Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Propranolol hydrochloride

Proprietary Product Name: Hemangiol

Sponsor: Pierre Fabre Medicament Australia Pty Limited

First round CER: 28 October 2013
Second round CER: 12 March 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
AE	Adverse event
ADR	Adverse drug reaction
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATU	Temporary authorization for use
AUC	Area under the plasma concentration time curve
BLQ	Below the level of quantification
BP	Blood pressure
bpm	Beats per minute
CER	Clinical Evaluation Report
CL/F	Apparent oral clearance
Cmax	Maximum plasma concentration
CHMP	Committee for Medicinal Products for Human Use (formerly the CPMP)
CPMP	Committee for Proprietary Medicinal Products (now the CHMP)
CRF	Case Report Form
CSR	Clinical Study Report
CV	Coefficient of variation
D, d	Day
dE*2000	Delta E*ab, year 2000 version: Unit for the IH color measurement (performed according to CIE LAB (Commission internationale de l'éclairage) colour space values.
DPB	Diastolic blood pressure
EC	European Commission
ECG	Electrocardiogram
eCRF	Electronic case report form

Abbreviation	Meaning
EMA	European Medicines Agency
EOS	End of study
EOT	End of treatment
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
H, h	Hour
Hb	Haemoglobin
Hct	Haematocrit
HR	Heart rate
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IH	Infantile hemangioma
ITT	Intention to treat
IVRS	Interactive voice recognition system
KM	Kaplan Meier
LC/MS-MS	Liquid chromatography-mass spectrometry (tandem MS)
LVEF	Left ventricular injection fraction
MCV	Mean corpuscular volume
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MedDRA	Medical Dictionary for Regulatory Activities
ms	Millisecond

Abbreviation	Meaning
PCSV	Potentially clinically significant value
PHACES	Posterior fossa brain anomalies, hemangiomas, arterial anomalies and cardiac defects and coarctation of the aorta
PK	Pharmacokinetics
PP	Per-protocol
PPK	Population pharmacokinetics
PR	Interval from start of the P-wave to start of the QRS complex
PT	Preferred Term (MedDRA)
QT	Interval from start of Q-wave to end of T-wave
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Friderica's formula
QTcP	QT interval corrected for heart rate in the paediatric population
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SCS	Summary of Clinical Safety
SD	Standard deviation
SOC	System Organ Class (MedDRA)
TEAE	Treatment emergent adverse event
T½	Terminal elimination half-life
US	United States
V0400 SB	Propranolol oral solution
vs	Versus
WBC	White blood count
W, wk	Week

1. Introduction

This is a Category 1 application to register a new dosage form, a new strength and a new indication for propranolol hydrochloride: Hemangiol (propranolol hydrochloride) 3.75 mg/mL Oral Solution.

Propranolol hydrochloride is a non-selective beta-blocker. The proposed indication is:

Treatment of proliferating infantile hemangioma requiring systemic therapy.

The approved indications [for currently registered propranolol hydrochloride tablets] are:

- Angina pectoris.
- Hypertension.
- Prevention of migraine.
- Cardiac dysrhythmias: certain intrinsic cardiac dysrhythmias; dysrhythmias associated with thyrotoxicosis; anxiety tachycardia; certain drug induced dysrhythmias (e.g., tachycardia due to digitalis or adrenaline overdosage).
- Essential tremor, including familial and senile tremor.
- Phaeochromocytoma (only with concurrent alpha-receptor blockade).
- Hypertrophic subaortic stenosis.
- Suspected or definite myocardial infarction.
- Fallot's tetralogy.

Comment: The proposed Hemangiol PI includes only the proposed new indication. It does not refer to the approved indications for propranolol hydrochloride.

2. Clinical rationale

Infantile hemangiomas (IHs) are common neoplasms composed of proliferating endothelial-like cells. IHs are the most common vascular tumours of childhood and have been estimated to occur in 3% to 10% infants (Frieden et al., 1997; Haggstrom et al., 2007; Hoornweg et al., 2005; Kilcline and Freiden, 2008). In a recent prospective Australian study, the incidence of superficial and mixed IHs over the first 6 weeks of life was found to be 2.6% (28/1065 babies) (Dickson et al., 2011).

IHs are benign tumours that are not usually present at birth, but appear within the first few weeks of life (Chen et al., 2013). In most cases proliferation continues for 3 to 6 months, although in rare cases it can continue for up to 12 months (Paediatrics Manual, Westmead, 2009). In a prospective cohort study of 526 IHs in 433 patients, most IH growth occurred before the age of 5 months (Chang et al., 2008). Spontaneous involution begins after the maximum size is reached, usually between 9 and 12 months of age, and is complete in 50% of children by the age of five and in 90% of children by the age of nine (Bruckner and Frieden, 2003; Paediatrics Manual, Westmead, 2009). Known risk factors for the development of IH are: female sex (female to male ratio of 2.4:1), Caucasian ethnicity, low birth weight (especially <1500 g), and infants of mother's with multiple gestations (Haggstrom et al, 2007; Sundine and Wirth, 2007; Drolet et al., 2008).

Treatment for IHs usually involves active observation only, as most follow an uncomplicated clinical course and 80-90% regress spontaneously (Storch and Hoeger, 2010). In a publication

by Bower's et al (1960), "140 children with 169 naevi [from a UK clinic] were watched until cured, or...for a minimum of 5 years" and approximately 50% of the naevi resolved by the age of 5 years and 70% by the age of 7 years. Furthermore, only about 6% of the naevi constituted "any cosmetic handicap". Bowers et al (1960) also noted that there was "almost exact agreement [between 49% of hemangiomas resolving with very good results by age of 5 and] and Lister's [Lister, 1938] figure of 53% excellent results at the age of 5".

Although most IHs are innocuous, some are associated with complications that can be life-threatening (Storch and Hoeger. 2010). In a prospective cohort study of a consecutive sample of 1058 children aged ≤ 12 years with IHs from 7 US paediatric dermatology clinics enrolled between September 2002 and October 2003, ~24% experienced complications related to their IHs (Haggstrom et al., 2006). The most commonly occurring complication was reported to be ulceration (16.0%), followed by threat to vision (5.6%), airway obstruction (1.4%), auditory canal obstruction (0.6%), and cardiac compromise (0.4%) (Haggstrom et al., 2007). It was observed that large size, facial location, and/or segmental morphology were the most important predictors of short-term outcomes as measured by complication and treatment rates for IHs. In addition, although most IHs are not worrisome, it has been estimated that approximately 12% are significantly complex requiring referral to specialists for consideration of treatment (Drolet et al., 2013). The sponsor provided a tabulated summary of the complications of IHs derived from a number of studies.

The Clinical Overview states that IHs "are extremely heterogeneous in terms of size, location, risk of complication, rate of proliferation and involution, and results after involution. For this reason, there is no established severity classification and the decision to treat by systemic therapy is individualized, weighing therapeutic risks against potential benefits. As soon as poor prognosis factors are present, a decision regarding treatment should be made without further delay, during the proliferative phase of the disease".

The Clinical Overview refers to Guidelines for the care of infants with HIs outlining the indications for treatment developed before the use of propranolol for treatment of the condition (Frieden et al., 1997). These general indications for treatment are:

1. Life-and function-threatening IHs (e.g., those causing impairment of vision, respiratory compromise caused by airway lesions, congestive heart failure, hepatic involvement).
2. IHs in certain anatomical locations that often leave permanent scars or deformity, especially the nose, lip, ear, and glabellar area.
3. Large facial IHs, especially those with a prominent dermal component (more likely to leave permanent scarring).
4. Smaller hemangiomas in exposed areas, such as the face and hands, may be considered for treatment with modalities unlikely to cause scarring or significant side effects.
5. Ulceration.
6. Pedunculated hemangiomas (likely to leave significant fibrofatty tissue after involution).

The Clinical Overview states that the target indication for the use of propranolol for the treatment of IHs includes the general criteria noted above (Frieden et al., 1997), as well as an enlargement of the criteria to include IH with a potential risk of disfigurement (not restricted to facial or exposed areas).

In order to avoid scarring, disfigurement, or interference with function a significant proportion of patients with IH will require systemic treatment (Haggstrom et al., 2007; Chen et al., 2013). In addition to systemic treatments, non-systemic therapies such as surgery and laser treatments have been used to treat IHs. There are currently no medicines approved in Australia for the treatment of IHs, and all medicines used to treat the condition are being used "off-label". The sponsor states that corticosteroids for the treatment of severe forms of angiomas in infants are

registered in only two countries (France, Germany), and there are currently no other products approved in any country for the treatment of IHs. Prior to 2008, corticosteroids (systemic, topical, or intralesional) were used for first-line therapy of IHs (Dickson et al., 2011; Chen et al., 2013), while other systemic therapies included interferon and vincristine (Chen et al., 2013).

Treatment of IHs with propranolol was first reported in 2008 (Léauté-Labrèze C et al., 2008), and since then there have been a number of further reports suggesting that propranolol is an effective treatment for IHs. Propranolol for the treatment of IHs has been reported to be replacing corticosteroids for first-line therapy of IHs (Dickson et al., 2011; Chen et al., 2013). The use of propranolol for the treatment of IHs has recently been the subject of a USA Consensus Conference sponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases and funded by the National Institute of Health (Drolet BA et al., 2013).

Three possible mechanisms of action of propranolol for the treatment of IH have been postulated: vasoconstriction, which is a classical consequence of beta-adrenergic blockade and might result in decreased perfusion of the IH lesion perfusion; inhibition of angiogenesis characterized by decreased proliferation of vascular endothelial cells, reduction in neovascularization and formation of vascular tubules, and reduction of the secretion of Matrix Metalloproteinase 9 which is crucial for endothelial cell migration; and apoptosis via beta2-adrenoreceptor mediated blockade of capillary endothelial cell proliferation (Storch and Hoeger, 2010; Summary of Clinical Pharmacology Studies.

> **Comment**: The sponsor provided a comprehensive an acceptable clinical rationale for propranolol for the treatment of proliferating IH requiring systemic therapy. The sponsor considers that there is an unmet need for treatment of IHs and seeks to register a propranolol formulation specifically designed for infants to meet this need. However, it is noted that there is a high spontaneous resolution rate for IHs and that, although some lesion can be life-threatening, the pivotal efficacy and safety study specifically excluded patients with life-threatening IHs and other high-risk lesions.

2.1. Orphan drug designation

Propranolol hydrochloride, sponsored by Pierre Fabre Medicament Australia P/L, was designated by the Therapeutic Goods Administration (TGA) as an orphan drug for *"the treatment of proliferating infantile hemangiomas requiring systemic therapy"* on 3 October 2012. The designated orphan indication and the proposed indication are identical.

2.2. Guidance

There are no TGA approved guidance documents specifically relating to the treatment of IHs.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

Module 5:

- 1 Phase I comparative bioavailability (BA) and bioequivalence (BE) study in healthy adult males;
- 1 Phase I pharmacokinetic (PK) and initial tolerability study in infants with IH, including a population pharmacokinetic (PPK) report;
- 1 pivotal Phase II/III efficacy and safety study in infants with IH;

- 1 protocol from an ongoing uncontrolled, extension study in infants with IH; Integrated Safety Study (ISS) tables and Statistical Analysis Plan (SAP); 4 Temporary Authorization for Use (ATU) reports identified as "reports of post-marketing experience", but actually reports of patients treated in France under a Compassionate Use Program (CUP); literature references.

Module 1:

- Application letter; application forms; proposed Australian Product Information (PI); proposed Australian Consumer Medicine Information (CMI); information about the sponsor's experts; orphan drug designation; details of compliance with meetings and pre-submission processes; overseas regulatory status including draft US and European prescribing information documents; summary of the BA/BE study; Risk Management Plan (RMP) for Australia.

Module 2:

- Quality overall summary; Nonclinical overview; Clinical overview; Summary of biopharmaceutics studies and associated analytical methods; Summary of clinical pharmacology studies; Summary of clinical efficacy; Summary of clinical safety; Literature references; Synopses of individual studies.

3.2. Paediatric data

The pivotal Phase II/III clinical and efficacy study (201) was undertaken in infants with proliferating IH aged from 30 to 150 days. The proposed indication for Hemangiol is applicable only to infants in this age group with proliferating IH requiring systemic therapy.

3.3. Good clinical practice

The studies forming the sponsor's clinical development program for the proposed product for the proposed indication were undertaken in compliance with the principles of good clinical practice.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

The submission included two studies providing pharmacokinetic (PK) data (study V004 SB 101 2A; study V00400 SB 1 02); these two studies will be referred to as study 1012A and study 102, respectively, in this Clinical Evaluation Report (CER). In addition to a non-compartmental PK analysis in infants with IH, study 102 also included a population pharmacokinetic (PPK) analysis in this patient group identified as V0400 101 and referred to as the PPK report in this CER. The two studies (including the PPK report) have been evaluated and relevant data from these studies (including the PPK report) have been included in the CER (text and supporting tables and figures). Studies 1012A, 102 and the PPK report are briefly outlined below (Table 1).

Table 1. Brief outline of the studies providing pharmacokinetic data.

Study	PK topic	Population (n)	Primary objective	Treatments
Study 1012A, Phase I, single-centre (France), single-dose, randomized, open-label, 2-period, crossover, washout ≥ 3 days.	BA/BE/PKs of oral solution and tablet formulations in healthy male adults.	Healthy male subjects; aged 20 to 41 years (12 m)	Evaluation of single-dose PK parameters of new propranolol oral solution compared with oral tablet	Propranolol HCL oral solution (5 mg/mL), 80 mg dose. Avlocardyl 40 mg tablets (propranolol HCl), dose 2 x tabs = 71.18 mg.
Study 102, Phase I, open-label, single-country (France), multi-centre (4), repeated dose (BID), 12 weeks duration.	Steady-state PKs of propranolol and 4-OH-propranol (metabolite) in infants with IH.	Infants with IH; Group 1 aged 35 to 90 days (inclusive); Group 2 aged 91 to 150 days (inclusive). (6 m & 16 f)	Characterize steady-state PKs of propranolol in infants with IH; PK assessment at D28 after 4 weeks treatment in Group 1 and at D84 after 12 weeks treatment in Group 2.	Propranolol oral solution (3.75 mg/mL) administered at a dose of 1 mg/kg/day from D0, 2 mg/kg/day from D7, and 3 mg/kg/day from D7 to D84. Dose given BID (morning and late afternoon).
PPK report based on data from study 102.	PPK	166 non-zero drug observations and 109 non-zero 4-OH metabolite observations. (10/G1 & 12/G2)	To describe PKs of propranolol and to describe the inter-subject variability in the PKs of the drug.	PKs of propranolol and 4-OH metabolite based on 22 patients sampled twice in the titration period (1-2 mg/kg/d) and six times in the fixed-dose period (3 mg/kg/d).

Note: BA = Bioavailability; BE = Bioequivalence; PKs = pharmacokinetics; BID = twice daily; m = males; f = females; D = day; IH = infantile hemangiomas.

4.2. Summary of pharmacokinetics

4.2.1. Bioavailability - healthy adult volunteers

4.2.1.1. Study 1012A - relative bioavailability in healthy adults

4.2.1.1.1. Introduction

The submission included one, single-centre (France), Phase I relative bioavailability study (1012A) in healthy adult volunteers comparing the PK profile of the oral solution of propranolol HCl to an EU marketed reference tablet formulation (Avlocardyl). This study was conducted prior to administration of the oral solution to infants. The dates of first and last enrollment were 22 June 2009 and 20 July 2009, respectively, and the report was dated 6 April 2012. The study was performed in compliance with Good Clinical Practice (CPMP/ICH/135/95), and the Declaration of Helsinki and subsequent amendments. The protocol was reviewed and approved by an Independent Ethics Committee (IEC) and authorized by the French health authorities (AFSSAPS). The study was sponsored by Pierre Fabre Dermatologie, Boulogne, France.

4.2.1.1.2. Objectives

The main objective was to evaluate the PK parameters of the new propranolol HCl oral solution formulation compared with the reference propranolol HCl tablet formulation after a single oral dose in 12 healthy subjects.

The secondary objectives were to document the clinical and biological tolerability of the two propranolol HCl formulations after single oral administration in 12 healthy subjects.

4.2.1.1.3. Inclusion, exclusion and withdrawal criteria

The inclusion criteria are generally consistent with PK studies in healthy volunteers. However, in order to obtain a homogeneous panel, the sponsor enrolled only healthy Caucasian male subjects aged from 18 to 45 years.

The exclusion criteria were extensive and aimed at excluding subjects in whom treatment with propranolol was contraindicated. The general exclusion criteria were consistent with PK studies in healthy male volunteers.

The withdrawal criteria were standard for clinical trials. The criteria included a requirement for the investigator to attempt to contact subjects who had withdrawn for any reason in order to obtain a final assessment. In addition, the criteria included a requirement for the investigator to take all appropriate therapeutic measures to manage adverse events.

Any volunteer dropping out of the study for any reason was replaced by another subject in order to have complete data for analysis from 12 subjects.

4.2.1.1.4. Methodology and Treatment

The study was a Phase 1, single-centre, open-label, randomized, single-dose, two-period crossover study with a wash-out of at least 3 days in healthy male subjects (aged between 18 and 45 years). The study treatment was propranolol HCl solution 5 mg/mL providing a propranolol (base) dose of 80 mg (i.e., 16 mL), and the reference treatment was Avlocardyl (propranolol HCl) 40 mg tablet providing a propranolol (base) dose of 70.18 mg (i.e., two tablets).

Subjects were randomized to receive a single oral fasting dose on Day 1, Period 1, of either propranolol HCl tablets (2 tablets of 40 mg) or propranolol HCl oral solution (16 ml of the 5 mg/ml solution), with the alternate treatment being given on Day 1, Period 2, following a washout of at least 3 days. Single dose was administered on the morning of Day 1, around 8 am, after an overnight fast of at least 10 hours. The oral solution was followed by 100 mL of water.

For each of the two treatment periods, subjects stayed in the clinical research centre from about 24 hours pre-dose to 24 hours post-dose (Day 2 morning). Including the screening period (15 to 2 days before the first administration), the total study duration for a subject was a maximum of 6 weeks. Safety and PK parameters were assessed as detailed in the study flow chart and the study schedule for the treatment phase.

4.2.1.1.5. Pharmacokinetic parameters

The PK analysis was carried using a non-compartmental model (KINETICA software). The PK parameters of Cmax, Tmax, AUC_{last}, AUC_{inf}, $\%AUC_{extra}$, CL/F, Vd/F, T½ and K_{el} were calculated for each formulation. Additionally, the relative bioavailability F(%) and Cmax ratio were calculated using Excel . The PK parameters were calculated using actual sampling times. All below the limit of quantification (BLQ) values in the absorption phase were substituted by zero before the calculation of the PK variables, except for BLQ values between evaluable concentrations which were treated as missing values. BLQ values in the terminal phase were ignored. The individual plasma propranolol concentration vs (theoretical) time profiles for each subject and treatment, as well as the mean plasma propranolol concentration vs (theoretical) time profiles for each

treatment, were presented graphically. These graphs were repeated using ln-transformed concentration plots.

Blood samples for propranolol plasma concentrations were taken for each period at the following times: pre-dose (T0), and then post-dose at 0h20, 0h40, 1h, 1h20, 1h40, 2h, 2h30, 3h, 4h, 6h, 8h, 10h, 12h, 16h, and 24h. Propranolol plasma concentrations were measured using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) assay. The method was linear from 0.5 to 250 ng/mL.

4.2.1.1.6. Statistical methods and sample size

Standard descriptive statistical methods were used to summarize both plasma concentration and PK parameters. Only quantifiable concentrations were taken into account for calculation of mean values, standard deviation and coefficient of variation. If more than half of the data were not quantifiable, descriptive statistics were not undertaken. No formal sample size calculations were undertaken.

The all patients treated (APT) data set included all subjects who took at least one dose of study medication and for whom at least one safety data assessment was available. The per-protocol (PP) data set was used for the PK analysis (i.e., subjects from the APT dataset having taken all study medications and without major protocol deviations). In this study, the PP and APT data sets were the same.

> **Comment**: The Statistical Analysis Plan (SAP) did not specify that administered propranolol doses were to be dose normalized. The administered propranolol tablet (reference) and solution (test) formulation contained doses corresponding to propranolol (base) 70.18 mg and 80 mg, respectively. However, the final CSR included Cmax and AUC_{inf} dose-normalized to propranolol 80 mg results for the tablet formulation. The Final Bioanalytical Report (which was provided as an appendix to the CSR) included the results for the two-sided 90% confidence intervals (CIs) for the ratio of the mean Cmax, AUC_{last} and AUC_{inf}. The CSR states that the ratios and 90% CIs were planned, but no reference to them could be identified in the SAP. In addition, if these parameters were planned it was unusual that the results were not included in the body of the CSR.

4.2.1.1.7. Subject disposition

A total of 30 subjects were screened for participation, and 18 of these were not included. The reasons for non-inclusion included medical history (4 subjects), abnormal biology (2 subjects), consent removed (2 subjects), abnormal vital signs (2 subjects), abnormal ECG (2 subjects), abnormal ECG and smoker (1 subject), abnormal physical examination (1 subject), concomitant treatment (1 subject), age out of range (1 subject), BMI > 28 kg/m^2 (1 subject), and not willing to stop physical activity (1 subject).

A total of 12 male subjects entered the study, and all completed the study. The mean age of the subjects was 28.9 years (range: 20 to 41 years), the mean weight was 71.1 kg (range: 62.9 to 82.4 kg), the mean height was 180.8 cm (range: 169.0 to 193.0 cm), and the mean BMI was 22.1 kg/m^2 (range: 19.6 to 24.8 kg/m^2).

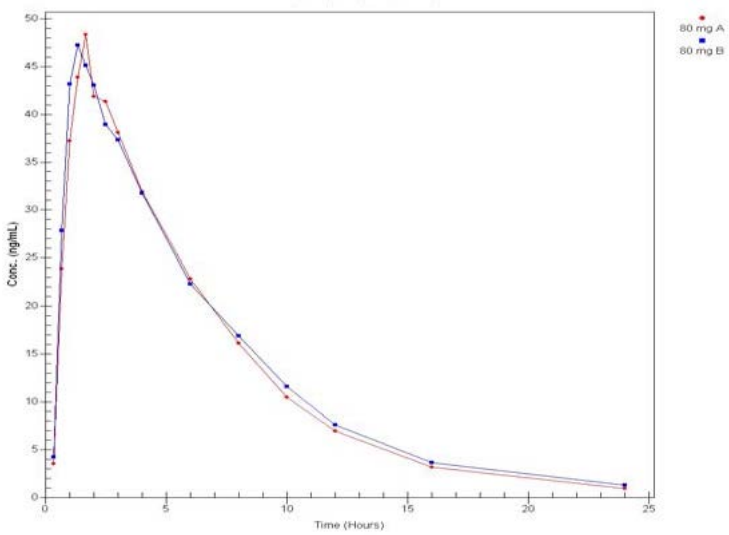
No major protocol deviations were reported (a major protocol deviation was an event that could significantly modify the interpretation of the study results). There were 5 minor protocol deviations and these were considered unlikely to have compromised the analysis or interpretation of the study results.

4.2.1.1.8. Pharmacokinetic results

The plasma concentration vs time profile of propranolol was similar for the tablet (dose normalized 80 mg) and the solution (80 mg) (see Figure 1, below). After single oral administration of both formulations, propranolol was quantifiable for all subjects from the first

sampling time at 0h20 post-dosing, except for 1 subject after tablet administration. Propranolol remained quantifiable until 24h post-dosing for all subjects following both formulations, except for 2 subjects following the tablet formulation for who propranolol was quantifiable until 16h post-dosing.

Figure 1: Study 1012A - Mean propranolol plasma concentration - time curves after administration of the reference tablet A (dose normalized 80 mg) and the test solution B (80 mg).



The main PK parameters for propranolol following single-dose administration of the two formulations are summarized below in Table 2.

Table 2: Study 1012A - Main arithmetic mean ± SD (%CV) propranolol PK results for tablet and solution formulations in healthy male subjects (n=12).

	Tablet (70.18 mg)	Tablet (80 mg dose-normalized)	Solution (80 mg)
Cmax (ng/mL)	52.8 ± 50.0 (%CV = 94.6)	60.2 ± 57.0	49.5 ± 13.2 (%CV = 27)
AUC_{inf} (h.ng/mL)	314.8 ± 288.4 (%CV = 91.6)	359 ± 328	328.2 ± 128.1 (%CV = 39.0)
AUC_{last} (h.ng/mL)	308.1 ± 288.0 (%CV = 93.5)	-	319.9 ± 125.4 (%CV = 39.2)
T½ hours	4.19 ± 0.63 (%CV = 15.1)	-	4.41 ± 0.63 (%CV = 14.3)
Tmax hours *	1.67 (range: 0.67, 3.00)		1.33 (range: 1.00, 2.00)
K_{el} (1/h)	0.17 ± 0.03 (%CV = 16.5)	-	0.16 ± 0.02 (%CV = 13.2)
CL/F (L/h)	372.6 ± 215.4 (%CV = 57.8)	-	269.7 ± 79.0 (%CV = 29.3)
Vd/F (L)	2277 ± 1359 (%CV = 59.7)	-	1705 ± 511 (%CV = 30.0)

* = median (Tmax)

The relative bioavailability of the propranolol solution was determined using the mean of the individual subject ratios of test solution/reference tablet for Cmax and AUC_{inf} after dose-normalization of both parameters to 80 mg. The arithmetic mean ratios for Cmax and AUC_{inf} are summarized below in Table 3. The results show that the dose-normalized Cmax of the solution is 22% higher than the tablet, and the dose-normalized AUC_{inf} of the solution is 20% higher than the tablet.

Table 3: Study 1012A - Mean solution/tablet ratio for dose-normalized Cmax and AUC_{inf} after single oral dose as tablet or solution formulation (expressed as arithmetic mean and [range]).

Arithmetic mean ratios	
Cmax ratio (solution/table) - F% (dose-normalized)	AUC_{inf} ratio (solution/tablet) - F% (dose-normalized)
1.22 [range: 0.32, 3.98]	1.20 [range: 0.5, 3.28]

The point estimates (90% CI) for the Cmax, AUC_{last}, and AUC_{inf} were summarized in the Final Bioanalytical Report. The results appear to be based on the mean geometric results for each of the parameters (not normalized for dose) found in the CSR. The results are summarized below in Table 4, and show that the two formulations (not dose normalized) were not bioequivalent as the 90% CI for each of the parameters was outside the standard bioequivalence interval of 0.80 to 1.25.

Table 4: Study 1012A - Point estimate (90% CI) for the test/reference (solution/tablet) for the Cmax, AUC_{last} and AUC_{inf} in healthy male subjects (n=12).

	Solution (80 mg)	Tablet (70.18 mg)	Point estimate	90% CI
Cmax (ng/mL)	47.98 (%CV = 26.87)	40.99 (%CV = 78.90)	1.17	0.85 - 1.61
AUC_{last} (h.ng/mL)	302.66 (%CV = 34.04)	244.27 (%CV = 72.43)	1.24	0.98 - 1.57
AUC_{inf} (h.ng/mL)	310.53 (%CV = 34.01)	251.88 (%CV = 70.29)	1.23	0.98 - 1.55

Comment: The dose-normalized (80 mg) propranolol plasma concentration - time profiles were similar for the solution and tablet formulations. The relative bioavailability (F%) dose-normalized to 80 mg results for the Cmax and the AUC_{inf} indicate that the bioavailability of the oral solution formulation is greater than the tablet formulation. Based on mean arithmetic dose-normalized propranolol (80 mg) Cmax and AUC_{inf} ratios derived from individual subjects, the Cmax and AUC_{inf} values were 22% and 20% higher for the solution than for the tablet, respectively. The range for the F% (dose-normalized) for both parameters suggests a high degree of inter-subject variability. Similarly, inter-subject variability of both the Cmax and AUC_{inf} for the tablet formulation (70.18 mg) were much higher than for the solution (80 mg), as can be seen from the %CV for the arithmetic and geometric mean values for these parameters. The median Tmax values for the solution (80 mg) and the tablet (70.18 mg) were similar (1.33 and 1.67 hours, respectively), indicating that the rate of absorption of the two formulations is similar. The mean T½ values for the solution (80 mg) and tablet (70.18 mg) were similar (4.41 and 4.19, respectively). However, both the mean CL/F and Vd/F values were higher for the tablet (70.18 mg) than for the solution (80 mg). The Vd/F values

were high for both formulations indicating that propranolol is extensively distributed following oral administration.

The study treatments were administered in the fasting state, but the proposed Hemangiol PI states that the medicine should be taken in the fed state. However, the approved propranolol PI states that the tablets can be taken with or without food suggesting that there are PK data indicating that food does not significantly affect the bioavailability of the medicine.

The propranolol oral solution formulation used in this study was not that proposed for registration in Australia and the propranolol oral tablet formulation (Avlocardyl) is not registered in Australia. However, the sponsor provided a justification for not providing a bioavailability study comparing the oral solution with Australian sourced tablets. The justification included a dissolution study comparing Avlocardyl, the French sourced propranolol hydrochloride 40 mg tablet used in the bioavailability study 1012A, and a US sourced propranolol hydrochloride 40 mg tablet. This study was used in the US submission as a justification for not providing a bioavailability study comparing US sourced tablets with the oral solution. The sponsor states that this in vitro dissolution study demonstrated that the French and the US sourced tablets could be considered to be equivalent. The dissolution profiles of the two tablets were similar and dissolution was very close to 100% after 15 minutes regardless of the pH.

The submission did not include a dissolution study comparing the Avlocardyl 40 mg tablet with an Australian sourced propranolol 40 mg tablet. The sponsor stated that it has been shown that the physicochemical and biopharmaceutical properties of propranolol hydrochloride (high solubility, high permeability) are such that it is unlikely that differences in the qualitative composition should have an effect on the dissolution profiles of different tablet formulas (Vogelpoel H et al., 2004), and "hence the bioavailability of the drug substance". The sponsor also stated that it "should be noted that French, US and Australian sourced tablets are conventional and given their qualitative composition are immediate-release tablets. Therefore, based on these data, we submit that the results of a bioavailability study comparing Australian sourced tablets would be equivalent to the results of the bioavailability study [1012A]". The sponsor's arguments concerning the comparability of the Avlocardyl 40 mg tablet and an Australian sourced propranolol 40 mg tablet based on the physicochemical and biopharmaceutical properties of propranolol is a matter for the Module 3 [quality] evaluator.

The sponsor did not specifically address the clinical issues relating to potential differences between the Avlocardyl 40 mg tablet and an Australian sourced propranolol tablet. Although propranolol is almost completely absorbed after oral administration (> 90%), it undergoes extensive first-pass metabolism resulting in an absolute bioavailability of between 5% and 50% (Vogelpoel H et al., 2004). As a result, there is considerable inter-subject variability in propranolol plasma concentration. Consequently, PK differences between propranolol oral tablet formulations might have significant clinical effects as regards the comparative efficacy and safety of the two formulations.

4.2.2. Pharmacokinetics in infants with infantile hemangiomas (IHs)

4.2.2.1. Study 102 - pharmacokinetics in paediatric patients

4.2.2.1.1. Introduction

Study 102 was a Phase I, multicentre, open-label, repeat-dose, study primarily aimed at assessing the pharmacokinetics (PKs) of propranolol in infants with infantile hemangiomas (IHs) requiring systemic therapy. The study was conducted in four centres in France. The dates

of first enrollments and last completion were 28 May 2010 and 7 June 2011, respectively, and the final version of the study report was dated 29 May 2012. The study was performed in accordance with the principles stated in the Declaration of Helsinki (1964) and its subsequent amendments, Good Clinical Practice (CPMP/ICH/135/95), and French legislation relating to the protection of individuals involved in biomedical research. The protocol was approved by an Independent Ethics Committee (IEC) and the Competent Authority. Informed consent was obtained from the parents of the participating infants. The study was sponsored by Pierre Fabre Dermatologie, Boulogne, France.

4.2.2.1.2. Objectives

The primary objective was to characterize the PKs of propranolol (administered as an oral solution) at steady-state in infants (after 2 or 10 weeks treatment at 3 mg/kg/day, depending on the age group) during the course of 12 weeks treatment for proliferating IHs requiring systemic therapy.

The secondary objectives were: (i) to characterize the PKs of a propranolol metabolite (4-OH-propranolol); (ii) to assess efficacy of propranolol on the evolution of the target IH over 12 weeks; and (iii) to document the safety profile of propranolol for the treatment of IHs.

4.2.2.1.3. Inclusion, exclusion and withdrawal criteria

The inclusion criteria were:

- Written informed consent for study participation obtained according to national regulations from the patient's parent(s) prior to performing any study procedures.
- Infants aged 35 to 150 days old, inclusive, at time of inclusion in the study.
- Presence of proliferating IH (target hemangioma) requiring systemic therapy: function-threatening IH, IH in certain anatomic locations that often leave permanent scars or deformity, large facial IH, smaller IH in exposed areas, severe ulcerated IHs, pedunculated IH.
- Affiliated with, or beneficiary of the social security.

The exclusion criteria were extensive. Of note, children with congenital hemangiomas were excluded from the study as were children with PHACES syndrome with central nervous system (CNS) involvement. PHACES is an acronym for the association of posterior fossa brain anomalies, hemangiomas, arterial anomalies, cardiac defects and coarctation of the aorta, eye anomalies, and sternal abnormalities or ventral developmental defects. Infants who had received specified prohibited medications within 15 days of inclusion were also excluded, as were breast fed infants of mothers who had taken these medications within the defined time interval.

The study included standard withdrawal criteria for clinical trials in children. In addition, the study included withdrawal criteria specific for adverse events known to be associated with propranolol (i.e., severe hypoglycaemia; clinically significant decrease in heart rate or blood pressure; severe bronchospasm). Worsening of the target IH from baseline from D14 onwards could also result in withdrawal.

Unless counter-requested by the parent(s), in all cases of treatment discontinuation available data were retained for safety analysis and collection of as much information as possible on treatment efficacy. Where possible, all patients were followed up to the end of the study (Day 96), regardless of the reason for treatment discontinuation. Patients permanently discontinued may have been prescribed a new treatment for IH at the discretion of the investigator.

> **Comment**: The sponsor states that the EMEA recommended that new born infants should not be included in the study. Infants born prematurely were also not allowed to enter the trial until they had reached term equivalent age.

4.2.2.1.4. Methodology

This was an open-label, multicentre, repeated-dose study. Infants were stratified to two groups according to age at inclusion. The time of PK-steady state assessment after initiation of treatment differed between the two age groups:

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

A total of 23 infants aged between 35 and 150 days were included in the study and received an oral solution of propranolol for 12 weeks for the treatment of IHs. The initial dose (1 mg/kg/day) was titrated in 1 mg/kg/day increments every week during the first 2 weeks followed by a maintenance dose of 3 mg/kg/day given twice daily (BID) for a further 10 weeks.

Screening procedures could have been carried out up to 7 days before the baseline visit (V) on Day (D) 0, or with the D0 procedures. Patients attended for a 5 further visits at intervals of 1 to 4 weeks: i.e., D7 ± 1 day, D14 ± 1 day, D28 ± 3, D56 ± 3, and end-of-treatment visit at D84 ± 3 days. A phone call was made to the parents two weeks after the end of study treatment at D96 (± 3 days) to collect any additional adverse event (AE) data.

During the titration period, 2 micro-blood samples (of 250 µL each) were obtained at the end of weeks 1 and 2. A further 6 serial micro-blood samples were obtained on 1 occasion at steady-state for propranolol and 4-OH-propranolol assays (D28 for Group 1; D84 for Group 2).

4.2.2.1.5. Treatment

The study drug consisted of an oral solution of propranolol (3.75 mg/mL) with excipients of saccharin sodium, sodium propionate, hydroxyethylcellulose, strawberry flavour, vanilla flavour, citric acid monohydrate, purified water.

All patients received open-label study treatment with propranolol oral solution for 12 weeks from D0, including a progressive titration over the first 2 weeks. The individual dose of propranolol depended on the infant's body weight. The required dose was calculated (and reported in the CRF) by the investigator at each visit and the parent(s) were instructed to administer the calculated dose using the provided pipette twice daily (BID) until the next visit. The dose to be administered by the parent(s) was recorded on the treatment box by the investigator. The method of administration was demonstrated to the parent(s) at D0. The solution was administered orally, without dilution, via graduated pipettes provided in the treatment kits. The pipettes were specifically designed to ensure an accurate dose and precise controlled administration of the oral solution to the buccal cavity of young infants.

Titration of propranolol was carried out over the first 14 days, with the dose being increased on D7 and D14.

- D0: 1 mg/kg/day (0.5 mg/kg in the morning and 0.5 mg/kg in the late afternoon);
- D7: 2 mg/kg/day (1 mg/kg in the morning and 1 mg/kg in the late afternoon);
- D14: 3 mg/kg/day (1.5 mg/kg in the morning and 1.5 mg/kg in the late afternoon).

Patients were assigned to receive propranolol oral solution for 12 weeks from D0, and no tapering of dose was considered necessary at the end of the treatment phase.

The doses were administered immediately prior to or after a meal. The second daily dose of propranolol was administered late in the afternoon to reduce the risk of hypoglycaemia during the night. In order to avoid the risk of hypoglycaemia, parents were instructed to temporarily discontinue administration of propranolol if the patient experienced vomiting or a prolonged

fasting period. Parents were instructed that on the evening before each PK visit, the last dose of treatment was to be administered at around 8 pm.

At D0, and at each dose increase at D7 and D14, the first administration of the new dose was carried out at the study site so that specific safety assessments could be performed. Temperature, heart rate, blood pressure, respiratory rate and pulmonary auscultation were assessed before the first administration and then every hour (± 30 minutes) for 4 hours after the first administration. Blood glucose level was measured by pin-prick test and an electrocardiogram (ECG) was performed before the first administration and at 2 hours (± 30 minutes) and 4 hours (± 30 minutes) after the first administration. The actions to be taken based on measurements of heart rate, blood pressure, respiratory rate and glycaemia are provided below in Table 5.

Table 5: Study 102 - Actions to be taken with respect to heart rate, blood pressure, and glycaemia.

Action to be taken	D0 – pre-dose	D7 and D14 – pre-titration	D0, D7 and D14 – 4 h safety assessment
Do not give study therapy (pre-dose/pre-titration) and continue to monitor the Patient on site	HR < 80 bpm or BP < 50/30 mmHg or glycaemia < 40 mg/dL	HR < 60 bpm or BP < 50/30 mmHg or glycaemia < 40 mg/dL	HR < 60 bpm or BP < 50/30 mmHg or glycaemia < 40 mg/dL
Permanently discontinue study treatment and continue to monitor the Patient on site	HR remains < 80 bpm or BP remains < 50/30 mmHg or glycaemia remains < 40 mg/dL	HR < 50 bpm for > 1 min or glycaemia < 30 mg/dL or HR remains < 60 bpm or BP remains < 50/30 mmHg or glycaemia remains < 40 mg/dL	HR < 50 bpm for > 1 min or glycaemia < 30 mg/dL or, after further monitoring (beyond the scheduled 4 h), HR remains < 60 bpm or BP remains < 50/30 mmHg or glycaemia remains < 40 mg/dL

If a potential safety issue was identified during the safety evaluations at D0, D7 and D14, the study drug was discontinued according to the criteria outlined in the above table. The patient continued to be monitored for safety on-site beyond the scheduled 4 hours if safety issues persisted. In the absence of any abnormalities, the patient was allowed to leave the site and continue study drug according to the protocol.

Before leaving the study site, parents were provided with a letter on safety monitoring during the treatment phase. The letter recommended actions to be taken under different scenarios, including, but not limited to: illness, asthenia (tiredness), mood changes, difficulty waking up, hypotonia (muscle weakness and fatigue), feeding difficulty, paleness and respiratory difficulty. Parents were advised to discontinue study treatment and contact the study doctor (or another doctor) immediately in the case of any safety issues. Parents were also provided with a patient diary to record any AEs between study visits and to log treatment administrations. Parents were specifically instructed on the potential risks, clinical features and management of hypoglycaemia and bronchospasm.

The list of prohibited medications to be avoided within 15 days before inclusion or at any time during the 12-week treatment period was extensive and is provided in the CSR. If any prohibited medications were considered medically necessary for the patient (and/or the mother while she was breastfeeding the patient) during the study treatment period the study drug was to be discontinued. All treatments for IH, including any surgical and/or medical procedures (e.g., laser therapy), were prohibited prior to and during the study. All medications other than the specified prohibited medications were authorized.

Treatment compliance was assessed at each post-baseline visit during the treatment period, with parents being instructed to bring back the investigational product (IP) box containing all

bottles of IP (used/unused). The bottles were weighed by the person in charge of treatment management in the centre and the weight recorded on the drug accountability form. This information was used to evaluate exposure to treatment. The investigator also qualitatively evaluated compliance (poor/average/good) at each visit and overall.

4.2.2.1.6. Pharmacokinetic parameters - primary objective

Pharmacokinetic parameters were determined for propranolol and 4-OH-propranolol as follows:

- Cmax - maximum plasma concentration estimated directly from the experimental data.
- Tmax - time to reach the maximal plasma concentration estimated directly from the experimental data.
- AUC_{last} - observed area under the plasma concentration time curve calculated according to linear-up/log-down trapezoidal rule from T0 (time of administration) to the last quantified concentration.
- AUCτ - observed area under the plasma concentration time curve between two drug administrations calculated according to linear-up/log-down trapezoidal rule, and τ corresponds to time elapsing between two drug administrations (12 hours).
- Cltot/F (only for propranolol) - apparent total plasma clearance or oral plasma clearance was calculated as the ratio of dose and AUCτ.
- Metabolite/parent drug ratio - calculated for Cmax and AUCτ.

During the titration period, micro-blood samples were taken on D7 and D14 for the determination of propranolol and 4-OH-propranolol plasma levels. At steady-state, 6 micro-blood samples were collected over a 9 hour-period at D28 for Group 1 or at D84 for Group 2. The micro-blood samples (250 µL) were obtained through puncture of a peripheral vein via an intravenous catheter after application of an appropriate local anaesthetic. The catheter was removed after the last D28 or D84 sample was obtained, or before in case of local intolerance. A total of 8 micro-blood samples per patient were required for analytical determinations. The total volume of blood collected per patient for PK purposes was 2 mL. The total amount of blood collected during the whole study was less than 12 mL. The timing of the micro-blood samples are summarized below in Table 6.

Table 6: Study 102 - Sampling times for micro-blood samples.

Day	Sampling time	Sample No
D7	Before new dose administration	P01
D14	Before new dose administration	P02
D28 or D84 (according to the group)	T0 (before morning dosing; 12 h after the previous evening dose) T1h T2h T4h Lunch T6h T9h*	P03 P04 P05 P06 P07 P08

* Before the afternoon dosing' T: time; h: Hour

Propranolol and 4-OH-propranolol plasma concentrations were measured using a validated LC/MS-MS method, with a quantification range of 0.50 to 250 ng/mL. For calculation of AUC_{last} and AUCτ, all BLQ values in the absorption phase were substituted by zero, except for BLQ values between 2 quantifiable concentrations, which were ignored. Terminal BLQ values were ignored.

4.2.2.1.7. Statistical methods and sample size

The PK analysis was undertaken in the Per-Protocol (PP) data set. The PP data set included patients who took all study medications and had no major protocol deviations. Major protocol deviations were those considered by the Validation Committee to be likely to significantly bias the interpretation of the main results of the study (i.e., PK results). Safety and tolerability were assessed in the all patients treated (APT) data set, which included all patients who received at least one dose of study medication and had available safety data from at least one post-baseline assessment. Efficacy was assessed in the intention-to-treat (ITT) data set, which included all patients who had received one dose of study medication and had at least one post-baseline efficacy assessment. In this study, the APT and the ITT data sets were the same, and the efficacy and safety/tolerability analyses were undertaken on the APT data set.

