

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205410Orig1s000

SUMMARY REVIEW



MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: March 07, 2014
FROM: Khin Maung U, M.D., Medical Officer, DCaRP
TO: Norman Stockbridge, M.D., Ph.D., Director, DCaRP
Cc: Thomas Marciniak, M.D., Medical Team Leader, DCaRP
Subject: Update to CDTL review of NDA 205-410 Hemangeol (Propranolol Hydrochloride Oral Solution)

BACKGROUND

My CDTL review filed in DARRTS on 07-Feb-2014 recommends approval of NDA 205-410 (b) (4) (Propranolol Hydrochloride Oral Solution, 3.75 ,g/mL propranolol) submitted by Pierre Fabre Dermatologie, the Applicant, pending their response to the changes suggested in the proposed labeling.

The approval recommendation is for the indication: "Treatment of proliferating infantile hemangioma requiring systemic therapy, to be initiated in patients aged 5 weeks to 5 months."

During the period 07-Feb-2014 to today, the following new information was obtained which required updating the CDTL review. The new information does not change the recommendation for approval of NDA 205-410.

CDTL REVIEW FINDINGS AND COMMENTS

(1) Proprietary name:

Initially, the **Office of Prescription Drug Promotion (OPDP)** determined that the proprietary name, (b) (4) was acceptable from a promotional perspective.

Also, the **Division of Medication Error Prevention and Analysis (DMEPA) review (by Kimberly De Fronzo** which was signed off by Irene Z. Chan on her behalf} on 07-Aug-2013 concluded that DMEPA

- (i) concurred with OPDP's assessment of the proprietary name, and
- (ii) found the proprietary name acceptable from both the promotional and safety perspectives.

On 03-Feb-2014, DMEPA informed Pierre Fabre that the name " (b) (4) had become unacceptable due to a recent regulatory change in which (b) (4) . On 05-Feb-2014, Pierre Fabre withdrew the proprietary name " (b) (4) and submitted a request for proprietary name review for the new name "HEMANGEOL."

DMEPA (Jacqueline Sheppard and Lisa Khosla) performed an expedited Proprietary Name Review (filed in DARRTS on 12-Feb-2014) and concluded that the name HEMANGEOL is acceptable.

CDTL comment: I concur with the DMEPA reviewers' conclusion.

(2) Revised Container Labels and Labeling

Following the proprietary name change, **DMEPA (Jacqueline Sheppard and Lisa Khosla)** also performed an expedited review of the revised Container Labels and Carton Labeling. DMEPA found that the applicant addressed all previous recommendations, but had a recommendation to be implemented prior to approval: "to revise container label and carton labeling with a statement alerting the dispenser to provide the Medication Guide to each patient."

CDTL comment: I concur with DMEPA reviewers' conclusion and recommendation.

(3) Facilities review/inspection:

On 07-Mar-2014, the CMC Reviewer, Prafull Shiromani, filed an addendum in DARRTS which contained the information: "The following Summary Report from the Office of Compliance was received on 07-Feb-2014, with an 'Acceptable' overall recommendation. There are no other CMC pending issues. Accordingly, this NDA is recommended for approval from a CMC perspective. The CMC Review was submitted to DARRTS on 31-Dec-2013."

Table 1 Manufacturing facilities scheduled for inspections by ORA

Application	FEI number	Establishment Name	Country Code	Profile Code (b) (4)	Responsibilities	Inspection Date	Compliance Status
NDA 205410					Manufacture, Packaging, Control and Batch release of Drug Substance	-	Acceptable
NDA 205410					Manufacture, Packaging, Control and Batch release of Drug Product	(b) (4)	Acceptable

CDTL comment: It appears that following the completion of FDA inspection of the (b) (4) manufacturing site in (b) (4), the Office of Compliance finalized their evaluation of FDA inspections of the manufacturing facilities in EES (Table 1). I concur with the CMC reviewer's recommendation for approval, which completes the action package for this NDA.

(4) Regulatory Evaluation:

Nisha Shah (OMPT/CDER/ORP/DRPI), Jennifer Stevens (OCOO), Beth Duvall (OMPT/CDER/OND) and Colleen L. Locicero (OMPT/CDER/OND/ODEI) contributed to the evaluation of the applicant's proposal of a two-step bridging approach. This regulatory evaluation was performed to make sure that the proposed approach is consistent with the bridging approaches for other 505(b)(2) applications.

From a regulatory perspective, the proposed bridging approach is not considered an optimal bridge. However, a key factor in the acceptability of this approach was that

the Division considered it to be appropriate from a scientific perspective. The Division's opinion is that there are no patient factors or formulation factors that would interfere with appropriate comparison of the confidence intervals of the compared products. The Division concludes that the bridge is scientifically sound, and that it can be considered that the applicant has adequately connected the dots such that the applicant can rely on NDA 16-418 for certain information rather than conducting those studies with the proposed product.

CDTL comment: Acceptability of the data supporting the bridging between the proposed propranolol solution product and the RLD propranolol product (Inderal[®] 40 mg tablets) under NDA 16-418 is necessary to leverage propranolol's non-clinical information. For this 505(b)(2) NDA, the applicant had conducted clinical trials to support safety and effectiveness for the pediatric indication. They proposed to rely on FDA's previous finding of safety and effectiveness for NDA 16-418 for Inderal (propranolol immediate release oral) Tablets and published nonclinical studies to fulfill the requirements for nonclinical studies. For this purpose, the applicant proposed a two-step bridging approach that included:

- (i) An *in vivo* bioavailability (BA) comparison between the proposed propranolol solution product and Avlocardyl[®], a French approved propranolol tablet formulation. This study demonstrated comparable BA profiles between the 2 formulations in 12 healthy adults.
- (ii) An *in vitro* dissolution test which demonstrated the equivalence of dissolution profiles of Avlocardyl[®] (the French propranolol tablet) and Propranolol HCl USP 40 mg tablets (Barr Laboratories, Inc., approved under ANDA 71-974). ANDA 71-974 is referenced to (RLD) NDA 16-418 (Inderal tablets). The applicant used the Propranolol HCl USP 40mg tablets, explaining that the Inderal[®] 40 mg tablet is no longer marketed in the US and could not be used as the reference listed drug (RLD) in the BE study supporting their product.

The ONDQA Biopharmaceutics reviewer (Kareen Riviere) concluded that the bridging between the proposed oral propranolol solution product and the US RLD Inderal[®] 40 mg tablets is adequately justified and acceptable based on supportive scientific data submitted (See CDTL review and BioPharm review for details). The BioPharm reviewer states that from the Biopharmaceutics standpoint, Hemangeol oral solution 3.75 mg/mL is recommended for approval.

On the basis of the fact that:

- (i) the BioPharm reviewer recommended that the bridging between the proposed oral propranolol solution product and the US RLD Inderal[®] 40 mg tablets is adequately justified and acceptable based on the supportive scientific data,
 - (ii) there are PK and Phase 2/3 data in the NDA, and
 - (iii) there are no patient factors or formulation factors that would interfere with appropriate comparison of the confidence intervals of the compared products,
- I concur that the two-step bridging approach is scientifically sound and acceptable.

Conclusion: The new information does not change the recommendation for approval of NDA 205-410.

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/s/

KHIN M U
03/07/2014

This addendum to CDTL review describes new information since filing of the CDTL review. The new information does not change the approval recommendation of the NDA.

THOMAS A MARCINIAK
03/07/2014

Cross-Discipline Team Leader Review

Date	07-Feb-2014
From	Khin Maung U, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 205-410
Application Type	505 (b) (2)
Applicant	Pierre Fabre Dermatologie
Dates of Submission	17-May-2013
PDUFA Goal Date	17-Mar-2014
Priority Designation	Standard Review
Proprietary Name / Established (USAN) names	(b) (4) / Propranolol Hydrochloride Oral Solution
Dosage forms / Strength	Oral solution: 4.28 mg/mL propranolol hydrochloride equivalent to 3.75 mg/mL propranolol base
Proposed Indication	Treatment of proliferating infantile hemangioma requiring systemic therapy to be initiated in patients aged 5 weeks to 5 months
Recommendation:	Approval
Advisory Committee Meeting	Not required

This CDTL review is based on completed reviews for the following disciplines:

Review Discipline	Reviewer	Team Leader
Clinical	Khin Maung U	Khin Maung U (CDTL)
Statistical	Yeh-Fong Chen	Hsein Ming J. Hung
Safety (REMS/MedGuide)	Lori Wachter	Mary Ross Southworth
Pharmacology/Toxicology	Baichun Yang	Thomas Papoian
Clinical Pharmacology	Divya Menon-Andersen	Jeffry Florian, Rajnikanth Madabushi
CMC	Prafull Shiromani	Kasturi Srinivasachar
BioPharm	Kareen Riviere	Angelica Dorantes
OPS/NDMS (Microbiology)	Erika Pfeiler	John Metcalfe
SEALD Endpoints Team	Eric Brodsky	
OSE-DMEPA	Kimberly De Fronzo	Irene Z. Chan
OSE-DMEPA	Jacqueline Sheppard	Lisa Khosla
OSE-DRISK	Somya Dunn	Kim Lehrfeld
OSI/DGCP	Susan Thompson	Kassa Ayalew
Project Manager	Quynh M. Nguyen	Edward Fromm
OPDP	Zarna Patel	
DMPP (PLR reviewer)	Sharon Mills	Barbara Fuller

1. Introduction

This CDTL review elaborates the rationale for recommending **approval**, under Section 505(b)(1) of the FD&C Act, of NDA 205-410 (b) (4) (Propranolol Hydrochloride Oral Solution, 3.75 mg/mL propranolol) submitted by Pierre Fabre Dermatologie, the Applicant, pending their response to the changes suggested in the proposed labeling.

The approval recommendation is for the indication: "Treatment of proliferating infantile hemangioma requiring systemic therapy, to be initiated in patients aged 5 weeks to 5 months."

Infantile hemangiomas (IH) are the most common benign vascular tumors of childhood occurring in about 3% to 10% of infants. IH 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, telangiectasias or residual lesions.

Corticosteroids are the only treatment registered in two countries (France and Germany) for treatment of severe forms of hemangiomas in infants, but their efficacy in IH is variable. In 2008, a 4-month-old infant treated with propranolol for obstructive cardiomyopathy was reported to have an unexpected rapid improvement of a nasal IH that was enlarging despite corticosteroid therapy¹. This initial result was further confirmed in ten more children with severe or disfiguring IH, and in a prospective study of 31 children with IH treated with propranolol²; this was followed by several publications of effectiveness of propranolol to treat IH. Propranolol is now widely used off-label for this indication, although it is not formulated for pediatric use.

Propranolol hydrochloride has monographs in the European and US Pharmacopoeia. In children, specific dosing recommendations have been established and its clinical use is accepted in hypertension, arrhythmias, tetralogy of Fallot, migraine spells, hypertrophic cardiomyopathy, pheochromocytoma and thyrotoxicosis. An oral solution is available in the US (Propranolol Hydrochloride, Roxane Lab.), but indicated in adults only.

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 oral dose 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.

The clinical development is based on 3 clinical studies including two pharmacokinetic (PK) studies – one in healthy adults (Study V00400 SB 1 01 2A) and one in infants with IH (Study V00400 SB 1 02). The third is a pivotal 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 pivotal clinical trial data to support the indication of propranolol to treat proliferating IH in a pediatric population.

There is a fourth clinical study (Study 301), which is an ongoing multicenter, open-label study of propranolol solution in infants with proliferating IH. This study is being

conducted at the request of the French Competent Authority (*Agence Nationale de Sécurité du Médicament et des Produits de Santé* [ANSM]) to allow the use of propranolol with adequate conditions of administration and follow up for infants requiring systemic treatment after participation in a previous clinical trial (Studies 102 and 201).

A fifth study is the Compassionate Use Program (CUP), also named Early Expanded Access in the US. It is on-going in France and Switzerland. 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 clinical studies above.

