patient 810115: Bazett QT_c 496 ms, Fridericia QT_c: 404 ms, pediatric QT_c: 427.8 ms, HR was 205/min). No patients had Fridericia or pediatric QT_c > 450 ms.

TEAEs of QT prolongation were reported for 3 patients during uptitration and 1 patient after uptitration. These TEAEs were asymptomatic and were not large prolongations.

Reviewer's Comments: Propranolol is not known to prolong the QT interval. The results indicate that the propranolol regimen does not induce QT interval prolongation in the indicated infant population.

ECGs in the Compassionate Use Program: Not reported.

ECGs in Scientific Publications: No reports indicating a safety signal were found.

Cardiac ultrasound in the Pooled Safety Population: Five patients had clinically significant abnormalities in 2D cardiac ultrasound examination, two in the placebo arm, one in the 1 mg/kg/day 3 months arm, one in the 1 mg/kg/day 6 months arm and one in the 3 mg/kg/day 3 months arm.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See Section 7.2.2.

7.5.2 Time Dependency for Adverse Events

Pooled Safety Population: TEAEs mostly occurred before or on the Week 12 visit. TEAEs that were more evenly distributed throughout the study tended to be non-specific childhood events such as teething, cough, URTI, bronchitis and bronchiolitis.

Compassionate Use Program: Not reported.

Scientific Publications: For the ADRs that were reported in the scientific publications, very little data were provided regarding the severity, relationship to treatment, and time of onset of each individual event. From the narratives, the only ADRS for which detailed time of onset was reported are: hypotension, diarrhea, and cold extremities which were noted to occur within the first days (<5 days) of propranolol treatment, and two events of asymptomatic hypotension and one event of heart rate 80 bpm occurred within 3 hours of treatment initiation.

7.5.3 Drug-Demographic Interactions

Pooled Safety Population: No notable differences in the safety profile were found in an analysis of patient subgroups (age, sex, IH localization, prematurity, or birth weight).

7.5.4 Drug-Disease Interactions

Pooled Safety Population: Not studied.

Compassionate Use Program and Scientific Literature: From an analysis of patients with high risk IH in the CUP and scientific literature, the safety profile in these cases appear equivalent to that of the pooled safety population. No new safety signal was identified.

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7.5.5 Drug-Drug Interactions

At the top-line meeting on 07-Dec-2012, Pierre Fabre stated that owing to the extensive knowledge accumulated with propranolol over the years in the adult population, and to ethical limitations associated with performing drug-drug interaction studies in infants, they did not carry out any specific interaction studies on the product and proposed to include in the corresponding sections of the PI the already known interactions of propranolol, adapted to the target population (infants).

The sponsor's proposal appears reasonable.

7.6 Additional Safety Evaluations

7.6.3 Pediatrics and Assessment of Effects on Growth

Pooled Safety Population: In Section 7.7.2 Postmarket Requirements and Commitments of this review, I recommend that the Division suggest to the sponsor to keep a registry of patients in Study 201 and Study 102, and follow them for any effect of propranolol on their growth and developmental milestones.

Compassionate Use Program: According to the Protocol for therapeutic use, prescribers will schedule 2 follow-up visits (at 12 and 24 months after treatment discontinuation) for patients who have been treated for at least 3 months. These visits will evaluate the neurological development and the growth of the patient.

7.6.4 Overdose, Drug Abuse Potential / Withdrawal and Rebound

Overdose:

Pooled Safety Population***:*** One patient on propranolol had a TEAE of overdose in the pooled safety population (evening dose of 0.5 mg/kg administered twice on one occasion) which was asymptomatic.

Compassionate Use Program***:*** One patient had an ADR of overdose in the CUP (1 mg/kg dose administered twice on one occasion) which was asymptomatic.

Scientific Publications***:*** 7 cases of propranolol overdose were reported in the scientific publications, of which 3 were symptomatic:

- Moderate hypotension in a patient having ingested a dose "10-fold higher than prescribed" (prescribed dosing not available) (Sanchez-Carpintero 2011),
- Severe hypoglycemic seizures within 2 weeks of treatment initiation in a patient having received twice the desired 2.5 mg/kg/day dose (Blatt et al. 2011),
- Restlessness, euphory and insomnia in a patient having received 10 times the dose (i.e., 20 mg/kg) (Zegpi-Trueba 2012).

In the asymptomatic 4 other cases, the administered overdose was: 4 mg/kg/day for 2 weeks, 8 mg/kg/day for 8 weeks, 5 mg for the first dose, and preparation from 40 mg tablets instead of 10 mg tablets for four doses (Haider 2010, Janmohamed 2011

[2 cases], and Phillips 2012, respectively).

Withdrawal: In the pooled safety population, the two regimens of 3 months propranolol followed by 3 months of placebo allowed evaluation of a withdrawal effect. TEAEs mostly occurred before or on the Week 12 visit. TEAEs that were more evenly distributed throughout the study tended to be non-specific childhood events such as teething, cough, URTI, bronchitis and bronchiolitis.

In these two regimens, all instances of "the patient's condition aggravated and drug ineffective" occurred in the 2nd 3 month phase, under treatment with placebo. For Study 201 in which SAE data is available for the follow-up period (after W24/EOT), SAEs that occurred in this period were sporadic, with no signal of withdrawal. The sponsor will submit follow-up safety data post-treatment withdrawal when the long term data to Week 96 become available and have been analyzed in 2014.

Rebound: Regrowth of IH after cessation of propranolol treatment, may occur in approximately 5% to 25% of patients, but less than 10% of patients require re-introduction of therapy. When re-treatment is required, the outcome is successful in almost all cases.

7.6.5 New safety signals reported

During the period 13-Oct-2012 to 12-Apr-2013 in Study 301, the sponsor reported 2 new safety signals from the analysis of the currently available data:

- Five (5) non serious cases of vasoconstriction were identified during the CUP. Although vasoconstriction is a pharmacologically well-known effect of propranolol, no cases were reported during the clinical development.
- In the literature review performed during the reference period, a Chinese publication reporting agranulocytosis in an 11-month-old infant treated with oral solution of propranolol (2 mg/kg/day) was identified.[62]

7.7 Additional Submissions / Safety Issues

7.7.1 Risk Management Plan

Regarding the drug product propranolol itself, its safety profile has been extensively documented over several decades of clinical use in adult patients, and in infants with cardiology indications.

For use in infants, the following risks were identified and evaluated in the submission: bradycardia, hypotension, hypoglycemia and exacerbation of bronchospasm/ bronchiolitis. The data in the submission in which patients were monitored during the clinical study and on the days of dose increments indicated that:

(i) the heart rate is the most adequate parameter to follow, and that a monitoring period of 2 hours post-treatment is sufficient to detect bradycardia; and

(ii) blood glucose monitoring on the days of uptitration did not reveal any signals of

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hypoglycemia that would be of concern, suggesting that hypoglycemia can be prevented with proper education of parents and guardians/caregivers on the importance of administrating propranolol oral solution during or right after a feeding.

The purpose of a REMS is to help the patient and/or the physician reduce the risks of a potentially fatal or serious adverse event.

The FDA Medication Guide Requirements Final Rule[63] states that:

(a) Medication Guides start with a presentation of the most important information patients should know about the product to use it safely and effectively, i.e., why the product poses a serious and significant public health concern requiring distribution of FDA-approved written patient information,

(b) Medication Guides will be required only for drug products of ''serious and significant concern," and

(c) "FDA now estimates that on average no more than 5 to 10 products per year would be determined to be of "serious and significant concern" and would thus require Medication Guides."

In the case of oral propranolol solution to treat IH in infants, a Medication Guide will not serve this purpose because

(i) hypoglycemia is prevented by frequent feeding or feeding during and immediately after the oral administration; parental education is the effective measure, and

(ii) reduction in heart rate and blood pressure observed were usually asymptomatic, with rapid development of tolerance to propranolol, and with only very rare instances reported in the literature.