The PK parameters were assessed using non-compartmental analysis (Phoenix WinNonlin, version 6.1). Actual sampling times rather than theoretical sampling times were used only if the deviation exceeded more than 10% of the theoretical sampling time. Standard descriptive statistics for plasma concentrations and PK parameters of propranolol and 4-OH-propranolol were provided. Only quantifiable concentrations were taken into account for calculation of mean values and CVs. If more than half of the data were not quantifiable, descriptive statistics were not undertaken. In addition, a PPK analysis assessed propranolol and 4-OH propranolol concentrations.

The primary objective of the study was the PKs of propranolol. There was no justification of the sample size. It was planned that 20 infants would be included in the study (10 infants in each stratification group). A sample size of 20 infants was deemed sufficient to reach the study objectives by the Paediatric Committee (PDCO) of the EMA and by the French Health Agency (AFSSAPS).

4.2.2.1.8. Patient disposition

The study included 23 patients from four centres in France (23 patients were screened and all were treated). Of the 23 patients, 10 were stratified to Group 1 (infants aged from 35 to 90 days at inclusion), and 13 were stratified to Group 2 (infants aged 91 to 150 days inclusive at inclusion). One (1) patient in Group 2 was withdrawn from the study by the sponsor prior to completion due to an increase in QTcB interval on D14. The demographic characteristics of the 23 patients in the APT are summarized below in Table 7.

Table 7: Study 102 - Demographic characteristics of the APT data set.

	35-90 Days n=10	91-150 Days n=13	Total n=23
Sex			
Missing	-	-	-
Male	3 (30.0%)	3 (23.1%)	6 (26.1%)
Female	7 (70.0%)	10 (76.9%)	17 (73.9%)
Age (Days)			
Missing	-	-	-
Mean (SD)	69.7 (13.8)	128.2 (20.9)	102.7 (34.6)
Min/Median/Max	50 / 72.0 / 89	91 / 134.0 / 152	50 / 95.0 / 152
Weight (KG)			
Missing	-	-	-
Mean (SD)	4.7670 (0.7338)	6.3273 (1.0165)	5.6489 (1.1872)
Min/Median/Max	3.600 / 4.8350 / 5.900	5.200 / 6.0000 / 8.500	3.600 / 5.5000 / 8.500
Height (cm)			
Missing	-	-	-
Mean (SD)	56.00 (3.87)	61.81 (2.73)	59.28 (4.34)
Min/Median/Max	50.0 / 56.75 / 61.0	57.5 / 62.00 / 67.0	50.0 / 60.00 / 67.0
Head circumference (cm)			
Missing	-	-	-
Mean (SD)	38.99 (1.53)	40.72 (1.55)	39.97 (1.74)
Min/Median/Max	36.0 / 39.35 / 40.9	37.5 / 41.00 / 43.0	36.0 / 40.00 / 43.0

Of the 23 patients in the APT, 19 were included in the PP data set for PK analysis (8 in Group 1 and 11 in Group 2). The reasons for exclusion of the 4 patients from the PP data set were: (i) no

available PK blood samples for 1 patient in Group 2, resulting in withdrawal from study during the titration period; (ii) missing blood samples for 1 patient in Group 2, with 2/5 of the PK blood samples collected after T0 at Visit 7 missing; (iii) the drug dosing interval (between 16.2 and 18.7 hours) was out of range (theoretical interval of 12 hours) for 3 patients (2 in Group 1, and 1 in Group 2). A patient may have had more than one reason for exclusion.

The reasons for exclusion of the 4 patients from the PP data set were considered to be major protocol deviations. There were numerous minor protocol deviations in the 19 patients in the PP data set for the PK analysis, but these were considered to have had no impact on the PK analysis.

4.2.2.1.9. Pharmacokinetic results

- Propranolol and 4-OH-propranolol plasma concentration

The mean plasma concentration - time profiles of propranolol and 4-OH-proranolol after repeated BID administration of propranolol 3 mg/kg/day for 2 weeks (Group 1) and 10 weeks (Group 2) were summarized by age group and by analyte. The results for both analytes are summarized below.

Propranolol:

During titration, after repeated oral BID administration of 1 mg/kg/day of propranolol the median concentrations of propranolol measured just before the morning administration (Cmin) on D7 (V3) were 4.63 ng/mL (range: 1.24, 12.5 ng/mL) and 3.74 ng/mL (range: 1.13, 29.9 ng/mL) in Groups 1 and 2, respectively.

During titration, after repeated oral BID administration of 2 mg/kg/day of propranolol the median concentrations of propranolol measured just before the morning administration (Cmin) on D14 (V4) were 9.39 ng/mL (range: 4.09, 15.8 ng/mL) and 6.82 ng/mL (range: 2.33, 25.5 ng/mL) in Groups 1 and 2, respectively.

At the target dose of 3 mg/kg/day, median Cmin levels were 22.4 ng/mL (range: 7.31, 36.8 ng/mL) on D28 in Group 1, and 10.1 ng/mL (range: 4.40, 47.4 ng/mL) on D84 in Group 2.

After titration and repeated oral BID administration of 3 mg/kg/day of propranolol for 2 weeks (Group 1) and for 10 weeks (Group 2), all plasma concentrations of propranolol measured between T0 and T9h were above the limit of quantification. Median Cmax levels were observed at 2 hours post-dose for both groups.

4-OH-propranlol:

During titration, Cmin values were BLQ for 5/8 patients on D7 and D14 in Group 1, and BLQ for 5/11 patients on D7 and 10/11 patients on D14 in Group 2. At the target dose of 3 mg/kg/day, median Cmin was 1.08 ng/mL (range: BLQ, 2.14 ng/mL) on D28 in Group 1, while individual Cmin levels were BLQ for 9/11 patients on D84 in Group 2.

After titration and repeated BID administration of 3 mg/kg/day of propranolol for 2 weeks (Group 1) and for 10 weeks (Group 2), all plasma concentrations of 4-OH-propranolol measured between T0 and T9h were above the limit of quantification, except for 2 patients in Group 1 (BLQ concentration at T9h post-dose), and 5 patients in Group 2 (BLQ concentration for 1 patient at T4h and 4 patients at T6h and/or T9h). Median Cmax levels were observed at 1.09 and 2 hours post-dose for Groups 1 and 2, respectively.

- Propranolol and 4-OH-propranolol pharmacokinetic parameters

The main PK parameters of propranolol and 4-OH-propranolol observed after repeated BID oral administration of propranolol for 4 weeks (Group 1) and for 12 weeks (Group 2) are summarized below in Table 8 (propranolol) and Table 9 (4-OH-propranolol). In the PK data set, deviations in actual sampling times of more than 10% from the theoretical sampling times were observed in 2 patients from Group 1 and 3 patients from Group 2. For these patients, actual

sampling times were used for AUC calculation. For 1 patient from Group 2, the PK analysis for the metabolite was not performed due to the lack of quantified concentrations (2 missing samples and 2 BLQ concentrations after administration of propranolol).

Table 8: Study 102 - Main pharmacokinetic parameters for propranolol after repeated twice daily oral administration of propranolol 3 mg/kg/day in infants for 2 weeks (Group 1) and for 10 weeks (Group 2).

Group		T_{max} (h)	C_{max} (ng/mL)	AUC_{9h} (h*ng/mL)	AUCτ (h*ng/mL)	CLtot/F (L/h)	CLtot/F/kg (L/h/kg)
1	N	8	8	8	8	8	8
	Geom Mean	2.00*	78.5	455	541	15.2	2.71
	Geom CV%	-	32.9	27.8	27.5	27.9	27.9
	Min	1.00	47.8	316	360	11.4	1.84
	Max	9.00	119	696	804	22.3	4.05
2	N	11	11	11	11	11	11
	Geom Mean	2.00*	79.2	373	430	25.5	3.27
	Geom CV%	-	103	72.4	73.0	79.1	73.3
	Min	1.00	21.3	102	116	7.55	1.18
	Max	4.00	448	972	1193	94.5	12.3

**median -: not calculated τ=12 h*

Table 9: Study 102 - Main pharmacokinetic parameters 4-0H-propranolol after repeated twice daily oral administration of propranolol 3 mg/kg/day in infants for 2 weeks (Group 1) and for 10 weeks (Group 2).

Group		T_{max} (h)	C_{max} (ng/mL)	Metabolite /parent C_{max} ratio	AUC_{9h} (h*ng/mL)	Metabolite /parent AUC_{9h} ratio	Metabolite /parent AUC_{τ} ratio
1	N	8	8	8	6	6	5
	Geom Mean	1.09*	6.16	0.0785	27.4	0.0593	0.0584
	Geom CV%	-	52.8	35.9	42.0	43.6	49.3
	Min	1.00	2.89	0.0524	16.8	0.0336	0.0321
	Max	2.00	14.4	0.132	53.8	0.108	0.105
2	N	10	10	10	7	7	2
	Geom Mean	2.00*	3.80	0.0503	16.2	0.0333	-
	Geom CV%	-	87.5	132	54.7	112	-
	Min	1.00	0.880	0.00712	5.29	0.00544	0.0356
	Max	4.00	10.9	0.202	23.8	0.0812	0.0407

**median -: not calculated τ=12 h*

Comments on pharmacokinetic results from study 102: Study 102 is considered to be a good quality PK study in infants with IH. The dosing regimen used in the study and the age group of the treated infants with IH were consistent with those proposed for approval. The sponsor notes that while the PKs of propranolol have been extensively documented in adults, information on the PKs of the drug are extremely limited in children. Overall, the primary PK parameters in infants from study 102 (corrected for body weight) are similar to those reported in the literature in adults.

A total of 23 infants (6 male and 17 female) with IHs were included in the study, and at inclusion, age ranged from 50 to 152 days and body weight from 3.6 to 8.5 kg. All 23 infants were given an oral solution of propranolol for the treatment of IH, and 22 completed 3 mg/kg/day for 10 weeks after a 2-week titration period at 1 mg/kg/day for 1 week and 2 mg/kg/day for 1 week. Steady-state PK parameters for propranolol and the 4-OH-propranolol metabolite were presented for 19 infants in the PP data set after repeated BID dosing of propranolol for 4 weeks for infants aged 35 to 90 days at inclusion (Group 1) and for 12 weeks for infants aged 91 to 150 days at inclusion (Group 2).

Trough concentrations of propranolol quantified before morning administration (Cmin) increased with dose. In Group 1, the median Cmin increased from 4.63 ng/mL on D7 following 1 mg/kg/day, to 9.39 ng/mL on D14 following 2 mg/kg/day, and to 22.4 ng/mL on D28 following 3 mg/kg/day. In Group 2, the median Cmin increased from 3.74 ng/mL on D7 following 1 mg/kg/day, to 6.82 ng/mL on D14 following 2 mg/kg/day, and to 10.1 ng/mL at D84 following 3 mg/kg/day. Most Cmin values for 4-OH-propranolol were BLQ during the titration period, and at weeks 4 and 12.

The geometric mean Cmax values were similar for Groups 1 and 2 (78.5 and 79.2 ng/mL, respectively), and the median Tmax was 2 hours for both groups. Geometric mean plasma exposure to propranolol was greater in Group 1 than in Group 2, based on the geometric AUCτ. However, in Group 2 the mean geometric AUCτ results demonstrated marked inter-subject variability with the geometric CV being 73.0%. Nevertheless, the geometric mean AUCτ in Group 2 (430 h.ng/mL) was within the range of values for the geometric mean AUCτ of Group 1 (360 to 804 h.ng/mL). Geometric oral clearance values, corrected by body weight, were similar in Groups 1 and 2 (2.71 and 3.27 L/h/kg, respectively). These values were in the same range as those reported in adults after oral propranolol administration (Mackichan et al., 1980; Walle et al., 1989; Routledge and Shand, 1979; and Walle et al., 1986).

Moderate inter-subject variability in the main PK parameters, as assessed by the geometric CV%, was observed in Group 1 (27.5% to 32.9%), while inter-subject variability in the main PK parameters was marked in Group 2 (72.4% to 103%). High inter-individual variability in the PK parameters of propranolol is a known characteristic of this drug.

Exposure to the 4-OH-propranolol metabolite accounted for 8% and 5% of parent drug at Cmax, and 6% and 3% of total exposure over 9 hours post-administration (AUC_{9h}) in Groups 1 and 2, respectively. These values are in the same range as those reported in the literature for adults after single oral administration of propranolol (Kopitar et al., 1986). From the data provided in Kopitar et al., 1986, it can be concluded that the exposure to the 4-OH-propranlol accounted for 10.6% of parent drug based on the mean AUC (ng.h/mL) values for 8 healthy male subjects following a single oral propranolol dose of 160 mg, and 11.3% for a single oral propranolol dose of 80 mg.

4.2.3. Population PK analysis 101 in patients with IH

4.2.3.1. Summary of the objectives and methodology of the population PK analysis

The submission included a population pharmacokinetic (PPK) analysis of the data from infants with IH from study 102. The PPK analysis was performed by Non-Linear Mixed Effect Modelling using NONMEM version 7.3, and NONMEM data sets were built using SAS software.

The main objectives of the PPK analysis were: (i) to describe the PKs of propranolol and its metabolite 4-OH-propranolol in infants; and (ii) to evaluate the between-subject variability and understand the source of variability of the PKs of propranolol in infants.

In non-linear mixed effects modelling, the mathematical model used in parameter estimation includes both fixed and random factors to describe the data.

The fixed effect parameters (θ) include the mean values of the relevant structural PK model (e.g., clearance) or a number of parameters which relate the structural model parameters to demographic and physiological variables (e.g., sex, weight, age).

The random effect parameters are of two types: those yielding inter-individual differences in parameter values not accounted for by the fixed effects (η), and those resulting in the intra-individual variation due to random fluctuations in an individual's parameter values, measurement error and all sources of error not accounted for by the other parameters (ε).

The selection of the structural PK model and error models was based on the NONMEM objective function value (OFV) and visual inspection of goodness of fit plots. The search for the final model, and the evaluation of covariates and the error models followed the strategy described below. The strategy aimed to ensure that no significant factors were missed and that no redundant factors remained in the model.

1. The structural PK model was identified using common variance models (exponential error model).
2. The best estimation method (FO or FOCE), the most appropriate between subject variance models and the residual error model were identified. The resulting model was called BASE.
3. Graphical exploration of the covariates was undertaken.
4. Selection of covariates by univariate analyses, at risk 0.05 (reduction of objective function of at least 3.84 for one additional parameter). The best model for each covariate to affect each of the parameters was selected at this stage.
5. In a multivariate analysis, all selected covariates were added together, the model fitted to data and a new value of the objective function was obtained and considered as a reference called FULL model.
6. Backward deletion until no covariate could be removed without significant increase of the objective function, using likelihood ratio test at $p<0.01$, objective function increase by at least 6.64 for one parameter. The resulting model was the FINAL model.

The FINAL model qualification (evaluation) was based on:

- Goodness of fitness plots: population and individual predictions vs observed measurements, population weighted residuals vs population prediction and time, and individual weighted residuals vs individual prediction and time
- Predictive performance check: Monte Carlo simulations were performed. The derived 5th, 50th and 95th percentiles from the simulated data were superimposed with observed concentrations and visually compared.

Comment: The strategy adopted to select and evaluate the final model is considered to be appropriate. The software used to perform the analysis is standard and well accepted for PPK analyses. The reporting of the PPK analysis was extensive and was consistent with the relevant TGA adopted Guidelines on reporting the results of population pharmacokinetic analyses (CHMP/EWP/185990/06).

4.2.3.2. PPK analysis data sets

The demographic characteristics of the PPK analysis were:

- A total of 22 patients (10 in Group 1 and 12 in Group 3) were used for the PK modelling. These 22 patients included 6 males (3 males in each Group) and 16 females (7 in Group 1 and 9 in Group 2).
- In Group 1, on day 0 (visit 2), ages ranged from 50 to 89 days (~1.7 to ~3 months) with a median of 72 days (~2.5 months). Body weights ranged from 3.60 to 5.90 kg with a median of 4.84 kg. In Group 1, on day 28 (visit 5), ages ranged from 77 to 118 days (~2.5 to ~4 months) with a median of 101 days (~3.5 months). Body weights ranged from 4.50 to 6.77 kg with a median of 5.60 kg.
- In Group 2, on day 0 (visit 2), ages ranged from 95 to 152 days (~3 to ~5 months) with a median of 135 days (~4.5 months). Body weights ranged from 5.20 to 8.50 kg with a median of 6.15 kg. In Group 2, on day 84 (visit 7), ages ranged from 180 to 243 days (~6 to ~8 months) with a median of 216 days (~7 months). Body weights ranged from 6.40 to 9.70 kg with a median of 7.65 kg.

The PPK analysis dataset included 166 non-zero observations of propranolol concentrations and 109 non-zero observations of 4-OH propranolol concentrations from 22 patients (10 in group 1 and 12 in group 2) sampled twice during the titration period (1 to 2 mg/kg/day) and 6 times during the fixed-dose period (3 mg/kg/day). The PPK analysis datasets included:

- 21/22 quantifiable and available concentration data of propranolol on Day 7 (1 mg/kg/day, 10 in Group 1 and 11 in Group 2).
- 2/22 quantifiable and available concentration data of 4-OH-propranolol on Day 7 (2 in Group 1 and none in Group 2).
- 18/22 quantifiable and available concentration data of propranolol on Day 14 (2 mg/kg/day, 9 in Group 1 and 9 in Group 2).
- 3/22 quantifiable and available concentration data of 4-OH-propranolol on Day 14 (3 in Group 1 and none in Group2).
- 128/132 quantifiable and available concentration data of propranolol after administration of 3 mg/kg/day (60 in Group 1 and 68 in Group 2).
- 104/132 quantifiable and available concentration data of 4-OH-propranolol after administration of 3 mg/kg/day (53 in Group 1 and 51 in Group 2).

4.2.3.3. Results

The PPK analysis was planned to combine both propranolol and 4-OH-propranolol concentrations for modelling. However, 4-OH-propranolol represented less than 10% of the propranolol plasma exposure and only 60% of concentration data were available and quantifiable. This did not give enough information to allow the estimation of PK parameters relating to the metabolite part of the model. Consequently, modelling was performed on propranolol concentration data only, using 166 concentrations in 22 patients (an outlier concentration was excluded from the propranolol data set).

The best structural model to describe the PKs of propranolol was a one-compartment disposition model with a first order absorption and a first order elimination. The between subject variability could be estimated on the apparent plasma clearance and the absorption rate. No between-subject variability was estimated on apparent volume of distribution. A three compartment model was not evaluated. Lag-time was not estimated.

The effect of weight was evaluated on plasma clearance and volume of distribution using allometric functions. The allometric coefficient was fixed to 0.75 for clearance and 1 for volume of distribution. Weight was found to affect plasma clearance, but not volume of distribution. The failure of weight to affect volume of distribution in infants was unexpected. The sponsor speculates that, as plasma samples were collected only for up to 9 hours after administration, there was not enough information to obtain a good estimate of the between subject variability or a covariate effect of weight on the apparent volume of distribution. The effects of the covariates of dose, age, time and sex were not evaluated on PK parameters. Due to the study design, the dose administered is highly correlated with age and visit (i.e., time effect), while sex was not a covariate of interest in infants. The propranolol final model for the parameter estimates is provided in the CSR.

The geometric mean of individual predicted CL/F values of propranolol using the final model for Groups 1 and 2 (16.3 and 24.3 L/h, respectively) were similar to the observed geometric mean CL/F values for Groups 1 and 2 (15.2 and 25.5 L/h, respectively). The similarity of the predicted CL/F results using the final model and observed CL/F results indicates good fit of final model to the observed data. The data support dose based on weight (mg/kg) rather than dose based on age (days). The individual CL/F values of propranolol predicted using the final model and the descriptive statistics for this parameter are summarized in the dossier.

The between individual variability on the plasma clearance was 44.2%, which is close to that observed on adult exposure (Kopitar et al., 1986). The between individual variability on the absorption rate was high (132%). However, sampling collection was not designed to accurately estimate the absorption rate.

The residual error was estimated using a proportional error model. The observed residual error of 30% was stated by the sponsor to be "reasonable for a limited, but not sparse sampling collection design in ambulatory patients".

> **Comment**: This was a good quality PPK study in 22 infants with IH aged from 50 to 152 days (actual age range) treated for 12 weeks with an oral solution of propranolol. The final PK model using a weight function on clearance was established and adequately predicted the PKs of propranolol in infants after repeated oral BID administration of 3 mg/kg/day. This analysis confirmed that the dose in mg/kg should be used rather than dose based on age. The Summary of Clinical Pharmacology Studies (included what appears to a post-hoc analysis of data from the PPK analysis to estimate the impact on the maximal plasma concentrations of the interval between the two intakes in the day. The simulation was performed for repeated 1.5 mg/kg/d BID administrations over 8 consecutive days, this duration being deemed sufficient to obtain the steady-state for propranolol. In order to assess the impact of the interval of administration between the morning and the late afternoon intakes on Cmax, the simulation was performed for a 9-hour and a 12-hour interval, using the demographic characteristics of the infant population of study 102. The simulated median Cmax (together with the 5th and 95th percentiles) was 67.1 ng/mL (25.9, 138) for the 9 hour interval between doses; and 61.2 ng/mL (23.6, 128) for the 12 hour interval between doses. The sponsor comments that the less than 10% difference in Cmax between the two dosing intervals "may be acceptable in light of the intrinsic variability of propranolol pharmacokinetics (around 30%)". The proposed dosing interval for treatment of infants with IH is 9 hours.

4.2.4. Comparison and analyses of PK results across studies

4.2.4.1. Pharmacokinetics in children

In the Summary of Clinical Pharmacology Studies, the PK profile of propranolol in infants with IH from study 102 was compared with PK profiles in infants from published data (Riopel and Walle, 1980; Ponce et al., 1973). The sponsor commented that published data on the PKs of propranolol in infants are sparse, and include "only a few studies in infants with cardiovascular disease". The comparative data are summarized below in Table 10.

Table 10: Pharmacokinetic parameters of propranolol in infants from study 102 and from the literature.

Source	Infants V0400 SB 1 02		Literature Infants	
Dose	1.5 mg/kg BID Group 1	1.5 mg/kg BID Group 2	2.4 to 4.4 mg/kg/d	4 mg/kg/d
C_{max} (ng/mL)	**47.8 to 119**	**21.3 to 448**	**16.5** to **114**[1]	**20** to **467**[2]
CL/F (L/h/kg)	**2.71**	**3.3**		
$T_{1/2}$ (h)	*	*	**3.9** to **6.4**[1]	

*In study 102, the sampling design did not allow an evaluation of T½;1. Riopel and Walle et al., 1980, n= 5, repeat oral doses every 6 hours, infants from 9 months to 6 years; 2. Ponce et al., 1973, n=15, repeat oral dose every 6 hours, infants from less than 2 years to 11 years. NB: The Cmax values from Riopel et al., 1980 appear to relate to mean steady state propranolol concentrations rather than Cmax concentrations (see below).

> **Comment**: In the sponsor's tabulated summary of the PKs of propranolol in children (Table 10 above), it is stated that the Cmax values from Riopel and Walle (1980) ranged from 16.5 to 114 ng/mL. However, the study report indicates that these concentrations

are mean steady state propranolol concentrations rather than Cmax values. The published literature identified by the sponsor included limited PK data on 20 children (19 with tetralogy of Fallot) from only two studies. The sponsor's conclusion that plasma levels observed in infants with IH from study 102 were in "accordance" with the published literature in children with cardiovascular disease should be interpreted cautiously due to the small number of children with data identified in the literature and the marked inter-subject variability in plasma/serum propranolol concentrations.

4.2.4.2. Pharmacokinetics in infants and adults

In the Summary of Clinical Pharmacology Studies, the PK profiles of propranolol were compared in healthy adults from study 101, infants with IH from study 102, and published data from adults (Mackichan et al., 1980; Walle et al., 1989; Routledge et al., 1979, and Walle et al., 1989). The comparative data provided by the sponsor are summarized below in Table 11.

Table 11: Pharmacokinetic parameters of propranolol in adults and infants.

	Geometric Mean PK Parameters (%CV)				
Source	**Adults** V0400 SB 1 01		**Infants** V0400 SB 1 02		**Literature Adults**
Dose	80 mg (1.11 mg/kg)	Dose corrected to 1.5 mg/kg	3 mg/kg given as 1.5 mg/kg BID Group 1	3 mg/kg given as 1.5 mg/kg BID Group 2	Variable
C_{max} (ng/mL)	47.98 (27%)	**64.8**	**78.5** (33%)	**79.2** (103%)	-
AUC* (h*ng/mL)	311 (34%)	**420**	**541** (28%)	**430** (73%)	-
CL/F (L/h)	258 (34%)	-	15.2 (28%)	25.5 (79%)	-
CL/F (L/h/kg)	**3.6** (34%)	-	**2.71** (28%)	**3.3** (73%)	**5.2** to **3**[1] **3.9** to **2.4**[2] **2.16**[3] **3.2**[4]

AUC: total area under the concentration versus time curve; * AUC_{inf} for adults and AUC_{12h} for infants; CL/F: apparent total plasma clearance; Cmax : maximum plasma concentration; CV: coefficient of variation; inf: infinity; 1. Mackichan et a l., 1980, single oral doses increasing from 10 to 40 mg, respectively. 2. Walle et al ., 1989, single oral dose of 80 mg in women and in men, respectively. 3. Routledge et al ., 1979, repeated oral administration of 80 mg three times a day. 4. Walle et al., 1986, single oral dose of 80 mg.

Comment: The published studies identified by the sponsor have been examined, and the accuracy of the data from these studies included in Table 11 (above) has been confirmed. Overall, it is considered that the submitted data suggest that the CL/F of propranolol (corrected for weight) is reasonably consistent in infants with IH and in healthy adults. In addition, the comparative Cmax and AUC data from studies 101 and 102 (expressed as mg/kg, normalized to 1.5 mg/kg in adults) suggest that exposure to propranolol based on these two PK parameters is also reasonably consistent in infants with IH and in healthy adults.

4.3. Evaluators overall conclusions on pharmacokinetics

The submission included two studies with PK data relating to the oral solution of propranolol (102A in healthy adults and 102 in infants with IH). In addition, the submission included a PPK analysis on data from infants with IH from study 102.

There was no study in either healthy adults or infants with IH comparing the proposed propranolol oral solution (3.75 mg/mL) with an Australian marketed propranolol tablet. The sponsor provided a justification for not submitting a relative bioavailability study comparing the oral solution with an Australian marketed product, but the justification included in vitro

dissolution data comparing the French sourced propranolol tablet with a US marketed tablet. The absence of a relative bioavailability study comparing the propranolol oral solution (3.75 mg/mL) proposed for registration with an Australian marketed propranolol tablet is considered to be a deficiency in the submission. However, this deficiency is offset to some extent by the presence of a study in infants with HI that adequately characterizes the PKs of propranolol in the proposed target population. There was no absolute bioavailability study comparing the proposed propranolol oral solution with an IV formulation of propranolol. However, the absence of such a study should not preclude approval of the solution, as it is well known that propranolol is almost completely absorbed following oral administration and undergoes significant first-pass hepatic metabolism.

In study 1012A, the relative bioavailability (BA) of a propranolol oral solution (5 mg/mL) and a propranolol tablet (40 mg) marketed in France were compared in 12 healthy adult males aged between 18 and 45 years in a cross-over trial. The sponsor considered this to be a supportive study in adults undertaken to evaluate the PKs of propranolol oral solution before it was administered to infants. In this study, the bioavailability of the oral solution was greater than the oral tablet assessed by both the Cmax (22% greater) and the AUC_{inf} (20% greater) following administration of single-doses of the two formulations dose-normalized to 80 mg. The plasma concentration - time profiles for the two formulations (dose-normalized to 80 mg) were comparable when measured over 24 hours following single-dose administration. The median Tmax values were similar for the oral solution 80 mg and the oral tablet 70.18 mg (1.33 [range: 1, 2] and 1.67 [range: 0.67, 3) hours, respectively), indicating rapid absorption following administration. The mean T½ values were similar for the oral solution 80 mg and the oral tablet 70.18 mg (4.41 and 4.19 hours, respectively), suggesting that both formulations are likely to be completely eliminated approximately 21 hours after dosing. Inter-subject variability in Cmax and AUC_{inf} values was moderate following single-dose administration of the oral solution (CV = 27% and 39%, respectively), while inter-subject variability in Cmax and AUC_{inf} values was marked following single-dose administration of the tablet formulation (CV = 95% and 92%, respectively).

In study 102, the steady-state PKs of propranolol and the 4-OH-propranol metabolite following administration of the 3.75 mg/kg solution BID were characterized using non-compartmental analysis in 23 infants with IH, stratified by age into two groups (Group 1 [n=10] aged 35 to 90 days, Group 2 [n=13] aged 91 to 150 days). All patients received 1 mg/kg/day from Day 0, 2 mg/kg/day from Day 7, and 3 mg/kg/day from Day 14 to Day 84. The assessment of steady-state PKs took place at Day 28 (i.e., after 4 weeks treatment) in Group 1 and at Day 84 (i.e., after 12 weeks treatment) in Group 2.

In study 102, during the titration period (repeated BID oral administration of propranolol at 1 and 2 mg/kg/day) and at the target dose (3 mg/kg/day), concentrations of propranolol quantified before the morning administration (minimum plasma concentration, Cmin) increased with dose. In Group 1, median Cmin increased from 4.69 ng/mL at Day 7 to 22.4 ng/mL at Day 28, and in Group 2, median Cmin increased from 3.74 ng/mL at Day 7 to 10.1 ng/mL at Day 84. For 4-OH propranolol, most Cmin levels were below the limit of quantification (0.5 ng/mL) during the titration period, and at steady-state at weeks 4 (Group 1) and 12 (Group 2).

In study 102, geometric mean propranolol steady-state Cmax levels were similar in the two age groups (78.5 and 79.2 ng/mL in Groups 1 and 2, respectively), while median Tmax values were 2 hours in both groups. The geometric mean propranolol $AUC_{0\text{-}9h}$ was higher in the younger age group than in the older age group (455 and 373 ng.h/mL, respectively), while the weight adjusted geometric mean total clearance of propranolol was lower in the younger age group compared with older age group (2.71 and 3.27 L/h/kg, respectively). Based on geometric CV% values, inter-individual variability in the key propranolol PK parameters was notably higher in the older age group (72.4% to 103%) than in the younger age group (27.5% to 32.9%). Plasma

exposure to the 4-OH propranolol metabolite assessed by the AUC_{9h} accounted for ~6% and ~3% of the parent compound in the younger and older age groups, respectively.

The submission included a population PK (PPK) analysis, based on data from study 102, aimed at describing the PKs of propranolol in infants and evaluating the between-subject variability in the PKs of propranolol. The PPK analysis included 166 non-zero observations of propranolol concentrations from 22 patients (10 in Group 1 and 12 in Group 3) sampled twice during the titration period (1 to 2 mg/kg) and 6 times during the fixed-dose (target-dose 3 mg/kg) period. A one compartment PK model with a first order absorption of drug from an oral dosing compartment and a first order elimination from the central compartment described the PKs of propranolol in infants. Irrespective of age group, the between-subject variability for apparent plasma clearance (CL/F) was estimated to be approximately 40%.

In the PPK covariate analysis, a statistically significant effect of body weight on propranolol CL/F was identified, with CL/F increasing with body weight according to an allometric function. Body weight was shown not to affect the apparent volume of distribution (Vd/F). The geometric mean values of the individual predicted CL/F results using the final model were 16.3 L/h and 24.3 L/h for infants from Groups 1 and 2, respectively. The predicted geometric mean CL/F values for Groups 1 and 2 were similar to the observed geometric mean CL/F values (15.2 and 25.5 L/h, respectively). The similarity of the predicted and observed geometric means for CL/F indicates good fit of the final model to the observed data. The PPK analysis supports dosing based on mg/kg rather than on age. In a post hoc analysis, the simulated median Cmax (together with the 5th and 95th percentiles) was 67.1 ng/mL (25.9, 138) for the 9 hour interval between doses, and 61.2 ng/mL (23.6, 128) for the 12 hour interval between doses.

5. Pharmacodynamics

There were no studies in the submission investigating the potential pharmacodynamic effects of propranolol in infants with IH.

6. Dosage selection for the pivotal studies

Study 201 is the pivotal efficacy and safety study. The sponsor states that the choice of doses and regimens was discussed with the European Medicines Agency (EMA) and the United States (US) Food and Drug Administration (FDA). The propranolol doses used in the original observations of efficacy of propranolol in infants with IH were 2 or 3 mg/kg/day and the mean durations of propranolol treatment in the series were 6.1 and 6.8 months (Leauté-Labrèze et al., 2008; Sans et al., 2009). The EMA and FDA recommended that there should be at least a 3-fold difference in doses studied since an investigation of smaller dose increments (for example, 1 to 2 mg/kg/day and 2 to 3 mg/kg/day) was not appropriate considering the widely known logarithmic pharmacological sigmoid dose response curve for propranolol and its receptor. The EMA also recommended that different treatment durations should be studied. After further discussion, it was agreed that the study would investigate two doses (1 and 3 mg/kg/day) over two durations (3 and 6 months). The proposed doses were within the ranges of doses reported to be effective in the treatment of IH, and doses recommended for propranolol in cardiovascular diseases.

> **Comment**: The selection of dose for the pivotal study is considered to be acceptable. The approved Australian PI for propranolol recommends (as a guide) propranolol 0.25 to 0.5 mg/kg three or four times daily as required for children with “cardiac dysrhythmias, phaeochromocytoma, thyrotoxicosis”, and up to 1 mg/kg repeated three to four times daily as required for “Fallot’s tetralogy”, and 10 mg once or twice daily initially for “migraine” increasing to 2 mg/kg in divided doses.

7. Clinical efficacy

7.1. Clinical studies providing efficacy data

The submission included two studies providing clinical efficacy data for the oral propranolol HCl solution (3.75 mg/mL) for the treatment of IH in infants (see Table 12, below). The pivotal efficacy study was V00400 SB 2 01 (referred to as study 201 in this CER), and supportive efficacy data were provided by study 102 (the primary objective of this study was assessment of the steady state PKs of propranolol).

Table 12: Study design and data sets for clinical studies 102 and 201.

Study No.	Design	Sites	Treatment (BID)	Treatment Duration	Total no. of Patients[1]	Analyzed for Efficacy[1]
V00400 SB 1 02	Multicenter, open-label, repeated dose, PK study.	4 in France	V0400SB 3 mg/kg/day	3 months	23	23
V00400 SB 2 01	Multicenter, randomized, double-blind, placebo-controlled, multiple-dose, adaptive Phase II/III study to compare 4 regimens of propranolol (1 or 3 mg/kg/day for 3 or 6 months) to placebo.	55 in 16 countries world-wide	V0400SB 1 mg/kg/day followed by placebo	3 months + 3 months	98	41
			V0400SB 1 mg/kg/day	6 months	102	40
			V0400SB 3 mg/kg/day followed by placebo	3 months + 3 months	100	39
			V0400SB 3 mg/kg/day	6 months	101	**101**
			Placebo	6 months	55	**55**

BID: twice a day; up-titration from Day 0 to 14. Received at least one dose of study treatment (and analyzed for safety for both studies). Intent-to-treat data sets. Stage 1+2 without overrun for Study 201: 2 regimens in bold were the only 2 planned regimens to be compared together for the primary efficacy analysis.

In addition to the primary data analysis at W24 (presented in the submitted CSR), the pivotal study also includes an on-going open-label extension period for an additional 72-weeks, with visits at Weeks 26, 48, 72 and 96, for patients who have completed 24-weeks of double-blind treatment. During the extension period, data will be collected on maintenance of efficacy in patients no longer being treated, and on patients for whom IH has recurred and the investigator considers re-treatment to be appropriate. The Summary of Clinical Efficacy included preliminary W48 data on 323 patients who had entered the 72-week extension period. The 72-week extension is still ongoing and the sponsor states that full results will be available in Q2, 2014. In addition to the submitted CSR for the pivotal study the preliminary W48 data from the on-going 72-week extension period has been reviewed in this CER.

7.2. Pivotal efficacy study 201

7.2.1. Study design, objectives, locations and dates

7.2.1.1. Overview

Study 201 was a Phase II/III, multinational, multicentre, randomized, placebo-controlled, double-blind, adaptive clinical trial designed to compare four regimens of propranolol (1 or 3 mg/kg/day for 3 or 6 months) to placebo in infants with proliferating infantile hemangiomas (IHs) requiring systemic therapy. The date of first enrollment was 24 February 2010, the date of last completion (week 24) was 8 May 2012, and the date of the CSR was 20 December 2012. The CSR included the primary analysis of the study based on data up to week 24.

The study was undertaken in 56 recruiting centres in 16 countries (Australia, Canada, Czech Republic, France, Germany, Hungary, Italy, Lithuania, Mexico, New Zealand, Peru, Poland, Romania, Russia, Spain and the USA). The co-ordinating investigator was located in France (CHU de Bordeaux Hospital). The study was sponsored by Pierre Fabre Dermatologie, represented by

the Institut de Recherche Pierre Fabre (IRPF), Boulogne, France. The study was performed in compliance with the principles of Good Clinical Practices (CPMP/ICH E6 2002, CPMP ICH E11 2000), the Declaration of Helsinki and subsequent amendments, and relevant country specific regulations relating to clinical trials. Parents or guardians provided written informed consent to the participation of their child in the study, and were free to withdraw their child from the study at any time.

An Independent Data Monitoring Committee (IDMC) was established with the following aims: to safeguard the interests of the study participants, investigators and the sponsor; to assess the appropriateness of the required study sample size; to assess the safety and efficacy of the interventions; to select none, one or two regimens of propranolol for further study in Stage 2 of the study; and to monitor the overall conduct of the study and to protect its validity and credibility. The IDMC comprised two clinicians and a statistician (all located in the USA).

The main purpose of this study was to evaluate the efficacy of propranolol treatment versus placebo in infants with proliferating IH requiring systemic therapy. Each patient was treated with the assigned study treatment until W24 (or premature discontinuation). Follow-up until W96 without treatment is planned for patients completing W24. The primary statistical analysis was undertaken on the W24 results. The submitted CSR covered only the methods and results of the first 24 weeks period.

The objectives of the first party 24 weeks of the study were:

- Primary objectives - to identify the appropriate dose and duration of propranolol treatment, and to demonstrate its superiority over placebo, based on complete or nearly complete resolution of the target IH at Week 24 (W24).
- Safety objective - to document the safety profile of the four treatment regimens of propranolol for the treatment of IH in infants aged 1 to 5 months (35 to 150 days) at inclusion.

7.2.1.2. Description of overall study plan

The study was a Phase II/III, multinational, multicentre, randomized, double-blind, placebo-controlled, multidose, adaptive clinical trial in infants with proliferating IHs requiring systemic therapy. Patients were randomized in a 2:2:2:2:1 ratio to receive one of four propranolol regimens or placebo. Randomization was stratified by age and IH localization (2:2:2:2:1 randomization ratio and IH localization were added following protocol amendment PA02, which extended the study to include non-facial hemangiomas and replaced the initial randomization ratio of 1:1:1:1:1 and deleted stratification criteria based on continent).

There were 11 scheduled visits planned during the first 24-weeks of the study: 1 screening visit (screening and baseline visits could take place on the same day); followed by 10 visits starting at baseline visit (D0) from 0 to 14 days after the screening visit, then D7, D14, D21, W5, W12, W16, W20 and W24 (end of study treatment: EOT).

The adaptive design of this Phase II/III study was organized in two stages: Stage 1, corresponding to the Phase II part of the study, compared the four propranolol regimens to placebo and an interim analysis was undertaken to identify one or two suitable propranolol regimens for further investigation; and Stage 2, corresponding to the Phase III part of the study, aimed to compare the efficacy of the selected single or two propranolol regimens to placebo at W24 after all patients had completed to treatment to this time-point or had been prematurely withdrawn from treatment. The planned study design and the actual study design are summarized in the CSR.

7.2.1.2.1. Interim analysis at end of Stage 1

An interim analysis was carried out by the IDMC at the end of Stage 1 after the first 40:20 (propranolol:placebo) patients per treatment arm had completed their W24 visit or had been

prematurely withdrawn from study treatment. The interim analysis was undertaken to select one or two "best" regimens of propranolol for Stage 2 of the study, where the "best" regimen was defined as the most efficacious of all regimens with a good safety profile. Efficacy was evaluated based on blinded centralized independent qualitative assessments of the target IH photographs for each patient. A futility criterion was included in the case that none of the four regimens was identified as potentially efficacious for further investigations in Stage 2 of the study. IDMC members were required to recommend to the sponsor whether to continue the study with one or two propranolol regimens, to stop the study for futility or safety purpose, or to increase the study sample size.

Recruitment was to continue to the five treatment arms in a 2:2:2:2:1 ratio after the first 40:20 (propranolol:placebo) patients had been randomized per arm and until the "best" regimen or regimens had been selected or the study terminated prematurely. All patients recruited in Stage 1 of the study were to be followed up in Stage 2 of the study, but only patients in the "best" propranolol regimen of regimens were to be included in the Stage 2 primary efficacy analysis at W24.

A total of 190 patients were randomized into Stage 1 of the study, and 188 were treated. The interim analysis was conducted on these 188 patients and the IDMC recommendation was to continue the trial, with one single active arm (3 mg/kg/day for 6 months) being compared with placebo at W24, without sample size re-estimation and/or adjustment. Accrual in the study continued while the interim analysis was being undertaken, and the planned sample size was reached on 24 November 2011 (460 patients randomized), which occurred before the IDMC recommendations were made (6 January, 2012).

7.2.1.2.2. Primary analysis in Stage 2 at W24

The study database was locked for the "primary analysis" when all patients in both stages of the study had completed W24 or had been prematurely withdrawn. The primary analysis was conducted by the Independent Statistician. The results for the primary W24 analysis presented in the CSR were unblinded at an individual patient level to an exclusive list of study personnel. The blind was maintained for the monitoring teams and all investigational site staff (except the International Coordinating Investigator, as reviewer and signatory of the present report) until the end of the study.

> **Comment:** The sponsor stated that adaptive design methodology was considered for this study in light of the unsatisfied medical need for a first-line treatment of proliferating IH with a good benefit/risk profile, and the ever increasing use of off-label propranolol for the treatment of IH in the absence of soundly based treatment guidelines. The sponsor indicated that the study design was established in line with recommendations made by both the European Medicines Agency (EMA) and the United States (US) Food and Drug Administration (FDA) during a Parallel Scientific Advice (teleconference held between the EMA, the FDA, the sponsor and other experts on January 30, 2009). The study design was then discussed through a Special Protocol Assessment in the US and a Pediatric Investigation Plan (PIP) in Europe. The chosen comparator was placebo. The use of corticosteroids as an active comparator was considered to be unacceptable, as these drugs were not approved to treat IH in the USA and several European countries. In the Australian context, the use of a placebo control is considered to be appropriate, as there are no drugs approved in this country for the treatment of IH.
>
> The sponsor stated that when recruitment to the study started in February 2010, "it became very quickly apparent that the extensive off-label use of propranolol to treat IH and the numerous communications concerning the good benefit/risk profile of the product made recruitment even more difficult than originally anticipated". Consequently, following discussions between the sponsor, the EMEA and the FDA the

protocol was amended in an attempt to facilitate further recruitment (PA02, 27 October 2010). The major changes included: (i) changing the study randomization ratio from 1:1:1:1:1 to 2:2:2:2:1 in Stage 1 and from (1:)1:1 to (2:)2:1 in Stage 2 in order to reduce the number of patients assigned to the placebo arm; (ii) increasing the complete or nearly complete resolution success rate estimate for the 3 mg/kg/day 6 months regimen to 55%, and decreasing the corresponding success rate estimates to 20% for the 1 mg/kg/day 3 months regimen and to 30% for the 1 mg/kg/day 6 months regimen for the new sample size calculation; and (iii) enlarging the target population to include non-facial IH requiring systemic therapy.