Pierre Fabre also submitted 15 key publications and 3 meta-analyses in the medical literature reporting the effect of oral propranolol in children with IH. These publications are also reviewed for additional safety information.

2. Background

The major points in the regulatory history of this Drug Product with FDA are as follows:

- 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 104,390 submitted
- 19-Aug-2009: 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:
- 15-Oct-2012: proprietary name (b) (4) granted conditional approval.

The adaptive design method of the pivotal clinical study (Study 201) was finalized incorporating the recommendations made by FDA and EMA after parallel scientific advice discussions, a Special Protocol Assessment (SPA) in the US, and a Pediatric Investigation Plan (PIP) in Europe.

On 07-Dec-2012, the sponsor met with the Division; 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 an exploratory comparison of the primary efficacy endpoint in these overrun patients to placebo-treated patients,
- (iv) Time point at which patients discontinued prematurely
- (v) Data related to persistent of treatment effect, regrowth of IH and scarring
- (vi) Efficacy data in infants with more severe IH – from literature reports and the CUP
- (vii) Safety data from patients in the CUP in France and Switzerland, and case reports

(b) (4) (Propranolol Hydrochloride Oral Solution - 3.75 mg/mL propranolol)

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

(viii) Definition of "inappropriate bradycardia" in infants

The discussion also included the appropriateness of a REMS which the sponsor planned to submit, and the need (or lack thereof) for drug-drug interaction studies.

3. CMC/Device

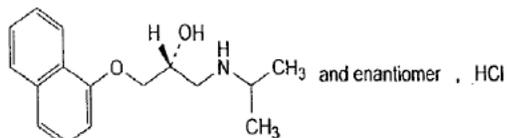
3.1 General product quality considerations

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: C₁₆H₂₁NO₂·HCl

Mean Molecular Weight: 295.8 Dalton

The CMC Reviewer (Pravall K. Shiromani) found that all drug substance analytical procedures are appropriate and that methods validation by DPA is not required since the analytical methods are conventional (i.e., a preliminary review earlier by CMC Reviewer Rao V. Kambhampati showed that the 7 criteria in IQP 5101 are not met).

CMC issues in the IR letter were addressed adequately by the applicant, specifically genotoxicity of the starting material ((b) (4)) and the intermediate ((b) (4)). The sponsor's risk management analyses found levels of ((b) (4)) ppm and ((b) (4)) ppm in industrial batches, which were far below the lowest TTC levels) described in the FDA and ICG-M7 guidelines ((b) (4)) ppm, respectively).

Regarding impurities, the drug substance is controlled according to USP, which the reviewer commented as adequate.

Analyses of 3 production batches show that all test results conform to the acceptance criteria and confirm the reproducibility of the synthesis.

The suitability of packaging was demonstrated by satisfactory stability data. The CMC reviewer commented that the overall stability program is adequate.

Initially, the product expiry date was found inconsistent between different sections of the prescribing information by the CMC reviewer (and also by the DMEPA reviewer, see section 12.3.1 of this CDTL review). Following an IR, the correct in-use expiry of 2 months is stated consistently in the revised label.

The applicant accepted FDA's recommendation to label the product as:

(b) (4), propranolol hydrochloride oral solution 4.28 mg/mL equivalent to 3.75

(b) (4) (Propranolol Hydrochloride Oral Solution - 3.75 mg/mL propranolol)

mg/mL propranolol,” which is now reflected in the revised label. This FDA recommendation was made to prevent medication errors which could result with the original label since there are other propranolol hydrochloride solutions in the market.

The CMC reviewer also agreed that the expected introduction concentration (EIC) at the point of entry into the aquatic environment is below 1 ppb/day limit, and that the NDA qualifies for a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR § 25.31(b).

The CMC reviewer does not have a list of deficiencies to be communicated to the applicant or any Phase 4 PMCs or Risk Management Steps to recommend.

The pending issue is the final evaluation of pre-approval inspection of one (b) (4) site. The Office of Compliance has made a “withhold” recommendation.

The CMC reviewer recommended approval from a Quality perspective, pending the acceptable recommendation for the above GMP inspection issue.

CDTL comment: I concur with the CMC reviewer’s evaluation and recommendation.

3.2 Facilities review/inspection

State whether all facilities inspections have been completed and whether Offices of Compliance and New Drug Quality Assessment have determined these facilities to be acceptable. If not, then the reason(s) for lack of inspections or lack of facilities acceptability should be described here.

OC/OMPQ/DGMPA for manufacturing facilities inspections (by Vibhakar J. Shah):

All necessary facilities were entered into EES. The Office of Compliance currently made a “withhold” recommendation. The final evaluation of pre-approval GMP inspection (scheduled for (b) (4)) of one GMP site (b) (4) in (b) (4) is pending.

Table 1 Manufacturing facilities scheduled for inspections by ORA

Application	FEI number	Establishment Name	Country Code	Profile Code (b) (4)	Responsibilities	Inspection Date	Compliance Status
NDA 205410					Manufacture, Packaging, Control and Batch release of Drug Substance	-	Acceptable
NDA 205410					Manufacture, Packaging, Control and Batch release of Drug Product	(b) (4)	Pending

CDTL comment: I will file an addendum to the CDTL review follow the Office of Compliance determination of the pending GMP inspection, when it is filed in EES.

3.3 Other notable issues (resolved or outstanding)

Where a consultative or collaborative review, such as with CDRH has occurred [e.g. a drug/device combination], a summary of the critical issues from the consult may be included here. Any and all unresolved issues should be stated. If disagreements exist between Centers in regard to any drug/device issue, these also should be described.

Not applicable.

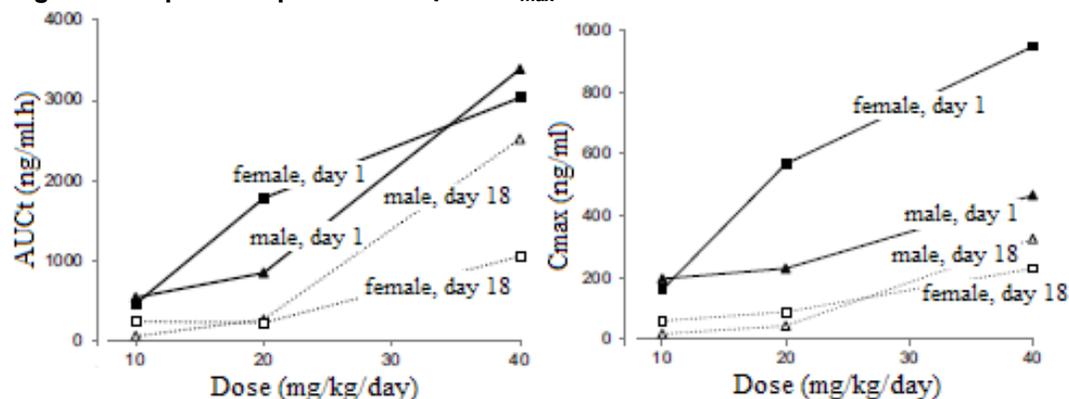
4. Nonclinical Pharmacology/Toxicology

General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).

The **pharm-tox reviewer (Baichun Yang)** described the sponsor's single nonclinical toxicology study (39331 RSR) in 32 male and 32 female juvenile Sprague-Dawley rats (in two Subsets of 16 for each sex at each dose level) conducted at (b) (4) in July 2012. Propranolol was administered by daily oral (gavage) administration from post-natal day (PND) 4 to day 21. This study was intended to cover the developmental period corresponding to human infancy, childhood and adolescence.

Toxicokinetics: Following propranolol administrations, systemic exposures to propranolol (C_{max} and AUC_t) increased with increasing dose, with no substantial gender effect on propranolol exposure (Figure 1); the increases were not dose proportional, and decreased after repeated administrations from day 1 to day 18 (no accumulation).

Figure 1 Propranolol plasma AUC_t and C_{max} vs. dose level



Source: Figure 2 in Pharm-Tox review

There were 5 premature deaths with no test-item related clinical signs. Body weight and weight gain were significantly lower at 20 and 40 mg/kg/day groups compared to controls, which was not present at the end of the treatment-free period.

The study showed that the propranolol-affected organs/systems in juvenile rats were neuromuscular development, kidney, and the lymphatic system:

- For neurologic developmental toxicity (manifested as hypoactivity and dose-related frequency of delayed air-righting reflex), the No Observed Adverse Effect Level (NOAEL) was 20 mg/kg/day (Mean $AUC_{0-24 h} = 221 - 261$ ng.h/mL).
- At the end of the treatment period, lower urine volumes in males at 40 mg/kg/day dose of propranolol and in females at 20 and 40 mg/kg/day doses were noted, with higher incidences of minimal renal cysts, and dilation of kidney pelvis/tubule in both sexes at 40 mg/kg/day dose. Histological examination was not done. By the end of treatment-free period, no abnormalities in urine volume were found.
- Dose-dependent increases (up to 40%, statistically significant) in white blood cells,

lymphocytes, basophils and large unstained cells were found at 20 and 40 mg/kg/day at the end of the drug free period. At the end of repeated dosing, higher incidence and degree of germinal centers in mandibular and mesenteric lymph nodes were found at 40 mg/kg/day. Lower weights of spleen and liver, associated with less hematopoiesis by these organs, were found at 40 mg/kg/day in both sexes. The limited extent of liver and spleen findings and the normal hematology and bone marrow histology suggest a slightly earlier switch of spleen/liver hematopoiesis to bone marrow hematopoiesis, which is considered to be of no toxicological significance.

Cardiovascular biomarkers evaluated were not detectable (plasma BNP-32 and C-Tn I levels lower than the limits of quantification) or not sensitive to show differences (plasma ANP levels) for cardiovascular functional changes.

There were no treatment-related reproductive findings or seminology findings; the NOAEL was considered to be 40 mg/kg/day (Mean AUC_{0-24 h} = 1051 – 2516 ng.h/mL).

The NOAEL for general toxicity was estimated to be 10 mg/kg/day (Mean AUC_{0-24 h} = 50 – 237 ng.h/mL) based on premature death at 40 mg/kg/day and the overall findings in the kidneys, white blood cells and lymph nodes described above.

The Pharm-tox reviewer commented that the juvenile rat study was well-designed and executed, and recommended the application approvable.

The Pharm-tox reviewer suggested revising the labeling to:

- (i) include the rat juvenile study and animal toxicology studies from the reference label,
- (ii) emphasize that (b) (4) is not intended to be prescribed to pregnant women, but add the adverse events reported in neonates whose mothers had received propranolol during pregnancy from the reference label, and
- (iii) add the information that bronchospasm and congestive heart failure have been reported in pediatric patients administered propranolol from the reference label.

CDTL comment: I concur with the Pharm-tox reviewer's the determination that the product is approvable, and the labeling change recommendations.

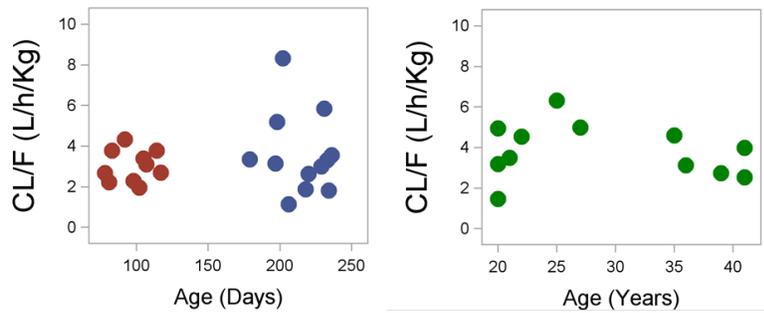
5. Clinical Pharmacology/Biopharmaceutics

5.1 General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

OCP – The Clinical Pharmacology reviewer (Divya Menon-Andersen) evaluated PK/PD study (Study # VS00400SB102) conducted in 23 infants with IH.