New § 208.1(c) of the Final Rule[63] describes *when* FDA may require a Medication Guide. Patient labeling will be required if the agency determines that one or more of the following circumstances exists:

(1) The drug product is one for which patient labeling could help prevent serious adverse effects.

(2) The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product.

(3) The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness. FDA believes that these circumstances will apply to a very small group of products.

Oral propranolol solution does not fit the Medication Guide statutes 2 and 3 (because the benefit is definitely and evidently much more than a "potential" risk of hypoglycemia, and patient adherence to directions for use is not crucial for "effectiveness"). It does not fit the very broad Medication Guide statue 1, because a "potential" for symptomatic hypoglycemia – which is not reported in the pivotal study, and reported rarely only in CUP and medical literature where there are associated conditions (fasting, vomiting, febrile illness, etc.) contributing to hypoglycemia or where hypoglycemia is not

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documented by blood glucose levels – does not qualify as an adverse effect of ‘‘serious and significant concern” as, for example, liver failure, agranulocytosis, *torsade de pointes* or intracranial bleeding, etc.

Reviewer's comments: Infants have lower glycogen stores (leading to a reduced fasting ability) and their glucose utilization rates are higher in the fasting state (by as much as 3-fold in the case of infants) partly due to their great brain mass relative to their body weight.[64] Propranolol may impair glucose homeostasis through inhibition of β-adrenergic mediated glycogenolysis, gluconeogenesis and lipolysis, and, therefore, propranolol can put the infants at risk of hypoglycemia.

I found eleven hypoglycemia (ten symptomatic) cases associated with propranolol therapy for IH reported in the literature (Table 45). In eight cases, an additional stressor such as an acute infection, prolonged fasting or oral corticosteroids causing adrenal insufficiency have been present and assumed to have precipitated all but one of these cases,[65,66,67,68] and two other cases were beyond the age group indicated (11 and 18 months old) at the time of starting treatment (see below).[69]

Table 45 Number of patients with submission-specific AEs

AE	Clinical Studies	CUP	Literature (case reports)
Symptomatic Hypoglycemia	0*	4	10§
Symptomatic Bradycardia	0*	2	1
Symptomatic Hypotension	0*	2	3
Bronchospasm/bronchiolitis exacerbation	4†	7	--

*There were 2 patients each with asymptomatic hypoglycemia or asymptomatic bradycardia, and 6 with asymptomatic hypotension.
†2 patients were on placebo; CUP = Compassionate Use Program. §11 patients, 10 symptomatic (see Section 7.4.2 of this review)

There were no cases of hypoglycemia in the clinical trials in this NDA.

In the CUP, there were four cases of hypoglycemia (Table 45). Two had symptoms (hypoglycemic seizure); both resulted from failure to give feeds to the child before administering propranolol, and in both there was no documentation of blood glucose levels so the probable cause of seizure is determined by “clinical reasoning.” It is also noteworthy that in these infants, propranolol was continued or re-administered without recurrence of hypoglycemia. (See Section 7.4.2 of this clinical review for details.)

The following two clinical studies describe the US experience with infants administered oral administration to treat IH:

- A recent US study[69] reported 3 patients with symptomatic hypoglycemia (documented by blood glucose levels) during treatment with propranolol (off-label use, given 2 mg/kg/day in 3 divided doses) for their IH. However, 2 of these 3 patients were beyond the age group indicated at the time of starting treatment (one was 11 months old, and the other 18 months old); both should not have been treated with propranolol as they have aged beyond the actively proliferating phase of IH (5 weeks to 5 months). The third patient, a 5-week old girl, was on propranolol 2 mg/kg/day for 8.5 months without AEs and with marked improvement

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of her IH. At the age of 10 months, she was found limp and pale 2½ hours after having a normal breakfast and receiving her morning dose of propranolol; the serum glucose was 20 mg/dL. This child had had symptoms of cough and runny nose 1 day prior, and a positive nasopharyngeal swab for respiratory syncytial virus. She was discharged from hospital the next day, and resumed propranolol treatment (2 mg/kg/day in 3 divided doses) for IH.

- In a recent study at the Yale Pediatric Vascular Anomalies Clinic, 31 children with IH were hospitalized for 24 hours during which they were administered oral propranolol at a dose of 2 mg/kg/day (no uptitration was done) and monitored for heart rate, BP and blood glucose at baseline and 1 to 3 hours before and after each dose.[70] Following oral propranolol administration, the heart rate decreased by 5 beats per minute (P<0.01) and systolic BP decreased by 4 mmHg (P<0.01) with no significant changes in diastolic BP or blood glucose; none were symptomatic, and all normalized within hours. Over the first 3 doses of propranolol administration, the effect on heart rate became attenuated suggesting rapid development of tolerance. The finding that there was no statistically significant decrease in blood glucose with oral propranolol therapy suggests that because the infants were frequent feeders, parental education on frequent feeding had been effective in preventing hypoglycemia. This study suggests that hospitalization for 24- to 48 hours during the initiation of propranolol therapy is not necessary, is costly, is disruptive to family life, and places the infants at risk of nosocomial infections, and that parental education on frequent feedings to decrease the chance of hypoglycemia was as effective as 24-hour hospitalization. These cases highlight the importance of frequent feedings; therefore, parental education on frequent feeding is an important and effective mechanism to prevent episodes of hypoglycemia.

Therefore, I think the emphasis should be to educate parents and caregivers to give frequent feeding, and/or to give feeds with the drug, which will be more effective to prevent hypoglycemia than a Medication Guide which is not appropriate and may detract from the message to give feeds to prevent hypoglycemia.

Based on the clinical data in the application (both in the controlled clinical trial and in the CUP) and comprehensive safety data reported in the medical literature, my opinion is that neither a REMS nor a Medication Guide is necessary for approval.

A physician communication plan does not help the patient or the physician because the application-specific adverse events are very rare at the symptomatic level. Symptomatic bradycardia and hypotension are rare; only three cases of symptomatic hypotension and one case of symptomatic bradycardia were reported in the medical literature (Table 45) with use of oral propranolol solution for the treatment of IH.[16] While the drop in BP persisted (antihypertensive effect) during treatment, the initial decrease in heart rate normalized over subsequent doses, suggesting rapid development of tolerance. Acute exacerbation of bronchospasm or bronchiolitis, which, too, is rare (Table 45), can be recognized by parents and guardians from the audible wheeze the child develops.

The sponsor also proposed to include the following statement in the PI:

(b) (4)

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(b) (4)

The above proposal appears reasonable.

Based on the above considerations, my opinion is that neither a REMS nor a Medication Guide is necessary for approval.

7.7.2 Postmarket Requirements and Commitments

None. However, I recommend that at the time of approval, the Division suggests to the sponsor in the approval letter to conduct the following studies:

(1) Keep a registry of all pediatric patients treated with propranolol in Studies 201 and 102 and follow them over the next 5-7 years for any effect of propranolol on their growth and developmental milestones. The following measures are examples of data that may be recorded and followed:

- Anthropometry to follow *physical growth* in pre-school age: weight, weight for age, weight for height; height, height for age; comparison to national/regional standards
- *Gross motor*: use of large groups of muscles to sit, stand, walk, run, etc., keeping balance, and changing positions.
- *Fine motor*: using hands to be able to eat, draw, dress, play, write, and do many other things.
- *Language*: speaking, using body language and gestures, communicating, and understanding what others say.
- Cognitive development: Thinking skills: including learning, understanding, problem-solving, reasoning, and remembering.
- *Social and emotional development*: Interacting with others, having relationships with family, friends, and teachers, cooperating, and responding to the feelings of others.