7.2.2. Inclusion and exclusion criteria

A patient was considered eligible if all of the following inclusion criteria were met:

- Written informed consent for patient study participation and for the use of patient images had been obtained according to national regulations from the parent(s) or legal guardian(s) prior to performing any study procedures.
- The patient was 35 to 150 days old, inclusive, at inclusion (D0),
- A proliferating IH (target hemangioma) requiring systemic therapy was present anywhere on the patient's body except on the diaper area, with largest diameter of at least 1.5 cm.
- If required by national regulations, the patient was registered with a social security or health insurance system and/or the parent(s) or legal guardian(s) registered with a social security or health insurance system.

The exclusion (non-inclusion) criteria were extensive. In particular, the exclusion criteria included patients with one or more life-threatening IHs, function threatening IHs (e.g., those causing impairment or vision, or respiratory compromise caused by airways lesions), ulcerated IHs (whatever the localization) with pain and lack of response to simple wound care measures, and where the diagnosis of soft tissue tumour as IH was not clinically certain, particularly in the case of sub-dermal lesions. In addition, patients who had been previously treated for IH with any medical or surgical treatment were excluded.

There were a number of criteria for discontinuation of the study drug and for withdrawal from the study. However, investigators were required not to discontinue study treatment before W24 because of "good efficiency". Where possible, all infants were to be followed up to the end of the study (W96/EOS), including those who had discontinued treatment. Follow-up data following discontinuation were required, unless parental consent for collection of data was withdrawn. Randomized patients prematurely withdrawn or lost to follow-up were not to be replaced, but the safety data from these patients could be analyzed if at least one dose of study drug had been administered.

> **Comment**: The study included only infants with low-risk proliferating IHs. Patients with high-risk proliferating IHs, including life-threatening IHs, function threatening IHs, and complicated ulcerated IHs were excluded from the study.

7.2.3. Study treatments

Patients were randomized (double-blind) in a 2:2:2:2:1 ratio to receive treatment with an oral solution of, respectively:

- propranolol 1 mg/kg/day for 3 months (regimen 1);
- propranolol 1 mg/kg/day for 6 months (regimen 2);
- propranolol 3 mg/kg/day for 3 months (regimen 3);
- propranolol 3 mg/kg/day for 6 months (regimen 4);

- placebo for 6 months.

The oral solutions of propranolol HCl were 1.25, 2.50, and 3.75 mg/mL in strength, and included excipients of saccharin sodium, sodium propionate, hydroxyethylcellulose, strawberry flavour, vanilla flavour, citric acid monohydrate, and purified water. The placebo solution contained the excipients without propranolol hydrochloride.

Treatment duration was 6 months (24 weeks), consisting of 3 months (12 weeks) of propranolol followed by 3 months (12 weeks) of placebo (1 or 3 mg/kg/day 3 month regimens), or 6 months of propranolol (1 and 3 mg/kg/day 6 month regimens), or 6 months of placebo. For the two 3 mg/kg/day dose regimens (3 months and 6 months), propranolol was titrated using 1 mg/kg/day increments during the first 3 weeks (i.e., D0 to D6, 1 mg/kg/day; D7, increase to 2 mg/kg/day; D14, increase to 3 mg/kg/day with this dose then being maintained through to 3 or 6 months). In the placebo 6 months regimen and the 1 mg/kg/day regimens, titration with placebo (i.e., dummy titration) was used in order to maintain the double-blind. No tapering of dose was planned at the end of the W24 treatment phase.

Study treatment was administered orally, twice daily (morning and late afternoon), immediately prior to, during, or after a meal (in case of vomiting the current dose was not re-administered). The second daily dose of the study treatment was administered in the late afternoon to reduce the risk of hypoglycaemia during the night while infants and parents/guardians were most likely to be asleep. The study drug was administered using a graduated pipette, without dilution. All patients received the same volume of product (0.4 ml/kg/dosing, morning and late afternoon), whatever the assigned treatment regimen. Doses were adjusted by the concentration of the administered products. The required volume of study drug was calculated by the investigator at each visit and followed by the parents/guardians until the next visit. The protocol specified two methods of calculating the dose, but the investigator was to use the same chosen method for a patient throughout the study.

At D0 and at each dose increase (or dummy increase) at D7 and D14, the first administration of the new or dummy dose of study drug was carried out at the study site so that a specific safety assessment could be performed. Temperature, heart rate, blood pressure, respiratory rate and pulmonary auscultation were measured before first administration of the study drug and then every hour (±30 min) for four hours after first administration. Blood glucose concentration was measured by pin-prick method, and an ECG was performed at 120±30 minutes before the first administration of the study drug and at 240 ±30 minutes after the first administration. The protocol specified actions to be taken based on heart rate, blood pressure and glycaemia.

ECGs were assessed by an independent physician during the treatment period in order to reduce the risk of treatment unblinding (e.g., due to bradycardia). Based on the ECG assessment, the independent physician advised the investigator whether or not it was safe to continue treatment with the study drug.

If a potential safety issue was identified during the D0, D7 or D14 evaluations, study treatment could be discontinued according to the protocol specified recommendations. The patient continued to be monitored for safety on-site beyond the scheduled 4 hours if safety issues persisted. In the absence of any abnormalities, the patient was allowed to leave the site and continue study treatment at home according to the protocol.

On D0, parents/guardians were instructed on administration of the study drug. Before leaving the study site, they received a letter explaining safety monitoring to be undertaken during the treatment phase. The letter recommended actions to be taken under different scenarios, including, but not limited to illness, asthenia (tiredness), mood changes, difficulty waking up, hypotonia (muscle weakness and fatigability), difficulty feeding, paleness, respiratory difficulty. Parents/guardians were advised to discontinue study treatment and contact the study doctor (or another doctor) immediately in the case of any safety issues. Parents/guardians were also

provided with a patient diary to record any adverse events in between study visits and to record treatment administrations.

In case of temporary treatment discontinuation, study treatment was to be reintroduced according to the following scheme: for 2 days, administration of half of the dose given before the temporary discontinuation, then administration of the full dose from the 3rd day onwards. In case of medical contra-indication (safety reason), the treatment was not reintroduced and was recorded as being prematurely discontinued.

The exclusion criteria listed medications prohibited for the patient (and/or mother if she was breastfeeding the patient) within the 14 days preceding randomization, and medications prohibited for the patient at any time during the study. If prohibited medications were considered medically necessary for the patient (and/or the mother if she was breastfeeding the patient) during the 6 months treatment period, study treatment had to be discontinued and the medication recorded in the eCRF. All treatments of IH, including any surgical and/or medical procedures, were prohibited prior to and during the study. All medications, other those specified as prohibited, were authorized.

The study included appropriate procedures for assessing treatment compliance based on the weight of the treatment bottles of the investigational product provided to the parents or guardians. One hundred percent (100%) compliance corresponded to the administration of 0.8 ml/kg/day of the investigational product throughout the study treatment period. The bottles (used/unused) were weighed at each relevant post-baseline visit by the person in change of treatment management at the individual study centres. The investigator undertook a qualitative evaluation of compliance (poor/average/good) at each visit, based on numbers of days of treatment missed (see Table 13, below). In the case of poor or average compliance, the investigator recorded the reasons in the eCRF.

Table 13: Study 201 - Investigator's qualitative assessment of compliance.

Compliance Visit	Good	Average	Poor
D7, D14, D21	less than 1 day of treatment missed	less than 2 days of treatment missed	at least 2 days of treatment missed
W5	less than 3 days of treatment missed	less than 6 days of treatment missed	at least 6 days of treatment missed
W8	*less than 4 days of treatment missed*	*less than 8 days of treatment missed*	*at least 8 days of treatment missed*
W12, W16, W20 and W24	*less than 6 days of treatment missed*	*less than 11 days of treatment missed*	*at least 11 days of treatment missed*

7.2.4. Efficacy variables and outcomes

7.2.4.1. Primary efficacy endpoint

The primary efficacy criterion was the evolution of the target IH from baseline to W24. The binary primary endpoint (success/failure) was evaluated for each patient based on blinded centralized independent qualitative assessments of W24 photographs of the target IH compared with baseline.

Treatment success was defined as a centralized assessment of complete or nearly complete resolution of the target IH at W24 compared with baseline, where nearly complete resolution was defined as a minimal degree of telangiectasis, erythema, skin thickening, soft tissue swelling and/or distortion of anatomical landmarks. The sponsor worked in association with an external IH expert advisory board to clearly define the criteria for nearly complete resolution.

At least two digital photographs of the target IH (using protocol specified standardized procedures) were to be taken by the on-site investigators for each patient at each scheduled

study visit from D0 to W96. The first photograph (Photograph 1) was taken with the image plane parallel to the target IH (front-on view) and the second photograph (Photograph 2) with the image plane at a different angle to that of the first photograph (side-on view) so that the thickness of the lesion could be clearly visualized.

The two photographs comprised the "group", and served the following purposes. Photograph 1 was used to identify the target IH, to qualitatively assess the target IH evolution between visits and to quantify the size and the colour of the target IH at baseline, W12 and W24. In each batch of photographs for centralized assessment of complete or nearly complete resolution, comparison time-points were mixed (i.e., readers were not aware if the comparison was between baseline or W12 or W24). Photograph 2 was used to qualitatively assess the target IH evolution between visits.

All photographs included a colour chart to enable colour and size calibration and a patient/visit identification card. Photographs (identified by patient-visit and front-on or side-on view) were uploaded to the study eCRFs at each site and sent to a central database where the system grouped them by patient-visit (two photographs per group). The groups of photographs at baseline (D0), W5, W8, W12, W16, W20, W24, W36 and W48 were paired by patient-visits and masked ready for two types of centralized qualitative assessments. Baseline was paired with W12, W24, W36 and W48 for Type 1 assessments (i.e., complete/nearly complete resolution of the target IH), and baseline, W5, W8, W12, W16 and W20 were paired with W5, W8, W12, W16, W20 and W24, respectively, for Type 2 assessments (i.e., 3-point score of improvement, stabilization, or worsening of the target IH)

Type 1 and Type 2 combined image assessment sessions were carried out by two blinded, independent, trained readers (different from the IDMC readers) on batches of no more than 30 paired groups of photographs of the same type. Paired photographs were presented in a random order to each reader for Type 2 assessments. Readers also evaluated the overall quality of the photographs for each combined image evaluation on a three-level scale (unevaluable, poor or good).

After paired sessions were carried out, the two independent readers met to discuss discrepancies between the evaluations of the same type for the same paired groups of photographs. The consensus reached for the discrepant evaluations was documented and considered as final for use in all applicable efficacy analyses.

7.2.4.1.1. Investigator's on-site qualitative assessments

The investigators made on-site qualitative assessments of the target IH evolution at each scheduled post-baseline visit compared to the previous scheduled visit (improvement, stabilization or worsening), and compared to baseline (complete/nearly complete resolution). For these on-site assessments, nearly complete resolution was defined as a minimal degree of telangiectasis, erythema, skin thickening, soft tissue swelling or distortion of anatomical landmarks and/or a minimal palpable component.

In the case of complete resolution of the target IH, investigators were asked to assess the level of sequelae (none, minimal or marked). Complete resolution with minimal sequelae was defined as minimal telangiectasis, macular discolouration and/or textural change, and complete resolution with marked sequelae was defined as marked textural change with or without distortion of anatomical landmarks or skin contours.

At all scheduled visits, on-investigators carried out other clinical assessments of the target IH (colour intensity, tenseness, superficial component, deep component, distortion of local anatomical landmarks). At each scheduled post-baseline visit, investigators also assessed non-target IHs in terms of complete resolution. In the case of complete resolution of all non-target IHs, investigators assessed the worst level of sequelae (none, minimal or marked). The use of any invasive procedures on the target and/or non-target IHs during the study was also documented in the eCRF.

7.2.4.1.2. Parents/guardians on-site qualitative assessments

The parents/guardians made on-site qualitative assessments of target IH evolution (improvement, stabilization or worsening) at each scheduled post-baseline visit compared with the previous scheduled visit.

7.2.4.1.3. Assessment of target IH complications

Target IH complications (functional impairment, ulceration and/or hemorrhaging) were assessed by the investigator at all visits using protocol specified grading criteria.

> **Comment**: The photographic criteria used to define complete or nearly complete resolution of IH has not been validated using the physical appearance of the lesion as assessed by clinical examination as the reference standard. Consequently, while assessment of the photographs using the specified criteria for complete or nearly complete resolution might be internally valid as regards consistency of outcome between assessors, the specified photographic criteria might be inconsistent with complete or nearly complete resolution determined by clinical examination. It is considered that complete or nearly complete resolution determined by clinical examination should be the "gold standard" against which the photographic criteria should be judged.
>
> The criterion for success was determined by the sponsor after discussions with the EMA and the FDA. The criterion for success (complete or nearly complete resolution at W24 compared to baseline) was included in protocol amendment number PA01, prior to any patient inclusion in the study. Initially, the sponsor proposed to consider overall stabilization/improvement of IH by W24 as a treatment success, as it considered that the goal of existing therapies (such as corticosteroids) had always been to stabilize IH growth. The EMA then suggested that improvement alone should be considered as a treatment success, and the consensus was to base the primary criterion on centralized blinded assessments of standardized photographs. The FDA then requested that the benefit of treatment should be based on a more stringent criterion such as full or rapid substantial resolution of IH. This led the sponsor and the external IH expert advisory board members to carry out an extensive review of recent data available from the use of off-label propranolol and resulted in the current primary criterion. However, it is considered that complete or nearly complete clinical resolution of IH is a particularly stringent endpoint to obtain. Clinically, it might have been more realistic for the primary criterion to have been improvement of the lesion rather than complete or nearly complete resolution.
>
> The sponsor considered that a quantitative assessment of change in size was not appropriate as a stand-alone primary efficacy criterion since IH does not necessarily reduce in size initially. The sponsor commented that the earliest signs of regression of a hemangioma are a fading of the colour of the lesion from a bright red to a dull red or pink, followed by the development of a grey-white hue at the centre of the lesion that spreads to the periphery, and a reduction in lesion tenseness (Sundine and Wirth, 2007).
>
> The sponsor stated that the readability and reproducibility of photographs was ensured by the use of a highly standardized procedure (summarized in the protocol) and the thorough training of investigators. Despite these standardized procedures, there inevitably remained several factors obstructing some quantitative aspects of photograph reproducibility, such as IH size and colour, particularly in infants who may not have stayed still for the photo or who would grow significantly over the 24-week period. For these reasons, quantitative assessments of size and colour density were only included as secondary efficacy endpoints. To maximize the objectivity and reproducibility of qualitative and quantitative central reading of the photographs, stringent reading procedures were put in place including, reader training, inter-reader

agreement assessment, intra-reader agreement assessment and adjudication sessions to resolve inter-reader discordances. The submitted data (electronic copy) included copies of the colour photographs (front-on and side-on) used to assess efficacy. The photographs included those taken at baseline and those taken post-baseline at weeks 5, 8, 12, 16, 20, and 24. The photographs are considered to be of good quality.

7.2.4.2. Secondary efficacy endpoint

The secondary efficacy criterion was success/failure (binary endpoint) based on the investigator's on-site qualitative assessment of complete resolution of the target IH at W48, where a treatment success was defined as complete resolution of the target IH without sequelae or with minimal sequelae at W48. This (post-W24) endpoint was not analyzed in the submitted CSR, and data collection relevant to this endpoint appears to be on-going.

7.2.4.3. Other secondary and exploratory efficacy endpoints

7.2.4.3.1. Centralized assessments of target IH:

- success/failure (binary endpoint) at W12, W36, and W48 compared to baseline (as defined for the primary efficacy criterion); and
- time to first sustained complete/nearly complete resolution (W12, W24, W36 or W48 compared to baseline).

7.2.4.3.2. Endpoints based on independent blinded Type 2 assessments of improvement stabilization or worsening of the target IH:

- endpoints for target IH evolutions based on a 3-point scale (improvement, stabilization, worsening) between paired patient visits (W5, W8, W12, W16, W20 or W24 compared to baseline, W5, W8, W12, W16 or W20, respectively);
- global improvement was also computed on the W5-W24 period (Yes/No), a binary endpoint of improvement between at least one pair of visits, without any assessments of worsening between the paired visits versus failure to improve (worsening between at least one pair of visits or stabilization between all paired visits). The definition of treatment failure ensured that a worsening of IH between, for example, W12 and W24 could be detected even if the IH was still in an improved state at W24 compared to baseline; and
- time to first sustained improvement (first improvement after which there was no worsening) of the target IH based on Type 2 (improvement, stabilization, or worsening) centralized qualitative assessments of paired patient-visits (W5, W8, W12, W16, W20 or W24 compared to baseline, W5, W8, W12, W16 or W20, respectively).

7.2.4.3.3. Investigator on-site qualitative assessments at each scheduled post-baseline visit compared with baseline:

- categorical endpoints for complete/nearly complete resolution of target IH, where nearly complete resolution was defined as a minimal degree of telangiectasis, erythema, skin thickening, soft tissue swelling, distortion of anatomical landmarks and/or a minimal palpable component;
- categorical endpoints for complete resolution (3-point scale: no sequelae; minimal sequelae defined as minimal telangiectasis, macular discoloration and/or textural change; marked sequelae defined as marked textural change with or without distortion of anatomical landmarks or skin contours);
- time to first sustained complete/nearly complete resolution; and
- time to first sustained complete resolution without sequelae or with minimal sequelae.

7.2.4.3.4. Separate investigator and parents/guardians on-site qualitative assessments of paired consecutive patient-visits (each scheduled post-baseline visit compared with the previous scheduled visit):

- categorical endpoints for target IH evolution (3-point scale: improvement, stabilization, worsening); and
- time to first sustained improvement (first improvement after which there is no worsening).

7.2.4.3.5. Other investigator on-site qualitative assessments at each scheduled post-baseline visit:

- categorical endpoints based on assessments of target IH complications: functional impairment/ ulceration/haemorrhaging;
- categorical endpoints based on qualitative assessments of complete resolution of non-target facial IH and non-facial IH at each scheduled post-baseline visit based on 3-point scale (no sequelae, minimal sequelae, marked sequelae as defined above); and
- categorical endpoints based on whether or not invasive procedures were carried out during the study on the target/non-target facial/non-facial IH.

7.2.5. Randomization and blinding methods

Randomization was centralized through an interactive voice recording system (IVRS). The IVRS was called at D0 to assign a unique treatment number to the patient that would provide the patient with sufficient investigational product (IP) for the full treatment period (from D0 to W24).

Randomization to Stage 1 was to one of five treatment arms (ratio 2:2:2:2:1). The randomization technique was stratified block randomization, with block size of 9. The stratification factors were: age (35-90 days and 91-150 days old at randomization), and IH localization (facial and non-facial).

Randomization to Stage 2 was planned to be done in a (2:)2:1 ratio with the same stratification factors as those used in Stage 1 and a block size of 3 (if three arms were dropped) or 5 (if two arms were dropped). However, randomization to Stage 2 was not implemented as the targeted sample size was reached before the IDMC made its recommendation on the propranolol regimen for primary analysis at W24 in in Stage 2.

The study was double-blinded. The measures undertaken to maintain blinding have been examined and are considered appropriate. The interim analysis was undertaken by an independent statistician and the IDMC to avoid unblinding of the study personnel. The primary W24 analysis was undertaken by an independent statistician. After the study database had been locked for the W24 analysis, the study results were unblinded (at an individual patient level) to an exclusive list of study personnel so that the primary CSR could be written and submitted to regulatory authorities. In order to continue to protect the integrity of the study and the validity of efficacy assessments from W36 to W96/EOS, the treatment blind will be maintained for the sponsor's monitoring/clinical team and all investigational site staff (except the international coordinating investigator, as reviewer and signatory of the submitted CSR) until the final study database is locked at the end of the study. Procedures were specified for unblinding in the case of emergency.

7.2.6. Analysis populations

The randomization data set includes all patients randomized by the IVRS.

The intention-to-treat (ITT) data set includes all randomized patients in Stage 1 and all patients in Stage 2 randomized to placebo or the selected regimen of propranolol and having received at

least one dose of study. This is the primary efficacy analysis data set. Patients were analyzed according to treatment assigned by the IVRS.

The per-protocol (PP) data set is a subset of the ITT data set and includes patients without major protocol deviations, except for major deviation for prohibited treatments (after randomization and before the W24 evaluation) that may be used to treat IH.

The ITT with overrun data set included all randomized patients in Stage 1 and all randomized patients in Stage 2 (including the overrun patients) who received at least one dose of study therapy. The overrun patients are the subgroup of patients in Stage 2 randomized in the unselected regimens.

The safety data set included all randomized patients who received at least one dose of study therapy during the first or second stage of the study. The safety analyses were performed in this data set, and patients were analyzed on treatment actually received.

The primary efficacy analysis ITT data set (all patients randomized in Stage 1 and all patients in Stage 2 in the selected regimens without over-run) comprised 55 patients in the placebo 6 month regimen and 101 patients in the 3 mg/kg/day 6 months regimens. These two treatment arms were the only arms compared in the primary efficacy analysis (W24 analysis). The details of all analysis data sets are provided below in Table 14.

Table 14: Study 201 - Number of randomized patients in each data set analyzed; randomized data set.

Stage Population	Placebo (N = 55)	V0400SB 1mg/kg/day 3mths (N = 99)	V0400SB 1mg/kg/day 6mths (N = 103)	V0400SB 3mg/kg/day 3mths (N = 101)	V0400SB 3mg/kg/day 6mths (N = 102)	Total (N = 460)
Stage1	25 (45.5%)	41 (41.4%)	41 (39.8%)	40 (39.6%)	43 (42.2%)	190 (41.3%)
Intention-to-treat	25 (45.5%)	41 (41.4%)	40 (38.8%)	39 (38.6%)	43 (42.2%)	188 (40.9%)
Per protocol	23 (41.8%)	38 (38.4%)	38 (36.9%)	37 (36.6%)	36 (35.3%)	172 (37.4%)
Safety	25 (45.5%)	41 (41.4%)	40 (38.8%)	39 (38.6%)	43 (42.2%)	188 (40.9%)
Stage2	30 (54.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	59 (57.8%)	89 (19.3%)
Intention-to-treat	30 (54.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	58 (56.9%)	88 (19.1%)
Per protocol	30 (54.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	57 (55.9%)	87 (18.9%)
Pooled (without overrun)	55 (100.0%)	41 (41.4%)	41 (39.8%)	40 (39.6%)	102 (100.0%)	279 (60.7%)
Intention-to-treat	55 (100.0%)	41 (41.4%)	40 (38.8%)	39 (38.6%)	101 (99.0%)	276 (60.0%)
Per protocol	53 (96.4%)	38 (38.4%)	38 (36.9%)	37 (36.6%)	93 (91.2%)	259 (56.3%)
Pooled (with overrun)	55 (100.0%)	99 (100.0%)	103 (100.0%)	101 (100.0%)	102 (100.0%)	460 (100.0%)
Safety	55 (100.0%)	98 (99.0%)	102 (99.0%)	100 (99.0%)	101 (99.0%)	456 (99.1%)

7.2.7. Sample size

The estimated success (complete/nearly complete resolution at W24) rates for the different regimens used for the sample size calculations were: 10% for placebo; 20% for 1 mg/kg/day 3 months; 30% for 1 mg/kg/day 6 months; 40% for 3 mg/kg/day 3 months; and 55% for 3 mg/kg/day 6 months. The success rate of 10% for placebo at W24 was a conservative estimate based on the natural history of IH (Bowers et al., 1960).

The targeted sample size was 450 (100:50 for propranolol:placebo): Stage 1 (n=180 consisting of 20 in the placebo arm and 40 in each of the propranolol treatment arms; Stage 2 + over-run (n=270 patients consisting of 30 in the placebo arm, 60 in the 1-2 selected propranolol treatment arms, and 40 to 60 the unselected [over-run] propranolol treatment arms).

The actual number of patients randomized in the study was 460: Stage 1 (n=190 consisting of 25 in the placebo arm and 40 to 43 in each of the propranolol arms; Stage 2 + over-run (n=270 patients consisting of 30 in the placebo arm, 59 in the selected propranolol treatment arm, and 58 to 62 in the unselected [over-run] propranolol treatment arms).

Assuming that only the most efficacious regimen was selected at the interim analysis, the sample size was calculated to achieve > 98% power (without taking into consideration the futility boundary) for an overall one-sided type I error rate of α=0.005.

The CPMP Points to Consider on Application with One Pivotal Study (CPMP/EWP/2330/99 2001) states that, for such an application, "statistical evidence considerably stronger than p<0.05 is usually required, accompanied by precise estimates of treatment effects". As such, the sponsor selected a one-sided significance level of 0.005 to provide stronger evidence of a successful treatment effect in the case of superiority of propranolol that would support marketing authorization approval based on a single pivotal phase III study.

7.2.8. Statistical methods

7.2.8.1. Primary efficacy endpoint

The primary efficacy analysis compared the complete/nearly complete recovery rate, based on centralized assessment at W24, for the selected propranolol regimen (i.e., 3 mg/kg/day 6 months) and placebo in the ITT data set.

The objective was to test the superiority of the selected regimen (null hypothesis of $H_{0,sel}$: $\theta \leq 0$ against the alternate hypothesis of $H_{1,sel}$: $\theta > 0$ using the methodology described by Posch et al (2005), for an adaptive confirmatory design with a single selection at an interim analysis. This methodology guarantees that the family-wise type I error rate is maintained at the nominal level of 0.005.

If the primary efficacy endpoint for a patient who completed the 24-week treatment period was missing for any reason (e.g., unevaluable photographs at baseline and/or W24), it was replaced by the investigator's on-site assessment of complete/nearly complete resolution at W24 and the patient was excluded from the sensitivity analysis of the primary efficacy analysis based on the PP data set. If both the primary efficacy endpoint and the investigator's assessment at W24 were missing, the patient was considered to be a treatment failure for ITT analysis, and the patient was excluded from the PP analysis.

7.2.8.2. Sensitivity and adjusted analysis of the primary endpoint

Sensitivity analyses of the primary endpoint were carried out on the PP data set, and on the ITT data set using a re-defined primary efficacy end-point (see review of primary efficacy end-point for definition of this endpoint). Logistic regression analysis of the primary endpoint in the ITT data set was also undertaken, using a model adjusted for the stratification factors and the randomization ratio.

7.2.8.3. Secondary efficacy endpoints and exploratory endpoints

None of the secondary efficacy endpoints analyzed at W24 were planned to be part of the overall type I error control. Consequently, all of these secondary endpoints are exploratory and all the p-values for all analyses of these endpoints are nominal rather than confirmatory. The statistical analysis plan (SAP) stated that a combination test computed exactly in the same way as for the primary endpoint will be used to analyze success/failure based on the investigator on-site qualitative assessment of complete resolution of the target IH at W48 (i.e., key secondary efficacy endpoint).

7.2.9. Participant flow

Overall, 512 patients were screened for entry into the study. Of the 512 screened patients, 510 (99.6%) had a signed informed consent form. Of the 510 patients screened and with a signed consent form, 460 (90.2%) were randomized, and 456 (89.4%) were treated (i.e., received at least one dose of study medication). Of the 4 randomized but untreated patients, the reasons for not receiving treatment were parents decision (n=2), and no treatment available at the site (n=2). Of the 510 patients screened and with a signed informed consent form, 50 (9.8%) were considered to be screening failures for one or more reasons (12 parent/guardian decision, 26 at least one inclusion/exclusion criterion not met, 15 for other reasons). The reasons for early treatment in the randomized data set are summarized below in Table 15.

Table 15: Study 201 - Reasons for premature treatment discontinuation; randomized data set.

Reasons for treatment discontinuation	Placebo (N = 55)	V0400SB 1 mg/kg/day 3mths (N = 99)	V0400SB 1 mg/kg/day 6mths (N = 103)	V0400SB 3 mg/kg/day 3mths (N = 101)	V0400SB 3 mg/kg/day 6mths (N = 102)	Total (N = 460)
Erroneous inclusion according to the protocol	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Treatment intolerance	0 (0.0%)	2 (2.0%)	0 (0.0%)	2 (2.0%)	0 (0.0%)	4 (0.9%)
Treatment inefficacy	32 (58.2%)	30 (30.3%)	7 (6.8%)	25 (24.8%)	9 (8.8%)	103 (22.4%)
Safety reason not linked to the protocol therapy	2 (3.6%)	1 (1.0%)	1 (1.0%)	3 (3.0%)	1 (1.0%)	8 (1.7%)
Patient's parent(s) or guardian(s) decision	7 (12.7%)	9 (9.1%)	6 (5.8%)[(1)]	13 (12.9%)[(2)]	4 (3.9%)	39 (8.5%)
Other	1 (1.8%)	5 (5.1%)[(3)]	2 (1.9%)	4 (4.0%)	2 (2.0%)[(4)]	14 (3.0%)
Overall	36 (65.5%)	36 (36.4%)	15 (14.6%)	36 (35.6%)	14 (13.7%)	137 (29.8%)

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

Comment: The primary efficacy endpoint analysis compared complete/nearly complete resolution of IH at W24 in the placebo and propranolol 3 mg/kg/day 6 months treatment arms. The percentage of patients who prematurely discontinued treatment was particularly high in the placebo arm compared with the 3 mg/kg/day 6 months arm (65.5%, 36/55 vs 13.7%, 14/102). The major reason for the marked imbalance in the percentage of patients discontinuing treatment prematurely in the placebo and 3 mg/kg/day 6 months arms was "treatment inefficacy" (58.2%, 32/55 vs 8.8%, 9/102). The major reason for premature discontinuation in each of the five treatment arms was "treatment inefficacy". Only 4 patients prematurely discontinued due to "treatment intolerance", all within the first week of treatment, including 2 in the 1 mg/kg/day 3 months arm (1 x long QTc at D7; 1 x AV block at D0) and 2 in the 3 mg/kg/day 3 months arm (1 x tiredness between D0 and D6, and 1 x bradycardia at D6).

7.2.10. Major protocol violations/deviations

In the randomized data set (n=460), at least one major protocol was reported in 31 (61.7%) patients: 2 (3.6%) in the placebo arm; 8 (8.1%) in the 1 mg/kg/day 3 months arm; 6 (5.8%) in the 1 mg/kg/day 6 months arm; 5 (5.0%) in the 3 mg/kg/day 3 months arm; and 10 (9.8%) in the 3 mg/kg/day 6 months arm. The most commonly reported major protocol deviations (groups) occurring in ≥ 1% of the total randomized population were: primary efficacy endpoint deviations, 2.6%, 12 patients; and compliance/exposure deviations, 2.4%, 11 patients. Overall, major protocol deviations were reported most commonly in the 3 mg/kg/day 6 months treatment arm. However, it is considered that the differences in the major protocol deviations between the 5 treatment arms are unlikely to have compromised the primary efficacy analysis. The major protocol deviations in the randomized data set are summarized in the CSR.

The overall mean (SD) treatment compliance over the duration of the study, as measured by weighing the returned bottles, was 97.0% (12.1%) with a range of 20% to 133%, and no evidence of differences in the 5 treatment arms (96% to 99%). According to the investigators' evaluation, the overall global compliance over the duration of the study was rated as good in 96.2% of patients, and ranged from 94.5% to 99.0% in the 5 treatment arms.

7.2.11. Baseline data

7.2.11.1. Demographics

Overall, for all patients treated (safety data set) the randomization strata and other baseline characteristics were well balanced across treatment regimens.

Of the total number of treated patients (n=456), 71.3% were female, with no obvious difference in sex ratio between randomized arms, although only 21% of the patients were male in the 3 mg/kg/day 3 months arm, compared with 30.6% to 31.4% in the other 4 arms. The mean (SD) birth weight was 3.0 (0.7) kg (range: 0.7, 5.4 kg).

The mean (SD) age at randomization was 103.9 (31.1) days, ranging from 35 to 156 days. The proportion of patients in the younger age group (35-90 days) was 36.6% compared with 63.4% in the older age group (> 90 days). Of the total number of treated patients (n=456), 26.8% had been born prematurely, ranging from 21.6% (1 mg/kg/day 3 month arm) to 34.5% (placebo arm).

The most frequent Race/Ethnicity combination was White/Non-Hispanic (72.1%), followed by White/Hispanic (7.2%) and Other/Hispanic (7.2%), American Indian-Alaska Native/Hispanic (3.3%), Other/Non-Hispanic (3.1%) and More than one race/Non-Hispanic (2.6%). All the other Race/Ethnicity combinations included less than 10 patients. The majority of patients were from Western Europe (51.5%). Of note, 7.0% (n=32) of patients were from Australia, and 1.1% (n=5) from New Zealand.

7.2.11.2. Medical history reported in at least 2 patients

The most frequently reported medical history preferred terms in treated patients (n=456) were: jaundice (+ jaundice neonatal) in 22 (4.8%) patients; neonatal respiratory distress syndrome, prematurity and respiratory distress, in 8 (1.8%) patients each; anaemia in 7 (1.5%) patients; infantile colic, circumcision, conjunctivitis, constipation and GORD, in 5 (1.1%) patients each; hyperbilirubinaemia neonatal, hypoglycemia neonatal and infantile apneic attack in 4 (0.9%) patients each; hyperglycemia, nasopharyngitis, bradycardia, bronchiolitis, dyspepsia, fetal growth restriction, hyperbilirubinaemia and hypoglycemia in 3 (0.7%) patients each.

7.2.11.3. Concomitant disease reported in at least 2 patients.

The most commonly reported diseases occurring in ≥ 1.0% of treated patients (n=456) were: anaemia (18, 3.9%); atrial septal defect (17, 3.7%); GORD (13, 2.9%); infantile colic (9, 2.0%); constipation (7, 1.5%); eczema (6, 1.3%); ALT increased (5, 1.1%); AST increased (5, 1.1%); and umbilical hernia (5, 1.1%).

7.2.11.4. Baseline characteristics of the target IH

The baseline characteristics of the target IH were similar for the 5 treatment. In treated patients (n=456), 318 (69.7%) had a facial IH and 138 (30.3%) had a non-facial IH. The frequency of facial IH varied between 64% (64 patients) in the 3 mg/kg/day 3 months arm and 72.7% (40 patients) in the placebo arm. Despite the protocol amendment to extend the inclusion criteria to include non-facial IHs, more than two thirds of patients had facial IHs.

The mean (SD) age of patients at the onset of IH was 15.5 (21.7) days, ranging from 12.9 (15.4) to 17.0 (29.2) days across the five treatment arms. In 98.5% (n=449) of patients, IH onset was before 90 days of life. The mean (SD) time from IH onset to entry into the study was 88.4 (35.9) days, ranging from 85.8 (38.2) to 91.7 (35.9) days across the five treatment arms.

The majority of the IHs were localized (406 patients, 89.0% overall, ranging from 87.3% to 90.8% across the 5 treatment arms). Segmental IHs were reported in 25 (5.5%) patients (ranging from 3.6% to 7.0% across the 5 treatment arms), and 25 (5.5%) IHs were of indeterminate subtype (ranging from 4.9% to 9.1% across the 5 treatment arms).

The most frequent primary anatomical locations of the target IH, by descending order of frequency, were: cheek (59, 12.9%); forehead, 49 (49, 10.7%); perioral, lower or upper lip, (41, 9.0%); scalp (39, 8.6%); peri-ocular region, (33, 7.2%); nasal tip (28, 6.1%); chest (25, 5.5%); other localizations (22, 4.8%), with the most frequent other localization being the temple (4,

0.9%); forearm (20, 4.4%); neck (18, 3.9%); abdomen (16, 3.5%); back (15, 3.3%); nasal sidewall (14, 3.1%); ear (11, 2.4%); glabella (11, 2.4%); and shoulder (9, 2.0%). Other localizations were observed with frequencies of less than 2%.

In 89.5% of patients (n=408), no secondary localization of the primary IH was reported. Only 6 patients (1.3%) had anomalies associated with the target IH: PHACES without CNS involvement in 1 patient and other anomalies in 5 patients (2x no precision; 1x small scab; 1x very firm and subcutaneous; 1x bluish purple target IH with coarse telangiectasia, not red).

Most of the target IHs presented a superficial component, consisting of a marked elevation in 157 patients (34.4%), a moderate elevation in 148 patients (32.5%) or a slight elevation in 114 patients (25.0%); the IH was flat in only 37 patients (8.1%). The target IH colour was most frequently bright red (in 223 patients, 49.1%) or dull red (in 146 patients, 32.2%).

A deep component was definitely present in 241 patients (52.9%), possibly present in 85 patients (18.6%) and absent in 130 patients (28.5%). The IH was more frequently firm (265 patients, 58.1%) rather than soft (178 patients, 39.0%). Distortion of anatomical landmarks were reported in 45.8% of the cases, slight in 130 patients (28.5%) and marked in 79 patients (17.3%).

The centralized quantitative assessment of the IH at baseline (safety data set) is provided in the dossier. The mean (SD) surface area of the target IH was 4.61 (4.88) cm^2, with a highly skewed distribution towards lesions with a lower surface area (median 2.7 [Q1 = 1.35, Q3 = 6.40]; and range 0.37 to 29.10 cm^2). The mean (SD) maximal diameter of the target IH was 2.41 cm (1.22), ranging from 2.39 (1.09) to 2.87 (1.77) cm across the 5 treatment arms. The mean (SD) colour of the target IH was 19.37 (7.87) dE*2000, ranging from 18.90 (6.71) to 20.37 (8.10) across the 5 treatment arms. The dE*200 (Delta E*ab, year 2000 version) was the unit for the IH colour measurement, and was performed according to CIE LAB (Commission internationale de l'éclairage) colour space values.

7.2.12. Results for the primary efficacy outcome

The results for the primary analysis of complete or nearly complete resolution of the IH at W24, centralized assessment of photographs, in the placebo and propranolol 3 mg/kg/day 6 month treatment arms are summarized below in Table 16.

Table 16: Study 201 - Primary endpoint complete/nearly complete resolution of IH at week 24; ITT data set

Complete/ Nearly complete	Placebo (n=55)	Propranolol 3 mg/kg/day 6 months (n=101)	p-value
yes	2 (3.6%)	61 (60.4%)	p < 0.0001
no	53 (96.4%)	40 (39.6%)	
missing	0	0	

The results for the sensitivity analysis in the PP data set for the primary efficacy endpoint (W24) were similar to those for the primary analysis in the ITT data set. In the PP data set, complete/nearly complete resolution of IH at W24 was 1.9% (1/53) in the placebo arm and 60.2% (56/93) in the propranolol 3 mg/kg/day 6 months arm; p<0.0001.

The results for the sensitivity analysis in the ITT data set based on the re-defined primary endpoint for complete/nearly complete resolution of the target IH (W24) were 27.3% (15/55) of patients in the placebo arm and 61.4% (62/101) of patients in the propranolol 3 mg/kg/day 6 months arm, p<0.0001. In this analysis, for patients who prematurely discontinued the study

drug the primary endpoint was re-defined as follows: (i) if the patient was withdrawn due to treatment intolerance, the primary endpoint remained a failure; and (ii) if the patient was not withdrawn due to treatment intolerance but if the closest centralized assessment from the end of treatment confirmed stabilization or worsening, the primary endpoint remained a failure, or if the closest centralized assessment from the end of treatment did not confirm stabilization or worsening, 50% of the patients concerned in each treatment group were selected at random and their primary endpoint was re-defined as a success.

An analysis of the primary endpoint was conducted, using an extension of the combination test for logistic regression and adjusting for the stratification factors and randomization ratio. The p-value for the adjusted logistic regression was statistically significant p<0.0001.

The results for the interim analysis for complete/nearly complete resolution of IH for the 5 treatment arms clearly showed that the most efficacious propranolol treatment regimen was 3 mg/kg/day 6 months (62.9%, 27/43 vs placebo 8.0%, 2/25; p < 0.0001). The results for the two stages of the study were consistent: in Stage 1 (data set used for the interim IDMC analysis), complete/nearly complete resolution occurred in 8.0% (2/25) of patients in the placebo arm and 62.8% (27/43) of patients in the propranolol 6 mg/kg/day 6 months arm, p<0.0001; in Stage 2, complete/nearly complete resolution occurred in 0% (0/30) of patients in the placebo arm and 58.6% (34/48) of patients in the propranolol 6 mg/kg/day 6 months arm, p < 0.0001.

> **Comment**: The primary efficacy analysis of complete/nearly complete resolution of the target IH at W24 (centralized assessment of photographs), was markedly higher in the propranolol 3 mg/kg/day 6 months arm than in the placebo arm (60.4%, 40/101 vs 3.6%, 2/55; p<0.0001). The results for the analysis of the primary efficacy endpoint in the sensitivity analyses in the PP data set and the ITT data set using a re-defined primary endpoint were consistent with the primary analysis in the ITT data set. The results for the primary efficacy end point in Stages 1 and 2 of the study were consistent with each other, and with the results for the primary efficacy endpoint analysis in the combined population (i.e., Stage 1 + Stage 2).
>
> In the analysis of the primary efficacy endpoint adjusted on stratification factors and randomization ratio in the ITT data set, the observed success rates were higher in the younger age stratum (35-90 days) compared with the older age stratum (>90 days) in both the placebo and propranolol 3 mg/kg/day 6 months arm. However, the placebo corrected complete/nearly complete success rates were similar in both the younger and the older age groups (57.6% vs 56.3%, respectively). The complete/nearly complete resolution rates in the propranolol 3 mg/kg/day 6 month arm was similar in patients with facial IH (60.6%, 45/71 vs placebo 5.0%, 2/50) and in patients with non-facial IH (60.0%, 18/30 vs placebo 0%, 0/15). The observed success rate in the propranolol 3 mg/kg/day 6 months arm was higher with the initial randomization ratio (1:1) than with the amended ratio (2:1), with 10 out of 13 patients (76.9%) showing complete/nearly complete resolution with the initial ratio (1:1) compared with compared with 51 out of 88 patients (58.0%) showing complete/nearly complete resolution with the amended ratio (2:1). However, the sponsor considers that the observed difference between the two randomization ratios "is likely to be explained by random variation and the small number of patients randomized with the 1:1 scheme and no conclusion can be drawn".

7.2.13. Results for the secondary efficacy outcomes

7.2.13.1. Centralized quantitative assessments; ITT data set.

The results for the centralized quantitative assessments of change in surface area, change in maximal diameter and change in colour from baseline to W24 are summarized below in Table 17.

Table 17: Study 201 - Centralized quantitative assessments, mean (SD) change from baseline to W24; ITT data set.

Change from baseline to W24	Placebo (n=55)	Propranolol 3 mg/kg/day 6 months	p-value
Change in surface area (cm^2); mean (SD)	0.464 (1.804)	-1.207 (2.439)	0.0093
Change in maximal diameter (cm); mean (SD)	-0.028 (0.743)	-0.179 (0.731)	0.4127
Change in color (dE*2000); mean (SD)	-0.054 (4.824)	-7.369 (7.430)	< 0.0001

7.2.13.2. Centralized qualitative assessment - success/failure at W12; ITT data set.

The proportion of patients with complete/nearly complete resolution of the target IH at W12 compared with baseline was notably higher in the 3 mg/kg/day 6 months arm than in the placebo arm (44.0%, 44/100 vs 3.6%, 2/55; p<0.0001).

7.2.13.3. Centralized qualitative assessments - time to first sustained complete/nearly complete resolution; ITT data set.

In the Kaplan-Meier (KM) analysis, the rates of sustained complete/nearly complete response at W12 and W24 were higher in the 3 mg/kg/day 6 months arm than in the placebo arm. The KM estimates at W12 for the 3 mg/kg/day 6 months and the placebo arms were 41.2% and 8.3%, respectively, and the KM estimates at W24 were 66.8% and 8.3%, respectively. The two KM curves differed significantly, and favoured the propranolol arm over the placebo arm (p<0.0001).