The Clin-Pharm reviewer found (Figure 2) that after normalizing for body weight, the propranolol clearance pharmacokinetics in infants {mean (±SD)= 3.3 (±1.7) L/h/Kg} is similar to that observed in adults {mean (±SD)= 3.8 (±1.3) L/h/Kg}.

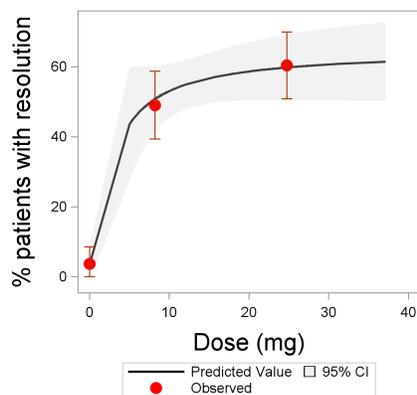
Figure 2 Propranolol Clearance normalized to body weight in adults and infants



Source: Figure 4 in Clin-Pharm Review

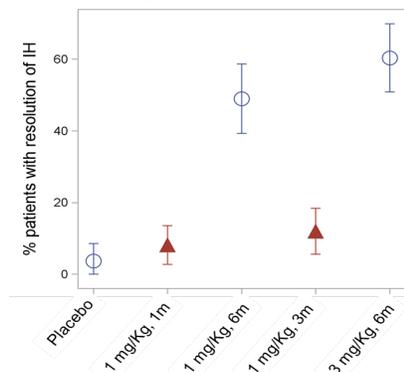
In Figure 3, the Clin-Pharm reviewer showed that the probability of complete/near complete resolution at week 24 appears to be dose dependent, with the highest dose evaluated (3 mg/Kg/day) close to the maximal effect and a further increase in the dose unlikely to result in a significant increase in response.

Figure 3 Probability of complete/near complete resolution (Primary endpoint) at Week 24



Source: Figure 2 in Clin-Pharm Review

Figure 4 Proportion (mean and 95% CI) of patients with complete/near complete resolution in all treatment groups at Week 24



Source: Figure 5 in Clin-Pharm Review

In Figure 4, over 50% of the patients in the 6 month duration arms achieved complete/

near complete resolution while only ~ 5 to 10 % of the patients randomized to the 3 month arms achieved complete/near complete resolution indicating that continued treatment for at least 6 months is needed for resolution of the hemangioma.

With regard to safety, the Clin-Pharm reviewer found no significant effect of propranolol treatment on blood pressure, heart rate, or blood glucose levels in infants.

The Clin-Pharm reviewer concludes that NDA 205-410 can be approved from a clinical pharmacology perspective provided agreement is reached with the applicant on labeling. The Clin-Pharm reviewer does not recommend Phase 4 Requirements or Commitments.

CDTL comment: I concur with the evaluation by the Clin-Pharm reviewer and the determination that the submitted clinical pharmacology data support approval. The Clin-Pharm reviewer's findings of dose-response and treatment duration effect further support the discussions in dose and duration of treatment recommendations (Please see Section 7.2 of CDTL review).

ONDQA – Biopharmaceutics reviewer (Kareen Riviere) evaluated the dissolution data in a relative bioavailability (BA) study (Study # VS004SB101), which was part of the applicant's two-step bridging approach that included:

- (i) An *in vivo* BA comparison between the proposed propranolol solution product and Avlocardyl[®], a French approved propranolol tablet formulation, which demonstrated comparable BA profiles between the 2 formulations in 12 healthy adults; and
- (ii) An *in vitro* dissolution test which demonstrated the equivalence of dissolution profiles of Avlocardyl[®] and Propranolol HCl USP 40 mg tablets (Barr Laboratories, Inc., approved under ANDA 71-974).

The applicant used the Propranolol HCl USP 40mg tablets, explaining that the Inderal[®] 40 mg tablet is no longer marketed in the US and could not be used as the reference listed drug (RLD) in the BE study supporting their product. However, Inderal[®] 40 mg tablets are still marketed and available in the US; the Biopharmaceutics reviewer's opinion is that it is possible the applicant did not have access to the US RLD product.

Acceptability of the data supporting the bridging between the proposed propranolol solution product and the RLD propranolol product (Inderal[®] 40 mg tablets) under NDA 16-418 is necessary to leverage propranolol's non-clinical information.

The BioPharm reviewer concluded that the bridging between the proposed oral propranolol solution product and the US RLD, Inderal[®] 40 mg tablets is adequately justified and acceptable based on the following supportive scientific data submitted:

- (i) Propranolol is a BCS class 1 drug substance. The 40 mg Avlocardyl[®], Propranolol HCl USP, and Inderal[®] tablets are expected to act as solutions *in vivo* since they are formulated and manufactured to be fast-dissolving immediate-release tablets.
- (ii) Avlocardyl[®], which contains mannitol (an inactive ingredient that may reduce the BA of drug products), is bioequivalent to the oral solution. Therefore, the Inderal[®] tablet, which does not contain mannitol, is expected to be bioequivalent to the oral solution.
- (iii) The 40 mg Avlocardyl[®] tablets and 40 mg Propranolol HCl USP tablets have similar dissolution profiles, and the 40 mg Propranolol HCl USP tablets and the Inderal[®] 40

(b) (4) (Propranolol Hydrochloride Oral Solution - 3.75 mg/mL propranolol)

mg tablets are bioequivalent. Therefore, it is expected that the 40 mg Avlocardyl[®] tablets and Inderal[®] 40 mg tablets will have similar dissolution profiles and similar *in vivo* performance.

(iv) There are PK data and Phase 2/3 data on the commercial formulation of the proposed product which provides further evidence of its efficacy and safety.

The BioPharm reviewer states that from the Biopharmaceutics standpoint, (b) (4) oral solution 3.75 mg/mL is recommended for approval.

CDTL comment: I concur with the reviewer's evaluation and recommendation.

5.2 Drug-drug interactions

No drug interaction studies were conducted.

6. Clinical Microbiology

Review of Product Quality Microbiology: CDER/OPS/ONDQA/NDMS Review (By Erika Pfeiler, Microbiologist): Early in the review process, the Product Quality Microbiology reviewer issued an IR to the sponsor to

- (i) identify potential sources for introduction of *Burkholderia cepacia* complex (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) use a validated method capable of detecting BCC organisms (as there are currently no compendial methods for detection of BCC).

The sponsor conducted studies which showed that

- (i) the residual risks for propranolol 3.75 mg/mL oral solution to be contaminated by BCC during the manufacturing process are considered under control and in compliance with current regulations,
- (ii) a high anti-microbial activity of the drug product was demonstrated on 2 strains of BCC, and
- (iii) analysis performed on 6 industrial scale batches demonstrated the absence of BCC in the drug product.

The Product Quality Microbiology reviewer considered these measures adequate, and commented that the microbiological quality of propranolol 3.75 mg/mL oral solution, including BCC, is controlled via suitable manufacturing and testing protocols.

The Product Quality Microbiology reviewer found the microbial limits specifications for Propranolol acceptable, and recommended approval.

CDTL comment: I concur with the Product Quality Microbiology reviewer's evaluation and recommendation.

7. Clinical/Statistical- Efficacy

7.1 Discussion of both the statistical reviewer review and the clinical efficacy review with explanation for CDTL's conclusions and ways that any disagreements were addressed.

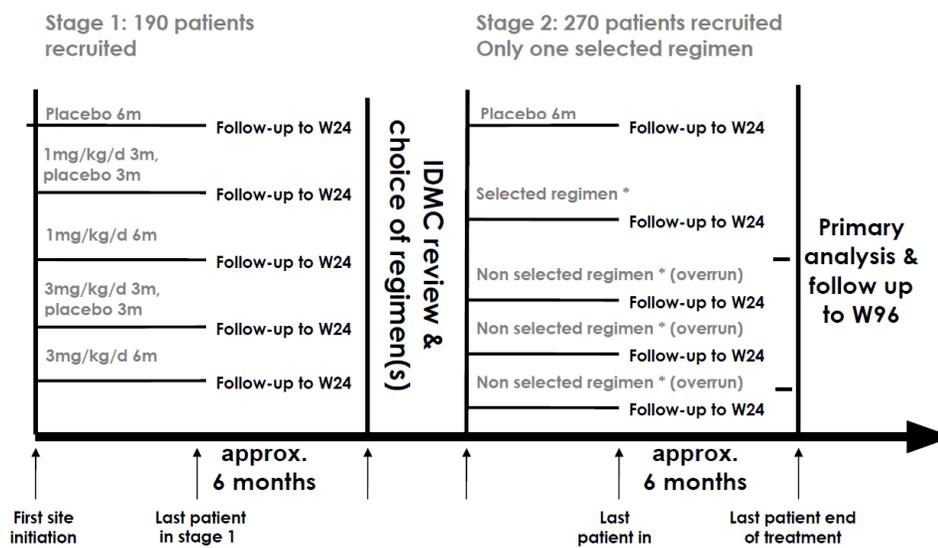
Note: CDTL and the primary clinical reviewer are the same. The primary clinical reviewer and the primary statistical reviewer (Yeh-Fong Chen) are in general agreement that the data submitted support approval of the NDA.

The pivotal study (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 weekly intervals) at the end of the first stage in a seamless phase II/III design³. The objective of the second stage of Study 201 was to demonstrate the efficacy of the selected dose regimen 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 (i) target IH evolution by the investigator's on-site qualitative (success/failure) assessments of complete/nearly complete resolution with an additional category of 'minimal palpable component', (ii) target IH evolution at paired consecutive visits, (iii) target IH complications, and (iv) parents'/guardians' qualitative assessment of target IH evolution at paired consecutive visits.

Figure 5 Actual Recruitment and Follow up
N = 460 patients



Five treatment arms (Figure 5; placebo and 4 regimens of propranolol with different

dose/duration combinations) were studied in Stage 1, in which 460 patients were randomized and 456 were treated 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.

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

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 the treatment assigned by the randomization code was not available on site. Thus, the number of ITT patients enrolled in Stage 2 was 88. The ITT data set totals 276 treated patients (188 in Stage 1 and 88 in Stage 2), not including the overrun patients. In the “per protocol” (PP) data set, 17 patients with major protocol deviations were excluded, thus counting 259 (i.e., 93.8% of 276 ITT data set).}

An interim analysis was conducted on 188 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 month arm and recommended continuing the trial with this regimen and the placebo, without sample size adjustment or re-estimation.

Patients who had already been assigned to a randomized regimen of propranolol at the time of the interim analysis continued their treatment according to their randomization (called “overrun patients”). Their data were not included in the primary efficacy analysis, but were included in the safety analysis and exploratory efficacy analyses.

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 about 98 weeks. This follow-up period is currently ongoing, and results will be available in Q2 2014.

Table 2 Complete or nearly complete resolution at Week 24 – 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. (Note: The sponsor’s p-values are one-sided.)

Analysis of the primary endpoint (Table 2) shows efficacy of the selected regimen, 3

mg/kg/day 6 month, versus placebo (ITT); the difference in rates of complete/nearly complete resolution of IH at W24 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 arm was 62.8% for Stage 1 and 58.6% for Stage 2. This statistically significant difference is also clinically meaningful.

The statistical reviewer confirmed the sponsor's primary endpoint analyses.

A sensitivity analysis using the PP data set for the primary efficacy endpoint 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 3).

Table 3 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

Table 4 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		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										
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										
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	
*P-value			1.0000		<0.0001		0.5614		<0.0001	

*P-values were obtained by two-sided Fisher's Exact test after Bonferroni Adjustment. Source: Sponsor's Table 1 of efficacy-information-amendment.pdf:2 from 007 submission.

A sensitivity analysis (Table 4) 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, and
- (iii) 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.

The pooled data was also analyzed by the sponsor (at the Division’s request in an IR letter) to 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 found to be statistically significant (Table 4). It appears that the 3-month regimens were not beneficial, whereas the 6-month regimens produced statistically significant benefit. This was confirmed by the statistical reviewer.