Justification: Studies in humans[1,2] indicates that prenatal beta blockade induces long-term neurological complications including impaired school performance, cognitive impairment, and psychiatric disorders; however, no studies to date have examined the long term neurological effects of acute or chronic beta blockade in one to two year old children. Extensive animal studies demonstrate that beta blockade in neonates induces long lasting neurological effects because of the inability of neonatal neural tissue to desensitize to beta adrenergic response,[3] and pre- and post natal modulation of beta adrenergic receptors with propranolol affects the long term levels of the noradrenaline metabolite 3-methoxy 4-hydroxyphenylglycol (MHPG) in the frontal cortex and striatum and serotonin signaling in the frontal cortex,[4] and induces a long term supersensitivity of the presynaptic alpha 2-adrenoceptor.[5]

While propranolol should definitely be used as a first line treatment in children suffering from disfiguring and/or life-threatening IHs, it should not be used in a

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widespread manner to treat merely cosmetic IHs. Appropriately controlled long term studies should be planned to evaluate the impact of use of propranolol in neonates and infants on their neurological, psychological and physical growth and development.

(2) Conduct a clinical trial of propranolol to show the effect of duration and dose of propranolol treatment:
   (a) comparing 2 mg/kg/day x 12 months vs 3 mg/kg/day x 6 months,
   (b) in all types of IH, including patients with PHACES syndrome, life-threatening IH, function-threatening IH, disfiguring IH, IH with ulcers and severe IH, and
   (c) using different clinical endpoints in addition to the number/proportion of patients who achieved complete/near complete resolution and time to resolution (e.g., rate, time and extent (nature) of regrowth, need for systemic retreatment with propranolol, need for local (topical) retreatment with beta-blockers, need for systemic retreatment with corticosteroids, etc.).

Justification: There is a varying regrowth rate of 6 – 12% after treatment of IH with propranolol 3 mg/kg/day x 6 months. According to the pathophysiology and natural history of IH, the active proliferative phase lasts from 5 weeks to about 14 months of life.[6] It is possible that the 6 months' treatment might not have covered the entire active proliferative phase in the patients who had regrowth. There is also the possibility of causing propranolol-resistant IH (PRIH) with an inadequate duration of treatment.[7] "Rebound growth" of focal hemangiomas have been reported after cessation of steroids as well as propranolol[8,9] whereas rebound growth after surgical resection is extremely unlikely.

8 Postmarket Experience

There is no post-marketing experience for the drug product for this indication in the proposed patient population of pediatric patients with IH.

9 Appendices

9.1 Literature Review/References

The sponsor submitted 17 key publications selected on the basis of their robust study designs and analysis of quantitative data for treating patients with IH. These are discussed in section 6.1.10 of this clinical review. Other relevant new information in the medical literature in the context of propranolol for IH is presented below.

A multicenter (14 centers in France), retrospective, observational study of 1130 patients treated with IH[7] showed that 10 (0.9%) had propranolol-resistant IH (PRIH), which was

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defined as no response to propranolol 2 mg/kg/day or 3 mg/kg/day after 4 weeks. The study found that PRIH occurred at all ages during early childhood and all proliferation stages, and in 2 patients after a short treatment interruption (designated secondary PRIH, although it is not known whether interrupting therapy could have triggered resistance.). There was a possibility that some IH that were not considered resistant in the study could have been due to spontaneous regression of IH that was propranolol resistant. Three PRIH cases received adjunctive systemic corticosteroids and achieved rapid responses, suggesting the possibility of a synergistic effect or systemic cortico-steroid effect; for PRIH adjunctive corticosteroids could be a useful second-line therapy.

A new AE of agranulocytosis was reported in one of 97 infants with IH treated with propranolol in a Chinese study[62]. Agranulocytosis (WBC count of 2.8 x 10^9/L and neutrophil count of 0.4 x 10^9/L) was found in an 11-month-old infant with IH who presented with fever (38.6^{o}C) after being administered propranolol (2 mg/kg/day) for 3 weeks. Bone marrow and viral serologic tests ruled out primary or virus-associated agranulocytosis. After discontinuation of propranolol and therapy with an anti-infective agent and granulocyte colony stimulating factor for 1 month, the patient recovered and blood parameters returned to normal.

9.2 Labeling Recommendations

9.2.1 Indications and usage

The indication and usage section of the label appears appropriate.

9.2.2 Dose considerations

As stated in Section 6.1.8 of this review, there is no clear dose-response, but the dose of 3 mg/kg/day in two divided doses appears to be the most appropriate. It is important to emphasize in the label that to prevent hypoglycemia the dose must be administered during or right after a feeding, and that regular feedings be maintained (also mentioned in Section 5.1 of the label).

9.2.3 Contraindications

This section in the label appears appropriate.

9.2.4 Warnings and Precautions

I modified this section to present Hypoglycemia first as the most important risk for an adverse event, and to emphasize feeding (both to maintain regular feedings and to give feeding with the dose of propranolol) to prevent hypoglycemia.

9.3 Advisory Committee Meeting

Not applicable.

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9.4 Detailed description of individual studies

9.4.1 Pivotal Study 201

TITLE: Protocol # V00400 SB 201: *"A randomized, controlled, multidose, multicentre, adaptive Phase II/III study in infants with proliferating infantile hemangiomas requiring systemic therapy to compare four regimens of propranolol (1 or 3 mg/kg/day for 3 or 6 months) to placebo (double-blind)."*

Note: Only the details of Study 201 that have not been described earlier in Sections 5, 6 and 7 of this review will be presented here.

Primary Objective: To identify the appropriate dose and duration of propranolol treatment and demonstrate its superiority over placebo based on the complete/nearly complete resolution of target IH at W24.

Safety objective: To document the safety profile of the four regimens of propranolol in the treatment of IH in infants aged 1 to 5 months at inclusion.

Long term objective: To study the long-term efficacy and safety of the four regimens of propranolol in the treatment of IH.

Investigator and sites: Christine Leaute-Labreze, MD, Bordeaux Hospital, France. Approx. 60 centers worldwide specialized in the management of hemangiomas.

Inclusion criteria: The patient is 35 to 150 days old, inclusive, at inclusion

Exclusion criteria: The patient was born prematurely and has not yet reached his/her term equivalent age (*e.g.* an infant born 2 months prematurely cannot be included before the age of 2 months)

Age at inclusion:
- Assuming 38-42 gestational weeks = full term
- Patients can only be included as of 5 weeks (35 days) of age
- So if an infant was born X days prior to the (38-5) 33rd gestational week, then the patient can only be included as of the age of 35 + X days
- For example, if the infant was 50 days premature, the infant cannot be included in the study until the age of 50 + 35 days or more

Experimental Design: Presented in Section 5 of this clinical review.

The trial conduct can be summarized as:
- The interim analysis (for regimen selection) was performed on the first 190 randomized (188 treated) patients from all five regimens having completed Week 24 (or prematurely withdrawn from treatment).
- After the interim analysis, all patients were kept in their randomization group.
- The total planned treatment duration was 6 months (24 weeks) even in the 3-month regimens that subsequently received placebo for a further 3 months.
- The primary efficacy criterion was evaluated at Week 24 (or premature discontinuation of treatment) for all patients, even in the unselected regimens.

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- The primary efficacy analysis did not concern the data from the Stage 2 patients randomized to the unselected regimens (referred to as "overrun" patients). However, a post-hoc analysis of the primary efficacy criterion for all patients treated has been performed (Section 2.7.3.3.3.4).

Type 1 and Type 2 evaluations are presented in Section 6 of this review. Type 1 and Type 2 combined image evaluation sessions were carried out by two blinded independent readers on batches of no more than 30 paired groups of photographs of the same type. The random order in which photographs were presented on a screen for assessment in paired sessions was different for each reader. No patient information was available to the independent readers.

After paired sessions were carried out, the independent readers were brought together for consensus meetings to discuss any discrepancies between two independent evaluations of the same type for the same paired groups of photographs. The consensus reached for the discrepant evaluations was considered final for use in all efficacy analyses.

Centralized quantitative assessments of the change in size and color density of the target IH at W12 and W24 compared directly to baseline were also performed for secondary efficacy analysis.