7.2.13.4. Centralized qualitative sustained improvement over time (3-point scale); ITT data set.

Sustained improvement over time based on the 3-point evolution scale (improvement, stabilization or worsening) was infrequently observed in the placebo arm: 5.4% at W5 vs Baseline; 3.8% at W8 vs W5; 4.2% at W12 vs W8; 4.8% at W16 vs W12; an 0% at both W20 vs W16 and W24 vs W20. Sustained improvement was markedly greater in the 3 mg/kg/day 6 months arm than in the placebo arm, with significant improvement being observed early in treatment (W5 vs Baseline, 88.0%), and then being maintained throughout the remainder of treatment. Further improvement was observed after W5 vs Baseline in a few patients in the 3 mg/kg/day 6 months arm: 13.1% at W8 vs W5; 9.2% at W12 vs W8; 10.5% at W12 vs W16; 2.2% at W20 vs W16; and 4.4% at W24 vs W20.

7.2.13.5. Centralized qualitative improvement - time to first sustained improvement (3-point scale); ITT data set.

In the 3 mg/kg/day 6 months arm, sustained improvement based on the 3-point evolution scale (improvement, stabilization or worsening) was observed at the first time point at which this endpoint was assessed (W5) in the majority of patients. In this treatment arm, the KM estimate of sustained improvement was 72.7% (72 patients) at W5 increasing to 79.5% (77 patients) at W24. In the placebo arm, sustained improvement was infrequent at all time points with KM estimates of 5.4% (2 patients) at W5 and 9.0% (3 patients) at W24. The KM estimates of time to

first sustained improvement were provided for W5, W8, W12, W16, W20 and W24. The difference was statistically significantly in favour of the active treatment arm compared with placebo (p<0.0001). The KM curves are provided in the CSR.

7.2.13.6. Centralized qualitative assessment - global improvement W5-W24; ITT data set.

Between W5 and W24, 3 patients (5.5%) in the placebo arm and 73 (73.0%) patients in the 3 mg/kg/day 6 months arm presented a global improvement from baseline (i.e., at least one assessment of improvement between paired visits without any worsening based on the 3-point evolution scale of improvement, stabilization or worsening). The difference was statistically significant in favour of the active treatment arm compared with placebo (p<0.0001).

7.2.13.7. Centralized assessment of photographs; ITT patients with over-run.

The results of the analysis of the primary efficacy endpoint (complete/nearly complete resolution) on all treated patients in the 5 arms (including overrun) are summarized below in Table 18. The complete/nearly complete resolution rates for the two 3 mg/kg/day arm were higher than the rates for the two corresponding 1 mg/kg/day arms, while the rates for the 6 month duration groups were higher than for the 3 month duration groups for both the 1 mg/kg/day and the 3 mg/kg/day doses.

Table 18: Study 201 - Primary efficacy endpoint; ITT data set with overrun.

	Placebo (N = 55)	V0400SB 1 mg/kg/day 3mths (N = 98)	V0400SB 1 mg/kg/day 6mths (N = 102)	V0400SB 3 mg/kg/day 3mths (N = 100)	V0400SB 3 mg/kg/day 6mths (N = 101)
Primary endpoint					
Complete or nearly complete resolution of target IH at week 24					
Overall					
n/missing	55 / 0	98 / 0	102 / 0	100 / 0	101 / 0
Yes	2 (3.6%)	8 (8.2%)	50 (49.0%)	12 (12.0%)	61 (60.4%)
No	53 (96.4%)	90 (91.8%)	52 (51.0%)	88 (88.0%)	40 (39.6%)
Stratification factor: Age at randomization					
35 - 90 days					
n/missing	20 / 0	36 / 0	38 / 0	36 / 0	37 / 0
Yes	2 (10.0%)	2 (5.6%)	21 (55.3%)	3 (8.3%)	25 (67.6%)
No	18 (90.0%)	34 (94.4%)	17 (44.7%)	33 (91.7%)	12 (32.4%)
> 90 days					
n/missing	35 / 0	62 / 0	64 / 0	64 / 0	64 / 0
Yes	0 (0.0%)	6 (9.7%)	29 (45.3%)	9 (14.1%)	36 (56.3%)
No	35 (100.0%)	56 (90.3%)	35 (54.7%)	55 (85.9%)	28 (43.8%)
Stratification factor: Target IH site					
Facial IH					
n/missing	40 / 0	71 / 0	72 / 0	64 / 0	71 / 0
Yes	2 (5.0%)	5 (7.0%)	34 (47.2%)	4 (6.3%)	43 (60.6%)
No	38 (95.0%)	66 (93.0%)	38 (52.8%)	60 (93.8%)	28 (39.4%)
Non-Facial IH					
n/missing	15 / 0	27 / 0	30 / 0	36 / 0	30 / 0
Yes	0 (0.0%)	3 (11.1%)	16 (53.3%)	8 (22.2%)	18 (60.0%)
No	15 (100.0%)	24 (88.9%)	14 (46.7%)	28 (77.8%)	12 (40.0%)

7.2.13.8. Investigator's on-site qualitative assessment of complete/nearly complete response (W24 results).

At W24, the investigator's assessment of the proportion of patients with complete/nearly complete resolution of the target IH was higher in the 3 mg/kg/day 6 months arm than in the placebo arm, but the difference between the two treatment groups was not statistically significant (26.7%, 24/90 vs 10.5%, 2/19; p=0.4419. The difference between the centralized

assessment and the investigator assessment was striking and is discussed further under *Evaluator's conclusions on clinical efficacy* below.

Complete resolution as assessed by the investigator occurred in no patients in the placebo arm at any visit between D7 and W24. In the 3 mg/kg/day 6 months arm, complete resolution as assessed by the investigator occurred in only 7 (7.8%) patients at W24 (5, 5.6% without sequelae, 2, 2.2%, with minimal sequelae, and 0, 0% with marked sequelae). The W24 results for the investigator assessment are summarized below in Table 19.

Table 19: Study 201 - Investigator's on-site assessment of complete/nearly complete resolution of target IH at W24 compared to baseline; ITT data set.

Overall/combined			
n/missing	19 / 36	90 / 11	0.4419
No	17 (89.5%)	66 (73.3%)	
Yes	2 (10.5%)	24 (26.7%)	
Nearly complete resolution	2 (10.5%)	17 (18.9%)	
Complete resolution without sequelae	0 (0.0%)	5 (5.6%)	
Complete resolution with minimal sequelae	0 (0.0%)	2 (2.2%)	
Complete resolution with marked sequelae	0 (0.0%)	0 (0.0%)	

7.2.13.9. Investigator's on-site qualitative assessment of IH - time to first sustained complete/nearly complete resolution.

In the 3 mg/kg/day 6 months arm, sustained complete or nearly complete resolution appeared gradually from W5 (1.0%) to W24 (25.1%, 23 patients). In the placebo arm, sustained complete or nearly complete resolution was observed in only 2 patients. In this treatment arm, the first patient with sustained complete/nearly complete resolution was observed at W12 (4.2%, 1 patient) followed by a second patient at W16 (8.7%), with no further patients being observed through to W24 (2, 8.7%). There was no statistically significant difference between the two KM curves for the 3 mg/kg/day 6 months and the placebo arms (p=0.5047).

7.2.13.10. Investigator's on site qualitative assessment of IH – time to first sustained complete resolution without sequelae or with minimal sequelae

In the placebo arm, no patient was considered to have achieved complete resolution without sequelae or with minimal sequelae. In the 3 mg/kg/day 6 months arm, sustained complete resolution without sequelae or with minimal sequelae was observed in 7.6% (KM estimate) in 7 patients at W24. It started at W12 (1.0%) with 1 patient, then 2 patients at W16 (2.1%) then 6 patients at W20 (6.5%) and 7 patients at W24 (7.6%). There were no statistically significant differences between propranolol 3 mg/kg/day and placebo for time to first sustained complete resolution without sequelae or with minimal sequelae at any time-point.

7.2.13.11. Investigator's on-site qualitative assessment sustained improvement

Investigator's on-site qualitative assessment of sustained improvement in IH, assessed by the 3-point evolution scale (improvement, stabilization or worsening), was achieved early in the 3 mg/kg/day 6 months arm, with KM estimates of 52.1% on D7 (50 patients), 64.6% on D14 (62 patients), 68.8% on D21 (66 patients), 70.9% at W5 (68 patients) and then a slower progression to reach 82.5% at W24 (76 patients). In the placebo arm, sustained improvement also started on D7 with a KM estimate of 11.1% (6 patients) and had a flatter progression, reaching a maximum of 32.4% on W16 (12 patients) and staying at this level through to Week 24. The difference between the two KM curves statistically significantly favoured propranolol 3 mg/kg/day 6 months compared with placebo (p<0.0001).

7.2.13.12. Parent/guardian on-site qualitative assessment of sustained improvement

Parent/guardian on-site qualitative assessment of sustained improvement in IH, assessed on the 3-point scale (improvement, stabilization or worsening), was achieved early in the 3 mg/kg/day 6 months arm, with KM estimates of 55.8% on D7 (53 patients), 64.2% on D14 (61 patients), 65.3% on D21 (62 patients), 67.4% at W5 (64 patients) and 85.6% at W24 (76 patients). In the placebo arm, sustained improvement also started on D7 with a KM estimate of 12.7% (7 patients) and reached a maximum of 45.0% on W16 (14 patients) and stayed at this level through to W24. The difference between the two KM curves statistically significantly favoured propranolol 3 mg/kg/day 6 months compared with placebo (p<0.0001).

7.2.13.13. Investigator's on site-site qualitative assess - target IH complications.

The grading system used for investigator on-site assessment of target IH complications is provided in the CSR.

- Functional impairment
  - Functional impairment occurred (or persisted in 1 case) on study treatment in 7 patients:
  - 4 patients on placebo (3 patients from the placebo arm [1 with persistent grade 1 eye impairment, 1 with treatment-emergent grade 2 eye impairment + grade 1 obstruction of visual axis, and 1 with grade 2 airway obstruction] and 1 patient from the 3 mg/kg/day 3 months arm [grade 1 eye impairment at the end of the placebo phase]); and
  - 3 patients on 1 mg/kg/day (2 patients in the 1 mg/kg/day 6 months arm [1 with grade 2 airway obstruction, and 1 with grade 1 airway obstruction] and 1 patient during titration [D7] in the 3 mg/kg/day 3 months arm [grade 1 obstruction of visual axis]).
  - Four (4) patients discontinued the study due to functional impairment: 3 placebo patients (1 for persistent eye impairment, 1 for eye impairment + obstruction of visual axis, 1 one for airway obstruction); and 1 patient in the 1 mg/kg/day 6 months arm (for airway obstruction).
  - In two (2) patients (both on propranolol), the functional impairment disappeared during the study treatment (1 patients with pre-existing grade 1 eye obstruction of visual axis in a patient from the 1 mg/kg/day 6 months arm, and 1 patient with grade 1 eye obstruction of visual axis that occurred on D7 and disappeared on D21 in the 3mg/kg/day 3 months arm).
  - There were no reports of functional cardiac impairment.
- IH bleeding/haemorrhaging
  - In the placebo arm, 1 patient had grade 1 bleeding ("mild without transfusion") on D14 (associated with grade 1 ulceration) and discontinued study treatment (for inefficacy) and study follow-up on D14.
  - In the 1 mg/kg/day 3 months arm, 1 patient presented an isolated grade 1 bleeding ("mild without transfusion", and without associated ulceration) at W16, with grade 0 afterwards at W20 and W24.
  - In the 1 mg/kg/day 6 months arm, 3 patients presented with bleeding: 1 patient entered the study with pre-existing bleeding ("mild without transfusion") on D0 (associated with grade 3 ulceration) and presented a grade 1 bleeding (with grade 2 ulceration) on D7; but no bleeding /haemorrhage occurred from D14 to W24; 2 patients had treatment-emergent bleeding - 1 patient with grade 1 bleeding ("mild without transfusion") with grade 1 ulceration on D14, bleeding was rated grade 0 at all the following visits (D21 to

W24); 1 patient with an isolated grade 1 bleeding ("mild without transfusion", without associated ulceration) on D21 (grade 0 afterwards from W5 to W24).

- In the 3 mg/kg/day 3 months arm: 1 patient had no bleeding on D0, then presented a grade 1 bleeding ("mild without transfusion") on D7 and D14 (with ulceration of grade 2 on D7 and grade 3 on D14, but from D21 to W24 no bleeding was reported.
- 3 mg/kg/day 6 months arm: 1 patient presented a grade 1 bleeding ("mild without transfusion") associated with a grade 1 ulceration on D14, and the patient had no bleeding afterwards from D21 to W24.

- Ulceration of the IH

This was reported in 2 patients in the placebo arm and both led to premature treatment, and in 6 (5.9%) patients in the propranolol 3 mg/kg/day 6 months (2 pre-existing that both resolved on treatment, and 4 treatment-emergent of which 2 led to premature withdrawal and 2 resolved on study treatment).

7.2.13.14. Investigator's on-site qualitative assessment - invasive procedures on IH

No invasive procedures were reported on the target IH at any visit.

7.3. Study 102 - efficacy data

The design of study 102 has been presented in the Pharmacokinetics Section of this CER. The primary objective of this study was to characterize the steady state PKs of propranolol following a dose regimen of 3 mg/kg/day for 12 weeks, including an initial titration period. The efficacy of propranolol on the target IH over 12 weeks was a secondary objective of this study in 23 infants, including 10 infants aged 35 to 90 days and 13 infants aged 91 to 150 days. Patients with life-threatening IHs were excluded from this study, but patients with other high-risk proliferating IHs could be included (e.g., IHs that were function threatening, IHs in certain anatomic locations that leave permanent scars or deformity, large facial IHs, severe ulcerate IHs, and pedunculated IHs).

Patients attended five post-baseline visits at intervals of 1 to 4 weeks: Days 7, 14, 28, 56, and at the end-of-treatment visit at Day 84. A phone call was made to the parents/guardians 2 weeks after the end of study treatment at Day 96 to collect additional AE data. The total treatment duration per patient was 12 weeks. Including the screening period, the maximum total study duration per subject was 15 weeks. There were no statistical analyses of the results. For the investigator's on-site qualitative assessments, investigators could use photographs or other methods according to their standard management of hemangiomas or preference. Investigator's assessments were conducted by the same evaluator wherever possible.

7.3.1. Efficacy assessments

- Investigator's on-site qualitative assessments of change in the target IH using a 3-point scale of improvement, stabilization or worsening for paired consecutive visits (i.e., at each scheduled post-baseline visit the change in the target IH was compared to the previous scheduled visit).
- Investigator's on-site qualitative assessments of complete/nearly complete resolution of the target IH, at each scheduled post-baseline visit compared to baseline. Nearly complete resolution was defined as a minimal degree of telangiectasis, erythema, skin thickening, soft tissue swelling, and distortion of anatomical landmarks and/or a minimal palpable component.
- Investigator's on-site assessment of target IH complications (cardiac impairment, ulceration of haemangioma, obstruction/stenosis of airway [bronchus, larynx, pharynx or trachea],

haemorrhaging/bleeding from haemangioma [each graded on a 0-5 scale]; eye impairment and obstruction of visual axis [each graded on a 0-3 scale]), at each scheduled visit.

- Parents on-site qualitative assessments of change in the target IH using a 3-point scale of improvement, stabilization, or worsening for paired consecutive patient-visits (i.e., at each scheduled post-baseline visit the change in the target IH was compared to the previous scheduled visit).

7.3.2. Results

The investigators assessment of change in target IH from the previous visit showed improvements in ≥ 72.7% of at each of the 5 assessment visits. Improvement at the first assessment visit on D7 (V3) was 86.4% (19/22) and at the last assessment visit on D84 (V7) was 72.7% (16/22). The proportion of patients showing improvement compared to the previous visit was maximal at D28 (V5) (95.5%, 21/22). No patients showed worsening from the previous visit for the 5 assessment visits.

At D84 (V7) complete/nearly complete resolution of the target IH (investigator's on-site assessment) was 36.4% (8/22; 4 patients in each age group).

At baseline, there were no major IH complications and no cardiac complications. All complications (mainly ulcerations) disappeared over time, confirming regression of the IH. By Day 28 (V5) all complications had disappeared except for one patient in Group 1 (infants aged 35-90 days) with Grade 1 ulceration. All patients were clear of complications by Day 56 (V6).

The parents/guardians assessment of change in target IH from the previous visit showed improvements in ≥ 63.6% of total patients at each of the 5 assessment visits. Improvement at the first assessment visit on D7 (V3) was 90.5% (19/22) and at the last assessment visit on D84 (V7) was 63.6% (14/22). The proportion of patients showing improvement compared to the previous visit was maximal at D14 (V4) (90.9%, 20/22). No patients showed worsening from the previous visit for the 5 assessment visits. The parent/guardian assessments were consistent with the investigator assessments for this efficacy parameter.

> **Comment**: This Phase 1, open-label, uncontrolled study provided evidence of efficacy in 22 infants with IH aged from 35 to 150 days treated with propranolol 3 mg/kg/day for 12 weeks (including an initial titration period). However, the primary objective of this study was assessment of the pharmacokinetics of propranolol rather than efficacy. The study was not designed as an efficacy study, and consequently, there were no power calculations to determine sample size and all efficacy data were descriptive. In view of the limitations of this study relating to the assessment of efficacy, it is considered that for regulatory purposed the efficacy data is exploratory rather than supportive.

7.4. Other efficacy data

7.4.1. Study 201 - extension data relating to maintenance of efficacy and re-treatment

The Summary of Clinical Efficacy included post-week 24 extension data from the on-going extension phase of study 201 planned to run for an additional 72-weeks, with visits at W36, W48, W72, and W96. The extension phase includes patients who have completed 24-weeks treatment and have elected to continue in the study. During the open-label extension period, investigators can re-initiate systemic therapy for IH if re-treatment is considered to be required. Re-initiation of systemic therapy for IH after W24 (i.e., at least 1 week after the W24 visit) could be considered to be an appropriate marker of unsatisfactory resolution of the condition following initial treatment.

The open-label 72-week extension is still ongoing and the sponsor states that full results will be available in Q2, 2014. All patients who completed the initial 24-week double-blind period of the

study and entered the 72-week open-label follow-up period have completed the W36 and W48 visits (or have been prematurely withdrawn). Sustainability of efficacy following cessation of propranolol at W24 based on the photographs taken at W36 and W48 has been assessed as of 31 December 2012. The photographs were analyzed according to the same methodology used for assessment of the primary efficacy criterion. The results are presented below in Table 20.

Table 20: Study 201 - IH response in the open-label extension period, W36 and W48.

	Placebo n=19	V0400SB 1mg/kg/day 3mths n=63	V0400SB 1mg/kg/day 6mths n=88	V0400SB 3mg/kg/day 3mths n=65	V0400SB 3mg/kg/day 6mths n=88
Week 36					
Number of available data	19	61	87	63	83
Not CR/NCR	13 (68.4%)	46 (75.4%)	44 (50.6%)	50 (79.4%)	39 (47.0%)
CR/NCR	6 (31.6%)	15 (24.6%)	43 (49.4%)	13 (20.6%)	44 (53.0%)
Week 48					
Number of available data	19	60	83	61	82
Not CR/NCR	13 (68.4%)	38 (63.3%)	38 (45.8%)	43 (70.5%)	33 (40.2%)
CR/NCR	6 (31.6%)	22 (36.7%)	45 (54.2%)	18 (29.5%)	49 (59.8%)

Source: Study V00400 SB 2 01, post-CSR additional information.

CR/NCR: complete or nearly complete resolution; W: week.

For patients having taken oral beta-blocker or other IH systemic treatment before the Type 1 assessment, the result of type 1 was considered as NOT CR/NCR

The proportion of patients for whom the investigator decided to re-initiate systemic therapy is summarized in below in Table 21.

Table 21: Study 201 - Patients receiving further systemic treatment at or after W24 of the double-blind treatment period.

	Placebo n=19	V0400SB 1mg/kg/day 3mths n=63	V0400SB 1mg/kg/day 6mths n=88	V0400SB 3mg/kg/day 3mths n=65	V0400SB 3mg/kg/day 6mths n=88
Entering the 72-week period	19 (100.0%)	61 (96.8%)	86 (97.7%)	65 (100.0%)	88 (100.0%)
Systemic treatment prescribed at Week 24*	1 (5.3%)	8 (12.7%)	8 (9.1%)	3 (4.6%)	1 (1.1%)
Oral Propranolol or other beta-blockers prescribed after Week 24**	1 (5.3%)	-	8 (9.1%)	6 (9.2%)	10 (11.4%)
Other IH systemic treatment prescribed after Week 24**	-	-	-	-	-

Source: Study V00400 SB 2 01, post-CSR additional information.

** treatment started the day of EOT or within 7 days post EOT, corresponding to lack of efficacy*

*** treatment started more than 7 days after EOT and before Week 48*

Note: the patient 711703 (V0400SB 1mg/kg/day 6mths) has been counted twice (in systemic treatment prescribed at W24 and in Oral Propranolol or other beta-blockers prescribed after W24), because this patient has taken beta-blocker the day of EOT during 2 weeks, following by 3 weeks without treatment and re-initiated after beta-blocker

> **Comment**: The preliminary extension data show that complete/nearly complete response can be maintained in the propranolol 3 mg/kg/day 6 months treatment arm at W48 (i.e., 59.8% [49/82] of patients at W48 compared with 60.4% [61/101] of patients at W24). The complete/nearly complete response rate in the placebo group at W48 was 31.6% (6/19), which was notably higher than that following the initial 6 months of double-blind treatment (3.6%, 2/55).

Of the 323 patients who completed the 24 week double-blind treatment period, 21 patients had further treatment for IH at or immediately (within 1 week) after W24. These patients are considered to show "lack of efficacy" at W24. As of 31 December 2012, 25 patients have received systemic treatment for IH with oral propranolol of other beta-blockers between W24 and W48 (i.e., treatment started more than 7 days after EOT and before W48). In these patients efficacy was considered to be non-sustainable. Of the 88 patients in the 3 mg/kg/day 6 months

arm, 11/88 (11.4%) required re-introduction of systemic treatment for IH starting more than 7 days after EOT and before W48 compared with 1/19 (5.3%) of patients in the placebo arm.

The Summary of Clinical Efficacy referred to data from 35 publications that showed re-growth of IH in 174 (14%) of 1282 patients included in the studies. However, the Summary noted that this figure is the "minimum possible percentage of patients experiencing regrowth: a more correct percentage based on the proportion of patients who initially responded to treatment and who completed treatment cannot be determined [from the provided data]". The summary also refers to a retrospective study from a single centre (Ahogo et al., 2013) that reported regrowth in 40 (25%) of 158 patients (all of whom had shown total or partial response to propranolol) following cessation of treatment. Of these 40 patients, 19 (12%) were considered major relapses with a true regrowth phase requiring retreatment and 21 were considered minor relapses. Propranolol was re-introduced for a second course for 14 patients and more than two courses for 5 patients. The analysis identified two independent factors associated with regrowth: segmental distribution (10-fold risk) and the presence of a deep component. Neither dose of propranolol nor age at initiation of treatment affected the risk of IH regrowth.

7.4.2. Compassionate use program

The Summary of Clinical Efficacy included a summary of data up to 12 October 2012 from the French Compassionate Use Program (CUP) for treatment of IH. The summary documented the reason for discontinuation in 159 of 660 patients treated with propranolol for IH in the CUP. The reasons for discontinuation included good efficacy in 134 patients (85.4%), poor efficacy in 6 patients (3.8%) and different reasons in 19 patients (11.9%).

An additional analysis of the CUP data was performed for data collected up to 31 December 2012 at 2 sites with the highest recruitment, comprising 209 patients with high risk IH of whom 138 had been definitively discontinued from treatment. The reason for discontinuation was documented for 137 patients and in 126 (92.0%) of these patients the reason was good efficacy. For these 126 patients, the mean (SD) propranolol dose after titration was 1.9 (0.7) mg/kg/day for a mean (SD) of 7.4 (3.1) months. The mean time since the first treatment discontinuation was 11.1 months

Of the 126 patients who discontinued for good efficacy, re-introduction of oral propranolol was reported in 4 (3%) patients, and in all cases the drug was re-introduced more than 2 months after the first treatment. The re-introduced oral dose of propranolol was 2 mg/kg/day for 3 patients, and 3 mg/kg/day for 1 patient. The reason for stopping the second course of propranolol in these 4 patients was linked to good efficacy in 3 patients and unknown in 1 patient. A third course of treatment with propranolol (on-going) was initiated in 1 patient.

7.4.3. Key publications

The Summary of Clinical Efficacy included the sponsor's review of data from "17 key publications" describing the use of propranolol for the treatment of IH. The sponsor comments that, despite the limitations of the studies, the analysis of the published data provides "an indication of the efficacy of off-label propranolol treatment in patients with high risk IH". The majority of patients in the studies showed a positive response in IH to propranolol treatment, ranging from 49% to 75% of patients in each study. The main limitations of these studies are the largely retrospective, observational, uncontrolled, open designs in small numbers of patient, the absence of standardization of the primary efficacy assessment, the variability of the planned dose (2 to 3 mg/kg/day), the variability of planned duration of treatment (3 months to unspecified time when the patient was older than 12 months or until satisfactory resolution of IH), the inclusion of some patients with high risk IH in all studies, the variability and/or absence of data on IH stage, and the variability and/or absence of data relating to patient age. The

primary efficacy results for the key publications reviewed by the sponsor are provided in an Appendix to the CER[1].

7.5. Evaluator's conclusions on clinical efficacy

The sponsor states that the efficacy analysis was based on a total of 1333 patients (23 in study 102, 456 in study 201, 159 analyzed in the CUP, and 695 in the key publications). However, it is considered that, for regulatory purposes, only the efficacy data from the pivotal Phase II/III study (201) are relevant for evaluating the efficacy of propranolol at the proposed dose for the proposed indication. In this study 460 patients were randomized 1:2:2:2:2 to placebo or one of four propranolol oral solution treatment regimens (1 mg/kg/day 3 months, 1 mg/kg/day 6 months, 3 mg/kg/day 3 months, or 3 mg/kg/day 6 months). The study included infants aged from 35 to 150 days (inclusive) with facial and non-facial IHs (largest diameter of at least 1.5 cm). The IHs treated in the pivotal study can be considered to be low-risk as infants were excluded if they had one or more life-threatening IHs, function threatening IHs, or complicated ulcerated IHs. In addition, in the total population the IH complication rate over the duration of the study assessed on-site by the investigators was low suggesting low-risk disease. The study excluded patients who had received previous medical or surgical treatment for IHs.

The pivotal study had an adaptive design allowing for the modification of key elements based on the results of an interim analysis (i.e., increased sample-size, selection of best propranolol treatment regimen or regimens, stop for futility or safety) with control of the pre-specified type 1 error. The interim analysis was undertaken by an IDMC and included data on 190 randomized patients of whom 188 patients from the five treatment arms had completed W24 (or had been prematurely withdrawn from treatment). Based on the results of the interim analysis, the IDMC recommended that the trial continue with one single active treatment arm (3 mg/kg/day 6 months) to be compared with placebo in the primary efficacy analysis at W24, no sample size adjustment/re-estimation and all patients being kept in their initial randomization arm. Accrual in the study continued while the interim analysis was being undertaken, and the planned sample size had been reached with 460 patients randomized before the IDMC recommendations were made.

The primary pre-specified efficacy endpoint was the proportion of subjects achieving complete or nearly complete resolution of the target IH at W24, assessed by centralized (blinded) reading of photographs, in the ITT population. The proportion of subjects achieving this endpoint was markedly higher in the propranolol 3 mg/kg/day arm than in the placebo arm, and the difference between treatment arms was statistically significant (60.4%, 61/101, vs 3.6% (2/55), respectively, $p<0.0001$). The results of the primary analysis were supported by sensitivity analyses in the PP data set, and the ITT date set using a re-defined primary efficacy endpoint. In addition, logistic regression analysis of the primary efficacy endpoint, adjusted for the stratification factors and the randomization ratio, statistically significantly favoured propranolol 3 mg/kg/day 6 months compared with placebo ($p<0.0001$). The observed placebo success rate of 3.6% was lower than the estimated rate on which the sample size calculations was based (10%), while the active treatment rate of 60.4% was higher than the estimated rate (55%).

The results for complete or nearly complete resolution of IH at W24 based on the photographic data assessed by 2 centralized readers differed markedly from the results for this outcome based on on-site investigator clinical assessment. Based on investigator assessment, complete or near complete resolution of the target IH at W24 compared with baseline was 10.5% (2/19) in the placebo arm and 26.7% (24/90) in the propranolol 3 mg/kg/day 6 months arm, nominal $p=0.4419$. Complete resolution as assessed by the investigator occurred in no patients in the

1 Not included here in the CER extract.

placebo arm at any visit between D7 and W24. In the 3 mg/kg/day 6 months arm, complete resolution as assessed by the investigator occurred in only 7 (7.8%) patients at W24 (5 patients, 5.6% without sequelae; 2 patients, 2.2%, with minimal sequelae; and no patients with marked sequelae). The difference in complete/nearly complete resolution rate between the two treatment arms based on investigator assessment was not statistically significant at any visit.

In the 3 mg/kg/day 6 months arm, centralized assessment identified 38 patients with complete/nearly complete resolution who were not assessed as complete/nearly complete resolution by investigator assessment, and 1 patient who was assessed as complete/nearly complete resolution by investigator assessment but not by centralized assessment. Sixty-two (62) patients were consistently assessed by centralized and investigators assessments, 23 as complete/nearly complete resolution and 39 as not complete/nearly complete resolution (see Table 22, below).

Table 22: Study 201 - Consistency between centralized and on-site investigator assessments of complete/nearly complete resolution of IH.

Complete/nearly complete resolution		Placebo (n=55)	V0400SB 3 mg/kg/day 6mths(n=101)
Centralized assessment (primary endpoint)	Investigator assessment		
Yes	Yes	0	23
Yes	No	2	38
No	Yes	0	1
No	No	53	39

The sponsor notes that the results of the investigator assessment of complete/nearly complete resolution of IH at W24 "clash strikingly" with the results of the centralized assessment, but considers that comparison of the two different assessment methods is "of limited significance" due to the dissimilarity between the methods used to assess the outcome. The sponsor states that assessment of complete/near complete response performed by two expert readers was used as the primary criterion in order to ensure both independence and reproducibility of assessments, and only took in to account the comparison of W24 photographs with baseline (W0) pre-treatment photographs. In contrasts, the investigators' assessment of the same criterion was by definition subject to greater heterogeneity (56 investigating sites versus 2 expert readers), less reproducibility (no training for this parameter, no validation of intra/inter reader reproducibility) and was also methodologically different since it was based on direct visual examination of the patient at W24 compared with the W0 photographs and additional medical data available at the investigator site arising from clinical examination of the patient.

However, in contrast to the sponsor's opinion it is considered that the difference between the two assessment methods as regards complete/nearly complete resolution of IH at W24 is a significant matter and should not be dismissed lightly. The investigators were required to undertake a detailed clinical assessment of the target IH at each visit, and the nature of this examination is considered to be consistent with that which would be undertaken in clinical practice and on which clinical decisions regarding treatment would be made. Furthermore, it can be reasonably assumed that the investigators chosen to contribute patients to this study would be physicians experienced in the assessment and management of infants with IH. Consequently, it is considered that it would be unwise to discount the clinical opinion of these physicians as regards complete or nearly complete resolution of IH. In addition, there is no evidence that the criteria used to determine complete/nearly complete resolution of IH based on photographic assessment has been validated against the same outcomes determined by clinical examination by experienced physicians. Overall, it is considered that the inconsistency between the two assessment methods raises more doubts about the reliability of photographic assessment of complete/incomplete resolution rather than about on-site investigator assessment. Furthermore, the striking inconsistency between the two assessment methods

raises significant uncertainty about the true effect of the propranolol 3 mg/kg/day 6 months regimen on complete/nearly complete resolution compared with placebo.

In contrast to the uncertainty concerning complete/nearly complete resolution, it is considered that the data from the pivotal study suggest that propranolol 3 mg/kg/day 6 months results in improvement in IH at W24 compared with placebo. However, the evidentiary weights given to these data is limited, as all secondary efficacy endpoints up to and including W24 were exploratory and p-values for the analyses of these endpoints were all nominal rather than confirmatory. The exploratory data suggesting that propranolol 3 mg/kg/day 6 months improve IH compared with placebo are summarized in the following two paragraphs.

In the centralized assessment, quantitative assessment of reduction in IH surface area, reduction in maximal IH diameter, and change in colour of the IH from baseline to W12 and W24 favoured propranolol 3 mg/kg/day 6 months compared with placebo, and the changes were nominally statistically significant for surface area and colour. In the centralized assessment, improvement in the target IH at W5 was observed in a greater percentage of patients in the propranolol 3 mg/kg/day arm than in the placebo arm (88.0%, 88 patients vs 5.4%, 2 patients, respectively). Further improvements in the propranolol 3 mg/kg/day 6 months vs placebo arm for the following pairs of visits were, respectively, 13.8% vs 3.8% for W8 vs W5, 9.2% vs 4.2% for W12 vs W8, 10.5% vs 4.8% for W12 vs W16, 2.2% vs 0% for W20 vs W16, and 4.5% vs 0% for W24 vs W20. Furthermore, between W5 and W24, global improvement from baseline (i.e., at least one assessment of improvement between paired visits without any worsening) was 73.0% (73 patients) in the 3 mg/kg/day arm and 5.5% (3 patients) in the placebo arm, nominal $p<0.0001$.

In addition, centralized, investigator and parent/guardian assessments, all showed greater sustained improvement in IH (KM estimates) at W5 and W24 in the 3 mg/kg/day arm than in the placebo arm. In the centralized assessment, sustained improvement was observed at W5 in 72.7% (72 patients) of patients in the 3 mg/kg/day arm and 5.4% (2 patients) in the placebo arm, with the corresponding results for the two treatment arms at W24 being 79.5% (77 patients) and 9.0% (3 patients), respectively. In the investigator assessment, sustained improvement was observed at W5 in 70.9% (68 patients) of patients in the 3 mg/kg/day arm and 20.1% (10 patient) in the placebo arm, with the corresponding results for the two treatment arms at W24 being 82.5% (76 patients) and 32.4% (12 patients), respectively. In the parent/guardian assessment, sustained improvement was observed at W5 in 67.4% (64 patients) of patients in the 3 mg/kg/day arm and 19.9% (10 patients) in the placebo arm, with the corresponding results for the two treatment arms at W24 being 85.6% (76 patients) and 45.0% (14 patients), respectively. For the three assessments, the difference in the KM estimates of time to first sustained improvement (W5 first assessment time-point) of the target IH over the 24 weeks of the study favoured active treatment over placebo, nominal $p<0.0001$.

Data suggesting that the IHs in the pivotal study were low-risk come from the infrequently occurring target IH complications in the total patient population, qualitatively assessed on-site by the investigators. Functional impairment due to the target IH occurred (or persisted in 1 case) on study treatment in 7 patients (3 [5.5%] in the placebo arm, and 4 [1.0%] in the combined propranolol arms). Ulceration of the target IH occurred on treatment in 13 patients (2 [3.6%] in the placebo arm and 11 [2.7%] in the combined propranolol arms). Bleeding/haemorrhaging of the IH occurred in 7 patients (1 [1.8%] in the placebo arm and 6 [1.5%] in the combined propranolol arms), and in all cases were pre-existing or occurred early in treatment (before or at D21). In all cases (apart from 1) the bleeding/haemorrhaging resolved at W5 at the latest.

The submitted data included preliminary data on patients from the pivotal study who have entered the 72-week open-label extension phase after completing the 24-week double-blind treatment period. Of the patients in the 3 mg/kg/day 6 months arm who entered the extension phase, 59.8% (49/82) were reported with complete/near complete resolution of IH at W48

(based on centralized assessment of photographic data) compared with 31.6% (6/19) in the placebo arm. The results showed that complete/nearly complete resolution at W24 can be maintained through to W48 in patients treated with propranolol 3 mg/kg/day (60.4%, 61/100 and 58.8%, 49/82, respectively), while the percentage of patients with complete/nearly complete resolution in the placebo arm actually increased from W24 to W48 (3.6%, 2/55 to 31.6%, 6/19). The preliminary results also showed that 11.4% (10/88) of patients in the propranolol 3 mg/kg/day 6 months arm required retreatment of IH with propranolol starting more than 7 days after the end of treatment but before week 48, compared with 5.3% (1/19) of patients in the placebo arm.

In summary, it is considered the evidence from the pivotal study showing a markedly increased rate of complete/nearly complete resolution in IH at W24 compared with placebo, based on centralized assessment (blinded) by two readers (primary efficacy endpoint), is unreliable due to the striking difference in this outcome when assessed (blinded) on-site by the study investigators (secondary exploratory efficacy endpoint). However, the efficacy data from the pivotal study suggest that propranolol 3 mg/kg/day 6 months can improve low-risk IH compared with placebo when assessed at W24, but the pivotal study was not designed to assess improvement, all data were exploratory, and all p-values were nominal rather than confirmatory. There is low level evidence from the CUP and the published data reviewed by the sponsor that propranolol can improve IH outcomes, but little regulatory weight can be given to this predominantly observational evidence.

8. Clinical safety

8.1. Studies with clinical safety data

The primary safety analysis in the submission includes pooled safety data on 424 patients from studies 102 (n=23) and 201 (n=401) treated with the sponsor's oral propranolol preparations.

Additional safety analyses in the submission included:

- sponsor's study 301, an on-going open-label study of propranolol in infants with proliferating IH, reporting serious adverse events (SAEs) in 1 patient in the 11 enrolled up to the cutoff date of 31 December 2012;
- cumulative data from 660 patients with IH (including high-risk disease) from the sponsor's French Compassionate Use Program (CUP) treated between 13 April 2010 and the cutoff date of 12 October 2012; and
- studies and individual case reports of 1367 patients with IH (including high risk disease) treated with oral propranolol presented in 60 publications from the scientific literature reviewed by the sponsor.

In total, the safety data provided in the submission included 1084 patients treated with the sponsor's oral propranolol preparations (424 pooled from studies 102 and 201, 660 in the French compassionate use program [CUP]), and 1367 patients from the scientific literature treated with other preparations of propranolol.

The sponsor stated that, "based on the pre-New Drug Application (NDA) meeting with the Food and Drug Administration (FDA), on 26 [April] 2012, and the [pre-submission] meeting with the European Medicines Agency (EMA) on 29 [November] 2012, it was agreed that, in order to obtain the fullest possible sample size for this submission, all the above listed sources of data were to be used for this analysis of the safety of oral propranolol in the treatment of IH. It was also agreed that the CUP data should be presented in [the dossier] Section 2.7.4.6, Post-Marketing Data. Moreover, the FDA agreed that it was appropriate to prepare a unique integrated 2.7.4/ISS document".

In this CER, the evaluation of safety primarily focuses on the data from the pivotal Phase II/III study (201), and the pooled safety data from studies 201 and 102 reported in the ISS/SCS. There is considerable overlap between the safety data for propranolol from the pivotal study and the pooled safety data reported in the ISS/SCS. This is to be expected as the 424 propranolol treated patients in the pooled safety population included 401 (94.6%) patients from pivotal study 201. Therefore, the pooled safety data for propranolol is primarily driven by the safety data from study 201. In addition, the safety results from the CUP have been considered, and brief mention of the data from the scientific literature reviewed by the sponsor has been provided.

8.2. Safety data - pivotal study 201 and pooled safety population 201/102

8.2.1. Overview

The safety analysis in pivotal study 201 was undertaken on the safety data set, which included 401 patients treated with propranolol and 55 patients treated with placebo. Adverse events were classified as: (i) treatment emergent adverse events (TEAE), i.e., any AEs that occur or worsen on study treatment or up to 5 days after the last day of study treatment; or (ii) non TEAEs, i.e., any pre-existing conditions or AEs occurring during the screening period that do not worsen on study treatment or up to 5 days after the last day of study treatment or any AEs that have an onset date more than 5 days after the last day of study treatment.

In the pivotal study, numbers and percentages of patients with at least one reported TEAE were tabulated by treatment group, by MedDRA system organ class (SOC) and by preferred term (PT) for all TEAEs, all AEs leading to drug discontinuation, all moderate TEAEs, all severe TEAEs, all related TEAEs (i.e., relationship to study treatment other than "not suspected"), and all TEAEs with an outcome "Not recovered", "is recovering" or missing. Data relating to serious adverse events (SAEs) and other significant AEs were also provided. The method of summarizing the data used in the pivotal study was also followed in the ISS/SCS for the pooled safety data.

8.2.2. Exposure

In the pivotal study safety population and the pooled safety population, actual extent of exposure was defined as the range of the days for which the patient was exposed to treatment (i.e., date of last intake of the drug [EOT] minus date of first intake of the drug plus 1 day). In the pivotal study, the data did not distinguish between propranolol for 3 months followed by placebo for 3 months (i.e., the data are described as 1 mg/kg/day for 3 months and 3 mg/kg/day for 3 months). In the pivotal study, all 5 treatment arms can be compared during the titration period (D0 to D21), then due to attrition in the placebo arm the 4 active treatment arms can be compared over the D21-W12 period, and after W12 the two active, 6 month treatment arms can be directly compared. The extent of exposure for the patients in the safety set from the pivotal study is summarized below in Table 23.

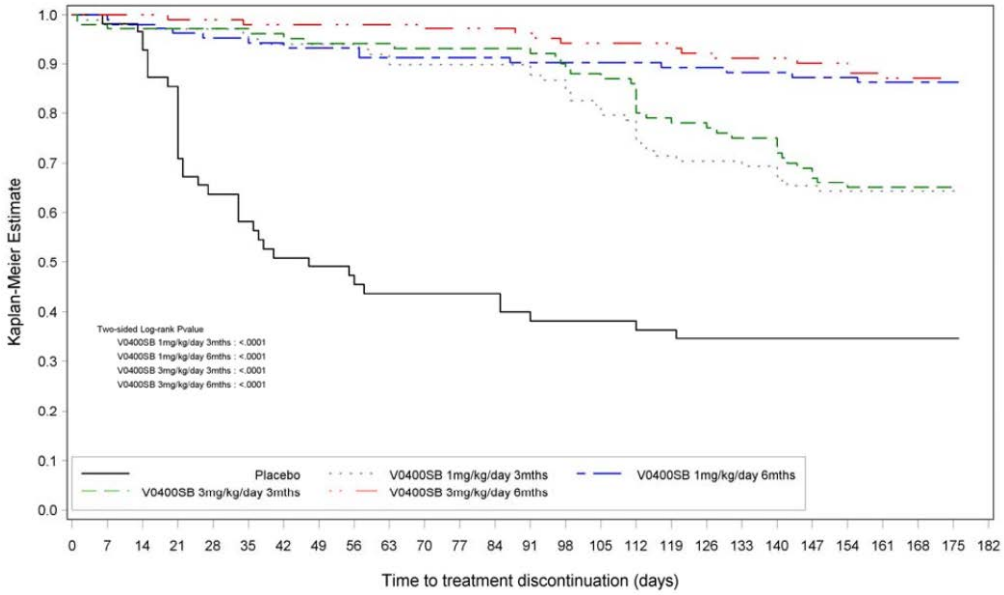
Table 23: Study 201 - Extent of exposure; safety set

	Placebo (N = 55)	V0400SB 1 mg/kg/day 3mths (N = 98)	V0400SB 1 mg/kg/day 6mths (N = 102)	V0400SB 3 mg/kg/day 3mths (N = 100)	V0400SB 3 mg/kg/day 6mths (N = 101)	Total (N = 456)
Extent of exposure*(in days)						
N/Missing	55/0	98/0	102/0	100/0	101/0	456/0
Mean (SD)	82.60 (67.31)	142.74 (43.73)	156.92 (39.89)	146.61 (38.45)	160.97 (26.59)	143.55 (48.32)
Q1 Q2 Q3	21.00 47.00 168.00	113.00 168.00 169.00	168.00 168.00 169.00	135.50 167.50 169.00	167.00 168.00 169.00	141.00 168.00 169.00
min max	6 176	1 214	7 220	7 176	19 190	1 220

** Estimated day of end of treatment (EOT) - day of first treatment administration + 1*

Treatment discontinuations over time in the pivotal study safety set are summarized below in Figure 2 by KM survival curves.