CDTL Comment: The statistical reviewer pointed out correctly that had the study been conducted as a “traditional” clinical trial with 5 treatment arms, both the 1 mg/kg/day 6 month and 3 mg/kg/day 6 month treatment groups could be considered as producing a statistically significant benefit over placebo. However, the analysis for the overrun group that received 1 mg/kg/day 6 month was pre-specified as exploratory. I think this *post-hoc* finding can not be used to support an indication for the 1 mg/kg/day 6-month regimen.

Another *post-hoc* exploratory analysis was done by the sponsor (at the Division’s request in an IR letter) for the pooled ITT with the overrun population as a group sequential trial (Table 5). This analysis maintains the parameters from the original analysis scheme, and uses a conservative O’Brien-Fleming rule (the nominal level of significance was set to 0.00125 (0.005/4) according to Bonferroni correction for multiplicity). The sequential design analyses (Table 5) show that the three-month regimens would have been stopped at the interim analysis for futility had the recruitment not been completed already at that time. Only the six month regimens showed statistically significant benefit.

Table 5 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

Source: Sponsor’s Table 2 of efficacy-information-amendment.pdf:2 from 007 Submission

CDTL Comment: Again, had the study been conducted as a sequential design clinical trial both the 1 mg/kg/day 6 month and 3 mg/kg/day 6 month treatment groups could be considered as producing a statistically significant benefit over placebo. However, the sequential analysis for the overrun group that received 1 mg/kg/day 6 month was pre-specified as exploratory only. Therefore, this *post-hoc* finding can not be used to support

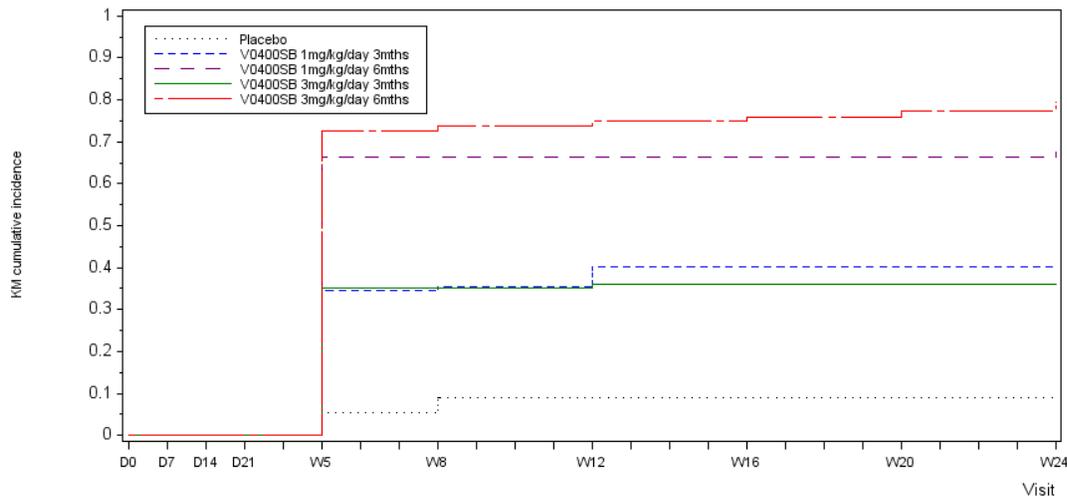
an indication for the 1 mg/kg/day 6-month regimen.

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 sustained improvement (defined as first improvement after which there is no worsening) occurs early, with 72.7% of the patients showing sustained improvement at W5 (Figure 6).

Figure 6 Cumulative incidence curves for the first sustained improvement (ITT with overrun)



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

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) compared to the centralized photographic assessment; non-standardized assessment may have created statistical noise causing a smaller observed difference.

In conclusion, the pivotal study shows that oral 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.

The statistical reviewer found the data quality of this NDA submission acceptable. The sponsor's primary analysis results were confirmed based on both the raw and derived data sets submitted to FDA.

CDTL comment: The primary clinical reviewer and the primary statistical reviewer agree that the efficacy findings support approval of the 3 mg/kg/day 6 months treatment for the treatment of IH requiring systemic therapy in infants 5 weeks to 5 months.

7.2 Discussion of notable efficacy issues both resolved and outstanding

Note: CDTL and the primary clinical reviewer are the same.

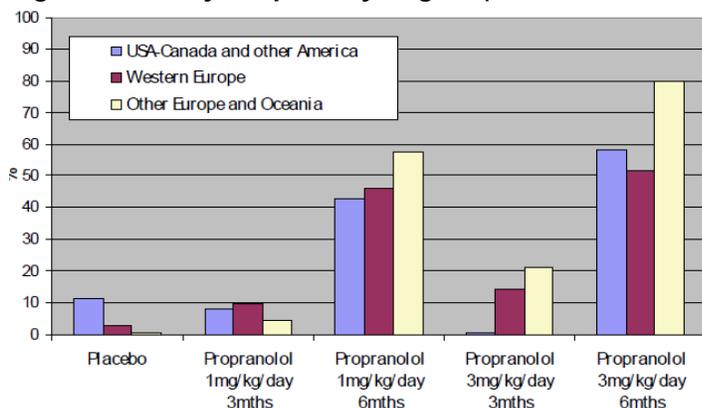
Statistical Reviewer's comments: Study 201 appeared to support propranolol's efficacy for both 3 mg/kg/day and 1 mg/kg/day 6 month regimens. However, there were differential dropout rates between the placebo and the study drug groups and between different regions/countries (most placebo dropouts were from Western Europe and France). The statistical reviewer stated that while it can be argued that a much higher dropout rate in the placebo group might lend an additional assurance for propranolol's efficacy, the fact that (i) the placebo group had a much higher dropout rate, (ii) most patients dropped out early and (iii) most of these placebo dropouts took propranolol (prohibited medication) after dropping out might have created a bias in favor of propranolol. Hence, the strength of evidence for efficacy of propranolol is probably overstated by the nominal p-value, an observation based on a number of sensitivity analyses made by the statistical reviewer.

CDTL comments: Including the dropout issue above noted by the statistical reviewer, I found a number of issues in Study 201 which needs to be evaluated as discussed below.

- (1) Randomization: Disproportionately fewer patients were randomized to placebo in non-European centers.

Figure 7 shows the exploratory analyses ITT data sets of the primary efficacy endpoint by region (USA-Canada and Other America vs. Western Europe vs. Other Europe and Oceania) performed by the sponsor (at the Division's request in an IR letter). In all 3 regions, the 3 mg/kg/day 6-month was consistently effective. No regional bias was found as a result of the disproportionate differences in placebo patients between the 3 regions. The PP data sets show similar results.

Figure 7 Primary endpoint by Region (ITT data set with overrun population)



CDTL Comment: The statistical reviewer's concern was about "the disproportionate number of placebo patients in Western Europe (France had 18% placebo patients and Western Europe had 14% whereas the overall placebo patients come to only 12%) and the number of placebo dropouts (86% of placebo patients in France and 74% of placebo patients in Western Europe dropped out compared to only 40% in Other Europe or 63% in North America)." The finding that the 3 mg/kg/day 6 month

regimen was consistently effective in all three regions with no evidence of a regional bias for the primary endpoint in both the ITT and PP data sets is reassuring.

- (2) 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 rapid efficacy of propranolol in the treatment of IH. Patients in the US and non-EU countries stayed on placebo longer than those 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 US and the non-EU countries reduced unblinding so that most placebo patients in US and the non-EU countries stayed longer in the trial.
- (3) Concomitant medications: The protocol specified that patients were ineligible for enrollment if they received at least one of the prohibited meds within 14 days for randomization – 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; for these drugs, a duration was not specified so patients were supposed have not received any of them at any point in time.

The statistical reviewer was concerned that "...more placebo patients took prohibited IH medication(s) (most of them after dropping out) and the prohibited IH medication they mostly took was the study drug, propranolol. For placebo dropouts, the mean number of days from randomization to when they took prohibited IH medication(s) was only 42 days, comparing with the other treatment dropouts taking prohibited medication, which were all more than 110 days..."

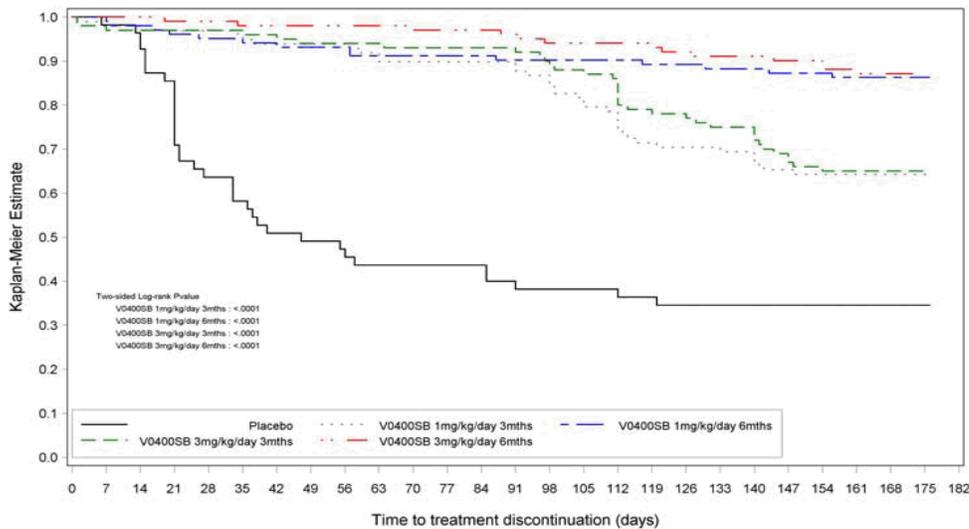
CDTL Comment: After discontinuation, the patient was not prohibited from taking any IH treatment at any point in time. When patients on placebo had no obvious cosmetic response, they dropped out early (decision by parents or their pediatricians) and then they were started on open-label propranolol; some patients 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 for off-label use). There is justification for this clinical action. Children with IH need to have definitive treatment started as soon as possible at a young age (<3 months preferably) because otherwise permanent skin lesions could result. Therefore, doctors and parents made efforts to start these placebo-treated children with IH immediately on some form of definitive IH therapy (usually propranolol or corticosteroids). This probably explains why the placebo-treated children with IH received off-label propranolol right after they left the study.

- (4) Discontinuations: 137 (29.8%) of the 460 randomized patients discontinued their treatment prematurely: 65.5% in the placebo 6 month regimen vs. 36.4% (1 mg/kg/day 3 month), 35.6% (3 mg/kg/day 3 month), 14.6% (1 mg/kg/day 6 month), and 13.7% (3 mg/kg/day 6 month) in the active regimens. For all regimens, treatment inefficacy was the most frequent primary reason for discontinuation; it was highest in the placebo 6 month 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%).

The pattern of discontinuation differed among the treatment arms (Figure 8):

- In the placebo arm, treatment discontinuation started early (as soon as at Week 2), with a very steep drop in the Kaplan Meier curve between Week 2 and Week 5; 49.1% of the patients had discontinued treatment at Week 5. Treatment discontinuations continued at a lower rate thereafter, reaching 65.5% at Week 20;
- In the active treatment arms, the treatment discontinuation rates were much lower than in the placebo arm

Figure 8 Kaplan Meier curve for Time to Treatment Discontinuation (Safety Data Set)



Source: CSR Study 201 Figure 5.