If a patient prematurely discontinued study treatment and/or received concomitant treatments that could be used to treat IH (*e.g.* corticosteroids, imiquimod, vincristine, alfa-interferon, beta-blockers or laser therapy), centralized assessments were carried out on photographs taken after the discontinuation of study treatment and/or the start of concomitant treatment (See Table 14).

Safety was assessed by the analysis of adverse events (AEs), safety laboratory investigations including pin-prick glycemia, physical examination findings (including height, weight, head circumference, pulmonary auscultation, and liver palpation measurements), vital signs, electrocardiogram (ECG) measurements, and neurodevelopment evaluation.

The following medications were prohibited for the patient at any time prior to or during the study:
- Systemic (oral, intra-venous or intra-muscular), intra-lesional or topical corticosteroids
- Imiquimod
- Vincristine
- Alfa-interferon
- Propranolol or other beta-blockers

Beta-blockers (including propranolol) were also prohibited for the mother prior to and during the study if she was breastfeeding the infant at the same time. The following medications were also prohibited for the mother within 14 days of randomization or during the study if she was breastfeeding the infant:
- Systemic (oral, intra-venous or intra-muscular) corticosteroids
- Vincristine
- Alfa-interferon

The study procedures, treatment flow chart and recruitment and follow-up procedures are outlined, respectively in Figure 16.

Figure 16 Study Procedures

Procedure		Treatment period										Follow-up period			
	Screening[1]	D0	D7 +/-1 day	D14 +/-1 day	D21 +/-1 day	W5 +/-3 days	W8 +/-3 days	W12 +/-3 days	W16 +/-3 days	W20 +/-3 days	W24 +/-3 days	W36 +/-7 days	W48 +/-7 days	W72 +/-7 days	W96/EOS +/-7 days
Informed consent	X														
Inclusion/exclusion criteria	X	X													
Review demographics	X														
Review medical history	X														
Randomisation (treatment assignment)		X													
Physical examination	X	X[2]	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (height, weight, head circum., temperature, HR, BP, RR, pulmonary auscultation, liver palpation) and glycaemia (pin-prick)[3]	X	X[2,4]	X[4]	X[4]	X	X	X	X	X	X	X	X	X	X	X
Neurodevelopment assessment	X										X				X
Two-dimensional cardiac ultrasound	X														X
ECG (evaluated by an independent physician from D0 to W24, inclusive)	X	X[2,4]	X[4]	X[4]	X			X			X	X	X	X	X
Laboratory examinations[5]	X							X			X				
Photographs of target IH based on standardised procedures		X	X	X	X	X	X	X	X	X	X	X	X	X	X
On-site qualitative assessments of efficacy[6]			X	X	X	X	X	X	X	X	X	X	X	X	X
Centralised qualitative assessment of efficacy								X	X	X	X				
Centralised quantitative assessments of target IH size and colour density		X						X			X				
Assessment of functional impairment related to target IH	X	X[2]	X	X	X	X	X	X	X	X	X	X	X	X	X
Scarring assessment												X	X	X	X
Review adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IVRS call	X[7]	X									X				
Demonstration of the use of study drug		X													
Dispense study drug to parent(s) or guardian(s)[8]		X	X	X	X	X	X	X	X	X					
Review previous/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect study drug and perform compliance assessment			X	X	X	X	X	X	X	X	X				

1. Same day as D0 if all procedures can be performed in one day (no more than D-14) 2. Not applicable if already performed at screening on D0 3. Glycaemia (pin-prick) only at D0, D7 and D14 (see Footnote 4)
4. Temperature, heart rate, blood pressure, respiratory rate and pulmonary auscultation will be measured before the first administration of a new or dummy dose of study drug and every hour for 4 hours after the first administration. Glycaemia (pin-prick) measured before administration and at 120 and 240 min after intake
5. Hematology: Hb, Hct, MCV, MCH, MCHC, RBC, reticulocyte count, WBC, platelet count and differential WBC (total and segmented neutrophils, bands, lymphocytes, monocytes, basophils and eosinophils) Chemistry: Total bilirubin, creatinine, glucose, AST, ALT, GGT, alkaline phosphatase, total proteins, K, Na, Cl;, Ca
6. Qualitative assessments of IH at screening, D0 (if screening not on D0) and each post-baseline scheduled visit. Includes target IH efficacy assessments (investigator & parent[s]) at each post-baseline scheduled visit compared to the previous scheduled
7. IVRS call to generate the patient's screening visit in the eCRF. The IVRS must also be called to report a screen failure
8. Twice daily (morning and late afternoon) treatment administration from D0 to W24 (on-site for the first administration of a new or dummy dose of study drug at D0, D7 and D14)
9. Diary filled in by parents and reviewed by investigators at each visit
10. If the first visit after last treatment intake (EOT visit) is prior to W24, the IVRS must be called to notify the EOT and the procedures planned at the next scheduled visit must be performed (prior to starting a new IH treatment, if applicable) along with the following procedures: laboratory examinations, ECG and neurodevelopment assessment. For patients who prematurely discontinue treatment on or prior to W20, only the W24 visit (excluding the laboratory examinations, ECG and IVRS call) and all follow-up visits (W36, W48, W72, W96/EOS) need to be performed after the EOT visit

Results

Patient Disposition: Presented in Section 6.1.3.

Data Sets Analyzed: See Section 6.1.2 of this review.

Baseline Demographic Characteristics: See Section 6.1.2 of this review.

Medical History and Concomitant Diseases: The most frequent medical history reported was jaundice (and neonatal jaundice) reported in 22 patients, followed by neonatal respiratory distress syndrome, prematurity, and respiratory distress, each reported in 8 patients; anemia in 7 patients; infantile colic, circumcision, conjunctivitis, constipation, and gastro esophageal reflux disease, each in 5 patients. Neonatal hyperbilirubinemia, neonatal hypoglycemia, and infantile apneic attack were reported in 4 patients. Hyperglycemia, nasopharyngitis, bradycardia, bronchiolitis, dyspepsia, fetal growth restriction, hyperbilirubinemia, and hypoglycemia were reported in 3 patients.

The most common concomitant diseases (observed in >5 patients) were: anemia (18 patients), atrial septal defect (17 patients), gastro esophageal reflux (13 patients), infantile colic (9 patients), constipation (7 patients), and eczema (6 patients).

Vital Signs, Physical Examination, ECG, and Cardiac Ultrasound Baseline Characteristics: Mean (SD) height was 60.1 (4.1) cm, weight was 5.9 (1.1) kg, body surface area was 0.31 (0.04) m^2, and head circumference was 40.0 (2.0) cm. Mean (SD) heart rate was 136 (17) bpm; systolic BP (SBP) was 92 (14) mmHg, and diastolic BP (DBP) was 55 (12) mmHg. The mean (SD) temperature was 36.7 (0.4)°C and mean (SD) respiratory rate at baseline was 43 (11) breaths per min.

Eleven patients (2.4%) had clinically significant abnormalities at physical examination at baseline, 1 in the placebo 6 months regimen, 2 in the 1 mg/kg/day 3 months regimen, 2 in the 1 mg/kg/day 6 months regimen (notably tachycardia at 180), 4 in the 3 mg/kg/day 3 months regimen, and 2 in the 3 mg/kg/day 6 months regimen. One patient in the 1 mg/kg/day 3 months regimen had clinically significant abnormalities at pulmonary auscultation (substernal systolic murmur II/VI parasternal). One patient in the placebo arm had an abnormality in neurodevelopmental assessment (slightly elevated axial muscular tension).

One single patient had a QT interval corrected for heart rate using Bazett formula (QTcB) above 480 ms in the 3 mg/kg/day 3 months regimen (QTcB 496 ms, QT interval corrected for heart rate using Fridericia formula [QTcF]: 404 ms, QT interval corrected for heart rate in the pediatric population [QTcP]: 427.8 ms, heart rate was 205/min); no patient had QTcF or QTcP above 450 ms.