Figure 2: Study 201 - Treatment discontinuation over time, KM survival curves for time to treatment discontinuation; safety set.



In the pooled safety population, the actual exposure data were analysed using two different data sets derived from the total pooled safety population, which included 424 propranolol treated patients (401 patients from the four active treatment arms in the pivotal Phase II/III study 201 and 23 patients from the Phase I open-label study 102 of propranolol 3 mg/kg/day for 3 months) and 236 placebo treated patients from the pivotal study).

One analysis compared all placebo (n=236), all propranolol 1 mg/kg/day (n=200), all propranolol 3 mg/kg/day (n=224), and all propranolol (n=424). In this analysis, the safety results for the placebo and active treatment components for the two 3 month active (1 mg/day and 3 mg/day) followed by 3 months placebo regimens were separated. Therefore, in this analysis the all placebo group (n=236) was derived from the pivotal study 201 and included 55 patients from the placebo for 6 months regimen, 88 placebo treated patients from the second 3 month phase of the 1 mg/kg/day 3 months regimen, and 93 placebo treated patients from the second 3 month phase of the 3 mg/kg/day 3 months regimen. The all propranolol 1 and 3 mg/kg/day groups included patients from the pooled regimens treated for 3 or 6 months; i.e., all 1 mg/kg/day group (n=200) included 102 patients from the 6 months regimen and 98 patients from the 3 months regimen; all 3 mg/kg/day group (n=224) included 101 patients from the 6 months regimen and 123 patients from the 3 month regimens.

One analysis compared placebo for 6 months (n=55), propranolol 1 mg/kg/day for 3 months (n=98), propranolol 1 mg/kg/day for 6 months (n=102), propranolol 3 mg/kg/day for 3 months (n=123), propranolol and propranolol for 6 months (n=101), and the total population (n=479).

> **Comment**: In the pivotal study, the mean duration of exposure in the placebo arm was about half that of the 3 mg/kg/day 6 months arm (i.e., 83 vs 161 days, respectively). Interpretation of the safety findings need to take into account the difference in treatment exposure among the placebo and active treatment arms. Differences in extent of exposure between placebo and active treatment are explained by the differences in premature treatment discontinuation rates, with most of the patients remaining on study treatment as long as they were on active treatment. In the randomized data set (pivotal study), 36 (65.5%) patients discontinued treatment prematurely in the placebo

arm compared with 14 (13.7%) patients in the 3 mg/kg/day 6 months arm, and the number of patients discontinuing due to treatment inefficacy in the two arms was 32 (58.2%) and 9 (8.8%), respectively. In the placebo arm, treatment discontinuation started early (as soon as W2), with a very steep decrease between W2 and W5, with 49.1% (27/55) of the patients having prematurely discontinued treatment at W5 and 65.5% (36/55) at W20. In contrast, in the 3 mg/kg/day 6 months arm, only 2.9% (3/102) of patients had discontinued prematurely at W5 and 11.8% (12/101) at W20.

8.2.3. Adverse events

8.2.3.1. Overall adverse event profiles

In pivotal study, at least one TEAE was reported in 95.0% (96/101) of patients in the 3 mg/kg/day 6 month arm, and 74.5% (41/55) of patients in the placebo arm (see Table 24, below). The TEAE data for the 1 and 3 mg/kg/day 6 months arms show a small dose response relationship in the proportion of patients with TEAEs, but there was no notable difference in the proportion of patients with TEAEs in the 1 and 3 mg/kg/day 3 months arms. The proportion of patients with at least one TEAE was greater in each of the propranolol arms than in the placebo arm, and the majority of patients in each of the four propranolol treatment arms experienced more that 2 TEAEs. The results are summarized below in Table 24.

Table 24: Study 201 - Summary of TEAEs; safety set.

	Placebo (N = 55)	V0400SB 1 mg/kg/day 3mths (N = 98)	V0400SB 1 mg/kg/day 6mths (N = 102)	V0400SB 3 mg/kg/day 3mths (N = 100)	V0400SB 3 mg/kg/day 6mths (N = 101)
Patients with at least one AE	41 (74.5%)	90 (91.8%)	90 (88.2%)	91 (91.0%)	96 (95.0%)
Patients with at least one TEAE	40 (72.7%)	89 (90.8%)	90 (88.2%)	91 (91.0%)	96 (95.0%)
Patients with one TEAE	13 (23.6%)	18 (18.4%)	16 (15.7%)	12 (12.0%)	16 (15.8%)
Patients with two TEAEs	7 (12.7%)	10 (10.2%)	6 (5.9%)	9 (9.0%)	13 (12.9%)
Patients with more than two TEAEs	20 (36.4%)	61 (62.2%)	68 (66.7%)	70 (70.0%)	67 (66.3%)
Patients with at least one AE leading to definitive study drug discontinuation	6 (10.9%)	4 (4.1%)	2 (2.0%)	7 (7.0%)	3 (3.0%)
Patients with at least one related TEAE	16 (29.1%)	44 (44.9%)	33 (32.4%)	35 (35.0%)	35 (34.7%)
Patients with at least one Serious AE	3 (5.5%)	5 (5.1%)	3 (2.9%)	9 (9.0%)	6 (5.9%)
Occurrence of TEAEs	143	516	478	468	520
Occurrence of AEs leading to definitive study drug discontinuation	7	4	2	10	3
Occurrence of related TEAEs	31	147	81	71	75
Occurrence of serious AEs	3	5	5	13	7

In pooled safety population at least one TEAE occurred in 65.3% (154/236) of patients in the all placebo group and 86.8% (368/424) of patients in the all propranolol group, and there was no marked difference in the proportion of patients with at least one TEAE between patients in the all 1 mg/kg/day (84.5%, 169/200) and the all 3 mg/kg/day (88.8%, 199/224) groups. The majority of patients in the propranolol groups experienced at least 3 TEAEs. The overall adverse event profiles for the pooled safety population is summarized below in Table 25.

Table 25: ISS/SCS - Summary of treatment emergent adverse events (TEAEs); safety set.

	All Placebo n=236	All V0400SB 1mg/kg/day n=200	All V0400SB 3mg/kg/day n=224	All V0400SB n=424
Patients with at least one TE AE	154 (65.3 %)	169 (84.5 %)	199 (88.8 %)	368 (86.8 %)
Patients with one TE AE	60 (25.4 %)	35 (17.5 %)	39 (17.4 %)	74 (17.5 %)
Patients with two TE AEs	47 (19.9 %)	24 (12.0 %)	36 (16.1 %)	60 (14.2 %)
Patients with at least 3 TE AEs	47 (19.9 %)	110 (55.0 %)	124 (55.4 %)	234 (55.2 %)
Patients with at least one TE AE leading to definitive study drug discontinuation	11 (4.7 %)	4 (2.0 %)	7 (3.1 %)	11 (2.6 %)
Patients with at least one related TE AE	35 (14.8 %)	75 (37.5 %)	79 (35.3 %)	154 (36.3 %)
Patients with at least one Serious TE AE	6 (2.5 %)	7 (3.5 %)	14 (6.3 %)	21 (5.0 %)
Total number of TE AEs	357	679	759	1438
Total number of TE AEs leading to definitive discontinuation of study drug	12	4	10	14
Total number of Related TE AEs	56	160	132	292
Total number of Serious TE AEs	6	9	19	28

** Related = events with a relationship to the study drug other than 'Not Suspected'*
*** Each patient was counted only once by Preferred Term*

8.2.3.2. TEAEs by System, Organ, Class (SOC)

In the pivotal study, SOCs occurring in at least 20% of patients in the propranolol 3 mg/kg/day 6 months group vs placebo were: Infections and Infestations (68.3%, 69/101 vs 40.0%, 22/55; p=0.0006); Gastrointestinal Disorders (54.5%, 55/101 v 29.1%, 16/55; p=0.0024); General and Administration Site Conditions (32.7%, 33/101 vs 21.8%, 12/55; p=0.1528); Skin and Subcutaneous Tissue Disorders (25.7%, 26/101 vs 18.2%, 10/55; p=0.2842); Respiratory, Thoracic and Mediastinal Disorders (23.8%, 24/101 vs 12.7%, 7/55; p=0.0989); and Psychiatric Disorders (21.8%, 22/108 vs 16.4%, 9/55; p=0.4178). All other SOCs in the 3 mg/kg/day 6 months group occurred in less than 10% of patients. TEAEs by SOC for the pivotal study are summarized in the submission.

In pooled safety population , the most commonly reported SOCs reported in at least 30% of patients in any group were: (i) Infection and Infestations - 41.9% (99/236) in the all placebo group, 56.5% (113/200) in the all 1 mg/kg/day group, 57.1% (128/224) in the all 3 mg/kg/day group and 56.8% (241/424) in the all propranolol group; Gastrointestinal Disorders - 20.8% (49/236) in the all placebo group, 48.5% (97/200) in the all 1 mg/kg/day group, 51.8% (116/224) in the all 3 mg/kg/day group and 50.2% (213/424) in the all propranolol group; and (iii) General Disorders and Administration Site Conditions - 13.6% (32/236) in the all placebo group, 30.5% (61/200) in the all 1 mg/kg/day group, 28.6% (64/224) in the all 3 mg/kg/day group and 29.5% (125/424) in the all propranolol group.

8.2.3.3. Common TEAEs

In the pivotal study, TEAEs reported in at least 5% of patients in the propranolol 3 mg/kg/day 6 months arm (in decreasing order of frequency) vs the placebo arm were: nasopharyngitis (33.7%, 34/101 vs 18.2%, 10/55); diarrhoea (27.7%, 28/101 vs 7.3%, 4/55); pyrexia (26.7%, 27/101 vs 9.1%, 5/55); teething (20.8%, 21/101 vs 10.9%, 6/55); bronchitis (16.8%, 17/101 vs 1.8%, 1/55); upper respiratory tract infection (13.9%, 14/101 vs 7.3%, 4/55); vomiting (12.9%, 13/101 vs 5.5%, 3/55); cough (11.9%, 12/101 vs 7.3%, 4/55); gastroenteritis (10.9%, 11/101 vs 3.6%, 2/55); peripheral coldness (9.9%, 10/101 vs 1.8%, 1/55); bronchiolitis (8.9%, 9/101 vs 5.5%, 3/55); dermatitis diaper (8.9%, 9/101 vs 3.6%, 2/55); toothache (8.9%, 8/101 vs 3.6%, 2/55); conjunctivitis (7.9%, 8/101 vs 3.6%, 2/55); vaccination complication (7.9%, 8/101 vs 3.6%, 2/55); sleep disorder (6.9%, 7/101 vs 1.8%, 1/55); middle insomnia (5.0%, 5/101 vs 5.5%, 3/55); nightmare (5.0%, 5/101 vs 1.8%, 1/55); and rash (5.0%. 5/101 v 1.8%, 1/55).

TEAEs that occurred at least 2-fold more commonly in the propranolol 6 mg/kg/day 6 months arm than in the placebo arm were considered to be of clinical interest. However, as the duration of exposure was approximately 2-fold greater in the propranolol 3 mg/kg/day 6 months arm

than in the placebo arm a ≥ 3-fold difference in the incidence of TEAEs between the two arms was chosen to signify clinical significance. TEAEs reported in at least 2% or patients in the 3 mg/kg/day 6 months arm and occurring at least 3-fold more commonly than in the placebo arm were: diarrhoea (27.7%, 28/101 vs 7.3%, 4/55); bronchitis (16.8%, 17/101 vs 1.8%, 1/55); gastroenteritis (10.9%, 11/101 vs 3.6%, 2/55); peripheral coldness (9.9%, 10/101 vs 1.8%, 1/55); sleep disorder (6.9%, 5/101 vs 1.8%, 1/55); ear infection (4.0%, 4/101 vs 0%, 0/55); pharyngitis (3.0%, 3/101 vs 0%, 0/55); viral infection (3.0%, 3/101 vs 0%, 0/55); GORD (3.0%, 3/101 vs 0%, 0/55); and AST increased (3.0%, 3/101 vs 0%, 0/55). TEAEs reported with a frequency of ≥ 2% in the propranolol 3 mg/kg/day 6 months arm are presented in the submission.

In the pooled safety population, TEAEs reported in at least 10% of patients in the pooled propranolol group (descending order of frequency) vs the all placebo group, respectively, were: nasopharyngitis (23.6%, 100/424 vs 15.3%, 26/236); pyrexia (21.2%, 90/424 vs 7.2%, 17/236); diarrhoea (18.9%, 80/424 vs 3.4%, 3/236); teething (15.3%, 65/424 vs 9.3%, 22/236); cough (11.8%, 50/424 vs 7.2%, 17/236); vomiting (10.6%, 45/424 vs 3.4%, 8/236); and URTI (10.1%, 43/424 vs 7.6%, 18/236). TEAEs reported in at least 2% of patients in either all propranolol group and occurring with a more than 3-fold incidence in the all propranolol group compared with the all placebo group in the pooled safety population are summarized in the submission.

8.2.3.4. Severity of TEAS

In the pivotal study, the majority of TEAEs in the five treatment arms were rated as mild or moderate in intensity rather than severe.

8.2.3.5. Time to onset of TEAEs

In the pivotal study, TEAEs generally occurred before or at the W12 visit. The break-down by time of onset (before or at W12 vs after W12) for the most frequently occurring TEAEs is summarized in the dossier. In the 3 mg/kg/day 6 months group, TEAEs generally occurred before or on the Week 12 visit. TEAEs that were more evenly distributed throughout the study tended to be non-specific childhood events such as teething, cough, URTI, bronchitis and bronchiolitis.

8.2.3.6. Outcome of TEAEs

Most patients recovered from their TEAEs. In the pivotal study, TEAEs reported as not recovered", "is recovering" or "missing" occurred in 20% (11/55) of patients in the placebo arm and 20% (20/101) of patients in the propranolol 3 mg/kg/day 6 months arm. TEAEs reported as "not recovered", "is recovering" or "missing" in at least 2% of patients in the propranolol 3 mg/kg/day 6 months arm vs the placebo arm were: teething (3.0%, 3/101 vs 5.5%, 3/55); toothache (2.0%, 2/101 vs 0%, 0/55); atopic dermatitis (2%, 1/101 vs 0%, 0/55); asthma (2.0%, 2/101 vs 0%, 0/55).

In the pooled safety population, the percentage of patients with at least 1 TEAE with an outcome of "not recovered", "is recovering" or "missing" was 9.3% (22/236) in the all placebo group, 20.0% (40/200) in the all 1 mg/kg/day group, 13.8% (31/224) in the all 3 mg/kg/day, and 16.7% (17/424) in the all propranolol group The only TEAEs with an outcome of "not recovered", "is recovering" or "missing" that occurred in at least 2% of patients in any group were (all placebo vs all 1 mg/kg/day vs all 3 mg/kg/day vs all propranolol, respectively): teething (2.1% vs 4.0% vs 2.3% vs 3.1); and eczema (0.4% vs 2.5% vs 0.4% vs 1.4%). Two (2) patients were listed as having recovered with sequelae: 1 treated with placebo (condition aggravated and vascular skin disorder); and 1 treated with 1 mg/kg/day (epilepsy). Eight (8) patients had TEAEs with unknown outcomes: 3 patients treated with placebo (teething, URTI and condition aggravated); 3 patients treated with 1 mg/kg/day (anaemia, GORD; and 1 patient

with both lower respiratory infection and teething); and 2 patients treated with 3 mg/kg/day (neutropenia and restlessness).

8.2.3.7. Treatment-related TEAEs

In the pivotal study, treatment-related TEAEs reported in at least 2% of patients in the 3 mg/kg/day 6 months arm (in decreasing order of frequency) vs the placebo arm were: peripheral coldness (8.9%, 9/101 vs 0%, 0/55); diarrhoea (7.9%, 8/101 vs 3.6%, 2/55); sleep disorder (6.9%, 7/101 vs 1.8%, 1/55); nightmare (5.0%, 5/101 vs 1.8%, 1); middle insomnia (4.0%, 4/101 vs 5.5%, 3/55); vomiting (3.0%, 3/101 vs 1.8%, 1/55); AST increased (3.0%, 3/101 vs 0%, 0/55); insomnia (3.0%, 3/101 vs 5.5%, 3/55); rash (2.0%, 2/101 vs 0%, 0/55); blood potassium increased (2.0%, 2/101 vs 0%, 0/55). Treatment-related TEAEs reported in at least 2% of patients in the placebo arm and more commonly than in the 3 mg/kg/day 6 months arm were: middle insomnia (5.5%, 3/55 vs 4.0%, 4/101); insomnia (5.5%, 3/55 vs 3.0%, 3/101); and frequent bowel movements (3.6%, 2/55 vs 1.0%, 1/101). Treatment-related TEAEs observed in 2 or more patients in the propranolol arms or at least 1 patient in the placebo arm are summarized in the submission.

In the pooled safety population, TEAEs that were considered related to the study drug were reported more frequently in the propranolol groups than in the placebo group. The percentage of patients with a least 1 treatment-related TEAE in the all placebo group, all 1 mg/kg group, all 3 mg/kg group and all propranolol group were 14.8% (35/236), 37.5% (75/200), 35.3% (79/244), and 36.3% (154/424), respectively. All of the treatment-related TEAEs occurring in at least 2% of patients in the all 1 mg/kg/day and all 3 mg/kg/day groups were known side-effects of propranolol documented in adults, with no unexpected safety signals detected.

In the pooled safety population, the most commonly reported treatment-related TEAEs occurring in at least 5% of patients in one or more of the treatment groups were (pooled placebo [n=235] vs pooled 1 mg/kg/day [n=200] vs pooled 3 mg/kg/day [n=224] vs pooled propranolol dose [n=424]; respectively): peripheral coldness (0% vs 8.0% vs 6.3% vs 7.1%); diarrhoea (1.3% vs 4.5% vs 6.3% vs 5.4%); sleep disorder (0.8% vs 6.0% vs 4.0% vs 5.0%); and nightmare (1.7% vs 2.0% vs 6.3% vs 4.2%). Most treatment related TEAEs were of mild or moderate severity. Four (4) patients experienced severe treatment-related TEAEs: 1 with nightmare in the 1 mg/kg/day 6 months group; 1 with increased serum alkaline phosphatase level in the propranolol phase of the mg/kg/day 3 months group; 2 patients with aggravated condition (1 in the placebo group and 1 in the propranolol phase of the 3 mg/kg/day 3 months group).

8.2.4. Deaths, serious adverse events and other significant adverse events

8.2.4.1. Deaths

There were no deaths in the pooled safety population.

8.2.4.2. Other serious adverse events (SAEs)

In the pivotal study, SAEs were reported in 5.5% (3/55) of patients in the placebo arm (3 events), 5.1% (5/98) of patients in the 1 mg/kg/day 3 months arm (5 events), 2.9% (3/102) of patients in the 1 mg/kg/day 6 months arm (5 events), 9.0% (9/100) patients in the 3 mg/kg/day 3 months arm (13 events), an 5.9% (6/101) patients in the 3 mg/kg/day 6 months arm (7 events). No dose dependent relationship for SAEs was observed for the 4 propranolol treatment regimens. The SAEs reported in the pivotal study are listed in the dossier.

- Of the 33 SAEs reported in the pivotal study, 26 occurred in 401 patients while on active treatment with propranolol (i.e., 0.06 events per patient) and 7 occurred in 236 patients while on treatment with placebo (i.e., 0.03 events per patient).

- In the 3 patients in the placebo arm the 3 SAEs were condition aggravated (x2) and drug ineffective (x1).
- In the 5 patients in the 1 mg/kg/day 3 months arm the 5 SAEs were drug ineffective in the placebo treatment phase (x1), bronchiolitis in the active treatment phase (x1), cystitis in the placebo treatment phase (x1), AV block second degree Mobitz 1 type in the active treatment phase (x1), and cataract operation in the active treatment phase (x1).
- In the 3 patients in the 1 mg/kg/day 6 months arm (all on active treatment) the 5 SAEs were bronchopneumonia and gastroenteritis in 1 patient, epilepsy in 1 patient, and ileostomy and inguinal hernia repair in 1 patient.
- In the 9 patients in the 3 mg/kg/day 3 months arm the 13 events were condition aggravated (ulceration of IH) in 1 patient in the active treatment phase, pyelonephritis in 1 patient in the active treatment phase, apathy and cyanosis in 1 patient in the active treatment phase, GORD in 2 patients both in the active treatment phase, bronchitis and rotavirus infection in 1 patient in the active treatment and placebo treatment phases respectively, bronchiolitis in 1 patient in the active treatment phase, viral infection and dehydration in 1 patient in the active treatment phase, and bradycardia and enterocolitis in 1 patient in the active treatment phase;
- In the 6 patients in the 3 mg/kg/day 6 months arm the 7 events (all on active treatment) were drug ineffective in 1 patient, pyrexia and inflammation in 1 patient, head injury in 1 patient, apathy in 1 patient, bronchiolitis in 1 patient, and bronchitis in 1 patient.

Of the SAEs reported in the pivotal study, 5 were assessed as related to the study drug by the investigator and/or the sponsor: 1x condition aggravated in 1 patient in the placebo arm; 1x AV block second degree Mobitz 1 type in the active treatment phase in the 1 mg/kg/day 6 months arm; 1x obstructive bronchitis in the active treatment phase in the 3 mg/kg/day 3 months arm; 1x condition aggravated (ulceration of IH) in the active treatment phase in the 3 mg/kg/day 3 months arm; and 1x bradycardia in the active treatment phase in the 3 mg/kg/day 3 months arm. The only treatment-related SAEs not categorized as a sudden unexpected serious adverse reaction (SUSAR) was bradycardia. Brief narratives of the 5 SAEs assessed by the investigator and/or sponsor are provided below.

- Condition aggravated: 1 patient in the placebo regimen experienced this SAE on D14. The event was of severe intensity and led to permanent discontinuation of the study drug. Corrective treatment was provided and the event was noted to have recovered with sequelae after 15 days.
- Atrioventricular (AV) block second degree): 1 patient in the active treatment phase in the 1 mg/kg/day for 3 months arm had this SAE diagnosed in the 240 minutes post-first dose ECG on D1. The event was of mild intensity and led to permanent discontinuation of the study drug. The event lasted less than 1 day and recovered without corrective treatment. On the basis of Holter monitor findings 7 months after the event, a pre-existing cardiologic disease was considered probable.
- Condition aggravated: 1 patient in the 3 mg/kg/day 3 months arm, experienced grade III ulceration of hemangioma on D23. The event was of severe intensity and led to permanent discontinuation of the study drug. Corrective treatment was provided, and the event was noted to have recovered after 47 days.
- Bradycardia and Enterocolitis: 1 patient in the active treatment phase in the 3 mg/kg/day 3 months arm. This patient, who had been born prematurely at 25 weeks of gestation, had been in an “extremely grave” condition since birth due to due to dysmaturity (hypoxic damage of the central nervous system, respiratory disorders, periventricular leucomalacia, prematurely induced anemia, hormonal replacement therapy, left inguino-scrotal hernia and retinopathy). During the titration period (on D6, while receiving 1 mg/kg/day), the

patient experienced fever, apnoea, bloating, and soft tools and was diagnosed with enterocolitis. Concomitantly, he presented significant bradycardia (90-100 bpm). Both events were of moderate intensity and led to permanent discontinuation of the study drug. Corrective treatment was provided for both events, and both were noted to have recovered (bradycardia after 3 days and enterocolitis after 9 days).

- Obstructive bronchitis: 1 patient in the 3 mg/kg/day 3 months regimen experienced this SAE considered to be possibly treatment-related by the sponsor, but not by the investigator. While on propranolol, the patient was hospitalized with obstructive bronchitis (associated with respiratory syncytial virus and rhinovirus) on D39. The event was graded severe, was reported as an SAE and led to temporary discontinuation of study drug. Of note, the patient also had a later SAE of rotavirus infection (while on placebo), but this was not considered related to study drug.

In addition to the 26 patients experiencing 33 SAEs in the pivotal study 201, 1 patient in study 102 experienced 3 SAEs while taking propranolol 3 mg/kg/day (crying, pallor, and acute otitis media).

The submission also included a summary of SAEs reported in the pivotal study post-W24. By the cutoff date of 12 December 2012, 319 patients had entered the follow-up period and 20 patients had experienced 30 SAEs. Of the 30 SAEs, 11 occurred in patients previously in a propranolol regimen, 2 occurred in patients previously in the 6 months placebo regimen, and 17 occurred in still blinded patients. SAEs occurring in 2 or more patients were: gastroenteritis 5 patients (2 previously in a propranolol regimen, 2 in patients still blinded, 1 previously in the placebo 6 months regimen); bronchiolitis 4 patients (3 previously in a propranolol regimen, 1 in a patient still blinded); and pneumonia 3 patients (2 in still blinded patients; 1 previously in a propranolol regimen). All other SAEs were reported in only 1 patient. All SAEs led to hospitalization, none were considered life-threatening, all were reported as recovered/resolved.

Of the SAEs in the pivotal study post-W24, all but 2 were considered as having no reasonable possibility of relation to study drug. The 2 exceptions were 2 SAEs in 1 patient (type 1 diabetes mellitus and ketoacidosis). Two months after the last administration of drug, the patient was diagnosed with type 1 diabetes mellitus and ketoacidosis, but blood glucose levels in the titration had been reported to have been normal. The investigator assessed the 2 events as possibly related to the study drug, but the sponsor considered there to be no reasonable possibility of relationship between the events and the study drug.

The ISS/SCS reported 1 SAE (bronchiolitis) in 1 patient from the open-label extension study 301 that occurred approximately 6 months after the last administration of propranolol. The patient recovered after corrective treatment, and the event was not considered to be related to study drug by the investigator or by the sponsor.

8.2.4.3. Other significant TEAEs

8.2.4.3.1. TEAEs leading to dose adjustment

In the pooled safety population, 4 patients had TEAEs leading to dose reduction: 1 patient in the 3 mg/kg/day 3 months group with QT prolongation on the ECG suspected to be related to treatment [study 102]; 1 patient with enteritis in the 3 mg/kg/day 3 months group not suspected to be related to treatment [study 201]; 1 patient in the 3 mg/kg/day 6 month group with diarrhoea not suspected to be related to treatment [study 201]; 1 patient in the placebo 6 months group with URTI not suspected to be related to treatment [study 201]. None of the events were severe and all patients recovered, except one (URTI: outcome unknown).

8.2.4.3.2. Temporary treatment discontinuation

In the pooled safety population, 63 patients had a temporary discontinuation in treatment due to TEAEs.

8.2.4.3.3. TEAEs during titration

All patients were monitored during the 2-week titration period with on-site observation on the first day of treatment (D0) and on the days of dose increase (D7, D14). In the pooled safety population, TEAEs reported in ≥ 2% of patients in the all propranolol group and ≥ 2% more frequently than in the placebo group during the titration period were: diarrhoea (12.5%, 23/424 vs 7.3%, 4/55); pyrexia (6.1%, 26/424 vs 3.6%, 2/55); peripheral coldness (6.1%, 26/424 vs 1.8%, 1/55); sleep disorder (5.7%, 24/424 vs 0%, 0/55); infantile colic (2.8%, 12/424 vs 0%, 0/55); and restlessness (2.4%, 10/424 vs 0%, 0/55).

TEAEs occurring in ≥ 2% of patients in the 3 mg/kg/day 6 months arm and ≥ 2% more commonly than in the placebo arm in the titration period were: diarrhoea (13.9%, 14/101 vs 7.3%, 4/55); peripheral coldness (7.9%, 8/101 vs 1.8%, 1/55); sleep disorder (6.9%, 7/101 vs 0%, 0/55); nightmare (4.0%, 4/55 vs 1.8%, 1/55); infantile colic (4.0%, 4/55 vs 0%, 0/55); GORD (2.0%, 2/55 vs 0%, 0/55); rash (2.0%, 2/55 vs 0%, 0/55); influenza (2.0%, 2/55 vs 0%, 0/55); abdominal distension (2.0%, 2/55 vs 0%, 0/55); and dry skin (2.0%, 2/55 vs 0%, 0/55).

8.2.5. Permanent treatment discontinuation due to TEAEs

In the pivotal study, TEAEs resulting in permanent treatment discontinuation were reported in 6 (10.9%) patients in the placebo arm (7 events), 4 (4.1%) patients in the 1 mg/kg/day 3 months arm (4 events), 2 patients in the 1 mg/kg/day 6 months arm (2 events), 7 (7.0%) patients in the 3 mg/kg/day 3 months arm (9 events) and 3 (3.0%) patients in the 3 mg/kg/day 6 months arm (3 events). In total, TEAEs resulting in treatment discontinuation were reported in 16 (4.0%) patients in the propranolol arms compared with 6 (10.9%) patients in the placebo arm. The TEAEs resulting in permanent treatment discontinuation in the pivotal study are listed in the submission.

In the placebo arm, the 7 TEAEs resulting in permanent treatment discontinuation: were gastroenteritis (mild) in 1 patient; bronchial obstruction (moderate) and upper airway obstruction (moderate) in 1 patient; condition aggravated/worsening of IH in 1 patient (severe, SAE); drug ineffective (mild, SAE) in 1 patient; condition aggravated/worsening of IH (severe, SAE) in 1 patient; and vascular skin disorder (moderate) in 1 patient. Of the 7 TEAEs, all were considered to be unrelated to the study drug, apart from 1 event of condition aggravated/worsening of IH.

In the 1 mg/kg/day 3 months arm, the 4 TEAEs resulting in permanent treatment discontinuation were: rash (mild) in 1 patient; ECG QT prolongation (moderate) 1 patient; drug ineffective (mild, SAE) in 1 patient; and AV block second degree/Mobitz 1 type (mild, SAE) in 1 patient. The 2/4 TEAEs suspected to be related to the study drug were drug ineffective and AV block second degree/Mobitz 1 type.

In the 1 mg/kg/day 6 months arm, the 2 TEAEs resulting in permanent treatment discontinuation were obstructive airways disorder (moderate) in 1 patient, and epilepsy (severe, SAE) in 1 patient. The obstructive airways disorder was suspected to be related to the study drug, while the epilepsy event was not suspected to be related to the study drug.

In the 3 mg/kg/day 3 months arm, the 9 TEAEs resulting in permanent treatment discontinuation were: asthma (mild) in 1 patient; bronchiolitis (mild) in 2 patients; fatigue (moderate) in 1 patient; condition aggravated/ulceration of IH (severe, SAE) in 1 patient; condition aggravated/regrowth of IH (moderate) in 1 patient; enterocolitis (moderate, SAE), bradycardia (moderate, SAE) apnoea (mild), and oliguria (mild) in 1 patient. The 5/9 TEAEs considered to be suspected to be related to the study drug were conditions aggravated (x2), bronchiolitis, fatigue, and bradycardia.

In the 3 mg/kg/day 6 months arm, the 3 TEAEs resulting in permanent treatment discontinuation were: bronchitis (moderate); bronchiolitis (mild); and drug ineffective (mild, SAE). The event of bronchitis was considered to have insufficient evidence to determine whether it was related to the study drug, while the other two events were considered to be unrelated to the study drug.

In the pooled safety population, 22 patients experienced 26 TEAEs leading to permanent study drug discontinuation: 11 (4.7%) patients/12 TEAEs in the all placebo group (n=236); 4 (2.0%) patients/4 TEAEs in the all 1 mg/kg/day group (n=200); 7 (3.1%) patients/10 TEAEs in the all 3 mg/kg/day group (n=224); and 11 patients (2.6%)/14 TEAEs in the all propranolol group (n=424). The only TEAEs resulting in permanent study drug discontinuation in more than 1 patient in the all placebo and all propranolol groups were (respectively): condition aggravated in 4 patients (3 [1.5%] vs and 1 [0.2%]); drug ineffective in 3 patients (2 [0.8%] vs 1 [0.2%]); and bronchiolitis in 3 patients (2 [0.8%] vs 1 [0.2%]). TEAEs leading to permanent study drug discontinuation in the pooled safety population are summarized below in Table 26.

Table 26: ISS/SCS - TEAEs leading to permanent study drug discontinuation; pooled safety population.

Preferred Term	All Placebo n=236	All V0400SB 1mg/kg/day n=200	All V0400SB 3mg/kg/day n=224	All V0400SB n=424
Patients with at least one TEAE leading to definitive study drug discontinuation	**11 (4.7%)**	**4 (2.0%)**	**7 (3.1%)**	**11 (2.6%)**
CONDITION AGGRAVATED	3 (1.3%)	-	1 (0.4%)	1 (0.2%)
DRUG INEFFECTIVE	2 (0.8%)	-	1 (0.4%)	1 (0.2%)
BRONCHIOLITIS	2 (0.8%)	-	1 (0.4%)	1 (0.2%)
FATIGUE	-	-	1 (0.4%)	1 (0.2%)
APNOEA	-	-	1 (0.4%)	1 (0.2%)
ASTHMA	-	-	1 (0.4%)	1 (0.2%)
BRONCHITIS	-	-	1 (0.4%)	1 (0.2%)
BRADYCARDIA	-	-	1 (0.4%)	1 (0.2%)
ENTEROCOLITIS	-	-	1 (0.4%)	1 (0.2%)
OLIGURIA	-	-	1 (0.4%)	1 (0.2%)
OBSTRUCTIVE AIRWAYS DISORDER	-	1 (0.5%)	-	1 (0.2%)
BRONCHIAL OBSTRUCTION	1 (0.4%)	-	-	-
NASAL OBSTRUCTION	1 (0.4%)	-	-	-
GASTROENTERITIS	1 (0.4%)	-	-	-
ATRIOVENTRICULAR BLOCK SECOND DEGREE	-	1 (0.5%)	-	1 (0.2%)
ELECTROCARDIOGRAM QT PROLONGED	-	1 (0.5%)	-	1 (0.2%)
EPILEPSY	-	1 (0.5%)	-	1 (0.2%)
RASH	1 (0.4%)	-	-	-
VASCULAR SKIN DISORDER	1 (0.4%)	-	-	-

Source: Table 2.7.4.2.1b and 2.7.4.2.15b (Section 5.3.5.3 – Vol. 1)
Note: Patients could have had more than 1 TEAE leading to discontinuation, therefore the sum of each column can be different to the total number of patients with at least 1 TEAE leading to discontinuation

8.2.6. Important identified TEAE risks

8.2.6.1. Hypoglycaemia (pivotal study).

In the pooled safety population, 2 patients with TEAEs of hypoglycaemia were reported in the all propranolol group (i.e., 2/424, 0.5%), both from the pivotal study. The 2 patients with hypoglycaemia in the pivotal study included: 1 in the 1 mg/kg/day 6 months arm on D14 (2.5 mmol/L before treatment); and 1 in the 3 mg/kg/day 6 months arm on D14 (2.9 mmol/L at 2 hours post-dose, associated with gastroenteritis present since D11 characterized by vomiting, diarrhoea, and poor feeding). Both events were considered to be of mild intensity. Both events were considered to be related to the study treatment by the investigator. Neither event was considered to be a SAE and neither event led to premature study treatment discontinuation.

8.2.6.2. Bradycardia (pivotal study)

In the pooled safety population, 2 patients with TEAEs of bradycardia were reported in the all propranolol group (i.e., 2/424, 0.5%), both from the pivotal study. The 2 patients with

bradycardia in the pivotal study included: 1 (1.0%) patient in the 1 mg/kg/day 6 months arm (on D167), and 1 patient in the 3 mg/kg/day 3 months arm (on D7). Neither event was considered to be severe, but both were considered to be related to the study treatment by the investigator. The TEAE in the 3 mg/kg/day 3 months arm was considered to be a SAE and led to premature discontinuation of treatment. The event occurred during the titration phase (D7) and was associated with enterocolitis, apnoea and oliguria. The characteristics of these events are summarized below in Table 27.

Table 27: Study 201 - Characteristics of bradycardia TEAE.

Treatment	Intensity	Relationship	Discontinuation	SAE	HR	Symptomatic	Period
1 mg/kg/day 6 months	Mild	Insufficient data	No	No	114	No information	>W12
3 mg/kg/day 3 months	Moderate	Suspected	Yes	Yes	105	No information	Titration

[Note: This table has been amended from the original to remove patient identifiers]

8.2.6.3. Hypotension (pivotal study)

In the pooled safety population, 5 patients with TEAEs of hypotension were reported in the all propranolol group (i.e., 5/424, 1.2%), all from the pivotal study. In the pivotal study, TEAEs of hypotension were reported in 6 patients (5 treated with propranolol, 1 treated in placebo), with similar frequencies in each treatment arm: 1 (1.8%) in the placebo arm; 2 (2.0%) in the 1 mg/kg/day 3 months arm; 1 (1.0%) in the 1 mg/kg/day 6 months arm (1.0%); 2 (2.0%) in the 3 mg/kg/day 3 months arm; and none in the 3 mg/kg/day 6 months arm. All first occurrences were reported before or at W12. None was of severe intensity. The investigator considered them to be related to the study treatment in 1/1 patient in the placebo arm, 2/2 patients in the 1 mg/kg/day 3 months arm, 1/1 patient in the 1 mg/kg/day 6 months arm, 0/2 patient in the 3 mg/kg/day 3 months arm and 0/0 patients in the 3 mg/kg/day 6 months arm. None were considered to be SAEs, none led to premature discontinuation of the study drug and none were considered to be SAEs. The characteristics of these events are summarized below in Table 28.

Table 28: Study 201 - Characteristics of hypotension TEAE

Treatment	Intensity	Relationship	Discontinuation	SAE	SBP/ DBP	Symptomatic	Period
Placebo	Mild	Suspected	No	No	76/30	No	D21-W12
1 mg/kg/day for 3 months	Mild	Suspected	No	No	51/34	No information	D21-W12
1 mg/kg/day for 3 months	Mild	Suspected	No	No	75/36	No information	Titration
1 mg/kg/day for 6 months	Mild	Insufficient data	No	No	47/38	No	D21-W12
3 mg/kg/day for 3 months	Mild	Not suspected	No	No	97/26	No information	Titration
3 mg/kg/day for 3 months	Mild	Not suspected	No	No	68/26	No information	Titration

[Note: This table has been amended from the original to remove patient identifiers]

8.2.6.4. Bronchospasm (pivotal study)

In the pivotal study, the safety analysis included a special search for events potentially linked to bronchospasm. During the blinded review of the data, a list of MedDRA terms considered to be linked or potentially linked to a bronchospasm was established. All AEs coded within the high level term (HLT) “Bronchospasm and obstruction” were considered “linked to bronchospasm”. In addition, AEs coded with the following low level terms (LLTs) of apnoea, asthma, asthma bronchial, bronchial hyperactivity, bronchitis asthmatic, bronchospasm, shortness of breath, wheeze and wheeze worsened were all considered to be potentially “linked to bronchospasm”,

as were AEs linked to bronchiolitis coded with the LLTs of "bronchiolitis" and "respiratory syncytial virus bronchiolitis".

In the pivotal study, 12 patients presented TEAEs potentially linked to bronchospasm, 1 (1.8%) patient in the placebo arm, no patients in the 1 mg/kg/day 3 months arm, 2 (2.0%) patients in the 1 mg/kg/day 6 months arm, 6 (6.0%) patients in the 3 mg/kg/day 3 months arm, and 3 (3.0%) patients in the 3 mg/kg/day 6 months arm. The results for TEAEs linked to bronchospasm or bronchiolitis are summarized below in Table 29, and the characteristics of the events are summarized in the submission.

Table 29: Study 201 - TEAEs linked to bronchospasm or bronchiolitis; safety data set.

Bronchiolitis or Bronchospams	Placebo (N = 55)	V0400SB 1 mg/kg/day 3mths (N = 98)	V0400SB 1 mg/kg/day 6mths (N = 102)	V0400SB 3 mg/kg/day 3mths (N = 100)	V0400SB 3 mg/kg/day 6mths (N = 101)
Bronchiolitis alone	3 (5.5%)	6 (6.1%)	6 (5.9%)	6 (6.0%)	9 (8.9%)
Bronchospasms alone	1 (1.8%)	0 (0.0%)	1 (1.0%)	5 (5.0%)	3 (3.0%)
Both	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (1.0%)	0 (0.0%)
None	51 (92.7%)	92 (93.9%)	94 (92.2%)	88 (88.0%)	89 (88.1%)

8.2.7. Other medically significant TEAEs

8.2.7.1. Cardiovascular TEAEs (pivotal study)

- Peripheral coldness (SOC: Vascular disorder) was reported in 1 patient (1.8%) in the placebo arm, 8 patients (8.2%) in the 1 mg/kg/day 3 months arm, 8 patients (7.8%) in the 1 mg/kg/day 6 months arm, 1 patient (1.0%) in the 3 mg/kg/day 3 months arm and 10 patients (9.9%) in the 3 mg/kg/day 6 months arm. The event was notably more common in three of the four propranolol treatment arms compared with placebo. All occurred before or at W12, and were considered to be related to the study drug by the investigator in 0/1 patient in the placebo arm, 8/8 patients in the 1 mg/kg/day 3 months arm, 8/8 patients in the 1 mg/kg/day 6 months arm, 1/1 patient in the 3 mg/kg/day 3 months arm and 9/10 patients in the 3 mg/kg/day 6 months arm (onsets on D1, D4 for 2 patients; D5, D12, D15 for 2 patients; D43 and D56). None was considered to be severe, none was considered to be a SAE, and none led to premature study drug discontinuation.
- Right bundle branch block (SOC: Cardiac disorders) was reported in 2 patients: 1 (1.0%) patient in the 1 mg/kg/day 6 months arm on D84, and 1 (1.0%) patient in the 3 mg/kg/day 6 months arm on D7. Neither event was considered to be related to the study treatment by the investigator. Neither event was of severe intensity, neither event was considered to be a SAE, and neither event led to premature study treatment discontinuation.
- Atrioventricular block second degree (SOC: Cardiac disorders) was reported in 1 patient in the 1 mg/kg/day 3 months arm after the first dose of study drug (0.5 mg/kg) on D0. The condition was diagnosed at the 240 minute post-dose ECG. It was not of severe intensity or a SAE. It resulted in permanent treatment discontinuation. The investigator suspected the event to be related to the study drug and the sponsor considered a causal relationship to be possible. Holter monitoring 7 months after the event showed one episode of second degree AV block and occasional first degree atrioventricular block, with spontaneous return of sinus rhythm. The sponsor's causal assessment remained possible, but Holter monitoring after the event revealed that the patient probably had a pre-existing cardiac disease.
- Cyanosis (SOC: Cardiac disorders) was reported in 1 patient in the 3 mg/kg/day 3 months arm, on D30. It was not of severe intensity. It was not considered to be related to the study drug by the investigator. It did not lead to premature study treatment discontinuation, but was considered to be a SAE.

- Electrocardiogram QT prolonged (SOC: Investigations) occurred in 3 patients, all from the 1 mg/kg/day 3 months arm (3.1%). Two cases occurred before or at W12 (1 on D7 and 1 on D15) and one after W12 (D168). None was considered to be of severe intensity. All were considered to be related to the study drug by the investigator. One led to premature study treatment discontinuation (the event that occurred on D7). None was considered to be a SAE.