Table 6 Statistical Reviewer’s Sensitivity Analyses for Study 201

Designated day or week to become responders n (%), p-value*	Placebo (N=55)	Propranolol 1 mg/kg/day 3 months (N=98)	Propranolol 1 mg/kg/day 6 months (N=102)	Propranolol 3 mg/kg/day 3 months (N=100)	Propranolol 3 mg/kg/day 6 months (N=101)
Day 14	37 (67.3%)	35 (36.1%) worse	29 (28.4%) worse	35 (35.7%) worse	35 (34.7%) worse
Day 21	31 (56.4%)	34 (35.1%) worse	28 (27.5%) worse	35 (35.7%) worse	35 (34.7%) worse
Week 5	20 (36.4%)	34 (35.1%) worse	27 (26.5%) worse	35 (35.7%) worse	34 (33.7%) worse
Week 8	9 (16.4%)	31 (32%) p = 0.039	26 (25.5%) p = 0.19	34 (35%) p = 0.019	33 (33%) p = 0.028
Week 12	7 (12.7%)	28 (29%) p = 0.025	23 (23%) p = 0.135	31 (32%) p = 0.011	33 (33%) p = 0.006
Week 16	4 (7.3%)	27 (28%) p = 0.003	22 (22%) p = 0.022	30 (31%) p = 0.001	31 (30.7%) p = 0.001
Week 20	3 (5%)	10 (10%) p = 0.31	21 (21%) p = 0.01	14 (14%) p = 0.10	27 (27%) p = 0.001

Note: p-values were two sided and calculated based on the primary analysis method; Source: Table 19 of Statistical Review

Statistical Reviewer’s sensitivity analyses (Table 6): The statistical reviewer

commented that since the primary endpoint only captured good response from patients who did not drop out, when a lot of placebo patients dropped out, there may be a concern that the final analysis comparing the response rate between the drug groups and placebo might exaggerate the true treatment effects. The statistical reviewer’s sensitivity analyses in Table 6 suggest that there seems to be a nontrivial impact on the p-values by assuming dropouts as failures. If all patients who dropped out after Week 8 are assumed to be responders, then the p-values in favor of propranolol do not achieve <0.00125. (Since this is a single trial using a soft endpoint, an alpha threshold should be <0.00125.)

Table 7 Statistical Reviewer’s Further Sensitivity Analyses for Week 8 (Study 201)

Change of Dropouts after Week 8 Being Responders	Placebo (N=55)	Propranolol 1 mg/kg/day 3 months (N=98)	Propranolol 1 mg/kg/day 6 months (N=102)	Propranolol 3 mg/kg/day 3 months (N=100)	Propranolol 3 mg/kg/day 6 months (N=101)
0.8	8 (15%)	26 (26.8%) p=0.087	25 (24.5%) p=0.144	31 (31.6%) p=0.024	32 (31.7%) p=0.019
0.5	6 (10.9%)	16 (16.5%) p=0.359	23 (22.6%) p=0.073	22 (22.5%) p=0.086	27 (26.7%) p=0.021
0.3	5 (9.1%)	8 (8.3%) p=0.843	22 (21.6%) p=0.048	13 (13.3%) p=0.467	28 (27.7%) p=0.006
0.1	2 (3.6%)	8 (8.3%) p=0.277	20 (19.6%) p=0.006	7 (7.1%) p=0.392	25 (24.8%) p=0.0008

Source: Table 19 of Statistical Review

One could argue that this assumption of making all dropouts after Week 8 as responders may be too strong. The statistical reviewer performed additional sensitivity analyses by giving each dropout patient a probability of being a responder (Table 7). By assigning patients who dropped out after Week 8 to have a 50% chance to be a responder, the p-value for the comparison between propranolol 3 mg/kg/day of 6 month regimen and placebo was at the level of 0.02.

CDTL comments: 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 they are more likely to seek open-label propranolol. I agree that these early treatment withdrawals which then became classified as “failures” could reduce the number of primary endpoint events in the placebo group, causing bias to make the treated group more likely to win in the ITT analysis. To understand the impact of these “failures” and the early placebo dropouts on the primary efficacy endpoint, I requested the sponsor to perform the following exploratory analyses:

- (i) use 168-day (24 W) as the cutoff and exclude any patient who took prohibited concomitant medications (which could include some patients on placebo who had been discontinued before W24) – i.e., analysis of “the completers”,
- (ii) consider those who dropped out before W24, not as “failures” but use some form of imputation method (such as multiple imputation method) to understand the noise associated with early discontinuation/failures from various causes.

In addition, I performed another “sensitivity analysis” in which ALL dropouts in the treated arms are considered as “failures” and ALL dropouts in the placebo arms as

“censored” (Avi’s Law).

The following summarizes the findings of the three sensitivity analyses I used:

- (i) Exploratory analysis of “the completers”: Table 8 shows the *post-hoc* analysis of data on “the completers” (patients who reached Week 24 and had photographs evaluated by central reading). There was a similar dose-response finding between the two 6-months treatment regimens (success rates of 69.3% and 56.8%, in the 3 mg/kg/day x 6 month and 1 mg/kg/day x 6 month regimens, respectively). Both of the 3-month regimens showed lower success rates close to that of placebo.

Table 8 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

Reviewer’s comment: In this exploratory analysis, any premature discontinuation was considered as a treatment failure. This analysis overestimates efficacy (which the statistical reviewer also noted), because in the placebo group patients were more likely to discontinue early when the lack of cosmetic benefit became obvious early to investigators and/or parents.

- (ii) Exploratory analyses using multiple imputation method: *Post-hoc* handling of early discontinuations was performed by the sponsor (at the Division’s request in an IR) 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 9) show a statistically significant treatment effect for propranolol 3 mg/kg/day 6 month (p=0.0006) and propranolol 1 mg/kg/day 6 month (p=0.0098).

Table 9 Primary endpoint: exploratory 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

Reviewer’s comment: This analysis using multiple imputation method confirms the robustness of the primary endpoint.

- (ii) In a third exploratory sensitivity analysis, I treated ALL dropouts in the 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).

Table 10 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%)
Primary Endpoint 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.

Reviewer’s comment: Using this very conservative analysis, the success rates in the 3 month regimens did not differ from placebo (Table 10), but the 6 month regimens remain significantly better than placebo, supporting the primary efficacy analysis.

Summary of sensitivity analyses: Overall, 2 patients (3.6%) in the placebo 6 month regimen and 61 patients (60.4%) in the 3 mg/kg/day 6 month regimen presented complete or nearly complete resolution of their IH at Week 24, with a combined p-value <0.0001 which shows that the difference was statistically significant (at the 0.005 level). The results were consistent between the two stages. These results were supported by an analysis on the Per Protocol data set and on the sensitivity analyses (above) which used different definitions of treatment failure.

(5) Dose considerations: (b) (4)

patients treated with the 3 mg/kg/day 6 month regimen:

- (i) had a higher success rate (60.4% had complete or near complete resolution at Week 24) compared to those treated with the 1 mg/kg/d 6 (49.0%)
- (ii) showed a more rapid response (87.1% of patients had improvement at Week 5) compared to those treated with 1 mg/kg/day 6 month (69.6%), and
- (iii) had a higher proportion who obtained sustained improvement post-treatment at Week 5 (71.3%) compared to those treated with 1 mg/kg/day 6month (61.8%).

However, patients treated with the 3 mg/kg/day 6 month regimen had more adverse events than the 1 mg/kg/d 6 month group.

Clinical Reviewer’s comments and discussion regarding the DOSE:

- (i) From the primary efficacy results (Table 4), the 3 mg/kg/day x 6 month regimen did not produce a proportionately larger response rate compared to the 1 mg/kg/day x 6 month regimen in a consistent manner. For a three-fold (one log)

increase in dose, the benefit obtained is about 11% more responders at 24 weeks (i.e., 60% vs. 49%). In Table 11, I have compiled the response rates in Study 201, the Compassionate Use Program (CUP) and the medical literature.

- (ii) In the 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 (Table 11). 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 as 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 the 3 mg/kg/day dose to accrue a response rate of 60%.

Table 11 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

- (iii) 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 11).

The response rates I have compiled in Table 11 suggest that even patients with high risk IH or more severe IH who were treated with propranolol at doses less than 3 mg/kg/day (~ 2 mg/kg/day) achieved a response rate comparable to that observed in patients in the pivotal clinical trial who received 3 mg/kg/day. Therefore, it may not be necessary to use the 3 mg/kg/day 6 month dose to obtain the 60% response rate.

Had the trial been pre-specified as a “traditional” 5-arm trial (Table 4) or as a group sequential design study (Table 5), BOTH the 1 mg/kg/day 6 month and the 3 mg/kg/day 6 month treatments would have been considered as providing statistically significant benefit over placebo.

However, from a regulatory perspective, the clinical trial was pre-specified as an adaptive design study. At the interim analysis of this adaptive design study, the 1 mg/kg/day 6 month group did show a statistically significant (35.5%; P<0.0042) benefit over placebo (Table 4), but the IDMC decided not to carry forward the 1 mg/kg/day x 6 month dose. While patient enrollment and randomization had been completed for all treatment arms at the time of interim analysis, any further analysis of the 1 mg/kg/day x 6 month dose following the interim analysis have to be considered *post-hoc* and “exploratory” in nature; the 1 mg/kg/day x 6 month dose was not pre-specified for primary efficacy analysis and, therefore, cannot be used to support an indication for regulatory approval.

It is noteworthy also that there appears to be a dose-response with the response rate in the 1 mg/kg/day x 6 month group (49%) being inferior to that in the 3 mg/kg/day x 6

month group (60%).

Therefore, from a strictly regulatory perspective, only the 3 mg/kg/day x 6 month regimen can be recommended for approval.

Table 12 Exposure (Dose and Duration of Treatment) to Propranolol in New Publications

Author	Year	No. Treated with Oral Propranolol	Mean / Target Dose of Propranolol	Duration of Treatment*
Anderson de Moreno	2013	5	2 mg/kg/day (TID), up-titration N/A	2-6 months in 4 patients (N/A for 1 patient)
Ben-Amitai	2012	10	2 mg/kg/day, after 3 days of up-titration from 0.5 mg/kg/day TID	9.7 (5-13) months
Clifford & May	2012	7	2 mg/kg/day after 1 week at 1 mg/kg/day (TID) if well tolerated	N/A
Dotan & Lorber	2013	1	3 mg/kg/day after 5 days at 1.5 mg/kg/day (TID)	> 5 months
Gan	2013	109	2 mg/kg/day after a 1-week up-titration starting at 0.5 mg/kg/day	6-12 months
Hasan	2013	36	3 mg/kg/day (TID), up-titration N/A	3.36 (2-7) months
Hermans	2013	174	2-2.5 mg/kg/day (after up-titration from 0.7-1 mg/kg/day TID) until the age of 9 months, then dose adjusted if needed. In 16 pts: 0.75-1.9 mg/kg/day; In 3 pts: 3 mg/kg/d	10.7 months in 113 completers
Hong	2013	45	2 mg/kg/day (TID) after an up-titration of 1-2 weeks starting at 0.5 mg/kg/day (TID)	6.5 (3-11) months
Jian	2013	97	2 mg/kg/day, up-titration N/A	6-12 months (planned)
Katona	2012	22	2 mg/kg/day (TID), no up-titration	6-14 months
Léauté-Labrèze	2013	7	3 mg/kg/day for 15 days then 4 mg/kg/day for 15 days	4 weeks in 6 patients (3 weeks in 1 patient)
Liu	2013	31	2 mg/kg/day (TID), no dose escalation	N/A (follow-up over the first 24 hours (3 first doses))
Ma	2013	89	1-3 months: 0.75 mg/kg/day; 4-12 months: 1 mg/kg/day (BID)	13.6 (5-16) months
Mc Gee	2013	24	2 mg/kg/day (22 infants) after 1 week of up-titration from 1 mg/kg/day TID (23 infants; 0.5 mg/kg/d in 1 infant)	Median 10.5 (3.5-14) months in 10 completers
Meng	2012	22	1 mg/kg/day (age <3 months), 1.5 mg/kg/day (age >3 months) (OD)	< 5 months
Ozyörük	2013	14	2 mg/kg/day (BID) without up-titration	Median 6 months (3-12 months) in 11 completers
Park	2013	83	2 mg/kg/day (TID) after 3-day up-titration from 0.5 mg/kg/day	8.7 (2.5-28) months
Rössler	2012	30	2 mg/kg/day after 1 mg/kg/d (BID) on the 1 st day	~6.5 months [198 (19-293) days]
Vassallo	2013	14	2 mg/kg/day, up-titration N/A	2.5 (1-4 months) in 12 completers
Vergine	2012	1	2 mg/kg/day (after ~1 week at 1 mg/kg/d)	~10 months (up to the age of 14 months)
Xiao	2013	64	2 mg/kg/day, no up-titration	Median 8.5 (4.5-14 months) in 53 completers
Yuan	2013	35	1 mg/kg/day for 3 months, then 1.5 mg/kg/day for 3 months (OD)	4-8 months
TOTAL		920		

On the other hand, there are considerations for the lower doses (than 3 mg/kg/day) to be recommended (particularly for patients who may not be able to tolerate the 3 mg/kg/day dose), because:

- (i) the Clin-Pharm reviewer noted that the primary endpoint appears to be dose dependent with the 3 mg/kg/day dose showing close to the maximal effect. The 1 mg/kg/day dose also appears to be high on the dose response curve (Figure 3). A further increase in the dose above 3 mg/kg/day appears unlikely to result in a significant increase in response. (Please see section 5.1 of this CDTL review.)
- (ii) even patients with high risk IH or more severe IH in the CUP (Table 11) achieved a response rate comparable to that observed in patients in the pivotal clinical trial when

most patients were treated with propranolol at a dose of 2 mg/kg/day, supporting the notion that it is not necessary to use the higher 3mg/kg/day dose to obtain the 60% response rate.