Five patients had clinically significant abnormalities in the 2-D cardiac ultrasound examination, two in the placebo 6 months regimen (left-to-right shunt, patent foramen ovale or atrio-septal defect II and intraventricular septal defect with aneurysm without blood flow - no hemodynamic changes), 1 in 1 mg/kg/day 3 months regimen (atrio-septal defect II 4 mm), 1 in 1 mg/kg/day 6 months regimen (2-3 small apical ventriculo-septal defects), and 1 in 3 mg/kg/day 3 months regimen (patent foramen ovale).

Target Hemangioma Baseline Characteristics: Regarding baseline IH characteristics, the study population was consistent with the study protocol and representative of the population of IH, except the high risk cases of IH that were excluded by the protocol: the mean (SD) age at IH onset was 15.5 (21.7) days; the majority of patients had IH that were localized (89.0%), 5.5% had segmental IH, and 5.5% had indeterminate subtype; in terms of localization, 69.7% had facial IH and 30.3% had non-facial IH; all IH with a superficial component, the majority with some degree of elevation (91.9%) and 52.9% had a definite deep component.

The most frequent IH localizations (>5%) were the cheek (12.9%), forehead (10.7%), perioral, lower or upper lip region (9.0%), scalp (8.6%), periocular region (7.2%), nasal tip (6.1%), and chest (5.5%). Only 6 patients (1.3%) had anomalies associated with the target IH: PHACE syndrome (posterior fossa brain anomalies, hemangiomas, arterial anomalies and cardiac defects and coarctation of the aorta, eye abnormalities and sternal abnormalities or ventral developmental defects) without central nervous system (CNS) involvement in 1 patient and other anomalies in 5 patients.

Interim Analysis See Section 6.1.4 of this review.

Primary Efficacy (Week 24) Analysis Results: See Section 6.1.4 of this review.

Results of the secondary endpoints: See Section 6.1.5 of this review.

Sample size: Approximately 450 patients were randomized overall (assuming that the IDMC did not recommend that the sample size be increased at the interim analysis).

Assuming 20% (for 1 mg/kg/day, 3 months), 30% (for 1 mg/kg/day, 6 months), 40% (for 3 mg/kg/day, 3 months) and 55% (for 3 mg/kg/day, 6 months) success rates (complete/nearly complete resolution of the target IH at W24) on the propranolol regimens and a 10% success rate on placebo, a total of 90 evaluable patients (36 in Stage 1 and 54 in Stage 2) on each regimen of propranolol selected at the interim analysis and 45 evaluable patients (18 in Stage 1 and 27 in Stage 2) on placebo would provide 98.4% power (if the most efficacious regimen at the interim analysis was selected) and 78.9% power (if the second most efficacious was selected) to test for superiority of propranolol over placebo with a maximum overall one-sided type I error rate of 0.005.

Stratification: Age 35 ~ 90 days / 91 ~ 150 days old at randomization, and IH localization as facial / non-facial. These factors were studied by the IDMC at the interim and final analyses.

Statistical Methods: The primary analysis was to test for superiority of the selected regimen(s) of propranolol *versus* placebo. The *p*-values from the first and second stages of the study were combined using the weighted inverse normal combination function. Simes' method was used to define an adjusted first stage *p*-value (and an adjusted second stage *p* value in the case where two regimens were chosen at the interim analysis) to ensure that the type I error rate was controlled at less than or equal to a nominal one-sided significance level of 0.005.

The primary efficacy analysis data set was the intention-to-treat (ITT) data set. The study was, however, powered based on the per protocol (PP) analysis of the primary efficacy endpoint. Assuming up to 10% of the patients in the ITT data set were excluded from the PP data set, a total of 100 patients were required to be randomized to each propranolol regimen studied in the primary analysis and 50 patients to placebo.

For the key secondary efficacy analysis at W48, a combination test computed in the same way as the primary endpoint was used to analyze success/failure based on the investigator on-site qualitative assessment of complete resolution of the target IH at W48. If the primary null hypothesis was rejected at the one-sided 0.005 significance level, the closed test procedure then allowed the key secondary endpoint to be tested on the ITT data set while maintaining the overall type I error rate at a nominal one-sided significance level ≤ 0.005.

Analyses of the safety criteria were carried out on the safety data set.

Long term follow-up analyses*:* Analyses of the follow-up period were made on the ITT data set after all patients had completed visit W96/EOS to assess stability of the response and long term tolerability of study treatments. If more than 10.0% of the ITT data set were excluded from the Per Protocol data set, the analysis was repeated on the PP data set.

The interim analysis was carried out after the first 40 patients randomized to each of the 4 propranolol regimens and the first 20 patients randomized to placebo had completed their W24 visit or been withdrawn prematurely from study therapy. The interim analysis was then performed (approx. 1 month).

If the study was to continue, one or two regimens of propranolol with good efficacy and tolerability would be selected for further investigation *versus* placebo in the primary analysis at the end of the second stage of the study.

The interim analysis does not allow for early stopping of the study for efficacy although a futility

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boundary was incorporated.

The IDMC could recommend to increase the sample size at the interim analysis if there was less than 80% conditional power (CP) to demonstrate superiority of the selected regimen (or at least one of the selected regimens in the case where two regimens were chosen) over placebo. The maximum permitted sample size increase was fixed at 100 additional patients per selected propranolol regimen and 50 additional patients on the placebo arm. If at least 50% CP (to demonstrate superiority of the selected regimen or at least one of the selected regimens in the case where two regimens were chosen) was not achieved with a total of 200 patients per selected propranolol arm and 100 patients on placebo, the study would be stopped for futility. The futility stopping rule only affected power, the type I error rate remained unchanged.

Randomization in the ratio 2:2:2:2:1 would continue to each treatment arm until none, one or two regimens were selected at the interim analysis. If one or two regimens were selected, randomization would then continue to the selected regimen(s) and placebo in the ratio (2:)2:1 until a total of 100 patients had been randomized to each selected propranolol regimen and 50 patients to placebo over the two phases of the study.

Randomization to all unselected regimens was permanently discontinued after the interim analysis decision. Patients already assigned to an unselected regimen of propranolol at the time of the interim analysis continued the treatment according to the protocol but efficacy data for these patients were not included in the primary analysis.

Safety endpoints were based on the following evaluations:

- Adverse events, height, weight, head circumference, temperature, heart rate, blood pressure, respiratory rate, pulmonary auscultation, liver palpation and global physical examinations (all visits)
- ECG measurements (D0, D7, D14, D21, W12, W24, W36, W48, W72 and W96/EOS)
- Laboratory examinations (Screening, W12 and W24)
- Two-dimensional cardiac ultrasounds (Screening, W96/EOS)
- Neurodevelopment assessments (Screening, W24 and W96/EOS)

Clinical and laboratory studies: The clinical, imaging and lab evaluation schedule are shown in Figure 16.

Handling of early withdrawals: Early withdrawals from the study therapy due to treatment inefficacy or intolerance or patients receiving, for any reason, prohibited treatments (after randomization and before the W24 evaluation) that could be used to treat IH (systemic [oral, intra-venous or intra-muscular], intra-lesional or topical corticosteroids, imiquimod, vincristine, alfa-interferon, beta-blockers other than the study treatment or laser therapy), i.e. in usual conditions for treating IH with appropriate formulation, dose and treatment duration, were considered as treatment failures for primary, sensitivity and key secondary efficacy analyses (ITT, PP). Patients receiving any other prohibited treatments before the W24 evaluation were excluded from the PP analysis data set.

SUMMARY

This is a multidose 2-stage adaptive design study with treatment regimen selection at the end of the first stage {methodology described in Posch *et al.* (2005)} in a seamless phase II/III design. 450 infants with IH {stratified by age (35 ~ 90 days / 91 ~ 150 days old) and IH localization (facial / non-facial)} were randomized to 5 treatment arms (placebo and 4 regimens of

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propranolol with different dose/duration combinations) in a 2:2:2:2:1 ratio (propranolol regimens:placebo).