8.2.7.2. Hepatic TEAEs (pivotal study)

- Hepatobiliary disorder (SOC) was reported in 1 (1.0%) patient in the 6 mg/kg/day 6 months arm. This event was cytolytic hepatitis of moderate severity reported on D37. The study drug was temporarily discontinued and the patient recovered. The event was not suspected to be related to study drug. The patient had abnormal high results at baseline for AST (341 UI/L), ALT (418 UI/L) and GGT (242 UI/L).
- AST increased (SOC: Investigations) was reported 1 (1.0%) patient in the 1 mg/kg/day 3 months arm, 2 (2.0%) patients in the 1 mg/kg/day 6 months arm, and 3 (3.0%) patients in the 3 mg/kg/day arm 6 months arm (i.e., 1.2%, 5/401, of all propranolol treated patients). The 3 events in the 3 mg/kg/day 6 months arm were considered to be related to the study drug by the investigator.
- ALT increased (SOC: Investigations) was reported in 2 (2.0%) patients in the 3 mg/kg/day 6 months arm (i.e., 0.5%, 2/401, of all propranolol treated patients).
- Transaminases increased (SOC: Investigations) was reported in 1 (1.8%) patient in the placebo arm.

8.2.7.3. Other (pivotal study)

- Neurodevelopment disorder (SOC: Psychiatric disorders) was reported in 1 (1.0%) patient in the 1 mg/kg/day 6 months arm after W12. The patient had an outcome of not recovered, recovering, or missing.
- Petit mal epilepsy (SOC: Nervous system disorders) of moderate severity was reported in 1 (1.0%) patient in the 3 mg/kg/day 3 months arm in the active treatment phase occurring between weeks 5 and 8.
- Epilepsy (SOC: Nervous system disorders) graded severe was reported in 1 (1.0%) patient in the 1 mg/kg/day 6 months arm on D150 and resulted in discontinuation of the study drug. The TEAE was not considered to be related to the study drug by the investigator.
- Intestinal obstruction (SOC: Gastrointestinal disorders) occurred in 1 (1.0%) patient in the 1 mg/kg/day 6 months arm, after W12.
- Pharyngeal oedema (SOC: Respiratory, thoracic and mediastinal disorders) was reported in 1 (1.0%) patient in the 1 mg/kg/day 3 months arm with an onset between W1-2.
- Lip swelling (SOC: Gastrointestinal disorders), possibly indicative of an allergic reaction, was reported in 1 (1.0%) patient in the 3 mg/kg/day 6 months arm with an onset between W12-16.
- Decreased appetite (SOC: Metabolism and nutrition disorders) was reported in 1 (1.8%) patient in the placebo arm, 4 (4.1%) patients in the 1 mg/kg/day 3 months arm, 1 (1.0%) patients in the 1 mg/kg/day 6 months arm, 5 (5.0%) patients in the 3 mg/kg/day 3 months arm, and 1 (1.0%) patient in the 3 mg/kg/day 6 months arm (i.e., 2.7%, 11/401, of all propranolol treated patients). All events of decreased appetite occurred on or before W12. All were considered to be related to the study drug by the investigator, except the patient in the 1 mg/kg/day 6 months regimen and 2 patients in the 3 mg/kg/day 3 months regimen. None of the TEAEs was considered to be severe in intensity.

- Rash (SOC: Skin an subcutaneous tissue disorders) was reported in 1 (1.0%) patient in the placebo arm, 3 (3.1%) patients in the 1 mg/kg/day 3 months arm, 3 (2.9%) patients in the 1 mg/kg/day 6 months arm, 3 (3.0%) patients in the 3 mg/kg/day 3 months arm, and 5 (5.0%) patients in the 2 mg/kg/day 6 months arm (i.e., 3.5%, 14/401, of all propranolol treated patients).
- No cases of anaphylactic reaction or angioedema were reported.

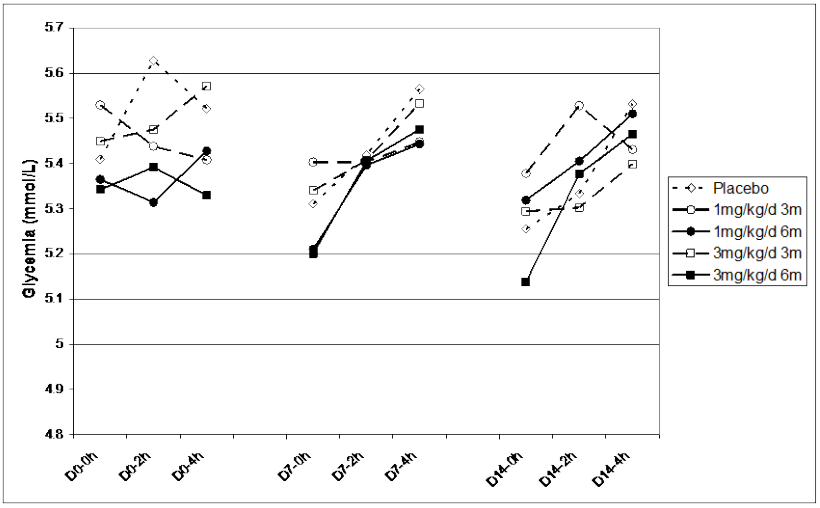
8.2.8. Laboratory tests

8.2.8.1. Blood glucose

8.2.8.1.1. Blood glucose measured by pin-prick testing

In the pivotal study, blood glucose levels were monitored by pin-prick in the titration phase on D0, D7, and D14 at pre-dose and then at 2 and 4 hours post-dose. There was no evidence of hypoglycaemia using pin-prick testing during the titration phase in the five treatment arms at 120 and 240 minutes following dosing on D0, D7 and D14 (see Figure 3, below).

Figure 3: Study 201 - Glucose pin-prick testing over the titration period.



In the pooled safety population, in the titration period mean pre-dose blood glucose levels on D0, D7, and D14 were similar for the all placebo, all 1 mg/kg/day and all 3 mg/kg/day groups (see Table 30, below). With the exception of a decrease in blood glucose level from pre-dose on D0+2h and D0+4h in the 1 mg/kg/day group, all changes in blood glucose levels from pre-dose were small increases.

Table 30: ISS/SCS - Blood glucose changes from pre-dose values in the titration period (D0, D7, D14) by pooled placebo or pooled dose of propranolol; pooled safety population.

Predose Value Change from predose		Blood Glucose (mmol/L)			
		All Placebo n=55	All V0400SB 1mg/kg/day n=200	All V0400SB 3mg/kg/day n=224	All V0400SB n=424
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Day 0 Predose value		5.406 (0.786)	5.444 (0.900)	5.429 (0.814)	5.436 (0.854)
			1mg/kg/day	1mg/kg/day	1mg/kg/day
Change from predose	D0 +2H	0.206 (0.972)	-0.069 (0.964)	0.009 (0.974)	-0.027 (0.969)
	D0 +4H	0.128 (0.954)	-0.023 (0.973)	0.017 (0.921)	-0.001 (0.944)
Day 7 Predose value		5.309 (0.662)	5.302 (0.791)	5.306 (0.846)	5.304 (0.819)
			1mg/kg/day	2mg/kg/day	
Change from predose	D7 +2H	0.120 (0.844)	0.108 (0.839)	0.154 (0.913)	0.133 (0.878)
	D7 +4H	0.267 (0.746)	0.135 (0.867)	0.225 (1.072)	0.183 (0.982)
Day 14 Predose value		5.252 (0.959)	5.346 (0.929)	5.256 (0.858)	5.298 (0.892)
			1mg/kg/day	3mg/kg/day	
Change from predose	D14 +2H	0.081 (1.046)	0.122 (1.029)	0.105 (0.883)	0.113 (0.953)
	D14 +4H	0.221 (1.041)	0.140 (0.868)	0.186 (0.871)	0.165 (0.869)

The normal range for blood glucose (3.33 to 5.83 mmol/L), was used to categorize patients into low, normal, or high blood glucose level groups. In the pooled safety population, in the titration period the majority of patients in each treatment group (61.1% to 75.0%) had no change in blood glucose level categories during the 4 hour post-dose period on D0, D7, and D14. The remaining patients in each treatment group were approximately evenly divided between increases and decreases in category. The patients with downward shifts in category the treatment groups are summarized below in Table 31.

Table 31: ISS/SCS - Patients with downward shift in blood glucose category compared to pre-dose according to normal range; safety population

Timepoint (Day+hour)	Decreasing Shift in Glycemia Category According to Normal Ranges			
	All Placebo n=55	All V0400SB 1mg/kg/day n=200	All V0400SB 3mg/kg/day n=224	All V0400SB n=424
	n (%)	n (%)	n (%)	n (%)
D0 +2H	9 (16.7%)	22 (11.5%)	29 (13.2%)	51 (12.4%)
D0 +4H	8 (14.8%)	27 (14.4%)	33 (15.1%)	60 (14.8%)
D7 +2H	8 (15.7%)	24 (12.9%)	29 (13.6%)	53 (13.3%)
D7 +4H	4 (7.7%)	22 (11.8%)	27 (12.6%)	49 (12.3%)
D14 +2H	6 (13.3%)	26 (13.9%)	29 (13.9%)	55 (13.9%)
D14 +4H	6 (13.6%)	15 (8.0%)	26 (12.2%)	41 (10.2%)

The number and percentage of patients with blood glucose level < 3.33 mmol/L in the pooled safety population are summarized below in Table 32. There were no reports of patients with blood glucose levels < 2.22 mmol/L.

Table 32: ISS/SCS - Patients with blood glucose < 3.33 mmol/L; safety population

Blood Glucose <3.33 mmol/L	All Placebo n=55	All V0400SB 1mg/kg/day n=200	All V0400SB 3mg/kg/day n=224	All V0400SB n=424
Baseline	-	1 (0.5%)	-	1 (0.2%)
D0 +2H	-	1 (0.5%)	-	1 (0.2%)
D0 +4H	-	2 (1.0%)	1 (0.5%)	3 (0.7%)
Predose D7	-	2 (1.0%)	3 (1.4%)	5 (1.2%)
D7 +2H	-	-	-	-
D7 +4H	-	1 (0.5%)	-	1 (0.2%)
Predose D14	-	4 (2.1%)	1 (0.5%)	5 (1.2%)
D14 +2H	-	2 (1.1%)	2 (1.0%)	4 (1.0%)
D14 +4H	-	-	1 (0.5%)	1 (0.2%)
Last Value on V0400SB	-	-	1 (0.4%)	1 (0.2%)
Last Value on Placebo	-	-	-	-

8.2.8.1.2. Critical blood glucose levels from blood biochemistry measurements

As well as monitoring blood glucose by pin-prick during the titration period, blood glucose levels were also measured as a blood biochemistry parameter throughout the study. Critical values from the literature were used to generate a listing of patients with critical glucose values < 2.6 mmol/L or > 20 mmol/L. There were 2 patients in the titration period with baseline critical values < 2.6 mmol/L detected routine monitoring (venous blood), and in both patients the blood glucose returned to normal levels during treatment (1 patient in the all 1 mg/kg/day and 1 patient in the all 3 mg/kg/day group). During the treatment, 2 patients with normal blood glucose levels at baseline developed critical values < 2.6 mmol at W24 (1 in all 1 mg/kg/day group and 1 in the 3 mg/kg/day group). Of the 2 patients with treatment emergent critical blood glucose levels < 2.6 mmol/L in the pooled safety population, 1 occurred in the placebo treatment phase in the all 1 mg/kg/day group, and 1 occurred on active treatment with propranolol in the 3 mg/kg/day group. Therefore, in the pooled safety population, 1 (0.4%) patient in the all placebo group (n=236) and 1 (0.2%) patient in the all propranolol group (n=424) with normal baseline blood glucose levels experienced treatment emergent critical blood glucose levels < 2.6 mmol/L at W24.

8.2.8.2. Haematology (pooled safety population)

Quantitative descriptive statistics were presented for the full range of haematology parameters including, summary values, proportion of values within, below or above the normal range of values, shift tables, and clinically significant abnormal changes. The sponsor stated that due to physiological changes in haematology values with age in the studied age range, interpretation of changes in overall mean values of mean changes should be interpreted with caution. The haematology parameters assessed were haemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), red blood cell (RBC) count, reticulocyte count, white blood cell (WBC) count, platelet count, differential WBC count (total and segmented neutrophils, bands, lymphocytes, monocytes, basophils and eosinophils). The haematology laboratory parameters were assessed at screening (baseline), W12 and W24. The normal ranges for the presented haematology parameters are provided in the submission. Clinically significant abnormalities in RBC parameters and clinically significant abnormalities in WBC and platelet parameters are summarized in the submission.

In the pooled safety population, the number of patients shifting from non-clinically significant (NCS) to clinically significant (CS) values were small in both placebo and propranolol treated patients. There were sporadic numbers of patients with post-baseline high of low clinically significant haematology values (normal ranges from local laboratories) in the pooled safety population, and no particular patterns emerged. No post-baseline CS values during the study were reported for MCHC, reticulocytes or banded neutrophils. For most other haematology parameters, post-baseline CS values occurred sporadically throughout the study (<2% of patients in each pooled dose group W12 and W24 time-points). In the pooled safety population, post-baseline high or low CS values (normal ranges from local laboratories) at W12 and/or W24 reported in ≥ 2% more patients in at least one of the treatment arms were:

- CS low hematocrit at W24 in 0.7% (1/147), 2.4% (2/85), and 1.2% (1/84) of patients in the all placebo, all 1 mg/kg/day and all 3 mg/kg/day groups, respectively.
- CS low hemoglobin at W24 in 0.7% (1/147), 2.4% (2/85) and 0% (0/84) of patients in the all placebo, all 1 mg/kg/day and the all 3 mg/kg/day groups, respectively;
- CS low segmented neutrophil at W12 in 0% (0/2), 7.0% (3/43) and 2.1% (1/48) of patients in the all placebo, pooled 1 mg/kg/day and the all 3 mg/kg/day groups, respectively.
- CS low MCV at W24 in 0% (0/147), 0% (0/85) and 2.4% (2/84) of patients in the all placebo, pooled 1 mg/kg/day and the all 3 mg/kg/day groups, respectively.

Most parameters had a trend towards more patients with post-baseline CS values treated with propranolol than with placebo. However, the sponsor comments that this observation should be interpreted with caution due to the high degree of variability in the data, physiological biological changes with age in infants (more important in the 6 months groups due to longer exposure) and the very low number of symptomatic changes. No trends over time were noted for any haematology parameter, nor was there a difference between the propranolol dose groups. In addition, no clear trends were observed between regimen groups in the safety population when analyzed by treatment regimens.

TEAEs associated with haematology abnormalities in the pooled safety population are summarized below in Table 33. None of the TEAEs associated with haematology abnormalities were serious, led to study drug discontinuation (temporary or definitive) or to dose modification.

Table 33: ISS/SCS - TEAEs associated with haematology abnormalities; safety population.

Preferred Term	All Placebo n=236	All V0400SB 1mg/kg/day n=200	All V0400SB 3mg/kg/day n=224	All V0400SB n=424
NEUTROPHIL COUNT DECREASED	-	2 (1.0%)	-	2 (0.5%)
NEUTROPHIL COUNT ABNORMAL	1 (0.4%)	1 (0.5%)	-	1 (0.2%)
BASOPHIL COUNT INCREASED	-	1 (0.5%)	-	1 (0.2%)
EOSINOPHIL COUNT INCREASED	-	1 (0.5%)	-	1 (0.2%)
PLATELET COUNT INCREASED	-	1 (0.5%)	-	1 (0.2%)
WHITE BLOOD CELL COUNT INCREASED	-	1 (0.5%)	-	1 (0.2%)
BLOOD IRON DECREASED	-	1 (0.5%)	1 (0.4%)	2 (0.5%)
ANAEMIA	-	2 (1.0%)	3 (1.3%)	5 (1.2%)
IRON DEFICIENCY ANAEMIA	-	3 (1.5%)	-	3 (0.7%)
NEUTROPENIA	-	1 (0.5%)	2 (0.9%)	3 (0.7%)
LEUKOPENIA	-	1 (0.5%)	-	1 (0.2%)
LYMPHOCYTOSIS	-	1 (0.5%)	-	1 (0.2%)
MONOCYTOSIS	-	1 (0.5%)	-	1 (0.2%)
HYPOCHROMASIA	-	-	1 (0.4%)	1 (0.2%)

In the pooled safety population, TEAEs associated with haematology abnormalities considered to be related to the study drug in the all propranolol group (n=424) vs the all placebo group (n=236) were: anaemia (0.2% vs 0%); and iron deficiency anaemia (0.2% vs 0%).

8.2.8.3. Biochemistry

The biochemistry laboratory parameters were summarized using similar descriptive statistical methods as those used to summarize the haematological parameters. Clinical chemistry laboratory parameters were measured at screening (baseline), W12 and W24. The following parameters were measured: total bilirubin, creatinine, glucose, aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase, total protein, calcium, potassium, chloride and sodium. The normal ranges for the biochemistry parameters; clinically significant hepatic biochemistry parameters' and other (non-hepatic) clinically significant biochemistry parameters are summarized in the submission.

In the pooled safety population, no change from baseline in category was the most common outcome for most biochemistry parameters. At least 70% of patients had no change from baseline for AST, ALP, creatinine, calcium, glucose, protein, sodium and chloride. Other parameters had a lower percentage of patients with no change (i.e., ALT [38.0-66.7%], potassium [50.7-62.9%] bilirubin [62.2-71.1%], GGT [61.9-94.8%]).

In the pooled safety population, post-baseline high or low CS values (normal ranges from local laboratories) reported in ≥ 2% more patients in at least one of the treatment arms at W12 and/or W24 were:

- AST high at W12 in 0% (0/23), 0% (0/162), and 2.3% (4/176) of patients in the all placebo, all 1 mg/kg/day and all 3 mg/kg/day groups, respectively.

- AST high at W24 in 2.1% (3/140), 2.6% (2/77) and 1.3% (3/180) of patients in the all placebo, pooled 1 mg/kg/day and the all 3 mg/kg/day groups, respectively.
- ALT high at W24 in 2.1% (3/142), 0% (0/82), and 1.2% (1/82) of patients in the all placebo, pooled 1 mg/kg/day and the all 3 mg/kg/day groups, respectively.
- ALP high at W24 in 3 (2.3%), 0% (0/72) and 0% (0/80) of patients in the all placebo, all 1 mg/kg/day and all 3 mg/kg/day groups, respectively.

In the pooled safety population, patients with post-baseline critical biochemistry results (according to literature-derived limits) were:

- 2 patients with isolated critical low calcium values: 1 patient in the 1 mg/kg/day 3 months regimen) had an isolated critical low value (1.45 mmol/L) at W24 (i.e., in the placebo phase); 1 patient in the 3 mg/kg/day 6 months regimen had a critical low value (1.37 mmol/L) at W24. Both patients with critical low calcium levels were from the pivotal study. Overall, in the pooled safety population, isolated critical low calcium levels were reported in 1 (0.4%) patients in the all placebo group (n=236) and 1 (0.2%) patient in the all propranolol group.
- 26 patients with 32 critical high potassium values (ranging between 6.1 and 8.4 mmol/L). When considering post-baseline critical high potassium values not present at baseline, 10 patients had critical high potassium values (ranging between 6.1 and 7.9 mmol/L): 3 patients in the 1 mg/kg/day 3 months regimen (2 in the placebo phase; 1 in the active phase); 1 patient in the 1 mg/kg/day 6 months regimen (1 in the active phase); 4 patients in the 3 mg/kg/day 3 months regimen (3 in the active phase, 1 in the placebo phase); and 2 patients in 3 mg/kg/day 6 months regimen (2 in the active phase). All 10 patients with post-baseline critical high potassium values were from the pivotal study. Overall, in the pooled safety population, isolated post-baseline critical high potassium levels were reported in 3 (1.3%) patients in the all placebo group (n=236) and 7 (1.7%) patients in the all propranolol group (n=424)

TEAEs associated with biochemistry abnormalities in the pooled safety population are summarized below in Table 34.

Table 34: ISS/SCS - TEAEs associated with biochemistry; safety population.

Preferred Term	All Placebo n=236	All V0400SB 1mg/kg/day n=200	All V0400SB 3mg/kg/day n=224	All V0400SB n=424
BLOOD POTASSIUM INCREASED	1 (0.4%)	1 (0.5%)	3 (1.3%)	4 (0.9%)
BLOOD CALCIUM INCREASED	-	1 (0.5%)	2 (0.9%)	3 (0.7%)
BLOOD IRON DECREASED	-	1 (0.5%)	1 (0.4%)	2 (0.5%)
ASPARTATE AMINOTRANSFERASE INCREASED	1 (0.4%)	2 (1.0%)	3 (1.3%)	5 (1.2%)
ALANINE AMINOTRANSFERASE INCREASED	-	-	2 (0.9%)	2 (0.5%)
TRANSAMINASES INCREASED	1 (0.4%)	-	-	-
BLOOD ALKALINE PHOSPHATASE INCREASED	2 (0.8%)	1 (0.5%)	1 (0.4%)	2 (0.5%)
BLOOD IMMUNOGLOBULIN E INCREASED	-	1 (0.5%)	-	1 (0.2%)
URINE CALCIUM/CREATININE RATIO INCREASED	-	1 (0.5%)	-	1 (0.2%)
PROTEIN TOTAL DECREASED	-	-	1 (0.4%)	1 (0.2%)
BLOOD CREATININE INCREASED	-	-	1 (0.4%)	1 (0.2%)
HYPERPHOSPHATASAEMIA	1 (0.4%)	-	-	-
HYPOGLYCEMIA	-	1 (0.5%)	1 (0.4%)	2 (0.5%)
HYPOCALCAEMIA	-	1 (0.5%)	-	1 (0.2%)

None of the TEAEs associated with biochemistry abnormalities were serious, led to study drug discontinuation (temporary or permanent) or to dose modification. One (1) patient had a severe TEAE of increased blood ALP level in the all 3 mg/kg/day group. In the pooled safety population, TEAEs associated with biochemistry abnormalities considered to be related to the study drug in the all propranolol group (n=424) vs the all placebo group (n=236) were: AST

increased (0.7% vs 0%); hyperkalaemia (0.7% vs 0%); alkaline phosphatase increased (0.5% vs 0%); hypoglycaemia (0.5% vs 0%); and ALT increased (0.2% vs 0%)

8.2.9. Vital signs

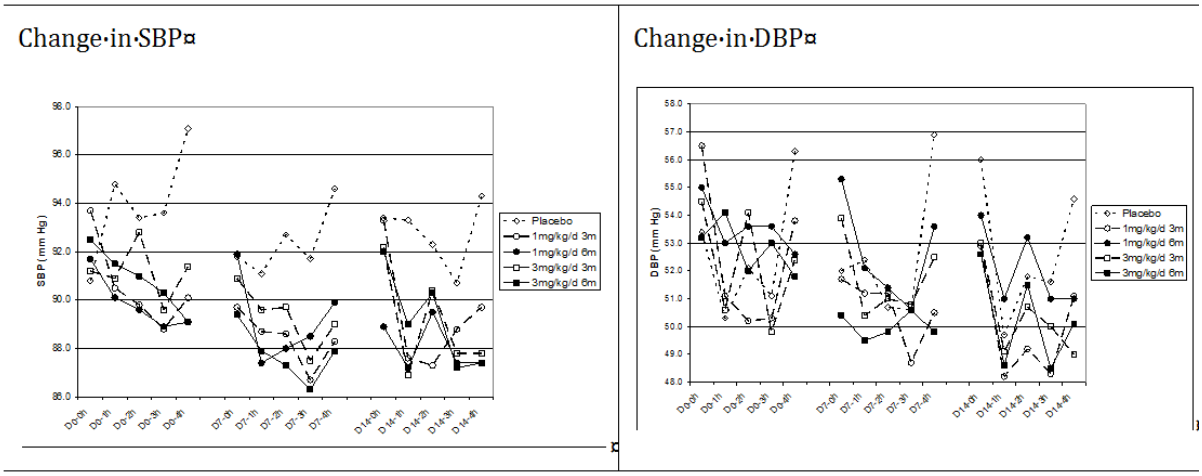
8.2.9.1. Blood pressure

8.2.9.1.1. Blood pressure in the titration period

The reference values for BP in the age groups were 65-85/45-55 mmHg (0-3 months), 70-90/50-65 mmHg (3-6 months), and 80-100/55-65 mmHg (6-12 months). In the pivotal study, mean baseline BP values were similar in the 5 treatment arms, with the SBP ranging from approximately 91 to 94 mmHg and the DBP ranging from approximately 53 to 56 mmHg.

In the titration period of the pivotal study, systolic and diastolic blood pressure (SBP, DBP) were monitored on D0, D7 and D14 pre-dose, and then post-dose at 1, 2, 3, and 4 hours. On D0, D7 and D14, both SBP and DBP increased at 4 hours following dose in the placebo arm, and decreased in the each of the 4 active treatment arms without a dose effect. The change in BP in the titration period over the 4 hours following dose on D0, D7, and D14 in the 5 treatment arms is summarized below in Figure 4.

Figure 4: Study 201 - Change in SBP (left panel) and DBP (right panel) during titration.



In the 3 mg/kg/day 6 months arm, in the titration period the highest mean (SD) reductions in SBP from baseline following dose (vs placebo arm at the same time-point) on D0, D7, and D14 were: -3.4 (17.7) mmHg vs +6.2 (19.1) on D0-4h; -2.9 (15.3) mmHg vs -0.4 (18.6) mmHg on D7-3h; and -5.0 (14.8) at 3 hours vs -2.5 (13.1) mmHg on D14-3h following dose.

In the 3 mg/kg/day 6 months arm, in the titration period the highest mean (SD) reductions in DBP from baseline following dose (vs placebo arm at the same time-point) on D0, D7, and D14 were: -1.3 (16.6) vs -1.5 (16.7) on D0-2h and -1.3 (16.2) vs -1.5 (16.7) on D0-4h; -1.1 (14.0) vs +0.6 (10.3) on D7-1h; and -4.2 (14.3) mmHg vs -3.5 (15.3) D14-3h.

8.2.9.1.2. Blood pressure change over the treatment period

- Systolic blood pressure

The mean SBP profile over the course of the study in the five treatment arms in the pivotal study, and the change in mean SBP from baseline over time, are summarized in the submission. In the placebo arm, mean SBP was stable through to W12, then increased through to W14. In the 3 mg/kg/day 6 months arm, mean SBP decreased over the first three weeks of the study then began to increase and approximately paralleled placebo from W16 through to W24. In the 3 mg/kg/day 6 months arm vs placebo arm, mean (SD) SPB values (mmHg) were: 92.5 (13.3) vs 90.8 (16.2) at baseline; 89.1 (13.4) vs 97.1 (14.9) at D0-4h post-dose; 87.9 (11.7) vs 94.6 (12.9) at D7-4h post-dose; 87.4 (12.1) vs 94.3 (14.4) at D14-4h post-dose; 89.3 (14.0) vs 91.6 (19.0) at

W5; 91.7 (11.7) vs 90.9 (14.8) at W12; 92.0 (14.1) vs 93.5 (9.4) at W16; and 96.5 (15.7) vs 96.2 (13.8) at W24.

In the pivotal study, the percentage of patients in the 3 mg/kg/day 6 months arm whose SBP fell from normal values at baseline to below normal values over the treatment period vs placebo arm were: 0% vs 1.9% at D0-4h post-dose; 0% vs 0% at D7-4h post-dose; 2.0% vs 2.1% at D14-4h post-dose; 3.1% vs 11.1% at W5; 7.3% vs 8.3% at W12; 4.3% vs 4.8% at W16; and 6.7% vs 10.5% at W24. The percentage of patients with shifts to decreasing SBP in the pooled safety population was presented. In the pooled safety population, most of the decreasing shifts in SBP were from high to low values.

In patients who had at least one SBP value lower than the normal range, many had between one and three low values. In most cases these low SBP values were not identified as clinically significant by the investigators. In the pivotal study, 23/55 (41.8%) patients in the placebo arm had at least one SBP value below the normal range during the study treatment period, including 16 during the titration period (D0-1h to D14), 9 between D21 and W12, and 3 after W12. In the pivotal study, 54/101 (53.5%) patients in the 3 mg/kg/day 6 months arm, had at least one SBP value below the normal range during the study treatment period, including 30 during the titration period, 27 between D21 and W12, and 27 after W12. The percentage of patients in the 3 mg/kg/day arm with SBP values below normal levels vs placebo arm over the treatment period were: 1.0% vs 9.1% at baseline; 3.0% vs 3.8% at D0-4h post-dose; 1.0% vs 0% at D7-4h post-dose; 10.1% vs 16.7% at W5; 10.3% vs 8.3% at W12; 16.0% vs 4.8% at W16; 12.1% vs 10.5% at W24.

- Diastolic blood pressure

The mean DBP profile over the course of the study in the five treatment arms, and the change in mean DBP from baseline over time is summarized in the submission. The patterns of DBP change over the treatment period in the placebo and 3 mg/kg/day 6 months arms was similar to the patterns of SBP change. In the 3 mg/kg/day 6 months arm vs placebo arm, mean (SD) DBP values (mmHg) were: 50.8 (11.1 vs 53.1 (11.6) at baseline; 51.8 (12.9) vs 56.3 (11.7) at D0-4h post-dose; 49.8 (11.3) vs 56.9 (13.2) at D7-04h post-dose; 50.1 (11.5) vs 54.6 (12,3) at D14-4h post dose; 52.1 (10.8) vs 54.1 (14.6) at W5; 54.8 (11.7) vs 53.5 (8.9) at W12; 55.6 (11.8) vs 54.8 (9.2) at W16; and 58.2 (12.6) vs 56.5 (8.4) at W24.

The percentage of patients in the 3 mg/kg/day 6 months arm whose DBP fell from normal values at baseline to below normal values over the treatment period vs placebo arm were: 11.0% vs 9.4% at D0-4h post-dose; 15.2% vs 5,6% at D7-4h post-dose; 17.0% vs 10.6% at D14-4h post-dose; 13.3% vs 16.7% at W5; 16.7% vs 12.5% at W12; 23.7% vs 14.3% at W16; and 22.5% vs 5.3% at W24. The percentage of patients with shifts to decreasing DBP in the pooled safety population was presented.

In the pivotal study, at least 90% of all patients had a least one DBP value lower than the normal range. In most cases, the low DBP values were not identified as clinically significant by the investigator. In the placebo arm, 49/55 (89.1%) patients had at least one DBP value below the normal range during the study treatment period, including 47 during the titration period (D0-1h to D14), 25 between D21 and W12, and 16 after W12. In the 3 mg/kg/day 6 months arm, 98/101 (97.0%) patients had at least one DBP value below the normal range during the study treatment period, including 83 during the titration period, 77 between D21 and W12, and 67 after W12.

The percentage of patients in the 3 mg/kg/day arm with DBP values below normal levels vs placebo arm over the treatment period were: 33.0% vs 36.4% at baseline; 36.6% vs 20.8% at D0-4h post-dose; 42.0% vs 24,1% at D7-4h post-dose; 39.4% vs 41.7% at W5; 42.3% vs 41.7% at W12; 44.7% vs 52.4% at W16; 42.2% vs 42.1% at W24.

8.2.9.1.3. BP (SBP/DBP) low potentially clinically significant values (PCSVs)

In this section, the results for low and very low BP are described for the 5 treatment arms in the pivotal study. The defined (SAP) blood pressure (SBP/DBP) categories for the pivotal study are summarized below in Table 35.

Table 35: Study 201 - Blood pressure categories

		Blood pressure		
Age		**0-3 months**	**3-6 months**	**>6 months**
Sub-categories	Very low BP (PCSV)	<50/30 mmHg[(a)]	<50/30 mmHg	<50/30 mmHg
	Low BP	<60/40 mmHg[(b)]	<65/45 mmHg	<70/50 mmHg
	Normal BP	≥60/40 mmHg[(c)]	≥65/45 mmHg	≥70/50 mmHg

a: if SBP<50 mmHg or DBP<30 mmHg
b: else if 50 mmHg ≤ SBP <60 mmHg or 30 mmHg ≤ DBP <40 mmHg
c: else if SBP ≥ 60 mmHg and DBP ≥ 40 mmHg

In the placebo arm, 78.2% (43/55) patients had at least one low BP measurement during the study, including 31 patients during the titration period (D0-1h to D14-4h), 15 patients between D21 and W12, and 7 patients after W12. In this arm, 18.2% (10/55) of patients had 17 very low BP measurements, including 8 patients (13 PCSVs including 12 between D7-1h and D14-4h) during the titration period, 3 patients (4 PCSVs) between D21 and W12, and none after W12. No patients were reported with very low SBP values.

In the 1 mg/kg/day 3 months arm, 83.7% (82/98) patients had at least one low BP measurement during the study, including 65 during the titration period, 46 between D21 and W12, and 35 after W12. In this arm, 11.2% (11/98) of patients had 20 very low BP measurements, including 10 (17 PCSVs including 11 between D7-1h and D14-4h) during the titration period, 2 (3 PCSVs) between D21 and W12, and none after W12. No patients presented with very low SBP values.

In the 1 mg/kg/day 6 months arm, 78.4% (80/102) patients had at least one low BP measurement during the study treatment period, including 60 during the titration period, 50 between D21 and W12, and 39 after W12. In this arm, 10.8% (11/102) of patients had very low BP measurements (15 PCSVs), including 9 during the titration period (13 PCSVs including 9 between D7-1h and D14-4h), 2 (2 PCSVs) between D21 and W12, and none after W12. Only one patient presented (once) with a very low SBP, at W5.

In the 3 mg/kg/day 3 months arm, 82.0% (82/100) of patients had at least one low BP measurement during the study treatment period, including 60 during the titration period, 56 between D21 and W12, and 34 after W12. In this arm, 19.0% (19/100) patients had very low BP measurements (52 PCSVs), including 18 (47 PCSVs including 31 between D7-1h and D14-4h) during the titration period, 4 (5 PCSVs) between D21 and W12, and none after W12. Only 2 patients presented (both once) with a very low SBP, both during the titration period.

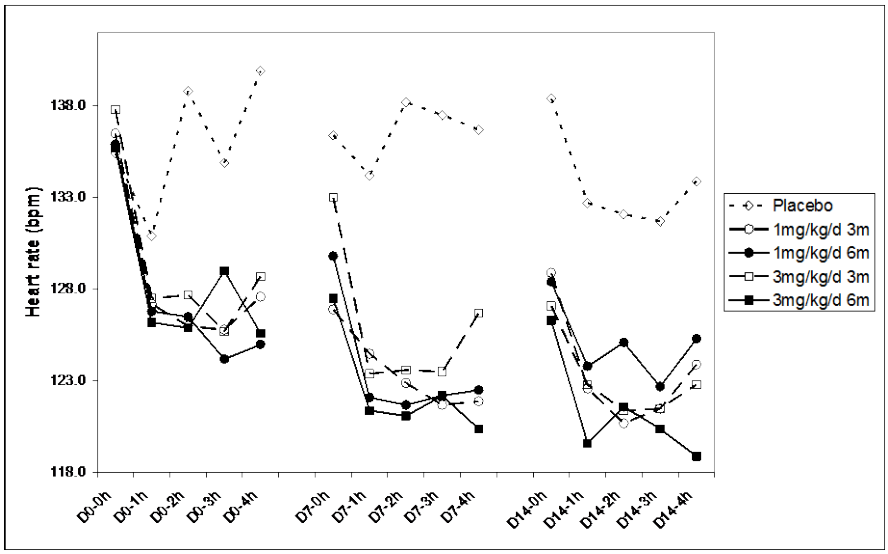
In the 3 mg/kg/day 6 months arm, 83.2% (84/101) of patients had at least one low BP measurement during the study treatment period, including 60 during the titration period, 51 between D21 and W12, and 40 after W12. In this arm, 20.8% (21/101) patients had very low BP measurements (40 PCSVs), including 20 (35 PCSVs including 23 between D7-1h and D14-4h) during the titration period, 4 (4 PCSVs) between D21 and W12, and 1 (1 PCSV) after W12. Only one patient presented (once) with a very low SBP, at D7-4h.

8.2.9.2. Heart rate (HR)

In the pivotal study, the reference values for HR based on age were 100-150 bpm (0-3 months), 90-120 bpm (3-6 months), and 80-120 bpm (6-12 months). In the study, mean baseline HR values were similar in the 5 treatment arms, ranging from 135 to 138 bpm. In the titration period, HR was measured on D0, D7, and D14 pre-dose and then post-dose at 1, 2, 3 and 4 hours.

The HR in the 4 active treatment arms was lower than in the placebo arm over the 4 hours following dose at D0, D7, and D14 (see Figure 5, below). In the 3 mg/kg/day 6 months arm, in the titration period the highest mean (SD) reductions in HR (bpm) from baseline following dose (vs placebo arm at the same time-point) on D7 and D14 were: -15.5 (20) vs +1.6 (24.7) on D7-4h; and -16.8 vs +0.1 (22.8) on D14-4h.

Figure 5: Study 201 - Heart rate during titration.



The mean HR profile over the course of the study in the five treatment arms, and the change in mean HR from baseline over time is summarized in the dossier. In the placebo arm mean HR increased during the first 2 weeks of treatment reaching a maximum of ~ 139 bpm at D14m and the decreased gradually over time with a minimum of ~120 bpm at W16, while in the 3 mg/kg/day 6 months arm HR decreased over time. In both the 3 mg/kg/day 6 months and placebo arms, HR was similar from W12 through to W24. In the 3 mg/kg/day 6 months arm vs placebo arm, mean (SD) HR values (bpm) were: 135.7 (18.1) vs 135.4 (21.5) at baseline; 125.6 (19.3) v 139.9 (12.2) at D0-4h; 120.4 (15.4) vs 136.7 (19.3) at D7-04h post-dose; 118.9 (16.0) vs 133.9 (21.0) at D14-4h post dose; 125.5 (15.5) vs 137.2 (12.8) at W5; 124.5 1(4.3) vs 126.6 (11.9) at W12; 119.3 (17.7) vs 120.2 (11.9) at W16; and 118.6 (15.4) vs 121.6 (10.2) at W24.

The results for the 5 treatment arms in the pivotal study for patients with at least one HR value below the normal level, and for patients with potentially clinically significant values (PCSV) defined a HR < 60 bpm are summarized below.

In the placebo arm, 8/55 (14.5%) had at least one HR value below the level of normal during the course of the study, and all of these values occurred in the titration period. One (1) patient had two PCSVs in the titration period (HR between 50 and 60 bpm) and discontinued from treatment. This patient's baseline HR was low normal (61 bpm).

In the 1 mg/kg/day 3 months arm, 22/98 (22.4%) patients had at least one HR value below the normal range over the study period; 20 during the titration period, 7 during the D21-W12 period and 2 after W12. One (1) patient had one PCSV during the D21-W12 period (51 bpm at W5), followed by normal HR values from W12 (130 bpm) to W24 (117 bpm). The baseline HR in this patient was 160 bpm.

In the 1 mg/kg/day 6 months arm, 16/102 (15.7%) patients had at least one HR value below the normal range over the study period; 13 during the titration period, 3 during the D21-W12 period and 3 after W12. One (1) patient had one PCSV after W12 (43 bpm at W16). This patient had a low HR measurement at W5 (51 bpm) and normal HR measurements at W12 (120 bpm) and W24 (117 bpm), and the baseline HR was 128 bpm.

In the 3 mg/kg/day 3 months arm, 17/100 (17.0%) patients had at least one HR value below the normal range over the study period; 14 during the titration period, 4 during the D21-W12 period and 1 after W12. No patients had PCSVs.

In the 3 mg/kg/day 6 months arm, 26/101 (25.7%) of patients had at least one HR value below the normal range during the course of the study, 19 during the titration phase, 11 during D21-W12, and 9 after W12. Five (5) patients had PCSVs (11 PCSVs after D0-1h).

The number of patients with both a HR decrease from pre-dose of ≥ 30 bpm and HR values < 80 bpm in the titration period in the pooled safety population are summarized below in Table 36. The proportion of patients meeting the criteria was notably higher in the all propranolol group than in the all placebo group (5.9%, 25/424 vs 1/55, 1.8%, respectively).

Table 36: Number of patients with both HR decreases from pre-dose ≥30 bpm and HR values < 80 bpm during titration; pooled safety population.

Value < 80bpm & Decrease from Predose ≥30bpm	All Placebo n=55	All V0400SB 1mg/kg/day n=200	All V0400SB 3mg/kg/day n=224	All V0400SB n=424
Actual daily dose	**Placebo**	**1mg/kg/day**	**1mg/kg/day**	**1mg/kg/day**
D0 +1H	1 (1.8%)	-	5 (2.3%)	5 (1.2%)
D0 +2H	-	-	1 (0.5%)	1 (0.2%)
D0 +3H	-	1 (0.5%)	-	1 (0.2%)
D0 +4H	-	1 (0.5%)	6 (2.7%)	7 (1.7%)
Actual daily dose		**1mg/kg/day**	**2mg/kg/day**	
D7 +1H	-	1 (0.5%)	1 (0.5%)	2 (0.5%)
D7 +2H	-	1 (0.5%)	2 (0.9%)	3 (0.7%)
D7 +3H	-	-	-	-
D7 +4H	-	-	-	-
Actual daily dose		**1mg/kg/day**	**3mg/kg/day**	
D14 +1H	-	-	-	-
D14 +2H	-	-	2 (0.9%)	2 (0.5%)
D14 +3H	-	-	2 (0.9%)	2 (0.5%)
D14 +4H	-	1 (0.5%)	1 (0.5%)	2 (0.5%)

Source: Table 2.7.4.4.1.HR.7b (Section 5.3.5.3 – Vol. 1)

8.2.9.3. Electrocardiograph

- In the pivotal study, ECG measurements were undertaken on D0, D7, D14, D21, W12 and W24, and assessed by an independent physician. Following each ECG assessment from D0 to W12, the independent physician advised the investigator whether or not it was safe to continue study therapy. ECG measurements included (PR, QRS, QT, QTc [Bazett's formula], and RR). The results described below are from the pivotal study.
- PR interval: On D0, the mean PR interval at 4 hours post-treatment increased by 2.3ms in the placebo arm compared with increases from 9.2 to 12.8ms in the 4 active treatment arms (with no dose effect). In the 3 mg/kg/day 6 months arm, the mean (SD) increase in the PR interval from baseline on D7 at 2 hours after dose was 8.6 (14.4)ms vs -0.1 (15.1) in the placebo arm and 4 hours after dose was 8.3 (15.2)ms vs 1.7 (14.7) ms in the placebo arm. The corresponding figures for D14 in the 3 mg/kg/day 6 month vs placebo arms were 10.1 (15.8)ms vs 1.2 (12.3)ms at 2 hours after dose, and 12.9 (34.6)ms vs -0.1 (13.3)ms at 4 hours after dose. At W12, the mean PR interval for the placebo and 3 mg/kg/day 6 months arm were 101.4 and 107.7ms, respectively, and at W24 the values were 101.4 and 111.1, respectively.
- In the total safety data set (n=456) in the pivotal study, mean (SD) baseline values for the QT interval (ms) corrected by different methods were: QTcB = 409.4 (27.9); QTcF = 354.7 (23.9); and QTcP = 369.2 (24.7). QTcB intervals at baseline were ≤ 450ms for 96.2% of patients, 450 to 480 for 3.5% of patients, and > 480ms for 0.2% of patients (1 patient in the 3 mg/kg/day 3 months arm with a QTcB of 496ms, QTcF of 404ms, QTcP of 427.8ms, HR of 205/min). No patients had baseline QTcF or QTcP intervals ≥ 450ms

- On D0, a small increase in mean QTcP of similar magnitude was observed in each of the 5 treatment arms between pre-treatment and 4 hours post-treatment. The highest increase was 7.7ms in the 3 mg/kg/day 3 months arm, and the lowest was 2.6ms in the 3 mg/kg/day 6 months arm, and an increase of 6.8ms was observed in the placebo arm. Smaller increases were observed on D7 and virtually no change on D14, except in the 1 mg/kg/day 6 months arms where an increase of 6.6ms was observed. After an initial increase in mean QTcP over the first 2 to 3 weeks of treatment in each of the 5 treatment arms (less marked in the placebo arm), the mean QTcP tended to decrease to the level of the baseline value or slightly lower (except in the placebo arm, where the W24 mean value was 18.5 ms above the W12 mean).
- QTcP values above 450ms were uncommon and there were no values above 480 ms. QTcP values from 450 to 480ms in the treatment arms in the pivotal study were: (i) placebo arm - 1 case (1.9%) at D0-4 hours post titration, 1 case (1.9%) at D7-2 hours post titration; (ii) 1 mg/kg/day 3 months arm - 2 cases (2.1%) at D0-2 hours post titration, 1 case (1.%1) at D14 pre-titration, 1 case (1.1%) at D14 2 hours post-titration; (iii) 1 mg/kg/day 6 months arm - 1 case (1.0%) at D14 4 hours post-titration and 1 case (1.1%) at W24; (iv) 3 mg/kg/day 3 months arm - 1 case (1.0%) at D14 pre-titration, 1 case (1.0%) at D14 2 hours post-titration and 1 case (1.5%) at W24; and (v) 3 mg/kg/day 6 months arm: 1 case (1.0%) at D7-4 hours post titration, 2 cases (2.0%) at D14 2 hours post-titration.