(iii) if the trial were analyzed as a “traditional” 5-arm trial or as a group sequential design study, BOTH the 1 mg/kg/day and 3 mg/kg/day treatments provided statistically significant benefit over placebo.

(iv) in 22 recent clinical studies (Table 12) on 902 patients with IH in the medical literature, and in patients with IH treated in the US pediatric dermatology practice (Table 13) the prevailing dose of propranolol used to treat the majority of patients is 2 mg/kg/day (range: 0.75 – 4 mg/kg/day).

CDTL comments: Based on the above considerations, I recommend that we ask the sponsor – in the approval letter – to study in a prospective clinical trial a dose of propranolol lower than 3 mg/kg/day (e.g., 2 mg/kg/day) for a duration of 12 months to minimize regrowth of IH. (See also discussion on duration of treatment below).

(6) Considerations regarding the DURATION of treatment:

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.² The proliferative phase of IH offers an important therapeutic window to halt progression of the IH and to induce early involution. In Study 201, the upper age limit at inclusion (5 months) and the maximum duration of treatment (6 months) were aimed at ensuring exposure to treatment during (but no later than) the proliferative phase when efficacy is most likely to occur. The dose and duration pre-specified in the SPA produced substantial success rates in the efficacy analysis (60.4% versus 3.6% with placebo), with a relatively low rate of patients needing re-treatment (11%) during the post-Week-24 off-treatment follow-up period. Thus, the sponsor argued that the efficacy results from Study 201 support the efficacy of the 6-month treatment duration.

Figure 9 Phases of Infantile Hemangioma



Growth and regression of IH. (Source: Storch CH & Hoeger PH. *Brit J Dermatol* 2010; 163: 269-74)

Clinical Reviewer’s comments regarding the DURATION of treatment: According to the

pathophysiology and natural history of IH (Figure 9), the active proliferative phase lasts **about 12 months** from the age of 5 weeks to about 14 months of life.⁴ I think this 12 month period is the duration for which propranolol treatment should be administered.

The reasons for recommendation the 12-month duration of propranolol treatment are:

- (i) In 22 recent clinical studies (Table 12) on 902 patients with IH in the medical literature, the majority of patients were treated with the dose of 2 mg/kg/day (range: 0.75 – 4 mg/kg/day), which is the prevailing pediatric dermatology clinical practice.
- (ii) Secondly, I base my considerations regarding the “duration of treatment” on the finding of consistency in sustainability of the initial treatment effect of propranolol after discontinuation in Study 201, the CUP and the medical literature (Table 13):

Table 13 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 ⁶ (1 – 3 mg/kg/day, 117 pts got 2 mg/kg/d)	158 / 158	40 (25%)	19 (12%)
Meta-analysis 35 studies ⁵	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

- (a) In Study 201, 10% of patients in the 3 mg/kg/day 6 month regimen required the re-introduction of a systemic treatment. The 6 month regimen might not have covered the entire active proliferative phase, causing regrowth or recurrence of IH that was also reported in the literature in 12% of propranolol-treated patients.
 - (b) In the CUP, the mean dose of propranolol after titration in the 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. Among the 126 patients who were discontinued for efficacy, 4 (3%) of patients required reintroduction of systemic propranolol treatment (i.e., fewer patients required re-treatment which could be attributable to a longer than 6 month treatment duration used in the CUP).
 - (c) A recent publication⁶ in which a cohort of IH patients was consecutively treated in one center (most of whom were treated with propranolol 2 mg/kg/day for a mean duration of treatment of 6.06 months) also showed that 40 of 158 infants (25.3%) showed IH regrowth, of which 19/158 (12%) patients had major regrowth requiring reintroduction of propranolol.
- (iii) Third, in 13 scientific publications on 573 patients treated with propranolol (Table 14), the regrowth rate ranged from 12% to 14%; the proportion of patients who required retreatment with propranolol ranged from 6% to 8% (Table 13). The duration of treatment was variable (range 3 months to 30 months), and the average propranolol dose was 2 to 3 mg/kg/day. In the publications with details related to re-treatment are available, 35 patients received re-treatment (i.e., 50% of the 70 patients who experienced regrowth and 6% of 573 propranolol-treated patients overall, which I have compiled in Table 13).

Table 14 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
⁷ 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
⁸ 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
⁹ Buckmiller, 2010	32	7.1 m (1.5 – 30 m)	Various	Planned: 2 mg/kg/day	NS	1	NS
¹⁰ 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
¹¹ 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
¹² 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
¹³ Leboulanger, 2010	14	5.2 m (0.7-16 m)	Airway	2.5 mg/kg/day	6 m	2/14 (14%)	1/2
¹⁴ Phillips, 2012	188	4 m (5 days-7 yr)	Various	2 mg/kg/day	8 m (10 days-30 m)	30/136 (22%)	NS/17
¹⁵ Price, 2011	68	4.9 m	Various	Planned: 2 mg/kg/day	7.9 m (3.5-14 m)	2	2/2
¹⁶ Saint-Jean, 2011	33	NS	Ulcerated	2 mg/kg/day	5.9 m	4	4/4
² Sans, 2009	32	Interventions - Early: 4.2 m Late: 31 m	Various	Planned: 2-3 mg/kg/day	6.1 m	7	NS/2
¹⁷ 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
¹⁸ 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.

CDTL comments: Based on the above considerations, I recommend that we ask the sponsor – in the approval letter – to conduct a prospective clinical trial in infants with IH using propranolol at a dose lower than 3 mg/kg/day (e.g., 2 mg/kg/day usually used in US pediatric dermatology clinical practice) for a duration of 12 months (and followed for 12 months) to determine whether (i) a lower dose will have lower risk of adverse events while being as effective as the 3 mg/kg/day dose, and (ii) a 12-week treatment regimen will have better sustained effect than the 6-month treatment regimen and minimize regrowth of IH. I suggest that the new clinical trial enroll all types of IH (e.g., life-threatening or function-threatening IH, severe IH, and IH with ulcers). In addition to the number/ proportion of patients who achieved complete/near complete resolution, additional endpoints should be used such as rate, time and extent (nature) of regrowth, and the need for retreatment {systemic or local (topical)}.

8. Safety

Note: CDTL and the primary clinical reviewer are the same.

8.1 Discuss the adequacy of the database, major findings/signals, special studies, foreign marketing experience, if any, and plans for postmarketing as discussed in the Pre-Approval Safety Conference (if NME will be approved)

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

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, many patients were treated up to 30 months.

8.2 General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.

Deaths:

- No death was reported in the pooled safety population.
- In the CUP, one death was reported (associated with AV block followed by cardiac arrest after lauromacrogol injection to sclerose esophageal varices).
- In the scientific publication one death was reported (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).

CDTL comment: The deaths do not appear attributable to propranolol treatment.

Serious Adverse Events (SAEs):

- In the pooled safety population, 36 SAEs were reported in 26 patients 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 continued 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.

Discontinuations:

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%).

Treatment-emergent adverse events (TEAEs):

In the pooled safety population, 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. 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.

CDTL comment: No unexpected safety signals were found.

8.3 Immunogenicity

Not applicable.

8.4 Special safety concerns

The submission-specific safety risks associated with propranolol (hypoglycemia, bradycardia, hypotension, and bronchospasm) were monitored during up-titration of propranolol doses in the clinical studies (102 and 201), and in the CUP. Case reports and narratives of patients who experienced the submission-specific adverse events were reviewed.

Hypoglycemia (Please see Section 7.4.2, pages 90-93 of my clinical review for details):

- In the pooled safety population in the clinical trials in this NDA, 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 four cases of hypoglycemia (Table 15). 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.”
- In the scientific publications, I found eleven cases of hypoglycemia (ten symptomatic) associated with propranolol therapy for IH (Table 15). In seven cases, an additional stressor such as an acute infection, prolonged fasting or corticosteroid use causing adrenal insufficiency were assumed to have precipitated hypoglycemia^{19,20,21,22} and

two other cases were beyond the age group indicated (11 and 18 months old) at the time of starting treatment (see below)²³.

Table 15 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 clinical review)

CDTL 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 larger brain mass relative to their body weight.²⁴ Propranolol may impair glucose homeostasis through inhibition of β -adrenergic mediated glycogenolysis, gluconeogenesis and lipolysis; therefore, theoretically propranolol can put the infants at risk of hypoglycemia. However, the blood glucose results in the clinical trials show no cause for concern.

There is no safety signal for hypoglycemia with propranolol treatment; almost all of the patients described above 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.

Hypotension: (Please see Section 7.4.3, pages 93-95 of my clinical review for details):

Blood pressure (BP) was monitored as an indicator of hypotension in the clinical studies.

- In the pooled safety population, there were no large reductions 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.
- In the CUP, 2 serious adverse reactions of hypotension were reported associated with too fast an increase in up titration; However, both continued on propranolol.
- In the scientific publications 4 events of hypotension were reported of which one was symptomatic (drowsiness, cold extremities); the BP values were not reported, and the symptoms resolved after treatment discontinuation.

Bradycardia: (Please see Section 7.4.3, pages 95-97 of my clinical review for details):

Heart rate was monitored as an indicator of bradycardia in the clinical trials.

- In the pooled safety population one patient 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 publications, 9 events of bradycardia were reported; none was symptomatic, all were transient and resolved after dose reduction or temporary discontinuation.

Bronchospasm: (Please see Section 7.3.5, pages 87-89 of my clinical review for details):

Bronchospasm is a known AE associated with propranolol. It was reported in:

- four patients in the pooled safety population (2 on placebo and 2 on propranolol),
- nine patients in the CUP (as bronchiolitis, presumed associated with a viral respiratory infection in 7 patients) and
- ten patients in the scientific publications.

None required hospitalization, all resolved and propranolol was able to be re-administered in most of these patients.

8.5 Discussion of primary reviewer's comments and conclusions

Note: CDTL and primary clinical reviewer are the same. See sections 8.1 to 8.4.

CDTL Comment: Overall, there are no new or unexpected safety signals.

8.6 Highlight differences between CDTL and review team with explanation for CDTL's conclusion and ways that the disagreements were addressed

Note: CDTL and primary clinical reviewer are the same. See section 8.7.

8.7 Discussion of notable safety issues (resolved or outstanding)

There are no outstanding notable safety issues.