An *interim analysis* was carried out after the first 40 patients randomized to each of the 4 propranolol regimens and the first 20 patients randomized to placebo had completed their W24 visit or been withdrawn prematurely from study therapy. This interim analysis was made by an independent data monitoring committee (IDMC) to either stop the study for safety or futility, or continue with the placebo arm and one or two 'best' regimens of propranolol, where the 'best' regimen was defined as the most efficacious of all regimens with a good safety profile.

After one or two regimens of propranolol are selected by the IDMC, all new recruits were randomized in the second stage in the same stratified blocks in a (2:)2:1 ratio between the chosen regimen(s) and placebo.

The primary efficacy criterion was the evolution of target IH from baseline to W24, evaluated in a binary (success/failure) manner based on the intra-patient *blinded centralized independent qualitative assessments* (Type 1) of W24 photographs of the target IH compared to baseline.

A key secondary efficacy endpoint was success/failure (binary endpoint) based on the *investigator on-site qualitative assessment* of complete resolution of target IH at W48.

When **all** of the patients in the study had completed their W24 visit or been prematurely withdrawn from study therapy, the treatments were unblinded to an exclusive list of study personnel (the sponsor, the (b) (4) biometry team), regulatory representatives, the independent statistician and the IDMC members. The blind continued to be maintained for the monitoring teams and all investigational site staff until the end of the trial.

The study duration was approximately 13 months for recruitment, 24 weeks of treatment and 72 weeks follow up (total = 96 week study duration per patient).

9.4.2 PK Study 101 2A

Protocol V00400 SB 1 01 2A: *Evaluation of pharmacokinetic parameters of a new propranolol hydrochloride formulation (oral solution) compared to the reference propranolol hydrochloride formulation (tablet) - A single-centre, randomized, open-label, single-dose, two-way crossover study.*

Objectives:

- Main objective: To evaluate the pharmacokinetic parameters of a new propranolol hydrochloride formulation (oral solution) compared to the reference propranolol hydrochloride formulation (tablet) after a single oral dose in 12 healthy subjects,
- Secondary objectives: To document the clinical and biological tolerability of the 2 propranolol hydrochloride formulations after single oral administration in 12 healthy subjects.

Subjects analyzed: 12 healthy subjects

Methods: A single-center, open label, randomized, single dose, two period crossover study with a wash-out interval of at least 3 days. Subjects were randomized to receive a single oral administration on Day 1 of each period either propranolol hydrochloride oral solution or propranolol hydrochloride tablet.

Screening period: Selection of subjects from Day –15 to Day –2: informed consent, medical history, record of concomitant diseases and/or treatments, medical examination with weight and height, vital signs, ECG and biology screening (hematology, biochemistry, urinalysis and hepatitis B, hepatitis C, HIV, serology).

Test product: Propranolol HCl oral solution: 5 mg/ml (expressed as base),

- Dose: Single administration of a dose of 80 mg (solution),
- Mode of administration: Orally administered at around 8 a.m. after an overnight fast of at least 10 hours. The subject swallowed 16 ml of the propranolol solution (without dilution), followed by 100 ml of the recipient rinsed water.

Reference product: Propranolol HCl tablet of 40 mg (corresponding to 35.09 mg base).

- Dose: Single administration of a dose of 70.18 mg (tablet).
- Mode of administration: Orally administered at around 8 a.m. after an overnight fast of at least 10 hours. Two tablets were taken with a 120 ml glass of water.

Duration of treatment: Single administration, 2 intakes separated by a wash-out of at least 3 days (2 tablets of 40 mg or 16 ml of the oral solution at 5 mg/ml). The duration of participation is at most 6 weeks, and the duration of treatment is 2 days (1 day for each period).

Evaluation Criteria: Pharmacokinetics

Blood samples for propranolol plasma levels determination were drawn via a catheter for each period at the following times: Pre-dose (T0), 0h20, 0h40, 1h, 1h20, 1h40, 2h, 2h30, 3h, 4h, 6h, 8h, 10h, 12h, 16h, and 24h after drug administration.

Blood samples were centrifuged, plasma was separated and frozen at – 20°C until assay.

Propranolol was assayed according to a validated analytical method (PKH/MOA/303, version 1. The method was linear from 0.5 to 250 ng/mL. QC samples were prepared in lithium heparinized human plasma at 1.50, 125 and 200 ng/mL.

The following pharmacokinetic parameters were determined for each formulation of propranolol:

- C_{max}: maximal observed concentration
- T_{max}: time to reach the Cmax
- AUC_{last}: area under the curve from t=0 to the last quantifiable point
- AUC_{inf}: area under the curve from t=0 to infinity
- Cl/F: apparent total plasma clearance
- Vd/F: apparent volume of distribution
- $T_{1/2}$: terminal elimination half-life
- k_{el}: elimination rate constant
- F% (relative bioavailability) was determined for the solution by comparison to the reference oral tablet formulation
- $\%AUC_{extra}$: percentage of extrapolated AUC
- C_{max} ratio (%): ratio of C_{max} between the solution and the tablet

Secondary criteria: Safety/Tolerability

- Physical examination, adverse events recording, vital signs, ECG, blood and urine for routine safety laboratory parameters.

Summary of results**:** Presented in Section 5.3 of this clinical review.

The plasma concentration profiles are similar after administration of both formulations. The mean ratio of AUC of the solution vs. the tablet was 1.2 indicating the absorption was 20%

higher for the solution compared to the tablet formulation.

The main pharmacokinetic parameters of propranolol (expressed as arithmetic mean ± SD (CV%) and [range], and [range] for T_{max}) are summarized in the table below:

	Formulation A Tablet (reference) 70.18 mg	Formulation A Dose-normalized 80 mg	Formulation B Solution (test) 80 mg
C_{max} (ng/mL)	52.8 ± 50.0 (95%) [11.6 – 204]	60.2 ± 57.0 [13.2 – 232]	49.5 ± 13.2 (27%) [31.4 – 75.0]
T_{max} (h)	1.67 [0.67 – 3.0]	-	1.33 [1.0 – 2.0]
AUC_{inf} (h*ng/mL)	315 ± 288 (92%) [87.1 – 1194]	359 ± 328 [99.3 – 1361]	328 ± 128 (39%) [201 – 679]
$T_{1/2}$ (h)	4.19 ± 0.63 (15%) [3.12 – 5.20]		4.41 ± 0.63 (14%) [3.69 – 5.74]

Relative bioavailability: Individual ratio of test/reference AUC (at equivalent dose) after administration of both the test solution and the reference tablet ranged from 0.5 to 3.28, with a high inter-individual variability. This variability is explained by the high variability (CV=92%) associated with the extent of absorption observed with the tablet.

Safety/Tolerability results: Clinical and biological tolerability was satisfactory, as no adverse events and no clinically relevant findings were reported at clinical examination as well as on laboratory parameters, vital signs or ECG parameters.

Conclusion: When comparing an equivalent oral dose of propranolol administered as a new propranolol hydrochloride solution (propranolol) and as a reference propranolol hydrochloride tablet, one can conclude that:

- The plasma concentration profiles are similar after administration of both formulations
- The rate of absorption is similar after administration of both formulations
- Based on individual comparison of AUC ratio, the extent of absorption is slightly higher (by about 20%) for the solution compared to the tablet formulation
- The inter-individual variability of the pharmacokinetic parameters is lower for the solution formulation.

9.4.3 PK Study 102 in infants

Protocol V00400 SB 1 02: *A multicentre, open-label, repeated-dose, pharmacokinetic study of propranolol in infants treated for proliferating infantile hemangiomas (IHs) requiring systemic therapy.*

Objectives:

Primary objective: To characterize the pharmacokinetics (PK) of propranolol (administered as an oral solution [V0400 SB]) at steady-state in infants during a treatment for proliferating IH requiring systemic therapy.