8.2.9.4. Neurodevelopmental assessment

Two (2) patients had an abnormal neurodevelopmental examination at W24/EOT in the pivotal study: 1 in the 1 mg/kg/day 3 months arm with both decreased axial tension and head turned to the left reported as AEs from D7 through to W24 (on-going); and 1 patient in the 1 mg/kg/day 3 months arm with a left hemiparesis.

8.2.9.5. Other

Other measurements included respiratory rate, temperature, head circumference, and weight. No clinical significant patterns of abnormalities associated with propranolol were observed for these parameters.

8.2.10. Safety in special groups

8.2.10.1. Age

- The ISS/SCS included a comparison of safety between patients aged 35-90 days and patients aged 91-150 days. The total pooled safety population included 37.0% (177/479) younger patients and 63.0% (301/479) older patients. In the pooled propranolol group, 85.4% (134/157) of patients in the younger age group experienced at least one TEAE compared with 87.6% (234/267) of patients in in the older age group, and the comparative percentages in the pooled placebo group were 54.4% (55/83) and 70.6% (108/153), respectively. TEAEs occurring in at least 5% of propranolol treated patients in either age category by treatment group are summarized in the dossier.
- TEAEs occurring in ≤ 2% of older patients compared with younger patients in the all placebo group and in ≥ 2% more older patients compared with younger patients in the all propranolol group were nasopharyngitis, pyrexia, cough, URTI, vomiting, and gastroenteritis.
- TEAEs occurring in ≤ 2% of younger patients compared with older patients in the all placebo group and in ≥ 2% younger patients compared with older patients in the all propranolol group were peripheral coldness, rhinitis, sleep disorder, conjunctivitis, agitation, irritability, and decreased appetite.

- No differences were observed between the age groups in the incidence of TEAEs of special interest (hypotension, bradycardia, bronchospasm and hypoglycemia), but low patient numbers for these events does not allow robust comparisons to be made.
- Potentially clinically significant hypotension (SBP or DBP), in the all placebo group occurred in 9.6% (8/83) of patients in the younger age group and 7.2% (11/153) of patients in the older age group. The corresponding values for potentially clinically significant hypotension in the active treatment groups for younger vs older patients, respectively, were: all 1 mg/kg/day group (18.9%, 14/74 vs 15.9%, 20/126); and all 3 mg/kg/day group (59.0%, 49/83 vs 54/141, 38.3%). In the all 3 mg/kg/day group, there were notably more younger patients with potentially clinically significant hypotension compared with older patients.
- Potentially clinically significant bradycardia (both HR decrease from pre-dose ≥ 30 bpm and HR < 80 bpm) in younger vs older patients, respectively, in the treatment groups were all placebo (7.2%, 6/83 vs 2.0%, 3/153); all 1 mg/kg/day group (6.8%, 5/74 vs 8.7%, 11/126); and all 3 mg/kg/day group (19.3%, 16/83 vs 25.3%, 32/126). The figures suggest a trend towards potentially clinically significant bradycardia in older compared with younger patients.
- The number of patients with QTcP prolongation was too small to make any meaningful comparisons between the two age groups.

8.2.10.2. Sex

- The ISS/SCS included a comparison of safety in males and females in the pooled safety population. The total pooled safety population included 71.4% (342/479) females and 26.8% (137/479) males. In the pooled propranolol group, 90.0% (108/120) of males and 85.5% (260/304) of females experienced at least one TEAE, and the comparative percentages in the pooled placebo group were 62.9% (39/62) and 66.1% (115/174), respectively. TEAEs occurring in at least 5% of propranolol treated patients in either sex by treatment group are summarized in the dossier.
- The only TEAE occurring in ≤ 2% of males compared with females in the all placebo group and in ≥ 2% of males compared with females in the all propranolol group was vomiting.
- TEAES occurring in ≤ 2% of females compared with males in the all placebo group and ≥ 2% of females compared with males in the all propranolol group were nasopharyngitis, rhinitis, sleep disorder, dermatitis diaper, vaccination complication, and peripheral coldness.
- No differences were observed between the sexes in the incidence of TEAEs of special interest (hypotension, bradycardia, bronchospasm and hypoglycemia), but low patient numbers for these events does not allow robust comparisons to be made.
- There were no marked differences between male and females as regards the incidence potentially clinical significant hypotension (SBP or DBP) throughout the course of the study. No trends between males and females were observed during the titration period for this event. No male patient had PCS hypotension after D21, and in the female subgroup there were sporadic reports of PCS hypotension up to W16.
- In the all placebo group, bradycardia (HR < 80 bpm and a HR decrease < 80 bpm during titration) occurred marginally more frequently in males (3.5%, 3/80) than in females (2.0%, 3/153). In the all propranolol group, bradycardia occurred notably more commonly in females (18.4%, 49/267) compared with males (10.8%, 17/157).
- The number of patients with QTcP prolongation was too small to make any meaningful comparisons between the sexes.

8.2.10.3. IH localization

- The ISS/SCS included a comparison of safety between patients with facial and non-facial IH localization. In the pooled propranolol group, 67.5% (110/63) of patients with facial IHs and 60.3% of patients with non-facial IHs experience at least one TEAE and the comparative percentages in the pooled propranolol group were 87.4% (263/301) and 85.4% (105/123), respectively. TEAEs occurring in at least 5% of propranolol treated patients by IH localization by treatment group are summarized in the dossier.
- TEAEs occurring in ≤ 2% more patients in the facial IH group compared with the non-facial IH group in the all placebo group and in ≥ 2% more patients in the facial IH group compared with the non-facial IH group in the all propranolol population were ear infection, diarrhoea, toothache, irritability, sleep disorder, middle insomnia, cough, and dermatitis diaper.
- TEAEs occurring in ≤ 2% more patients in the non-facial IH group compared with the facial IH group in the all placebo group and in ≥ 2% more patients in the non-facial IH group compared with the facial IH group in the all propranolol group were rhinitis, influenza, viral URTI, constipation, infantile colic, pyrexia, vaccination complication, and peripheral coldness.
- No differences were observed between the sexes in the incidence of TEAEs of special interest (hypotension, bradycardia, bronchospasm and hypoglycemia), but low patient numbers for these events do not allow robust comparisons to be made.

8.2.10.4. Other groups (intrinsic factors)

- The ISS/SCS included a review of TEAEs in infants who were born prematurely and had reached the corrected age of 35 days before inclusion in the study. TEAEs occurring in at least 5% of premature patients in any pooled propranolol group were reported as being generally similar to TEAEs occurring in the general population.
- The ISS/SCS included a review of TEAEs grouped by birth weight (<1500 g, 1500-2500 g, 2500-4000 g, and ≥ 4000 g). However, there was a marked imbalance in patient numbers in the birth weight categories making meaningful comparisons across the subgroups difficult (i.e., relatively small numbers of patients in the < 1500 g and ≥ 4000 g categories). No differences were reported in the TEAE profiles in the four weight categories.

8.3. Compassionate Use Program (CUP)

Module 5 [of the dossier] included 5, six-monthly safety reports, covering the period from 13 April 2010 to 12 October 2012, prepared by the sponsor and submitted to the French Competent Authority relating to temporary authorization for use (Authorisation Temporaire d'Utilisation [ATU]) of oral propranolol (3.75 mg). The first ATU was approved in France on 13 April 2010, and the therapeutic indication was proliferating IHs which are life-threatening or give rise to a functional risk, and ulcerative hemangioma not responding to simple treatment in infants unable to be included in a clinical trial. France is the only country for which patient safety data have been received by the sponsor. The ISS/SCS included a summary of the data from the ATU reports (as did the Clinical Overview).

8.3.1. Summary

The main safety information from the ATU reports is summarized below:

- Up to 12 October 2012, a total of 660 patients have been included in France in the CUP. For the 619 patients with data available, mean (and median) propranolol 3.75 mg/mL dose was 2 mg/kg/day. Mean treatment duration was 246.1 days (= 8.1 months), median treatment

duration was 215 days (= 7.1 months), and range of treatment duration was 8 to 673 days for patients with a completed treatment discontinuation form (n=159).

- Demographic data were provided on 637 patients (76.2% female, 23.8% male). The mean age (at inclusion) was 170 days (= 5.6 months), ranging from 2 to 2282 days (i.e., 6.2 years). Median birth weight was 2.96 kg (range: 0.65-4.6 kg) for 553 patients, and 21.9% (139/636) of patients had been born prematurely.
- Of the 637 patients with data, the IH was facial in 65.8% (n=419), on the body in 63.7% (n=234), and multiple (≥ 3) on the body in 7.5% (n=48). Of the patients with data, facial IHs with largest diameter > 1.5 cm were present in 87.6% (332/379) of patients, while internal localization was present in 10.1% (63/626) of patients with IHs on the body. As regards complications of IHs, functional impairment was present in 73.4% (450/613) of patients, severe ulceration was present in 39.2% (235/599) of patients, and vital function was at risk in 15.3% (90/587) of patients. All patients had high-risk IH.
- Of the 618 patients with available data, 79.9% (n=494) had received no previous treatment for IH. Of patients who had received previous treatment for IH, 6.8% (n=42) had received propranolol of other beta-blockers alone.
- In patients treated in France under the CUP since 13 April 2010, 6.9% (44/660) have experienced adverse drug reactions (ADRs) (19 [2.9%] serious cases), including a total of 81 ADRs (26 serious) which have been reported to the sponsor. One of the cases was fatal, but the causal relationship between the event and treatment with propranolol was considered by the sponsor to be doubtful.

8.3.2. Frequently reported ADRs:

- The SOC in which ADRs were reported most frequently was “infections and infestations”, with 18 ADRs of which 6 were considered serious. This was followed by the “psychiatric disorders” (14 non-serious ADRs). In addition, a notable proportion of the ADRs reported were considered serious for the following SOCs: “cardiac disorders” (5/6 ADRs); “metabolism and nutrition disorders” (4/5 ADRs); “respiratory, thoracic, and mediastinal disorders” (4/7 ADRs); and “vascular disorders” (3/6 ADRs).
- The most frequently reported ADR was bronchiolitis (11 ADRs), for which 5 events were considered serious. The next most frequently reported ADRs were sleep disorder (5 ADRs, none serious), diarrhoea (3 ADRs, none serious), bronchitis (3 ADRs, none serious) and agitation (3 ADRs, none serious). ADRs with 2 reports were: bradycardia (2 ADRs considered serious), hypotension (2 ADRs considered serious), bronchospasm (2 ADRs considered serious), hypoglycemia (2 ADRs considered serious), hypoglycemic seizure (2 ADRs considered serious), decreased appetite (1 ADR considered serious), nightmare, abnormal behavior, somnolence, vasoconstriction, pyrexia (both in a context of infection) and medication error. Only 1 event was reported for all other ADRs. ADRs and serious ADRs by SOC and preferred term are summarized in the dossier.

8.3.3. ADRs resulting in dose reduction, temporary or permanent treatment discontinuation,

The dose of propranolol was reduced in 4 patients with ADRs (1 with erythema and vasoconstriction; 1 with initial insomnia, sleep disorder; 1 with agitation, abnormal behaviour, decreased appetite; 1 with a serious bronchospasm). For the previously listed events identified with an asterisk, causality was considered to be possible, and for all other events causality was considered to be doubtful.

The dose of propranolol was temporarily discontinued due to ADRs in 9 patients, including 17 events (1 patient with somnolence; 1 patient with bronchiolitis; 1 patient with diarrhoea, abdominal pain, flatulence; 1 patient with bronchiolitis [severe], incorrect dose administered; 1

patient with 3 episodes of bronchiolitis [severe]; 1 patient with purpura [severe]; 1 patient with hypotension [severe]; 1 patient with bronchitis, nasopharyngitis; 1 patient with abnormal behaviour, sleep disorder, peripheral vasoconstriction). Causality was considered to be probable or possible for the previously listed events identified with an asterisk, and for all other events causality was considered to be doubtful or not applicable.

The dose of propranolol was permanently discontinued due to ADRs in 15 patients (30 events). The events were: bradycardia, sinus arrest in 1 patient; bronchiolitis (2 episodes resulting in 1 temporary and 1 permanent discontinuation); bronchiolitis in 1 patient; bronchiolitis in 1 patient (3 episodes resulting in 2 temporary discontinuations and 1 permanent discontinuation); hypoglycaemia, asthenia, somnolence in 1 patient; middle insomnia, nightmares in 1 patient; respiratory arrest, shock, bronchiolitis in 1 patient; bronchospasm, bronchiolitis (dose decrease and then permanent discontinuation); respiratory distress, bronchiolitis in 1 patient; complete AV block and fatal acute cardiac failure in 1 patient; diarrhoea in 1 patient; chills, agitation, crying, pyrexia in 1 patient; asthma, cough in 1 patient; bronchiolitis, apathy in 1 patient; and hypoglycaemic seizure, bradycardia, medication error in 1 patient. Causality was considered to be probable or possible for the previously listed events identified with an asterisk, and doubtful or not applicable for all other events. The ADRs included 8 serious ADRs (1x complete heart block and fatal heart failure; 1x case of bradycardia and sinus arrest; 4x cases of severe or recurrent bronchiolitis; 2x cases of severe hypoglycaemia (1 with asthenia, somnolence; 1 with hypoglycaemic seizure, bradycardia, medication error).

8.3.4. Serious ADRs as potential risks for infants treated with propranolol

The following serious ADRs were identified in the CUP as important risks for the IH population treated with propranolol: bradycardia, aggravation of AV conduction; hypotension; bronchospasm; bronchial hyper-reactivity reactions; and hypoglycaemia and related seizures. In the 660 patients included in the CUP, patients with ADRs fulfilling the criteria for the important identified risks are listed below. The CUP included detailed case narratives for all patients with the important identified risks.

- Aggravation of pre-existing conduction disorder (intensification of AV block): There was 1 patient (aged 5 months) with serious complete AV block and serious acute cardiac failure (fatal) in which the causality relationship of both events to treatment was considered doubtful by the sponsor and by the French Health authority. The patient presented with biliary atresia diagnosed at 6 weeks of age with hepato-splenomegaly, icterus, portal hypertension, without hepatocellular insufficiency. Hepatic porto-enterostomy, was performed at day 57, but failed. At the time of the fatal event the patient was aged 5 months. There was no contraindication to propranolol for the treatment of a painful ulcerated IH on her back, and treatment was initiated at dose of 1 mg/kg/day increasing to 2 mg/kg/day three days later. The events occurred ~13 days after initiation of treatment. During treatment daily ECGs had been unremarkable. On the day of her death, prophylactic sclerotherapy was undertaken under GA with propofol, suxamethonium, sevoflurane and sulfentanil. Grade II varices were identified and endoscopic sclerotherapy was performed with administration of Aetoxisclerol, followed by octreotide with continuous iv infusion. About 15 minutes after Aetoxisclerol the patient experienced bradycardia followed by grade III AV block with circulatory failure, and transient asystole. Standard intensive treatment methods were instituted, but after initial haemodynamic stabilization deterioration occurred followed by death. Transthoracic ECG identified severe biventricular dysfunction. The causal relationship between the reported events and propranolol were considered to be doubtful by both the sponsor and the Health Authority, considering the cardiac safety measures that had been initiated since the introduction of propranolol, the underlying diseases, and the numerous concomitantly taken medications.
- Bradycardia: There were 2 patients with bradycardia: 1 patient aged 4 months with numerous episodes of serious bradycardia with serious sinus arrest identified by Holter

monitoring during the titration period, causality considered by the sponsor to be possible; 1 patient aged 9 months with severe bradycardia (30 bpm) related to delayed identification of severe hypoglycaemia due to failure to temporarily discontinuation propranolol during a fasting period.

- Hypotension: There were 2 patients with asymptomatic hypotension (causality considered by the sponsor to be possible for both patients): 1 patient aged 3 months with serious hypotension was considered to be due to rapid dose escalation inconsistent with the recommended titration regimen; 1 patient aged 8 months with asymptomatic hypotension.
- Bronchospasm and bronchial hyper-reactivity reactions: There were 16 patients with bronchospasm and bronchial hyper-reactivity reactions including 2 serious life threatening cases of bronchiolitis, 2 serious cases of bronchospasm, 9 cases of bronchiolitis alone; and 3 non-serious cases of bronchitis Most of these patients had IH localized on the face or lip, with ocular complications or risk of ulceration. There was one case of subglottic IH and one case with a risk of breathing difficulty. The age of the patients was between 2.5 and 14 months. In total, 12 of these respiratory disorders occurred during winter-time; 6 occurred in the first months of treatment and 6 occurred in the 2-3 months of treatment, dose was 1 mg/kg/day for 6 cases and 2 mg/day for 9 cases. Familial history included atopy in one case, and asthma and smoking in two parents in one case. Action taken on the drug was continuation at the same dose for 3 cases, decrease of dose for 1 case, temporary discontinuation for 3 cases, permanent discontinuation for 8 cases, and the compassionate use renewal was refused due to 3 episodes of bronchiolitis for 1 case.
- Hypoglycaemia and related seizures: There were 4 patients with hypoglycaemia: 1 patient with asymptomatic hypoglycaemia after the first dose, treatment with propranolol was continued, no other episodes; and 3 patients with symptomatic hypoglycaemia (1 with asthenia and excessive sleepiness during the first week of treatment, treatment permanently discontinued; 1 with hypoglycaemia seizure, 6 months after beginning treatment in the context of dehydration associated with gastroenteritis during which propranolol had not been discontinued; 1 with hypoglycaemia seizure 6 months after initiation of treatment while receiving propranolol associated with not eating, followed by severe bradycardia, treatment permanently discontinued.

8.4. Scientific literature

The ISS/SCS included a review undertaken by the sponsor of the AE data from 60 publications involving 1367 patients treated with propranolol for IH. The sponsor noted that there were very few details in the literature regarding how the formulation of off-label, oral propranolol was manufactured. No publications relating to the use of the proposed Pierre Fabre formulation oral solution formulation of propranolol were identified. The majority of patients reported in the publications were treated with propranolol 2 mg/kg/day (range 1-4 mg/kg/day) for up to 30 months, except for 3 patients reported in one publication who received higher doses (3-6 mg/kg/day).

The safety profile of propranolol was consistent with that from the CUP and the clinical trial program. Bradycardia, hypotension, hypoglycemia and related seizure, and bronchospasm and bronchial hyper-reactivity reactions were experienced by a small proportion of patients receiving oral propranolol. Sleep disorders, diarrhoea, and cold extremities were the most frequent other non-serious ADRs reported. Hyperkalemia was also considered as a potential risk associated with IHs with large ulceration. No other new reactions emerged from the publications and no predisposing factors were identified for any ADR. No predominant onset time was identified for any ADR except for hypotension, diarrhoea and cold extremities, which mainly occurred within the first 5 days of treatment. Propranolol was usually considered well tolerated, but full data on safety were generally not provided.

8.5. Evaluator's overall conclusions on clinical safety

8.5.1. Number of patients with safety data

The safety data provided in the submission included information on a total of 2,451 patients with IH treated with propranolol (424 patients from the clinical trial program, 660 patients from the French CUP, and 1367 from the scientific literature identified by the sponsor). The key safety data are considered to be from the pivotal study, which included 456 patients in the safety set aged between 35 and 150 days at inclusion with proliferating IH requiring systemic therapy (401 patients in the propranolol arms, and 55 patients in the placebo arm).

8.5.2. Exposure to propranolol

In the pivotal study, the mean duration of treatment in the 3 mg/kg/day 6 months arm was approximately 2-fold greater than in the placebo arm (i.e., 161 days [range: 1, 220 days] vs 83 days [range: 6, 176 days]), and similar patterns were observed between the placebo arm and each of the other three active treatment arms. The pattern of increased length of treatment in the active arms compared with the placebo arm reflects the lower rate of permanent treatment discontinuations in the active arms compared with the placebo arm, due primarily to differences relating to discontinuations due to inefficacy. In the placebo arm, permanent treatment discontinuation due to inefficacy was approximately 6.6-fold higher than in the 3 mg/kg/day 6 months arm (58.2% vs 8.8%, respectively).

In the clinical trial program, a total of 155 patients have been exposed to propranolol for ≥ 24 weeks (74 in the 3 mg/kg/day 6 months arm, 80 in the 1 mg/kg/day 6 months arm, and 1 in the 1 mg/kg/day 3 months arm). The clinical trial exposure numbers are small, but adequate given the safety data from the CUP and the scientific literature relating to the use of propranolol in children with IH. In addition, reassurance is provided by the extensive exposure to propranolol in adults, and the absence of safety signals in children suggesting that the safety profile of the drug will be significantly different in children and adults.

8.5.3. Treatment-emergent adverse events (TEAES)

TEAEs occurred notably more commonly in propranolol treated patients than in placebo treated patients, despite the difference in the length of treatment between the two treatment groups. In the pooled safety population, TEAEs were reported in 65.3% (154/236) of patients in the all placebo group and 86.8% (368/424) of patients in the all propranolol group, with no marked difference between the all 1 mg/kg/day and all 3 mg/kg/day groups (84.5%, 169/200 vs 88.8%, 199/224, respectively). TEAEs reported in at least 10% of patients in the all propranolol group (n=424) vs the all placebo group (n=236) were (in descending order of frequency in the active arm): nasopharyngitis (23.6% vs 15.3%); pyrexia (21.2% vs 7.2%); diarrhoea (18.9% vs 3.4%); teething (15.3% vs 9.3%); cough (11.8% vs 7.2%); vomiting (10.6% vs 3.4%); and URTI (10.1% vs 7.6%).

In the pivotal study, TEAEs reported in at least 5% of patients in the propranolol 3 mg/kg/day 6 months arm (n=101) vs the placebo arm (n=55) were (in descending order of frequency in the active arm): nasopharyngitis (33.7% vs 18.2%); diarrhoea (27.7% vs 7.3%); pyrexia (26.7% vs 9.1%); teething (20.8% vs 10.9%); bronchitis (16.8% vs 1.8%); URTI (13.9% vs 7.3%); vomiting (12.9% vs 5.5%); cough (11.9% vs 7.3%); gastroenteritis (10.9% vs 3.6%); peripheral coldness (9.9% vs 1.8%); bronchiolitis (8.9% vs 5.5%); dermatitis diaper (8.9% vs 3.6%); toothache (8.9%, 8/101 vs 3.6%); conjunctivitis (7.9% vs 3.6%); vaccination complication (7.9% vs 3.6%); sleep disorder (6.9% vs 1.8%); middle insomnia (5.0% vs 5.5%); nightmare (5.0% vs 1.8%); and rash (5.0% vs 1.8%).

In the pivotal study, TEAEs reported in at least 2% of patients in the 3 mg/kg/day 6 months arm and occurring at least 3-fold more commonly than in the placebo arm were considered to be clinically significant. The events meeting this criteria (3 mg/kg/day 6 months [n=101] vs placebo [n=55]) were: diarrhoea (27.7% vs 7.3%); bronchitis (16.8% vs 1.8%); gastroenteritis

(10.9% vs 3.6%); peripheral coldness (9.9% vs 1.8%); sleep disorder (6.9% vs 1.8%); ear infection (4.0% vs 0%); pharyngitis (3.0% vs 0%); viral infection (3.0% vs 0%); GORD (3.0% vs 0%); and AST increased (3.0% vs 0%).

In the pivotal study, the majority of TEAEs were reported to be mild or moderate in intensity, to have occurred before or at W12 (i.e., before switch to placebo in the 1 and 3 mg/kg/day 3 months treatment arms), and to have resolved by W24.

8.5.4. Treatment-related treatment emergent adverse events

In the pooled safety population, treatment-related TEAEs were reported more frequently in patients in the all propranolol group than in all placebo group (36.3%, 154/424 vs 14.8%, 35/236). Treatment-related TEAEs occurring in at least 2% of patients in the all propranolol group (n=424) and/or the all placebo group (n=236) were (respectively) in descending order of frequency in the active treatment group: peripheral coldness (7.1% vs 0%); diarrhoea (5.4% vs 1.3%); sleep disorder (5.0% vs 0.8%); middle insomnia (4.7% vs 1.7%); nightmare (4.2% vs 1.7%); vomiting (2.6% vs 0.4%); constipation (2.4% vs 0.4%); decreased appetite (2.4% vs 0%); somnolence (2.4% vs 0%); restlessness (2.1% vs 0.8%); hypersomnia (2.1% vs 0.4%); and insomnia (1.4% vs 2.1%). Four (4) patients experienced severe treatment-related TEAEs: 1 with nightmare in the 1 mg/kg/day 6 months arm; 1 with increased serum alkaline phosphatase level in the active treatment phase of the 3 mg/kg/day 3 months arm; and 2 patients with aggravated condition (1 in the placebo group, and 1 in the active treatment phase in the 3 mg/kg/day 3 months arm).

In the pivotal study, 34.7% (35/101) of patients in the 3 mg/kg/day 6 months arm experienced at least one treatment-related TEAE compared with 29.1% (16/55) of patients in the placebo arm. Treatment-related TEAEs reported in ≥ 2% of patients in the 3 mg/kg/day 6 months arm (n=101) and/or the placebo arm (n=55) were (in decreasing order of frequency in the active treatment arm): peripheral coldness (8.9% vs 0%); diarrhoea (7.9% vs 3.6%); sleep disorder (6.9% vs 1.8%); nightmare (5.0% vs 1.8%); middle insomnia (4.0% vs 5.5%,); vomiting (3.0%, vs 1.8%); AST increased (3.0% vs 0%); insomnia (3.0% vs 5.5%); rash (2.0% vs 0%); blood potassium increased (2.0% vs 0%); and frequent bowel movements (1.0% vs 3.6%).

8.5.5. Deaths and other serious adverse events

There were no deaths in the pooled safety population. However, there was 1 (0.15%) death in the CUP reported in 660 patients (complete heart AV block and acute cardiac failure) considered by the sponsor and French health authority to be of doubtful relationship to treatment considering that cardiac safety measures had been initiated following the introduction of propranolol, the nature of the underlying non-cardiac disease, and the numerous concomitantly taken medications.

In the pivotal study, SAEs were reported in 5.5% (3/55) of patients in the placebo arm (3 events), 5.1% (5/98) of patients in the 1 mg/kg/day 3 months arm (5 events), 2.9% (3/102) of patients in the 1 mg/kg/day 6 months arm (5 events), 9.0% (9/100) patients in the 3 mg/kg/day 3 months arm (13 events), an 5.9% (6/101) patients in the 3 mg/kg/day 6 months arm (7 events). The proportion of patients with SAEs was similar in the placebo and propranolol 3 mg/kg/day 6 months arms (5.5% vs 5.9%, respectively). No dose dependent relationship for SAEs was observed for the 4 propranolol treatment regimens.

Of the 33 SAEs reported in the pivotal study, 26 occurred in 401 patients while on active treatment with propranolol (i.e., 0.06 events per patient) and 7 occurred in 236 patients while on treatment with placebo (i.e., 0.03 events per patient). The most commonly reported SAEs were condition aggravated, drug ineffective and bronchiolitis each in 3 patients, and bronchiolitis in 2 patients, all other SAEs occurred in 1 patient each. SAEs led to temporary treatment discontinuation in 8 patients and permanent treatment discontinuation in 9 patients. All patients recovered from their SAEs, except for 2 patients who recovered with sequelae after permanently discontinuing the study drug (epilepsy and condition aggravated).

Of the SAEs reported in the pivotal study, 5 were assessed as related to the study drug by the investigator and/or the sponsor: 1x condition aggravated in 1 patient in the placebo arm; 1x AV block second degree Mobitz 1 type in the active treatment phase in the 1 mg/kg/day 6 months arm; 1x obstructive bronchitis in the active treatment phase in the 3 mg/kg/day 3 months arm; 1x condition aggravated (ulceration of IH) in the active treatment phase in the 3 mg/kg/day 3 months arm; and 1x bradycardia in the active treatment phase in the 3 mg/kg/day 3 months arm. The only one of the 5 events not categorized as a SUSAR was bradycardia.

The submission also provided SAE data from the pivotal study reported post-W24 at the cutoff date of 31 December 2012. In this period, 319 patients had entered the cut-off phase and 20 (6.3%) patients had experienced at total of 30 SAEs. There were no unexpected SAEs in the preliminary data from the post-W24 extension phase of the pivotal study. One (1) patient from on-going study (301) enrolling previously treated patients from studies 102 and 201 had experienced 1 SAE (bronchiolitis).

8.5.6. Permanent treatment discontinuation and other significant adverse events

TEAEs resulting in permanent treatment discontinuation occurred more commonly in patients treated with propranolol than in patients treated with placebo. In the pooled safety population, TEAEs resulting in permanent treatment discontinuation were reported in 4.7% (11/236) of patients in the all placebo group compared with 2.6% (11/424) of patients in the all propranolol group. The only TEAEs resulting in permanent study drug discontinuation in more than 1 patient in the combined all placebo and all propranolol groups were: condition aggravated in 4 patients (3 [1.5%] in the all placebo group, and 1 [0.2%] in all propranolol group); drug ineffective in 3 patients (2 [0.8%] in the all placebo group, and 1 [0.2%] in the all propranolol group); and bronchiolitis in 3 patients (2 [0.8%] in the all placebo group, and 1 [0.2%] in all propranolol group).

In the pivotal study, TEAEs resulting in permanent treatment discontinuation were reported in 6 (10.9%) patients in the placebo arm (7 events), 4 (4.1%) patients in the 1 mg/kg/day 3 months arm (4 events), 2 patients in the 1 mg/kg/day 6 months arm (2 events), 7 (7.0%) patients in the 3 mg/kg/day 3 months arm (9 events) and 3 (3.0%) patients in the 3 mg/kg/day 6 months arm (3 events). The proportion of patients discontinuing treatment due to permanent TEAEs was greater in the placebo arm than in the 3 mg/kg/day 6 months arm (10.9% vs 3.0%, respectively). No dose dependent relationship for TEAEs resulting in permanent treatment discontinuation was observed for the 4 propranolol treatment regimens.

Dose reductions due to TEAEs were reported in 4 patients in clinical trial program (3 in propranolol treated patients and 1 in a placebo treated patients), and temporary treatment discontinuations due to TEAEs were reported in 63 patients (58 in propranolol treated patients and 6 in placebo-treated patients).

8.5.7. Important identified risks associated with propranolol

Important risks in infants with IHs treated with propranolol include bradycardia, intensification of AV block, hypotension, hypoglycaemia including related seizures; bronchospasm and bronchial hyper-reactivity reactions.

The most frequently observed important risks observed with propranolol related to bronchospasm and bronchial hyper-reactivity reactions. In the pooled safety population, TEAES of bronchospasm and bronchial hyper-reactivity reactions were reported in 86 (20.3%) out of 424 propranolol treated patients. Of these 86 patients, 11 (2.6%) had TEAEs grouped under the term bronchospasm, 29 (6.8%) had TEAEs grouped under the term bronchiolitis, and 46 (10.8%) had TEAEs grouped under the term bronchitis. In the CUP, 16 (2.4%) of 660 patients experience these reactions.

In the pooled safety population, TEAEs of hypotension were reported 5 (1.2%) out of 424 propranolol treated patients. Three (3) cases were observed in all 1 mg/kg/day group at 3

weeks, 2 months and 2.5 months, and 2 cases were observed during the titration phase in the 3 mg/kg/day 3 months regimen. All 5 events were reported before or at W12. All were asymptomatic, all were of mild intensity, none was a SAE, and none required corrective treatment or dose adjustment. All were considered by the investigator to be possibly related to treatment with the study drug. In the CUP 2 (0.3%) of 660 patients experienced hypotension.

In the pooled safety population, TEAEs of bradycardia were reported in 2 (0.5%) of 424 propranolol treated patients, and both were considered by the investigator to be related to the study drug. Both patients had been participants in the pivotal study, 1 (1.0%) in the 1 mg/kg/day 6 months arm (after W12, on D167), and 1 (1.0%) in the 3 mg/kg/day 3 months arm (before or at W12, on D7) considered to be a SAE and resulting in permanent treatment discontinuation. In the CUP, 2 (0.3%) of 660 patients were each reported to have experienced bradycardia (serious ADRs).

In the pooled safety population, 1 (0.2%) out of 424 propranolol treated patients experienced a TEAE of intensification of AV block following the first dose of propranolol (0.5 mg/kg/day) considered by the sponsor to be possibly related to treatment, and resulting in permanent treatment discontinuation. In the CUP, 1 (0.15%) of the 660 patients experienced complete AV block and fatal heart failure considered to be unrelated to treatment for the reasons provided above under the heading “Death and other serious adverse events “.

In the pooled safety population, TEAEs of hypoglycaemia were reported in 2 (0.5%) out of 424 propranolol treated patients. Both events occurred during the titration period at D14, one event at 1 mg/kg/day and one event at 3 mg/kg/day, and both events were of mild intensity (2.5 mmol/L and 2.9 mmol/L, respectively). In 1 patient (2.5 mmol/L) the D14 event had been preceded by gastroenteritis since D11 with vomiting, diarrhoea and poor feeding. No hypoglycaemic symptoms were reported for either of the cases and blood glucose levels normalized spontaneously. In the CUP 4 (0.6%) of 660 patients experienced hypoglycaemia.

8.5.8. Laboratory assessments

Overall, the analysis of haematology and biochemistry laboratory parameters does not give cause for concern or generate new safety signals. The assessment ‘blood glucose levels’ was specifically targeted in the clinical study program, and was monitored by pin-prick in the titration period and routinely in venous blood throughout the course of the study. In the pooled safety population, there were no cases in the placebo (n=55) or all propranolol (n=424) groups of potentially clinically significant blood glucose values (< 2.22 mmol/L) measured by pinprick at +2h and +4h post-dose on the first day of treatment (D0) or on both days of increased dose (D7 and D14) in the titration period. In the pooled safety population, 1 (0.4%) patient in the all placebo group (n=236) and 1 (0.2%) patient in the all propranolol group (n=424) with normal baseline blood glucose levels experienced treatment emergent critical blood glucose levels < 2.6 mmol/L detected by routine monitoring of venous blood at W24.

8.5.9. Vital signs - Blood Pressure

In the pivotal study, during the titration period, the proportion of patients with SBP and DBP values below the normal range were similar for the placebo group and the grouped 1 mg/kg/day and grouped 3 mg/kg/day regimens. The proportion of patients in the placebo, grouped 1 mg/kg/day and grouped 3 mg/kg/day regimens with SBP values below the normal range during the titration period were 29% (16/55) vs 33.0% (66/200) vs 29.4% (59/201), respectively, and the corresponding results for DBP were 85.5% (47/55) vs 82.0% (164/200) vs 83.1% (167/201), respectively. Over the course of the pivotal study, SBP and DBP values below the normal range were frequently observed in all five treatment arms (SBP: 41.8% in the placebo arm, 50.0% to 53.5% in the active arms; and DBP: 89.1% in the placebo arm, and 87.3% to 97.0% in the active arms). The results show that reductions in BP in the placebo and active treatment arms were predominantly diastolic.

In the pivotal study, almost all very low SBP/DBP potentially clinically significant values (PCSVs < 50/30 mmHg whatever the age) were DBP values, and occurred during the titration period. The proportion of patients with PCSVs from D7-1h to D14-4h in the titration period was similar for the grouped 3 mg/kg/day regimen and the placebo regimen (14.4%, 29/201, 52 events vs 14.5%, 8/55, 12 events), and lowest in the grouped 1 mg/kg/day regimen (7.0%, 14/200, 20 events). The proportion of patients with PCSVs notably decreased after the titration period in each of the treatment arms

8.5.10. Vital signs - Heart Rate

In the pivotal study, there was a decrease in HR of about 7 bpm, on-average, from baseline in the propranolol treatment arms during the titration period. In the pivotal study, HR values below the normal range occurring in at least one patient over the course of the study were 14.5% (8/55), 22.4% (22/98), 15.7% (16/102), 17.0% (17/100) and 25.7% (26/101) in the placebo, 1 mg/kg/day 3 months, 1 mg/day/kg 6 months, 3 mg/kg/day 3 months, and 3 mg/kg/day 6 months arms, respectively.

In the pivotal study, low HR PCSVs (<60 bpm) occurred infrequently in all treatment arms and the rates were 1.8% (1/55), 1.0% (1/98), 1.0% (1/102), 0% (0/100) and 5.0% (5/101) in the placebo, 1 mg/kg/day 3 months, 1 mg/day/kg 6 months, 3 mg/kg/day 3 months, and 3 mg/kg/day 6 months arms, respectively.

8.5.11. Vital signs - ECG

No clinically significant ECG abnormalities appear to have been identified by routine monitoring.

8.5.12. Vital signs - Other

No significant differences were observed in the pivotal study between propranolol and placebo treated patients as regards respiratory rate, temperature, head circumference, and weight.

8.5.13. Special groups

The safety patterns were different between the two age groups and the two sexes, but the observed differences are unlikely to be clinically significant and provide no support for dose adjustment based on age or sex.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

In the pivotal study, the proportion of infants aged from 30 to 150 days achieving complete/nearly complete resolution of proliferating IH requiring systemic therapy at W24 was markedly higher in the propranolol 3 mg/kg/day arm than in the placebo arm, based on centralized (blinded) reading of patient photographs in the ITT data set (60.4%, 61/101, vs 3.6%, 2/55, respectively, p<0.0001). The absolute difference between the active and placebo treatment arms (56.8%) indicates that approximately 2 patients need to be treated with propranolol 3 mg/kg/day 6 months in order for 1 of them to show a complete or nearly complete resolution in their IH at W24 based on photographic data (i.e., number needed to treat [NNT] = 2). However, the results for the primary efficacy analysis for complete/nearly complete resolution of IH at W24 are strikingly inconsistent with the results for this outcome based on investigator assessment in the propranolol 3 mg/kg/day 6 months and placebo arms (26.7%, 24/90, vs 10.5%, 2/19, respectively, p=0.4419).

The sponsor claims that the difference between the results for the two assessment methods for complete/nearly complete resolution in IH at W24 is insignificant, due to notable differences in

the methods used to assess the outcome. However, the difference in outcome between the two methods is considered to be important, and the data from investigator assessment based on clinical examination by physicians experienced in the management of IH cannot be dismissed. In particular, it is considered that the difference in outcome between the two assessment methods raises concerns about the validity of the photographic criteria to satisfactorily identify clinically meaningful complete/nearly complete resolution of IH. Overall, the inconsistency between the evidence for complete/nearly complete resolution of IH at W24 from blinded centralized assessment (2 readers) and blinded on-site investigator assessment is considered to raise uncertainty about the true effect of propranolol compared with placebo on this endpoint. Therefore, it is considered that the pivotal study has not satisfactorily established that treatment with propranolol 3 mg/kg/day for 6 months results in clinically significant complete/nearly complete resolution of IH at W24 compared with placebo.

It is considered that the pivotal study provides some evidence suggesting that treatment with propranolol 3 mg/kg/day for 6 months might result in clinically meaningful improvement of IH compared with placebo at W24. However, it is considered that all evidence suggesting that propranolol 3 mg/kg/day for 6 months provides a treatment benefit relating to improvement at W24 is exploratory. The pivotal study was not designed to investigate improvement in outcome in IH between baseline and W24, and p-values for all secondary efficacy endpoints up to and including W24 were nominal rather than confirmatory. Therefore, for regulatory purposes there are no pivotal data establishing that propranolol 3 mg/kg/day 6 months can improve IH compared with placebo at W24.

Improvement in the surface area, maximal diameter and colour of the IH from baseline to W12 and W24 were observed in the propranolol 3 mg/kg/day arm compared with placebo. Global improvement from baseline between W5 and W24 was notably greater in the propranolol 3 mg/kg/day 6 months arm than in the placebo arm (73.0%, 73 patients, vs 5.5%, 3 patients, nominal $p<0.0001$), based on central assessment of the 3-point scale in the ITT population.

There was consistency as regards nominal statistical significance across centralized, investigator, and parent/guardian assessments for the sustained improvement results (KM estimates) at W5 and W24 for the propranolol 3 mg/kg/day 6 months and placebo groups, based on the 3-point scale. The KM estimates for the three assessment methods, respectively, for propranolol 3 mg/kg/day 6 months vs placebo, respectively, at W5 were 72.7% (72 patients) vs 5.4% (3 patients), 70.9% (68 patients) vs 20.1% (10 patients) and 67.4% (64 patients) vs 19.9% (10 patients), and the KM estimates for the corresponding results at W24 were 79.5% (77 patients) vs 9.0% (3 patients), 82.5% (76 patients) vs 32.4% (12 patients), and 85.6% (76 patients) vs 45.0% (14 patients). The results for the KM estimates over the course of the study were nominally significant ($p<0.0001$) for each of the three assessment methods. However, it is noted that the absolute difference between the two treatment arms for the endpoint at both W5 and W24 is notably different for the investigator and parent/guardian assessments compared with the centralized assessment, with improvement being assessed more conservatively both by investigators and parents/guardians than by centralized readers.

With respect to treatment-emergent IH complications reported in the pivotal study in the ITT population in the placebo and 3 mg/kg/day 6 months arms: treatment-emergent IH functional impairment was reported in 2 patients in the placebo arm, both of whom prematurely withdrew from treatment, and no patients in the active 3 mg/kg/day 6 months arm; treatment-emergent IH ulceration was reported in 2 patients in the placebo arm, both of whom prematurely withdrew from treatment due to inefficacy, and in 4 patients in the active 3 mg/kg/day 6 months arm (2 patients resolved while on treatment, 2 led to premature withdrawal from treatment due to inefficacy); and treatment-emergent IH bleeding/haemorrhaging was reported in 1 patient in the placebo arm resulting in premature withdrawal from treatment due to inefficacy, and 1 patient in the active 3mg/kg/day 6 months arm that resolved while on

treatment. Overall, IH complications in the pivotal study were infrequent and confirm that the IHs in this study were low-risk.

There are no confirmatory data in the submission demonstrating that propranolol 3 mg/kg/day 6 months can satisfactorily maintain efficacy following cessation of therapy. The submission included preliminary data from the pivotal study on patients who entered a 72-week open-label extension phase after completing the 24-week double-blind treatment period. Of the patients in the 3 mg/kg/day 6 months arm who entered the extension phase, 59.8% (49/82) were reported with complete/near complete resolution of IH at W48 (based on centralized assessment of photographic data) compared with 31.6% (6/19) in the placebo arm. The preliminary results showed that complete/nearly complete resolution at W24 can be maintained through to W48 in patients in the propranolol 3 mg/kg/day arm (60.4%, 61/100 and 58.8%, 49/82, respectively), while the percentage of patients with complete/nearly complete resolution actually increased from W24 to W48 in the placebo arm (3.6%, 2/55 to 31.6%, 6/19). The preliminary data also showed that 11.4% (10/88) of patients in the propranolol 3 mg/kg/day 6 months arm required retreatment of IH with propranolol starting more than 7 days after the end of treatment, but before week 48, compared with 5.3% (1/19) of patients in the placebo arm.

The efficacy data relating to treatment of IH with propranolol from the CUP are entirely observational, while the efficacy data from the sponsor's review of the scientific literature are primarily observational. The data from these two sources suggest that treatment with propranolol can improve IH in children treated with propranolol.