9. Advisory Committee Meeting

According to the FDA Guidance for the Public and FDA Staff on Convening Advisory Committee Meetings (Draft Guidance, August 2008), "When considering whether to convene such a meeting, FDA should consider the following three factors:

- (a) *Is the matter at issue of such significant public interest that it would be highly beneficial to obtain the advice of an advisory committee as part of the agency's regulatory decision-making process?*

Reviewer's Answer: No. The indication in this NDA is treatment of proliferating infantile hemangioma requiring systemic therapy in infants 5 weeks to 5 months old, which is not of significant public interest.

- (b) *Is the matter at issue so controversial that it would be highly beneficial to obtain the advice of an advisory committee as part of the agency's regulatory decision-making process?*

Reviewer's Answer: No. There are no major controversial issues.

(c) *Is there a special type of expertise that an advisory committee could provide that is needed for the agency to fully consider a matter?*

Reviewer's Answer: No.

Since none of the above factors is met, an advisory committee meeting is not necessary.

10. Pediatrics

10.1 Peds exclusivity board review - PPSR/WR



10.2 PeRC Review Outcome-PMCs, deferrals, waivers, pediatric plan, peds assessment

Not applicable.

11. Other Relevant Regulatory Issues

Financial disclosure: The applicant submitted certification that the clinical investigators and sub-investigators who participated in Studies 201 and 102 had no disclosable financial interest and that they remained fully blinded throughout the study.

The applicant also submitted that Dr. Christine Labreze (principal and coordinating investigator for the pivotal Study 201) and Dr. Jean-Benoit Thambo (cardiologist of the clinical center 0501), who are the inventors of the use of β -blockers in the treatment of IH and participated in Studies 201 and 102, (b) (4)

(b) (4) and claimed to have no direct financial arrangement with the investigators).

Office of Compliance/Office of Scientific Investigation audits (by Susan

Thompson): Analysis of the primary efficacy endpoint results by sites showed that no particular site had efficacy data that was a clear outlier for GCP inspections. The Division requested OSI for GCP inspection of the conduct of the pivotal Study 201 at two sites (#0508 in Toulouse, France, and #5001 in Lima, Peru) which enrolled large numbers of patients, and showed relatively strong positive results. At the third site (#7105 in San Diego, California) all subjects who received the intended marketing dose (3 mg/kg/day x 6 months) were adjudicated negative, which appeared unusual.

The EMA had also selected Site #0508 in France (similar to our selection), and a different site (#5002) in Lima, Peru for inspections.

Site #5001 (FDA selection) randomized 16 subjects and completed 15 with 1 premature discontinuation; Site #5002 (EMA selection) randomized 17, and treated 17 with 1 premature discontinuation. We selected Site #5001 for inspection because it had a larger number (and proportion) of positive patients compared to site #5002:

- Site 5001 had 5 positive patients in the dose regimen intended for marketing (3 mg/kg/day 6 months), and 4 more who were positive with a different dose regimen i.e., 9 of 15 (56%) randomized were positive at Site #5001.
- 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.

EMA had already scheduled inspections in France and Peru, as well as of the sponsor, Institut de Recherche Peirre Fabre (IRPF); therefore, OSI decided to obtain the results of EMA inspections prior to scheduling similar or identical inspections. If serious findings impacting on study data integrity or subject safety were identified by EMA, OSI would then issue inspections to be conducted by ORA. Since no such findings were identified, the results of EMA inspections in France (clinical investigator and sponsor) and Peru were included as part of the Clinical Inspection Summary (together with the results of the domestic inspection of site #7105 by ORA) filed by OSI on 09-Dec-2013.

FDA inspection of Site #7105 was unremarkable. An important issue identified at the foreign sites and the sponsor was a failure to precisely describe 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 appeared 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).

The OSI Reviewer recommended that the data was considered adequate and could be used in support of the pending application.

CDTL comment: I concur. The above determination by the OSI reviewer is appropriate.

12. Labeling

12.1 Proprietary name

The Office of Prescription Drug Promotion (OPDP) determined that the proposed proprietary name, (b) (4) is acceptable from a promotional perspective.

The Division of Medication Error Prevention and Analysis (DMEPA) review (by Kimberly De Fronzo) {signed off by Irene Z. Chan on her behalf} on 07-Aug-2013 concluded that DMEPA

- (i) concurs with OPDP's assessment of the proposed proprietary name, and
- (ii) finds the proposed proprietary name acceptable from both the promotional and safety perspectives.

This is accompanied by the provisos that the proposed proprietary name must be

(b) (4) (Propranolol Hydrochloride Oral Solution - 3.75 mg/mL propranolol)

- (i) re-reviewed 90 days prior to approval of the NDA, and
- (ii) re-submitted for review if any of the proposed product characteristics as stated in the 22-May-2013 submission are altered.

Following a recent regulatory change, DMEPA informed Pierre Fabre on 03-Feb-2014 that the name (b) (4) is unacceptable because of (b) (4). On 05-Feb-2014, Pierre Fabre withdrew the proprietary name (b) (4) and submitted a request for proprietary name review for the new name "HEMANGEOL." During an internal labeling meeting on 05-Feb-2014, DMEPA informed the Division that an expedited review will be made to meet the PDUFA goal date.

CDTL comment: I will file an addendum to the CDTL review following DMEPA's assessment of the new proprietary name.

12.2 Address important issues raised by brief discussion of OPDP and DMEPA comments

The applicant wanted a claim that (b) (4) is "sugar free" because there is no sucrose or glucose in it. I checked the CFSAN definition of "sugar free" which is a label claim on a packaged food if the food has <0.5 g of sugar per serving per 21 CFR 101.60(c) and 101.9(c)(6)(ii).

The OPDP reviewer (Zarna Patel) commented that OPDP finds claims of "sugar free" and "alcohol free" on carton and container labeling acceptable, as long as they are disseminated with the PI. (Please also see Section 12.3.1 below.)

CDTL comment: I concur. The above determination by the reviewer is accurate.

12.3 Physician labeling

12.3.1 Carton and immediate container labels (if problems are noted)

The DMEPA reviewer (Jacqueline Sheppard) evaluated the proposed container label, carton and package insert labeling for areas of vulnerability that can lead to medication errors. The DMEPA reviewer finds that the proposed label and labeling can be improved to promote the safe use of the product and to mitigate the risk for confusion with other commercially available propranolol solutions, specifically:

- (i) use of the name of the active moiety, propranolol, instead of the name of the salt, propranolol hydrochloride according to USP,
- (ii) inconsistencies in expiry dates in different parts of the label and package insert,
- (iii) placement of the statement "Alcohol/Sugar free" (which is found acceptable) on the side panel of the container label, and
- (iv) clarification of the amount of liquid (feeds such as milk) in which the medication can be diluted before being administered to the infant.

Following an IR, the applicant made a correction of the in-use expiry of 2 months which is now stated consistently in the revised label.

The applicant also accepted FDA's recommendation to label the product with the

(b) (4) (Propranolol Hydrochloride Oral Solution - 3.75 mg/mL propranolol)

propranolol hydrochloride salt concentration as: (b) (4) propranolol hydrochloride oral solution 4.28 mg/mL equivalent to 3.75 mg/mL propranolol," which is reflected in the revised label. This FDA recommendation was made to prevent medication errors which could result with the original label since there are other propranolol hydrochloride solutions in the market which are labelled based on the salt concentration (Please see also the CMC reviewer's evaluation in Section 3.1 and DMEPA review in Section 12.1 of this CDTL review).

The DMEPA reviewer also recommended changes to the bottle container label and the carton labeling which were communicated to the applicant. The applicant submitted revised container label and carton labeling on 20-Dec-2013. On 15-Jan-2014, the DMEPA reviewer determined that the applicant had implemented all recommended changes and found the revisions acceptable. DMEPA has no further recommendations.

CDTL comment: I concur. The above determination by the reviewer is appropriate.

Office of Prescription Drug Promotion (OPDP) review by Zarna Patel: The OPDP reviewer provided comments on the proposed Patient Package Insert (PPI), particularly from the perspective that some portions of the labeling language may be used in promotional materials. The reviewer has no additional comments on the revised Carton and Container Labeling. The PPI with OPDP comments is placed in the DCRP e-Room for further edits and discussion.

CDTL comment: I concur with the OPDP reviewer's assessment and comments.

12.3.2 Patient labeling/Medication guide (if considered or required)

Division of Medical Policy Programs (DMPP) and Office of Prescription Drug Promotion (OPDP) review by Sharon Mills and Zarna Patel: In this collaborative review of the proposed patient labeling Patient Package Insert (PPI) and Instructions for Use (IFU) for (b) (4) the reviewers converted the proposed PPI to a Medication Guide (MG) on the basis that "The drug product is one for which patient labeling could prevent serious adverse effects." The reviewers also simplified wording, clarified concepts, removed redundant information, incorporated their comments into the appended IFU, and ensured that the MG met FDA regulations and Guidance criteria. The MG and IFU were placed in the DCRP e-Room for further edits and discussion.

CDTL comment: The reviewers' edits made the PPI and IFU easier to read and understand. However, I do not agree that a Medication Guide is required. My opinion is that a Medication Guide is NOT necessary for approval {please see section 12.3.2 of this CDTL review and section 7.7.1 (pages 101 to 104) of my clinical review for discussion on the need (or lack thereof) for a Medication Guide}.

OSE-DRISK review (by Somya Dunn): The DRISK reviewer evaluated the need for a Risk Evaluation and Mitigation Strategy (REMS) for (b) (4). The submission did not contain a REMS proposal. The DRISK reviewer concluded that "... no AEs of particular interest or preclinical safety signals have been identified that cannot be discussed and communicated through approved labeling." The DRISK reviewer's recommendation is that a REMS is not required.

The DRISK reviewer recommends that the Patient Package Insert (PPI) proposed by the sponsor be converted to a Medication Guide focusing on the risk of hypoglycemia, and its prevention and corrective measures as the first discussed risk in the Medication Guide. The DRISK reviewer's reason is that while pharmacies are not required to distribute a PPI when the medication is dispensed, a Medication Guide is required to be distributed at the time of dispensing, and would serve as a reminder to the caregiver about the importance of prevention of hypoglycemia weeks or months after the initial counseling has taken place.

CDTL comment: I concur with the DRISK reviewer's assessment that a REMS is not required.

However, I do not agree that a Medication Guide is required. My opinion is that a Medication Guide is NOT necessary for approval (please see discussion below, and Section 7.7.1 (pages 101 to 104) of my clinical review for discussion on the need (or lack thereof) for a Medication Guide).

Clinical Reviewer and CDTL evaluation and comments regarding patient labeling/Medication Guide:

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.

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 from case studies of 1,367 patients treated with propranolol for 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.

Also, Medication Guide will not be useful because (i) hypoglycemia 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.

Only 11 cases (10 symptomatic) of hypoglycemia associated with propranolol therapy have been reported in case studies of 1,367 patients with IH treated with propranolol in the medical literature. In eight cases, an additional stressor such as an acute infection, prolonged fasting or oral corticosteroids causing adrenal insufficiency were present and assumed to have precipitated all but one of them; 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 660 patients with severe IH treated with propranolol in the CUP, there were four cases of hypoglycemia of which two had symptoms (probable 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.”

Therefore, there appears to be no evidence to support the contention that “...The drug product is one for which patient labeling could prevent serious adverse effects,” because symptomatic hypoglycemia arising to the level of a serious adverse effect – the condition intended to be prevented by the proposed Medication Guide – is rarely reported and is not really documented in the clinical trial, the CUP or the medical literature involving a total exposure of 2,451 pediatric patients treated with propranolol for IH.

Please also see Section 8.4 and Section 11 of this CDTL review, and Section 7.7.1 (pages 101-104) of my clinical review for more detailed discussions.