Secondary objectives:

- To characterize the PK of a propranolol metabolite (4-OH-propranolol)
- To assess the efficacy of propranolol on the evolution of the target IH over 12 weeks
- To document the safety profile of propranolol in the treatment of IH

Study Design: An open-label, multicenter, repeated-dose study. Infants were stratified to 2 groups according to their age at inclusion, which defined the timing of their PK assessment at steady-state:

- Group 1: aged from 35 to 90 days inclusive at inclusion; PK assessment after 4 weeks of treatment
- Group 2: aged from 91 to 150 days inclusive at inclusion; PK assessment after 12 weeks of treatment

Infants received propranolol (3 mg/kg/day given twice daily after a 2-week titration period). Patients attended 5 further visits at intervals of 1 to 4 weeks: D7±1 day, D14±1 day, D28±3 days and the end-of-treatment visit at D84±3 days.

During the 2-week titration period, 2 micro-blood samples were collected at D7 and D14. Six serial micro-blood samples were collected over a 9-hour period at steady-state (after 4 or 12 weeks of treatment for the lower and higher age groups, respectively) for propranolol and 4-OH-propranolol assay: T_0 (just before morning dosing, 12h after the previous evening administration) and 1h, 2h, 4h, 6h and 9h after the morning dosing.

Subjects analyzed: Twenty (20) infants 35 ~ 150 days old with proliferating IH were planned (10 infants in each stratification group). Twenty three (23) infants were included (10 in group 1, 13 in group 2).

Duration of treatment: 12 weeks

Administration: Propranolol oral solution twice daily (morning and late afternoon). The dose was calculated by the Investigator at each visit and followed by the parent(s) until the next visit.

Efficacy criteria: Pharmacokinetic criteria (primary):

- Bioanalysis for propranolol and 4-OH-propranolol plasma concentration quantification using a validated LC/MS-MS method.
- A non-compartmental approach to assess PK parameters: C_{max}, T_{max}, AUC_{last}, AUC_{ζ}, Cl_{tot}/F (only for propranolol) and metabolite/drug ratio for C_{max} and AUC_{ζ}.

Efficacy criteria (secondary)

Investigator on-site qualitative assessments of: change in the IH for paired consecutive patient-visits, complete/nearly complete resolution of the IH at each post-baseline visit compared to baseline, and target IH complications at each scheduled visit; Parent(s)' on-site qualitative assessment of change in the IH for paired consecutive patient-visits.

Safety criteria:

- Adverse events
- Height, weight, head circumference, temperature, heart rate (HR), systolic/diastolic blood pressure (SBP/DBP), respiratory rate, pulmonary auscultation, liver palpation and global physical examinations (all post-baseline visits)
- Electrocardiogram (ECG) measurements (D0, D7, D14 and D84): QT corrected for HR according to Bazett (QT_{cB}), Fridericia (QT_{cF}), and Pediatric (QT_{cP}) formulae
- Laboratory examinations (Baseline and D84)

Patients' disposition and data sets: All 23 included patients (10 in group 1, 13 in group 2) were treated and analyzed for safety and efficacy (APT data set). Of the 23 APT patients, 1 patient of Group 2 prematurely withdrew at D19 following an out-protocol adaptation of dose due to an

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AE. This patient together with 3 other patients (1 of Group 1 and 2 of Group 2) had missing PK samples or an out-of-range drug dosing interval; they were excluded from the PK analysis. Thus 19 patients (9 in group 1 and 10 in group 2) were included in the PK analysis (PK data set).

Pharmacokinetic results: The PK results are described in Section 5.3 of this clinical review.

Efficacy results

For on-site assessments by the Investigator, improvement in the IH for paired consecutive visits was reported for the majority of patients at all post-baseline assessments in Groups 1 and 2. All 23 patients showed improvement in the target IH at either Visit 3 (D7) or Visit 4 (D14) and 11 patients showed improvement at all 5 paired assessments. None of the target IH worsened since the previous visit at any post-baseline assessment.

At Visit 7 (D84), complete/nearly complete resolution of the IH was seen in 8 (4 in each group) of the 22 patients.

Assessments by the parents were consistent with those made by the investigators.

Safety results

No deaths occurred during the study. One patient in Group 2 experienced 3 non-drug-related SAEs (hospitalization for mild pallor, crying and for moderate acute otitis media). One patient in Group 2 was prematurely withdrawn following an out-protocol treatment adaptation due to a drug-related AE: a prolonged QT_{cB} at 4 h post-dose (1 mg/kg) on D14: 467 ms; not associated with prolonged QT_{cF} and QT_{cP}) and returning to normality 1 h later (427 ms).

Overall, 75 treatment-emergent AEs (TEAEs) were reported for 20/23 patients. The most common TEAEs (reported for ≥ 3 patients), were diarrhea, nightmare, pyrexia, nasopharyngitis, peripheral coldness, conjunctivitis, cough, bronchitis and toothache. Two severe TEAEs were reported (pyrexia and blood alkaline phosphatase increased). Related TEAEs (relationship to study drug other than 'not suspected') were reported for 7 patients in Group 1 and 8 patients in Group 2. Nightmare (5/23 patients), peripheral coldness (4/23 patients) and diarrhea (2/23 patients) were the most commonly reported related TEAEs.

Three abnormal laboratory values were assessed as clinically significant by the Investigator. One patient had elevated alkaline phosphatases (ALP) at the final study visit which returned to normal range at 1-month post-study follow-up. There were also individual occurrences of elevated MCV and potassium at the final study visit for 2 patients; no repeat test data were reported.

There were small decreases in supine SBP, DBP, HR and respiratory rate measurements compared to baseline within 4 h of the first dose of propranolol at each up-titration visit. There were no clinically relevant changes in mean body temperature or physical findings over time during the study.

For QT_{cP}, all patients remained ≤450 ms throughout the study and the majority of patients (81.8% to 95.5%) at all time-points had changes in QT_{cP} that were ≤30 ms. Only one clinically significant QT_c (QT_{cB}) was reported during the study (prematurely withdrawn patient).

Conclusion

Once corrected by the body weight, primary PK parameters for propranolol determined in infants are similar to those reported in the literature for adults.

Treatment with propranolol for 12 weeks of proliferating IH in infants resulted in a rapid

improvement (within 7-14 days) in all patients. Resolution of the target IH was seen as early as D28 and by D84, 36.4% (8/22) patients had resolution of their target IH. In addition, complications of IH disappeared over time, confirming the regression of the IH.

Propranolol was well tolerated in the overall study population.

9.4.4 Study V00400 SB 3 01 (Study 301 – Open-label study)

Study 301 is the ongoing multicenter, open-label study of propranolol solution in infants with proliferating IH to allow the use of propranolol with adequate conditions of administration and follow up in infants requiring this systemic treatment after participation in a previous trial Study 102 and Study 201 within the previous 6 months. The number of patients enrolled is expected to be around 100.

Propranolol will be administered up to 6 months, depending on the evolution of the target hemangioma and the benefit/risk ratio as assessed by the investigator. At D0 and each dose increase (D7 and possibly D14), the first administration of the new dose of study drug will be carried out at the study site so that a specific safety assessment can be performed. In particular, temperature, heart rate, blood pressure, respiratory rate and pulmonary auscultation will be measured before the first administration and then every hour (±30 min) for four hours after the first administration. Furthermore, glycaemia will be measured (pin-prick) and an ECG will be performed before the first administration and at 120 min (±30 min) and 240 min (±30 min) after the first administration. Immediately after each ECG evaluation, the investigator will verify whether or not there are clinically significant abnormalities that require the study treatment to be permanently discontinued (or in the case of any doubt in terms of patient safety). If a potential safety issue is identified during the different evaluations at D0, D7 and possibly D14, the study therapy will be permanently discontinued for intolerance. In the absence of any abnormalities, the patient will be allowed to leave the site and continue study therapy according to the protocol.

If there is worsening of target IH during the treatment period for which the investigator considers it is necessary for the patient's well-being to administer another treatment of his/her choice, the study drug will be permanently discontinued.