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 recommendation is that a Medication Guide is NOT necessary for approval.**

I think the emphasis should be to educate parents and caregivers to feed the infant frequently, and/or to give feeds with the drug. This action will be more effective to prevent hypoglycemia than a Medication Guide which may detract from the message to the parent or caregiver to give feeds to prevent hypoglycemia.

An additional consideration is to put the message: “Give (b) (4) dose with feeds,” on the bottle and the bottle carton. This message will always be available and visible to the parent or caregiver **every** time the bottle is handled to administer the dose.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended 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 (424 patients in the clinical trials, 660 patients in the CUP and 1,367 patients with IH treated with propranolol in the scientific publications showed no new unlabeled safety signals in infants with IH.

Based on review of the 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.

The regulatory reason to approve is:

There is substantial evidence consisting of adequate and well-controlled investigations, as defined in §314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling {§ 21 CFR 314.125(b)(5)}.

13.2 Risk Benefit Assessment

For Benefit Assessment, 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.

The pivotal Study 201 is a single randomized, placebo-controlled, multi-dose, 2-stage, seamless Phase II/III adaptive design study. The results of the primary endpoint (rate of complete/nearly complete resolution of IH at W24 (assessed by central reading of the photographs) analysis show efficacy of the selected regimen, 3 mg/kg/day 6 month vs. placebo; the difference was 60.4% with propranolol vs. 3.6% with placebo (ITT), which is statistically significant ($p < 0.0001$) and also clinically meaningful. A sensitivity analysis of the per-protocol (PP) data set shows similar results.

There were no differences in the primary efficacy endpoint between 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 month over placebo was also found on two of the three centralized quantitative assessments: surface and color of hemangioma.

The pivotal study results were supported by the results of the PK Study 102.

In the CUP, too, 60.3% (126 of 209) patients with high risk IH obtained good efficacy.

In 15 key publications and 3 meta-analyses in the medical literature reporting the effect of propranolol in children with IH, the beneficial response rate ranged from 50% to 100%.

The results in Study 201, the CUP and the medical literature suggest that up to 10% of patients required re-introduction of treatment after discontinuing propranolol (10% in Study 201, 3% in the CUP and 6-8% in key publications).

For Risk Assessment, safety was evaluated on 2,451 patients treated with propranolol (424 patients in the clinical trials, 660 patients in the CUP and 1,367 patients with IH treated with propranolol in the scientific publications). 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 in the studies in children with IH treated with propranolol in the scientific literature.

There were no new or unexpected safety signals in the important known risks of propranolol in infants (hypoglycemia, hypotension, bradycardia, and bronchospasm). Patient monitoring after treatment initiation and after up-titrations in dose showed that the heart rate was the most adequate parameter to follow and that a monitoring period of 2 hours post-treatment could be considered sufficient to detect bradycardia. Educating parents/caregivers to provide frequent feeding to the infant and/or to feed the infant just before dosing with propranolol was shown to prevent hypoglycemia.

Based on the risk benefit assessment, oral propranolol at the dose of 3 mg/kg/day (in two divided doses) for 6 months can be considered an effective and safe treatment to be started in infants 5 weeks to 5 months old with IH requiring systemic therapy.

13.3 Recommendation for Postmarketing Risk Management Activities (includes restricted distribution, RiskKAPs, REMS)

None.

13.4 Recommendation for other Postmarketing Study Commitments

None.

13.5 Recommended Comments to Applicant

I recommend that the Division advise/inform the sponsor in the AP letter to suggest the following postmarket studies (*please also see section 7.7.2 (pages 105-107) of my clinical review for more details*):

- I. **Keep a registry of all pediatric patients treated long term with propranolol** and follow them over the next 5 - 7 years for any effect of propranolol on their growth and developmental milestones. The following are examples of data to record and follow:
 - *Anthropometry (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, keep balance, and change positions.
 - *Fine motor*: using hands to eat, draw, dress, play, write, and do 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/responding to feelings of others.

Justification:

- (1) IHs are quite common, occurring in 3-10% of newborns after the first month of life. So, it is in the interest of child health and US public health to have some measure of follow up for this large population of young, developing infants with IH treated long term with propranolol.
- (2) Propranolol has been shown to significantly impair retention of emotionally arousing memories while not affecting neutral memories in adult subjects.
 - (a) Cahill et al (1994)²⁵ studied 15 healthy volunteers who received placebo and 20 who received propranolol using the recognition (multiple-choice) memory test for 3 phases of the arousal and neutral stories (4-min slide shows). They showed that propranolol treatment selectively impaired the retention of memory for the more emotional (arousal) stories but did not block these subjects' subjective emotional reactions to the neutral stories assessed immediately after viewing.
 - (b) McGaugh, Cahill and Roozendaal (1996)²⁶ mentioned comparable results in another experiment examining the effect of β -blockers on enhanced memory induced by physically induced arousal (increased muscle tension), in which

elderly subjects taking β -blockers did not show enhanced retention by arousal. The experiment suggests that memory storage is influenced by activation of the β -adrenergic systems and the amygdala, and that β -blockers will reduce it.

- (c) In another study, Cahill and van Stegeren²⁷ demonstrated that β -blockade markedly impaired gender-related differences in memory retention of information central versus peripheral to the story following emotionally arousing information in adult human volunteers receiving propranolol.
- (3) Studies in pregnant women^{28,29,30,31,32} indicate that prenatal β -blockade induces fetal growth retardation and long-term neurological complications including impaired school performance, cognitive impairment, and psychiatric disorders.
- (4) Apart from the above studies in adults whose neurological pathways are largely developed at the time of β -blockade, it is not known what β -blockade could do to the susceptible developing brain of a neonate.³³ No studies to date have examined the long term neurological effects of acute or chronic β -blockade in one to two year old children.
- (5) For cosmetic IHs that are small and non-life threatening, propranolol will certainly be used off-label after approval, despite the labelled indication specifying that propranolol be used for treatment of proliferating IH requiring systemic therapy. Therefore, it is important to have information related to the long term effect of propranolol in young, developing healthy infants.
- (6) I think the sponsor can keep a registry not only of infants with IH treated with propranolol in Study 201 or 301 but also propranolol-treated infants post-approval.
- (7) I do not think a placebo controlled group is needed for this observational study. Infants are followed by their primary health caregiver for developmental milestones. That the sponsor keep a registry of propranolol-treated infants IH to follow their developmental milestones is a justifiable request.
- (8) The nature of this observational follow up study is "exploratory." It is not derived from a known serious safety issue. Therefore, we do not need a PMR/PMC.
- (9) I think practicing pediatricians will, on their own initiative, carry out growth and developmental follow up studies of infants with IH treated long term with propranolol if the sponsor does not take up the suggested observational study or if FDA does not make the suggestion in the approval letter.

II. **Conduct another clinical trial in infants with IH to show the effect of the dose and duration 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 life-threatening IH, function-threatening IH, IH with ulcers, severe IH and PHACES syndrome, 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 β -blockers, need for systemic retreatment with corticosteroids or other agents).

Justification: (Please also see discussion of my rationale for selection of dose and duration of propranolol for treatment of IH on pages 21 to 26 of this CDTL review.)

DOSE Considerations:

I think a lower dose than 3 mg/kg/day can be recommended (e.g., for patients who may not be able to tolerate the 3 mg/kg/day dose), because:

- (i) The primary endpoint is dose dependent with the 3 mg/kg/day dose showing close to the maximal effect, and the 1 mg/kg/day dose also high on the dose response curve (Figure 3). (Please also see section 5.1 of this CDTL review.)
- (ii) Even patients with high risk IH or more severe IH in the CUP, most of whom were treated with propranolol at a dose of 2 mg/kg/day (equivalent to 1.75 mg of propranolol base as used in the pivotal Study 201), achieved a response rate comparable to that observed in patients in the pivotal clinical trial (Table 11). This supports the notion that the higher 3mg/kg/day dose may not be necessary to obtain the 60% response rate observed in Study 201.
- (iii) If the pivotal trial (Study 201) were analyzed as a “traditional” 5-arm trial (Table 4) or as a group sequential design study (Table 5), BOTH the 1 mg/kg/day 6 month and the 3 mg/kg/day 6 month treatments provided statistically significant benefit over placebo.
- (iv) In 22 recent clinical studies on 902 patients with IH (Table 12) in the medical literature, and in patients with IH treated with propranolol in key publications submitted with the NDA (Table 14) the prevailing dose of propranolol used to treat the majority of patients is 2 mg/kg/day (range: 0.75 – 4 mg/kg/day).

Based on the above observations, I recommend that the Division suggests to the sponsor – in the approval letter – to study in a prospective clinical trial a dose of propranolol lower than 3 mg/kg/day (e.g., 2 mg/kg/day) for a duration of 12 months in comparison to the 3 mg/kg/day 6 month regimen.

DURATION of treatment considerations:

The reasons for recommending the 12-month duration of propranolol treatment are:

- (i) According to the pathophysiology and natural history of IH (Figure 9), the active proliferative phase lasts **about 12 months** from the age of 5 weeks to about 14 months of life.⁴ I think this 12 month period is the duration for which propranolol treatment should be administered.
- (ii) In 22 recent clinical studies on 902 patients with IH (Table 12) in the medical literature, patients with IH in a large number of reported studies were treated for a duration more than 6 months (7 to 14 months, and as much as up to 28 months), which appears to be the prevailing pediatric dermatology clinical practice.
- (iii) Sustainability of the initial treatment effect of propranolol after discontinuation in Study 201, the CUP and the medical literature (Table 13) is better when infants with IH are treated for >6 months.

- (a) In Study 201, 10% of patients in the 3 mg/kg/day 6 month regimen required the re-introduction of a systemic treatment.
- (b) In the CUP, patients with high risk IH were treated with 1.9 (SD ±0.7) mg/kg/day for 7.4 (SD ±3.1) months; the rate of retreatment was 3%.
- (c) A recent publication⁶ of a cohort of IH patients consecutively treated in one center (mostly, propranolol 2 mg/kg/day for a mean duration of 6.06 months) showed 25.3% had IH regrowth, and 12% required propranolol retreatment.
- (iv) In 13 scientific publications on 573 patients treated with propranolol (Table 14), the regrowth rate ranged from 12% to 14%; the proportion of patients who required retreatment with propranolol ranged from 6% to 8% (Table 13). The duration of treatment was variable (range 3 months to 30 months, Table 14), and the average propranolol dose was 2 to 3 mg/kg/day (Table 14). In publications in which details related to re-treatment are available, 50% (35 of 70 patients who experienced regrowth) received re-treatment, making 6% (36 of 573 propranolol-treated patients) who received re-treatment overall (Table 13).
- (v) I think the 6 months' treatment may not have covered the entire active proliferative phase in patients who had regrowth. "Rebound growth" of focal hemangiomas have been reported after cessation of steroids as well as propranolol^{34,35}. There is also the possibility of causing propranolol-resistant IH (PRIH) when treatment is given for an inadequate duration.³⁶

Based on the above considerations, I recommend that we ask the sponsor – in the approval letter – to conduct a prospective clinical trial in infants with IH using propranolol at a dose lower than 3 mg/kg/day (e.g., 2 mg/kg/day usually used in US pediatric dermatology clinical practice) for a duration of 12 months (and followed for 12 months) to determine whether (i) a lower dose will have lower risk of adverse events while being as effective as the 3 mg/kg/day dose, and (ii) a 12-week treatment regimen will have better sustained effect than the 6-month treatment regimen and minimize regrowth of IH. I suggest that the new clinical trial enroll all types of IH (e.g., life-threatening or function-threatening IH, severe IH, and IH with ulcers). In addition to the number/proportion of patients who achieved complete/near complete resolution, additional endpoints should be used such as rate, time and extent (nature) of regrowth, and the need for retreatment {systemic or local (topical)}.

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KHIN M U

02/07/2014

Recommend approval pending sponsor's response to recommended labeling changes.

THOMAS A MARCINIAK

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