Similarly, if there is a rebound growth of target IH during the follow-up period, another treatment of the investigator's choice may be given to the patient.

In both above cases, the concomitant medication is to be fully documented in the case report form and the patient is followed up to W96.

9.4.5 Compassionate Use Program (CUP)

See Section 5.3 of this clinical review.

9.4.6 Key Publications

See Section 6.1.10 for my review of the 15 key publications and 3 meta-analyses.

9.4.9 Comparison of Efficacy Results of Pivotal Studies

Not applicable. There is only one pivotal study.

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/s/

KHIN M U

12/20/2013

Based on review of the clinical data submitted in this NDA, the recommended regulatory action is approval (§21 CFR 314.110) pending the sponsor's response to agree to the suggested changes in the proposed labeling.

THOMAS A MARCINIAK

12/20/2013

CLINICAL FILING CHECKLIST FOR NDA 205-410 – (b) (4)

NDA Number: 205-410 Applicant: Pierre Fabre Dermatologie Stamp Date: 17-May-2013

Drug Name: (b) (4) NDA/BLA Type: NDA

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	√			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	√			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	√			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	√			
5.	Are all documents submitted in English or are English translations provided when necessary?	√			
6.	Is the clinical section legible so that substantive review can begin?	√			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	√			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	√			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	√			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	√			
11.	Has the applicant submitted a benefit-risk analysis for the product?	√			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	√			505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: V00400 SB 201 Study Title: A randomized, controlled, multi-dose, multi-center, adaptive phase II/III study in infants with proliferating infantile hemangiomas requiring systemic therapy to compare four regimens of propranolol (1 or 3 mg/kg/day for 3 or 6 months) to placebo (double blind) Treatment arms: 5 (placebo and 4 regimens of propranolol: 1 mg/kg/day 3 months then placebo 3 months, 1 mg/kg/day 6 months, 3 mg/kg/day 3 months then placebo 3 months, 3 mg/kg/day 6 months). Sample Size: 460 patients (randomized 2:2:2:2:1 ratio, propranolol regimens : placebo) Stage 1: 190 patients: (Placebo: 25, active arms: 40 to 43) Stage 2 + overrun*: 270 patients (Placebo: 30, selected active arm: 59, unselected active arms	√			

Reference ID: 3332332

	Content Parameter	Yes	No	NA	Comment
	[overrun]: 58 to 62) Location in submission: Module 5, under section 5.3.5.1				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	**YES** √	**NO**	**NA**	
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	√			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	√			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			√	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	√			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			√	Propranolol is not known to prolong the QT interval.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	√			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			√	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	√			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	√			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	√			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	√			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	√			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			√	
PEDIATRIC USE					

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.
[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

Reference ID: 3332332

CLINICAL FILING CHECKLIST FOR NDA 205-410 – (b) (4)

	Content Parameter	Yes	No	NA	Comment
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	√			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			√	Parents administer to babies 1-5 months old
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			√	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	√			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	√			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	√			
34.	Are all datasets to support the critical safety analyses available and complete?	√			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	√			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	√			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	√			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	√			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	√			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None at this time.

Filed in DARRTS 21-Jun-2013

Reviewing Medical Officer (Khin Maung U, MD) Date (26-Jun-2013)

Clinical Team Leader (Thomas Marciniak, MD) Date (2-Jun-2013)

Reference ID: 3332332

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/s/

KHIN M U
06/26/2013

THOMAS A MARCINIAK
06/27/2013

Memo to file

Date: 31-May-2013
To: Norman Stockbridge, Division Director, DCRP
From: Khin Maung U, Medical Officer, DCRP
Cc: Quynh M. Nguyen, RPHM, DCRP
Subject: Opinion on Priority Review request for NDA 205-410 ([redacted] (b) (4))
Sponsor: Pierre Fabre Dermatologie
Indication: Treatment of proliferating infantile hemangiomas

Sponsor's proposal

Pierre Fabre requests priority review, stating that the following points underscore the need for Priority Review for [redacted] (b) (4) for the treatment of proliferating IH requiring systemic therapy:

- IH requiring systemic therapy is an orphan disease, which can create serious and life-threatening medical complications in small children, including airway involvement, impediment of feeding, ophthalmologic complications often requiring surgery, associated structural anomalies such as cardiac defects, increased risk of visceral involvement, and hepatic lesions including congestive heart failure and hyperthyroidism;
- There is currently no FDA-approved treatment for IH;
- Patients who experience proliferating IH represent a clear unmet medical need;
- [redacted] (b) (4) is specifically formulated and developed for pediatric use;
- Phase 2/3 study with [redacted] (b) (4) demonstrated statistically significant and sustained clinical improvements in IH patients compared to placebo and a favorable safety profile;
- The magnitude of the treatment effect is clinically relevant and significantly greater than any effects previously reported with historical treatments; [redacted] (b) (4) stands as a clear leader as a first-line treatment for IH requiring systemic therapy.

Reviewer's comments

The sponsor submitted that [redacted] (b) (4) fills an unmet, urgent medical need where no satisfactory alternative therapy exists.

However, corticosteroids, INF alpha and vincristine have been recommended for use by the American Academy of Dermatology's Guidelines (1997)[1] since about 15 years ago. Recently, timolol maleate, a nonselective beta blocker used in ophthalmic solutions to treat glaucoma, has been evaluated as a topical 0.5% or 0.1% timolol maleate gel-forming solution to treat patients with IH.[2]

The efficacy and safety information of currently available treatment compared to [redacted] (b) (4) are summarized in Table 1.

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[1] Frieden IJ, Eichenfild LF, Esterly NB, Geronemus Rk, Mallory SB, the Guidelines/Outcomes Committee. Guidelines for care of hemangiomas of infancy. *J Amer Acad Derm* 1997;37:631-7.
[2] Chakkittakandiyil A, Phillips R, Frieden IJ, et al. Timolol maleate 0.5% or 0.1% gel-forming solution for infantile hemangiomas: a retrospective, multicenter, cohort study. *Pediatr Dermatol* 2012;29(1):28-31.

Table 1 Efficacy/safety profiles of currently available treatments for Infantile Hemangioma

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GI: gastrointestinal; IFN: interferon; IH: infantile hemangioma; KMS: Kasabach-Merrit syndrome; tx: treatment. [3]Enjolras et al. 1990; [4]Bennett et al. 2001; [5]Frieden et al. 2005 ; [6]Ezekowitz et al. 1992 ; [7]Enjolras et al. 2004; [8]Barrio et al. 2005; [9]Boon et al. 2006; [10]Barlow et al. 1998 {Source: Sponsor's references}
[11] Efficacy data in NDA

The response rates obtained with the other available drugs (Table 1) appear to be as good as or better than that obtained with (b) (4) (60%) although the endpoints used to evaluate efficacy may be variable; corticosteroids produce a 84% response rate, INF alpha a 40-50% response rate (with regression starting at 2-12 weeks), Vincristine a 78% response rate (in 7 of 9 infants) and timolol a 99% response rate (72 of 73 patients improved).

Although propranolol hydrochloride solution beats placebo in the pivotal trial in the NDA, whether it can beat a positive control such as corticosteroids or INF alpha or vincristine, is not known.

While these four available alternative therapies to (b) (4) are not FDA-approved, they are considered by practicing pediatricians and pediatric dermatologists as acceptable therapeutic modalities; it is simply that these drugs have not been submitted to FDA for a claim related to treatment of infantile hemangioma although substantive clinical data exist in the medical literature. In addition, the MAPP does not require that the alternative therapies be FDA-approved.

Reviewer's Recommendation

There are four other equally (or more) effective therapeutic agents currently available for the treatment of infantile hemangioma. (b) (4) can thus be considered as merely one of the drugs Pierre Fabre Dermatologie effective for the treatment of infantile hemangioma. Therefore, I do not recommend granting a Priority Review.

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/s/

KHIN M U
05/31/2013

NORMAN L STOCKBRIDGE
05/31/2013