9.2. First round assessment of risks

There is a notably increased risk of adverse events associated with propranolol compared with placebo. Some of these risks, while occurring infrequently, are particularly clinically significant (i.e., bronchospasm, hypotension, bradycardia, hypoglycaemia, and AV conduction disorders). The risks of treatment with propranolol can be mitigated by careful patient selection based on history (including family history) and clinical examination undertaken prior to treatment, careful monitoring of heart rate, blood pressure, and possibly ECG over at least the first 4 hours following the initial dose (D0) and following dose increase in the titration period (D7 and D14), and prompt recognition of adverse events occurring while on treatment followed by permanent treatment discontinuation, temporary treatment discontinuation and/or symptomatic treatment as appropriate.

The risks of propranolol in adults are well known as the drug has been in clinical use for at least the last 40 years. While the drug has been used less extensively in children than in adults, there is no reason to expect that the safety profile will differ in the two populations. Overall, the risks of treatment observed in infants were consistent with the known safety profile of propranolol and generated no new safety signals.

The most clinically important identified risks with propranolol in infants include bronchospasm and bronchial hype-reactivity reactions, bradycardia, intensification of AV block, hypotension, and hypoglycaemia including related seizures. In order to mitigate the risks of propranolol in infants the proposed Hemangiol PI recommends that treatment of infants with HI should be initiated by physician's with expertise in treatment of the condition, and in a controlled setting having facilities to manage adverse events requiring urgent treatment should they arise. This is considered to be a prudent recommendation, and should apply not only to the day of initiation of treatment, but also to the days of dose increase in the titration period (i.e., D7 and D14).

The most frequently reported important identified risks in the safety population were bronchospasm and bronchial hyper-reactivity. These risks were reported in 20.3% (86/424) of propranolol treated patients in the safety population. Of the 86 patients experiencing this bronchial reactions, 11 (2.6%) had TEAEs grouped under the term bronchospasm, 29 (6.8%)

had TEAEs grouped under the term bronchiolitis, and 46 (10.8%) had TEAEs grouped under the term bronchitis. In the CUP, 2.4% (16/660) patients experience these reactions.

The important identified risk of hypotension (TEAE) was reported in 1.2% (5/424) of propranolol treated patients in the safety population (all considered by the investigator to be possibly related to treatment). In the pivotal study, BP values below the normal range were frequently observed in the active treatment arms and in the placebo arm, and reductions in DBP were reported more commonly than reductions in SPB. In the pivotal study, almost all very low SBP/DBP PCSVs (< 50/30 mmHg) occurred during the titration period, and were low DBP rather than low SBP values. Over D7-1h to D14-4h of the titration period, the proportion of patients in the pivotal study with very low PCSVs SBP/DBP was similar in the grouped 3 mg/kg/day and placebo regimens (14.4%, 29/201, 52 events vs 14.5% 8/55, 12 events, respectively), and lowest in the grouped 1 mg/kg/day regimen (7.0%, 14/200; 20 events). The proportion of patients with very low PCSVs SBP/DBP decreased after the titration period in each of the treatment arms. In the CUP, hypotension was reported in 0.3% (2/660) of patients.

The important identified risk of bradycardia (TEAE) was reported in 0.5% (2/424) of propranolol treated patients in the safety population. In the safety population, both cases were from the pivotal study and both resulted in permanent treatment discontinuation. In the pivotal study, low HR PCSVs (< 60 bpm) occurred infrequently in all treatment arms with the rates being 1.8% (1/55), 1.0% (1/98), 1.0% (1/102), 0% (0/100) and 5.0% (5/101) in the placebo, 1 mg/kg/day 3 months, 1 mg/day/kg 6 months, 3 mg/kg/day 3 months, and 3 mg/kg/day 6 months arms, respectively. In the CUP, hypotension was reported in 0.3% (2/660) of patients.

The important identified risk of hypoglycaemia (TEAE) was reported in 0.5% (2/424) of propranolol treated patients in the pooled safety population. In the pooled safety population, both events (2.5 mmol/L and 2.9 mmol/L, detected by pin-prick) occurred in the titration period and both events resolved spontaneously. One of the events was preceded by 2 to 3 days of gastroenteritis (vomiting, diarrhoea, poor feeding), but propranolol dosing was not stopped. Routine blood biochemistry during the treatment period (venous blood) revealed 2 patients with critical blood glucose values (< 2.6 mmol/L) during the titration period, with levels returning to normal while on propranolol, and 2 patients with isolated critical values at Week 24 (1, 0.4%, in the all pooled placebo group [n=256] and 1, 0.2%, in the all propranolol group [n=424] of the pooled safety population). In the CUP, hypoglycaemia was reported in 0.6% (4/660) of patients.

The important identified risk of intensification of AV block (TEAE) was reported in 1 (0.2%) of 424 propranolol treated patients. This event occurred almost immediately after the first dose (0.5 mg/kg) of propranolol and was considered by the sponsor to be possibly related to treatment, although there is some evidence that the event might have been related to a pre-existing cardiac disorder. In the CUP, complete AV block associated with acute heart failure resulting in deaths occurred in 1 (0.15%) of 660 patients. The events were not considered by the sponsor to be related to the study drug due to the presence of confounding factors. Of note, in the pivotal study right-bundle branch block was reported in 2 propranolol treated patients as a TEAE, and QT prolongation was reported in 3 patients as a TEAE.

There were no reports of AV block being detected by routine, repeat ECG monitoring in the clinical trial program. The sponsor proposes that routine ECG not be undertaken before initiation of treatment. The sponsor states that in the clinical development program, ECG before initiation of treatment did not identify a single condition likely to interfere with tolerability to propranolol, while echocardiography before the initiation of treatment resulted in the non-inclusion of 1 patient on the basis of a questionable intra-cardiac mass of doubtful clinical relevance.

The risk of experiencing at least one TEAE was greater in patients treated with propranolol compared with placebo. In the pooled safety population, TEAEs were reported in 65.3%

(154/236) of patients in the all placebo group and 86.8% (368/424) of patients in the all propranolol group, with no marked difference between the all 1 mg/kg/day and all 3 mg/kg/day groups (84.5%, 169/200 vs 88.8%, 199/224, respectively). In the pooled safety population, TEAEs reported in at least 10% of patients in the all propranolol group (n=424) vs the all placebo group (n=236) were (in descending order of frequency): nasopharyngitis (23.6% vs 15.3%); pyrexia (21.2% vs 7.2%); diarrhoea (18.9% vs 3.4%); teething (15.3% vs 9.3%); cough (11.8% vs 7.2%); vomiting (10.6% vs 3.4%); and URTI (10.1% vs 7.6%).

In the pivotal study, TEAEs reported in at least 5% of patients in the propranolol 3 mg/kg/day 6 months arm (n=101) vs the placebo arm (n=55) were (in descending order of frequency): nasopharyngitis (33.7% vs 18.2%); diarrhoea (27.7% vs 7.3%); pyrexia (26.7% vs 9.1%); teething (20.8% vs 10.9%); bronchitis (16.8% vs 1.8%); URTI (13.9% vs 7.3%); vomiting (12.9% vs 5.5%); cough (11.9% vs 7.3%); gastroenteritis (10.9% vs 3.6%); peripheral coldness (9.9% vs 1.8%); bronchiolitis (8.9% vs 5.5%); dermatitis diaper (8.9% vs 3.6%); toothache (8.9% vs 3.6%); conjunctivitis (7.9% vs 3.6%); vaccination complication (7.9% vs 3.6%); sleep disorder (6.9% vs 1.8%); middle insomnia (5.0% vs 5.5%); nightmare (5.0% vs 1.8%); and rash (5.0% vs 1.8%).

In the pivotal study, clinically significant TEAEs defined as occurring in least 2% of patients in the 3 mg/kg/day 6 months arm (n=101) and with at least a 3-fold higher incidence than in the placebo arm (n=55) were: diarrhoea (27.7% vs 7.3%); bronchitis (16.8% vs 1.8%); gastroenteritis (10.9% vs 3.6%); peripheral coldness (9.9% vs 1.8%); sleep disorder (6.9% vs 1.8%); ear infection (4.0% vs 0%); pharyngitis (3.0% vs 0%); viral infection (3.0% vs 0%); GORD (3.0% vs 0%); and AST increased (3.0% vs 0%). In the pivotal study, the majority of TEAEs in the treatment arms were reported to be mild or moderate in intensity, to have occurred before or at W12, and to have resolved by W24.

The risk of experiencing a treatment-related TEAE was greater in patients treated with propranolol compared with placebo. In the pooled safety population, the percentage of patients with a least one treatment-related TEAE in the all placebo group was 36.3% (154/424) compared with 14.8% (35/236) in the all placebo group. In the pivotal study, 34.7% (5/101) of patients in the 3 mg/kg/day 6 months arm experienced at least one TEAE compared with 29.1% (16/55) of patients in the placebo arm. Treatment-related TEAEs reported in ≥ 2% of patients in the 3 mg/kg/day arm (n=101) and/or the placebo arm (n=55) were: peripheral coldness (8.9% vs 0%); diarrhoea (7.9% vs 3.6%); sleep disorder (6.9% vs 1.8%); nightmare (5.0% vs 1.8%); middle insomnia (4.0% vs 5.5%,); vomiting (3.0%, vs 1.8%); AST increased (3.0% vs 0%); insomnia (3.0% vs 5.5%); rash (2.0% vs 0%); blood potassium increased (2.0% vs 0%), and frequent bowel motions (1.0% vs 3.6%). Only three of these events (middle insomnia, insomnia, frequent bowel motions) occurred more commonly in the placebo arm than in the propranolol 3 mg/mg/kg/day 6 months arm.

There were no deaths reported in the pooled safety population. However, there was 1 death reported in a propranolol treated patient in the CUP due to complete AV block and acute cardiac failure (mentioned above). In the pivotal study, the risk of experiencing a SAE was similar in the propranolol 3 mg/kg/day 6 months and placebo arms (5.9%, 6/101, 7 events vs 5.5%, 3/55, 3 events, respectively). Of the total number of SAEs reported in the pivotal study (33 events), 26 events occurred in 401 patients while on propranolol (i.e., 0.06 events per patient), and 7 events occurred in 236 while on placebo (i.e., 0.03 events per patient).

Of the SAEs reported in the pivotal study, 5 were assessed as related to the study drug by the investigator and/or the sponsor: 1x condition aggravated in 1 patient in the placebo arm; 1x AV block second degree Mobitz 1 type in the active treatment phase in the 1 mg/kg/day 6 months arm; 1x obstructive bronchitis in the active treatment phase in the 3 mg/kg/day 3 months arm; 1x condition aggravated (ulceration of IH) in the active treatment phase in the 3 mg/kg/day 3 months arm; and 1x bradycardia in the active treatment phase in the 3 mg/kg/day 3 months arm. The only one of the events not categorized as a sudden unexpected serious adverse

reaction (SUSAR) was bradycardia. Preliminary data from the post-week 24 extension to the pivotal study raises no additional concerns relating to SAEs.

Permanent treatment discontinuation due to TEAEs occurred more commonly in patients treated with placebo than patients treated with propranolol. In the pivotal study, permanent treatment discontinuations due to TEAEs were reported in 10.9% (6/55) of patients in the placebo arm and 4.0% (16/401) of patients in the combined propranolol arms. In the pooled safety population, 4.7% (11/236) of patients in all placebo group had at least one TEAE resulting in permanent treatment discontinuation compared with 2.6% (11/424) of patients in the all propranolol group. The only TEAEs resulting in permanent treatment discontinuation in ≥ 2 patients in the pooled safety population all occurred in the all placebo group (n=236) and were condition aggravated (3, 1.3%), drug ineffective (2, 0.8%) and bronchiolitis (2, 0.8%). Temporary treatment discontinuations occurred in 63 patients in the pooled safety population, and the dose of propranolol was reduced in 4 patients in the clinical trial program.

There were no data from the clinical studies of the risks of propranolol in infants with high-risk IH, but the CUP included patients with high-risk IH. There were no data in the clinical studies on the risks of concomitant use of propranolol and other drugs. Therefore, all the known risks of interactions between the propranolol and other drug should be considered to apply to the use of the drug for the treatment of infants with IH. There were no data on the treatment of infants with IH with concomitant hepatic, renal, cardiac and/or respiratory disease. Therefore, it is considered that all infants with IH with these concomitant conditions should not be treated with propranolol.

9.3. First round assessment of benefit-risk balance

No assessment of the benefit-risk balance of propranolol at the proposed dose for the proposed indication can be made due to the absence of pivotal data satisfactorily establishing the benefits of the drug compared with placebo.

10. First round recommendation regarding authorisation

It is recommended that the submission to register Hemangiol for the treatment of proliferating infantile hemangioma requiring systemic therapy be **rejected**. The reasons for this recommendation are as follows:

1. In the pivotal study, the marked benefit of treatment with propranolol 3 mg/kg/day 6 months compared with placebo for the primary efficacy endpoint of complete/nearly complete resolution of IH at W24, based on blinded central assessment of photographs by 2 readers, was not confirmed by blinded on-site assessment of this endpoint by investigators. The difference in outcome between the two assessment methods is considered to be important, and the results of the on-site investigator assessment by physicians experienced in the management of IH cannot be dismissed. The inconsistency between the results for complete/nearly complete resolution of IH at W24 for the two assessment methods is considered to raise uncertainty about the true effect of propranolol compared with placebo for this outcome. Therefore, it is considered that the pivotal study has not satisfactorily established that treatment with propranolol 3 mg/kg/day for 6 months results in clinically significant complete/nearly complete resolution of IH at W24 compared with placebo.
2. In the pivotal study, there are data suggesting that propranolol 3 mg/kg/day 6 months might improve IH outcome at W24 compared with placebo. However, all evidence suggesting that the proposed dose provides a treatment benefit relating to improvement at W24 for the proposed indication is exploratory. The pivotal study was not designed to investigate improvement in outcome in IH between baseline and W24, and p-values for all

secondary efficacy endpoints up to and including W24 were nominal rather than confirmatory.

3. There are no pivotal data indicating that treatment benefits observed at W24 can be maintained following cessation of treatment. The available data suggesting that this might be the case are preliminary and considered to be exploratory.
4. There is no information on spontaneous regression of the target IH in patients in the pivotal study who prematurely withdrew from the study due to "treatment inefficacy" (32/55, 58.2%). If a substantial number of these patients spontaneously regress over time, then this might have implications for the assessment of the benefit-risk balance of propranolol, even it could be established that improvement occurred significantly earlier with treatment than with placebo. This is considered to be particularly important given that the patients in the pivotal study had low-risk IHs.

11. Clinical questions

11.1. Pharmacokinetics

1. For study V00400 SB 1 01 2A, please confirm that the point estimates and 90% CIs provided in the Final Bioanalytical Report ([dossier] table 10) for the Cmax, AUC_{last}, and AUC_{inf} were derived from the geometric mean ratios (solution 80 mg/tablet 70.18 mg) summarized in the CSR ([dossier] tables 14.2.3-1 and 14.2.3-2). If this is confirmed, please explain why dose-normalized 80 mg geometric means were not used to calculate the point estimates for Cmax, AUC_{last}, and AUC_{inf}, and provide point estimates (solution/tablet) based on the dose-normalized geometric means for the parameters. Why were the bioequivalence data not included in the body of the CSR?
2. Please justify why the propranolol oral solution formulation proposed for registration in Australia was not used in study V00400 SB 1 01 2A.
3. Please supply a justification addressing the relevant clinical issues relating to the in vivo PKs of propranolol in humans for not comparing the oral solution used in study V00400 SB 1 01 2A with an Australian sourced propranolol 40 mg tablet rather than Avlocardyl 40 mg tablets.

11.2. Efficacy

1. In the pivotal study, was any attempt made to validate the photographic criteria used to define complete or nearly complete resolution of IH at W24 against the actual physical appearance of the lesion as assessed by clinical examination undertaken by physicians experienced in the assessment and management of IH?
2. Please provide the number of patients with complete resolution and the number of patients with nearly complete resolution contributing to the total number of patients with complete/nearly complete resolution for the primary efficacy endpoint analysis in the pivotal study (i.e. 61 patients on propranolol 3 mg/kg/day 6 months, 2 patients on placebo).
3. The inclusion criteria for the pivotal study included a proliferating IH (target hemangioma) "requiring systemic therapy". Were investigators instructed to document their reasons for considering that an individual patient's IH required systemic therapy? If so, what were these reasons?
4. Does the sponsor have any information on the outcome of the IHs (e.g., spontaneous regression) in the patients in the placebo arm in the pivotal study who withdrew

prematurely due to lack of efficacy (32/55; 58.2%)? If not, does the sponsor intend to obtain this information and, if so, over what time-period will such information be collected?

5. In the pivotal study (CSR) is stated that the centralized readers evaluated the overall quality of the photographs for each combined image evaluation on a three-level scale: unevaluable; poor; good. What was the outcome of this quality assessment?

[Additional clinical efficacy questions raised in the consolidated TGA request for information are shown below in Section 12.3]

11.3. Safety

1. Please provide a tabulated summary of patients in the pooled safety population with temporary treatment discontinuations by treatment group (i.e., all placebo [n=236], all 1 mg/kg/day [n=200], all 3 mg/kg/day [n=224], and all propranolol [n=424]). The table should summarize the data in the same manner as the data for TEAEs resulting in permanent treatment discontinuation summarized in the ISS/SCS ([dossier] table 23). In addition, please provide information on the mean duration (and range) of the total temporary treatment discontinuations for each of the treatment groups.
2. Please provide the proportion of patients in the pivotal study (201) and the pooled safety population with HR values less than 80 bmp in each treatment arm during the course of treatment, and indicate the number (and percentage) of these events occurring during and after the titration period. The proposed Hemangiol PI recommends that specialist advice be sought for patients with bradycardia (HR < 80 bpm). Please explain why the cutoff figure of 80 bpm was chosen as the point for intervention.
3. Please provide the number and percentage of patients with first, second, and third degree heart block identified by routine ECG monitoring in the safety population in the first 4 hours following the first dose (D0) and following dose increase in the titration period (D7, and D14).
4. Please provide the number and percentage of patients with first, second, and third degree heart block identified by routine ECG monitoring in the safety population during the course of the study.
5. Were any patients permanently or temporarily discontinued from treatment due to abnormalities detected by routine ECG monitoring in the clinical development program. If so, please provide information on these patients
6. In the clinical development program, how many patients had routine echocardiography undertaken before treatment with propranolol was initiated and confirm that only one patient was excluded from treatment because of detected abnormalities.
7. In the ISS/SCS (CTD 2.7.4), patients with at least one TEAE occurring on the days of dose increase are presented by pooled dose of V0400SB or placebo for D1 in [the dossier] table 2.7.4.2.29b ([dossier] section 5.3.5.3 – Vol. 1), for D7 in table 2.7.4.2.30b (section 5.3.5.3 – Vol. 1) and for D14 in table 2.7.4.2.31b (section 5.3.5.3 – Vol. 1). The summary states that on D1, D7 and D14, no TEAEs were experienced in the pooled placebo group. However, this statement appears to be inconsistent with the tables referred to in the summary which suggest that 4, 2, and 5 patients in the placebo group experienced adverse events on D0, D7, and D14, respectively. Please comment on this apparent discrepancy.

[Additional clinical safety questions raised in the consolidated TGA request for information are shown below in Section 12.4]

12. Second round evaluation of clinical data submitted in response to questions

12.1. Overview

The sponsor's Response to TGA questions included clinical data submitted in response to the clinical questions raised by the clinical evaluator and the TGA clinical reviewer following the first round clinical evaluation of the submission. The approach adopted to the evaluation of this clinical data has been to repeat the question in full using the numbering system found in the sponsor's response, followed by the sponsor's response to the question provided in full (complete) or in abridged and/or edited form, and the clinical evaluator's comment on the response. The evaluation of the clinical data submitted in the sponsor's Response to the questions, and the first and second round clinical evaluation reports have been prepared by the same clinical evaluator.

12.2. Pharmacokinetics

12.2.1. Question 1

For study V00400 SB 1 01 2A, please confirm that the point estimates and 90% CIs provided in the Final Bioanalytical Report ([dossier] table 10) for the Cmax, AUC_{last}, and AUC_{inf} were derived from the geometric mean ratios (solution 80 mg/tablet 70.18 mg) summarized in the CSR ([dossier] tables 14.2.3-1 and 14.2.3-2). If this is confirmed, please explain why dose-normalized 80 mg geometric means were not used to calculate the point estimates for Cmax, AUC_{last}, and AUC_{inf}, and provide point estimates (solution/tablet) based on the dose-normalized geometric means for the parameters. Why were the bioequivalence data not included in the body of the CSR?

12.2.1.1. Sponsor's response (complete)

The applicant confirms that the point estimates and 90%CIs provided in table 10 of the Final Bioanalytical Report of study V00400 SB 1 01 2A are derived from the non dose-normalized geometric mean ratios summarized in the [dossier] tables 14.2.3-1 and 14.2.3-2 of the CSR.

Initially, study V00400 SB 1 02 2A was aiming at assessing the pharmacokinetic characteristics of a single 80 mg dose of propranolol solution (V0400) in comparison to the same dose of a reference tablet formulation (Avlocardyl). Additionally, a statistical analysis (ANOVA and 90%CI) on geometric mean ratios of the PK parameters was planned. Results of the pharmacokinetic analysis were reported in the Final Bioanalytical Report and included in the CSR.

After the CSR of study V00400 SB 1 01 2A was finalized (version dated January 20th, 2010 available in the Trial Master File), a mistake in the expression of propranolol dose for the tablet (expressed as propranolol hydrochloride) and the solution (expressed as propranolol base) was pointed out: administered doses were not equivalent between the two formulations (80 mg and 70.18 mg for the solution and the tablet, respectively).

The CSR was amended accordingly (version dated April 6th, 2012). Actual administered doses were corrected, individual PK parameters (Cmax, AUC_{last} and AUC_{inf}) were dose normalized to 80 mg for the Tablet formulation and the corresponding individual relative bioavailabilities were calculated (results are given in [dossier] table 14.2.3-3). With regard to statistics, results of the point estimates and 90% CIs previously calculated were removed from the body of the CSR. Because demonstrating the bioequivalence between the solution and the tablet was not in the objectives of study V00400 SB 1 01 2A, no additional statistical analysis was performed with the 80mg dose-normalized PK parameters.

12.2.1.2. Clinical evaluator's comment

The sponsor's response is satisfactory. [dossier] table 14.2.3-3 in the report for study V00400 SB 1 01 2A has been reviewed. The table provides dose-normalized (80 mg) test [solution]/reference [tablet] results for the Cmax and the AUC_{inf} for each of the 12 individual subjects with evaluable data, and mean values for each of these two parameters. The mean Cmax ratio (solution/tablet) was 1.22 (range: 0.32, 3.98), indicating that the mean Cmax was 22% higher for the solution compared with the tablet, and the mean AUC_{inf} ratio (solution/table) was 1.20 (range: 0.5, 3.28), indicating that the mean AUC_{inf} was 20% higher for the solution compared with the tablet. No 90% CI was provided for either of the two parameters, but it can be reasonably inferred from the point estimates that the upper bound of the 90% CI for both parameters will be greater than 1.25 and that the 90% CIs will not be completely enclosed within the standard bioequivalence limits of 0.80-1.25.

12.2.2. Question 2

Please justify why the propranolol oral solution formulation proposed for registration in Australia was not used in study V00400 SB 1 01 2A.

12.2.2.1. Sponsor's response (complete)

Study V00400 SB 1 01 2A was an early biopharmaceutic study using a development solution at 5 mg/mL of propranolol (administered as propranolol hydrochloride). This study aimed at evaluating the pharmacokinetic characteristics of this propranolol solution in comparison to a well-known EU marketed reference before the initiation of the clinical programme aiming at determine the therapeutic dose in infants.

For the Phase II/III study, the solution strength has been changed from 5 mg/mL to 3.75 mg/mL in order to meet specific study requirement such as doses to be tested, volume to be administered and double-blind design. Hemangiol is a solution of propranolol hydrochloride dosed at 3.75 mg/mL (expressed as propranolol base).

Taking into account the solubility characteristics of propranolol, which is highly soluble whatever the tested pH, no issue regarding a potential difference in propranolol solubility in both formulations (3.75 mg/mL versus 5 mg/mL) is anticipated, supporting that the outcome of the early biopharmaceutic can be extended to Hemangiol, which is the formulation proposed for registration in Australia.

12.2.2.2. Clinical evaluator's comment

It is recommended that the Module 3 evaluator comment on the sponsor's response. A section in the dossier relates to the pharmaceutical development of the product and is headed "Initial Risk Assessment of Drug Substance Attributes". The section notes that, according to the Biopharmaceutics Classification System (BCS), propranolol hydrochloride is a class 1 drug substance (high solubility, high permeability). The section also includes an assessment of the effect of pH on the solubility of the propranolol hydrochloride solution.

12.2.3. Question 3

Please supply a justification addressing the relevant clinical issues relating to the in vivo PKs of propranolol in humans for not comparing the oral solution used in study V00400 SB 1 01 2A with an Australian sourced propranolol 40 mg tablet rather than Avlocardyl 40 mg tablets.

12.2.3.1. Sponsor's response (complete)

Pierre Fabre has developed a new oral solution of propranolol hydrochloride for use in infants for the treatment of HI. Study V00400 SB 1 01 2A was an early development study in which the

pharmacokinetic characteristics of this new propranolol solution were evaluated in comparison to a European marketed reference (Avlocardyl).

Propranolol hydrochloride is a well-known compound characterised by a high solubility (whatever the tested pH) and a high permeability (almost completely absorbed after oral administration in human). These characteristics allow classifying propranolol hydrochloride as a Class I compound according to the Biopharmaceutics Classification System (BCS).

During the development, the applicant has compared in vitro the dissolution profile of the EU propranolol hydrochloride tablet (Avlocardyl 40mg) to a US propranolol hydrochloride USP tablet 40mg (Barr Laboratories, Inc). Methodologies were those recommended in the FDA guidance for bioavailability and bioequivalence studies and the USP 31-NF 26 method given for the Propranolol HCl tablet. Data demonstrated that both dissolution profiles were similar. Based on the BCS I classification of propranolol hydrochloride, it can be concluded that the EU propranolol hydrochloride tablet (Avlocardyl 40mg) used in clinical study V00400 SB 1 01 2A and the propranolol hydrochloride USP tablet 40mg (Barr Laboratories, Inc) are bioequivalent (report V0400SLDAR-RE000501).

The Australian reference formulation of propranolol hydrochloride tablet is Inderal 40mg. A table [comparing] the respective excipient composition of the European, the US and the Australian formulations was provided.

All three reference products contain propranolol which is a BCS Class I compound. All three reference products are immediate-release tablets and have only minor differences in their excipient composition. Therefore the changes in excipient composition are not expected to have an impact on their biopharmaceutic characteristics.

In conclusion, considering that propranolol hydrochloride is a BCS Class I compound, that a specific in vitro dissolution study has demonstrated that both the EU and US reference formulations are close to a 100% dissolved after 15 minutes (whatever the tested pH) and that the Australian reference formulation had only minor differences in its excipient composition not impacting its dissolution characteristics compared to the EU and the US reference formulations, the conclusions of the V00400 SB 1 01 2A study can be extrapolated the conclusions of the V00400 SB 1 01 2A study can be extrapolated to the Australian formulation Inderal 40mg, and no clinical issues are anticipated.

12.2.3.2. Clinical evaluator's comment

The sponsor's response is satisfactory. However, it is recommended that comment on the response be obtained from the Module 3 [quality] evaluator.

12.3. Efficacy

12.3.1. Question 1

In the pivotal study, was any attempt made to validate the photographic criteria used to define complete or nearly complete resolution of IH at W24 against the actual physical appearance of the lesion as assessed by clinical examination undertaken by physicians experienced in the assessment and management of IH?

12.3.1.1. Sponsor's response (complete)

12.3.1.1.1. Overview:

- The primary efficacy criterion was success/ failure based on the centralized blinded assessment of photographs of the target IH at W24 compared to baseline. A treatment success was defined as complete/nearly complete resolution of the target IH at W24 compared to baseline. Complete/nearly complete resolution was also assessed by central

readers at W12. Nearly complete resolution was defined as a minimal degree of telangiectasis, erythema, skin thickening, soft tissue swelling and/or distortion of anatomical landmarks. Central readers did not differentiate in their evaluation of success the cases of complete vs the cases of nearly complete resolution.

- Investigator-assessed onsite qualitative evaluation included several criteria, including complete/nearly complete resolution of target IH (yes/no). Complete resolution was defined as complete resolution without sequelae, complete resolution with minimal sequelae, and complete resolution with marked sequelae. Nearly complete resolution was defined as a minimal degree of telangiectasis, erythema, skin thickening, soft tissue swelling, distortion of anatomical landmarks, and/or a minimal palpable component. This was assessed at each post-baseline visit compared to baseline.
- As summarised in Table 37, complete/ nearly complete resolution with the selected propranolol regimen (3 mg/kg/day for 6 months) at W24 was reported for more patients with the primary centralised assessment (60.4%) than with the Investigators' on-site assessment (26.7%).

Table 37: Complete/nearly complete response of target IH at W24 (ITT population)

	Complete/ nearly complete resolution of target IH at W24 (ITT population)			
	Primary endpoint		**Investigators Assessment**	
	Placebo n=55	V0400SB 3 mg/kg/day 6mths n=101	Placebo n=55	V0400SB 3mg/kg/day 6mths n=101
n/ unevaluable	55/ 0	101/ 0	19/ 36	90/ 11
Yes	2 (3.6%)	61 (60.4%)	2 (10.5%)	24 (26.7%)
No	53 (96.4%)	40 (39.6%)	17 (89.5%)	66 (73.3%)
Efficacy analysis:	p<0.0001		P=0.4419	

The discrepancy in results between the primary centralised analysis and one of the secondary endpoints based on Investigators' assessment cannot be explained by a lack of validity of the primary endpoint, as documented below:

- The primary centralised efficacy endpoint was developed in collaboration with an external expert advisory board, and was designed to be robust and reproducible (see below for details).
- The centralised assessment was performed by two trained expert readers (see below for details) whilst the Investigators' assessment was more heterogeneous, since there were 56 sites spread over 16 countries.
- The robustness of the centralised assessment was ensured by the following precautions:
  - Performance of standardised photographs, using standardised equipment, and featuring colorimetric scales for harmonisation
  - Real time quality assurance in order to ensure that photographs would meet criteria for interpretation, and repetition of photographs when needed
  - Blinded assessment by trained readers
  - Independent reading with reconciliation in case of discrepancy, with no external influence

  - Demonstration of the intra and inter-reader reproducibility by analyses of successive batches, reintroduction of photographs in further batches, all allowing calculation of kappa coefficients, which met a priori defined thresholds

- The robustness of the primary endpoint was confirmed by several sensitivity analyses which, despite using very conservative assumptions favouring the placebo arm, all provided highly clinically and statistically significant results.
- Based on this evidence, it is argued that the difference between the centralised interpretation of the primary efficacy parameter and the Investigators' assessment cannot be due to a bias in the centralised assessment, but is most likely attributable to subjectivity in the definition of complete/near complete resolution which may be influenced by differences in training, standard treatment used in the centres and expectations (of Investigators and parents).
- From a statistical point of view, based on the Investigators' onsite assessment of complete/ near complete resolution, propranolol was not statistically significantly more effective than placebo. However, this analysis only takes into account patients in whom an evaluation at W24 was performed, and therefore does not take into account the large difference between groups in terms of early discontinuation, mostly due to insufficient efficacy. When data from the Investigators' onsite assessment were analysed using the same rules as applied to the primary centralised variable, a statistically significant benefit with propranolol was observed. In this analysis, data were transformed into a binary outcome of success/failure. In this analysis, discontinuations due to treatment inefficacy and patients who received prohibited medications were handled as treatment failures (see below for details).
- The results of efficacy obtained by central readers are converging with most other Investigator based assessments, including the 3-point evaluation of improvement (stabilisation, improvement, worsening) which was consistently in favour of propranolol across the centralised assessment, Investigators' assessment and the parents' assessment (see below for details). The consistency of results for time to first sustained improvement and time to first worsening across the centralised and Investigators' assessments shows that propranolol leads to early halt of IH progression and early improvement of the lesion.

12.3.1.1.2. Development of Primary Efficacy Variable

At the initiation of the phase 2/3 study, there were no official validated assessments or tools for the measurement of IH improvement/resolution. Therefore Pierre Fabre worked closely with both the regulatory agencies and experts in the field to develop the primary efficacy criterion in the pivotal study 201 that adequately reflected the natural course and clinical presentation of IH in its many different forms. Initially, Pierre Fabre proposed to consider overall stabilization/improvement of IH by Week 24 as a treatment success, since the goal of existing therapies (such as corticosteroids) has always been to stabilize IH growth. However, the EMA Paediatric Committee (PDCO) suggested that improvement alone should be considered as a treatment success (Summary Report propranolol hydrochloride 000511-PIP01-08-1251387960291) and the consensus was to base the primary criterion on centralized blinded assessments of standardized photographs, to limit any bias potentially linked to the heterogeneity of IH. The FDA then agreed to a more stringent primary outcome of near complete resolution (104390 Meeting Minutes propranolol IH 10-Nov-09). A quantitative assessment of change in size was not considered appropriate as a stand-alone primary efficacy criterion since IH does not necessarily reduce in size initially. Indeed, the earliest signs of regression of a hemangioma are a fading of the colour of the lesion from a bright/dull red to pink, followed by the development of a grey-white hue at the centre of the lesion that spreads to the periphery and a reduction in lesion tenseness (Sundine and Wirth 2007).

Taking all of this into account, Pierre Fabre and the external IH expert advisory board (four members, three of whom were study Investigators1) carried out an extensive review of recent

data available from the use of off-label propranolol, leading Pierre Fabre to propose the following primary endpoint: complete/nearly complete resolution of target IH at Week 24. Pierre Fabre worked in association with the external IH expert advisory board to clearly define 'nearly complete resolution' as: a minimal degree of telangiectasias, erythema, skin thickening, soft tissue swelling, and/or distortion of anatomic landmarks. It should be noted that this efficacy criterion is more stringent than most efficacy criteria reported in the scientific literature.

12.3.1.1.3. Validity of centralized readings

A charter was defined in order to ensure standardization of imaging, including photograph acquisition, central reader training, validation and monitoring. The full charter for these tasks is available in the Study 201 CSR.

- Photograph acquisition

For photograph acquisition, a very detailed standardized procedure was defined in the protocol for which Investigators received thorough training and were qualified on tests prior to the study. This procedure included image colour and size calibration, subject lighting and background, patient position, and the angle and distance between the camera and patient. Furthermore, in order to assure that a high quality of material was provided to the central readers, a quality control check was performed within 1 hour of acquisition of each photograph, allowing repetition of the photograph in case of unacceptable quality.

- Central readers training

The centralized readers were chosen for their expertise in paediatric dermatology. They were not Investigators in the study, nor did they have financial conflicts of interest. Prior to commencing independent blinded reading sessions, the independent readers underwent training sessions managed by the imaging team from Cardinal Systems (the CRO in charge of imaging). Training sessions focused on the evaluations that were to be carried out by the independent readers and the reading workstation that they would use to evaluate IH evolution during the independent blinded reading sessions. Readers were trained to evaluate complete/ nearly complete resolution (type 1 assessment) and to assess worsening/stabilization/ improvement of IH (type 2 assessment).

- Central readers monitoring

Inter-reader variability testing: Qualitative evaluations: After each batch reading by both readers and the verification of the results, the Kappa statistic was used to test inter-variability: If a batch had an acceptable Kappa value (≥0.6) then all evaluations in the batch for which both readers had marked YES or NO were considered as the final result for analysis purposes. Other evaluations (NA/NA and disagreements) were collected in the adjudication database to be decided by consensus at a later date. Any batch with an unacceptable Kappa value (<0.6) was re-read in its entirety at a later date (the order of the photographs was changed for the next reading but the same comparisons remained). If the re-read was unsuccessful (Kappa still <0.6) then the batch was adjudicated in its entirety in an adjudication session.

Intra-reader variability testing: Qualitative evaluations: During the study readings and after the first successful batch, at least one visit pair from the previously assessed successful batch was reinserted into a follow-up batch to check if readers made the same assessments again. In particular, the reader performed repeat image evaluations of randomly determined cases. These cases were re-introduced and re-read during the course of the study (approximately 5% of all visit pairs read). The reader was not informed which pairs in a batch were repeat image evaluations. In the case of discrepancies compared to the reader's first evaluation, only the first evaluation was taken into account for the study.

12.3.1.1.4. Robustness of centralized primary endpoint (Study 201)

The robustness of the primary efficacy endpoint and the centralized readings was demonstrated by the consistency of results across the populations and subgroups assessed. Table 38 shows that the results of the centralised evaluation of the primary binary endpoint were similar between all the populations analysed. The rate of complete/ near complete resolution was 60.4% in the ITT population and 60.2% in the PP population. A sensitivity analysis confirmed the results of the primary analysis (significant superiority of the active treatment regimen) despite the relaxation of the definition of failures resulting in a high increase of the success rate in the placebo regimen (from 2 to 15 patients: 3.6% to 27.3%) when only one additional patient in the active treatment regimen was considered a success. In this sensitivity analysis of the ITT population, 61.4% of patients had complete/ near complete resolution. To further demonstrate the robustness of the primary analysis, an additional post-hoc analysis was performed. This was similar to the planned sensitivity analysis in that:

- patients who discontinued treatment due to intolerance remained a treatment failure
- patients who discontinued treatment for reasons other than treatment intolerance were classed as treatment failures if the closest centralized assessment (Type 2) from the end of treatment confirmed stabilization or worsening.

This unplanned sensitivity analysis differed from the planned analysis in that, if the closest centralized assessment (Type 2) from the end of treatment did not confirm stabilization or worsening:

- 50% of the patients concerned in each of the four V0400SB group were selected at random and their primary endpoint was redefined as a success.
- 60% of the patients concerned in the placebo group were selected at random and their primary endpoint was redefined as a success. The rate of 60% corresponds of the rate of success of the selected arm (V0400SB 3mg/kg/day 6 months).

In this sensitivity analysis (see Table 38), the success rate with propranolol (61.4%) was in line with other analyses of the primary criterion.

In the ITT and PP populations, and in the two sensitivity analyses, propranolol had a highly significant treatment effect ($p<0.001$). This was tested in the same way as for the primary analysis of the primary efficacy criterion.

Table 38: Primary analysis results: Complete of nearly complete resolution at week 24, central reading.

Primary endpoint: Complete or nearly complete resolution of target IH at week 24				
		Placebo (N = 55)	V0400SB 3 mg/kg/day 6mths (N = 101)	P value
ITT set	**Overall/combined**			
	n/missing	55 / 0	101 / 0	<.0001
	Yes	2 (3.6%)	61 (60.4%)	
	No	53 (96.4%)	40 (39.6%)	
PP set	**Overall/combined**			
	n/missing	53 / 0	93 / 0	<.0001
	Yes	1 (1.9%)	56 (60.2%)	
	No	52 (98.1%)	37 (39.8%)	
Planned sensitivity analysis of ITT set*	**Overall/combined**			
	n/missing	55 / 0	101 / 0	<.0001
	Yes	15 (27.3%)	62 (61.4%)	
	No	40 (72.7%)	39 (38.6%)	
Unplanned post-hoc sensitivity analysis of ITT set	n/missing	55 / 0	101 / 0	<.001
	Yes	17 (30.9%)	62 (61.4%)	
	No	38 (69.1%)	39 (38.6%)	

CSR Tables 18, Table 19 and Table 105, and UNPL_central_Response_ANA_sens2

* For patients who prematurely discontinued the study drug:

- If the patient was withdrawn from study therapy for treatment intolerance, the primary endpoint remained a failure.
- If the patient was not withdrawn from study therapy for treatment intolerance:
- If the closest centralized assessment (Type 2) from the end of treatment confirmed stabilization or worsening, the primary endpoint remained a failure.
- If the closest centralized assessment (Type 2) from the end of treatment did not confirm stabilization or worsening, 50% of the patients concerned in each treatment group were selected at random and their primary endpoint was redefined as a success.

Subgroup analysis of the centralised primary endpoint consistently supported the primary analysis. The success rate with propranolol was similar between the ITT and PP populations for each of the subgroups analysed (age group, IH localization, randomization schedule) (Table 39). The consistency of results across analysis populations and across subgroups reinforces the robustness of the primary evaluation method and does not suggest bias in the evaluation of photographs.

Table 39: Primary analysis results, by subgroup and population

Primary endpoint Complete or nearly complete resolution of target IH at week 24	ITT Population		PP Population	
	Placebo (N = 55)	V0400SB 3 mg/kg/day 6mths (N = 101)	Placebo (N = 55)	V0400SB 3 mg/kg/day 6mths (N = 101)
Age 35 - 90 days				
n/missing	20 / 0	37 / 0	18 / 0	35 / 0
Yes	2 (10.0%)	25 (67.6%)	1 (5.6%)	23 (65.7%)
No	18 (90.0%)	12 (32.4%)	17 (94.4%)	12 (34.3%)
Age > 90 days				
n/missing	35 / 0	64 / 0	35 / 0	58 / 0
Yes	0 (0.0%)	36 (56.3%)	0 (0.0%)	33 (56.9%)
No	35 (100%)	28 (43.8%)	35 (100%)	25 (43.1%)
Facial IH				
n/missing	40 / 0	71 / 0	38 / 0	66 / 0
Yes	2 (5.0%)	43 (60.6%)	1 (2.6%)	40 (60.6%)
No	38 (95.0%)	28 (39.4%)	37 (97.4%)	26 (39.4%)
Non Facial IH				
n/missing	15 / 0	30 / 0	15 / 0	27 / 0
Yes	0 (0.0%)	18 (60.0%)	0 (0.0%)	16 (59.3%)
No	15 (100%)	12 (40.0%)	15 (100%)	11 (40.7%)
Randomization ratio 1:1				
n/missing	12 / 0	13 / 0	10 / 0	10 / 0
Yes	2 (16.7%)	10 (76.9%)	1 (10.0%)	9 (90.0%)
No	10 (83.3%)	3 (23.1%)	9 (90.0%)	1 (10.0%)
Randomization ratio 2:1				
n/missing	43 / 0	88 / 0	43 / 0	83 / 0
Yes	0 (0.0%)	51 (58.0%)	0 (0.0%)	47 (56.6%)
No	43 (100%)	37 (42.0%)	43 (100%)	36 (43.4%)
Overall/combined				
n/missing	55 / 0	101 / 0	53 / 0	93 / 0
Yes	2 (3.6%)	61 (60.4%)	1 (1.9%)	56 (60.2%)
No	53 (96.4%)	40 (39.6%)	52 (98.1%)	37 (39.8%)
Logistic regression analysis	p<.0001		p<.0001	

12.3.1.1.5. Difference between centralised and Investigators' evaluation for primary criterion

Differences in evaluation methods: As discussed above, the centralized readers had side by side photographs of baseline and W24 to make their judgment taking into account the baseline IH. Importantly, readers were blinded to treatment, site number, patient characteristics, tolerance etc. In addition, readers underwent rigorous training, validation and monitoring to ensure reproducibility of evaluations. It is therefore argued that all precautions were taken in order to avoid any bias due to expectations, parent's perceptions, or any other external influence.

In contrast, the Investigators did not receive specific training in the assessment of complete/ near complete resolution and validation of inter- or intra-Investigator reproducibility could not be performed considering the logistics of the study (56 centres in 16 countries).

12.3.1.1.6. Differences in analytical methods may impact statistical significance

In the analysis of the primary centralised variable, but not the Investigators' onsite assessment, the SAP defined that missing data, premature discontinuations and patients who received additional treatment for IH were handled as treatment failures. Using this methodology, all patients were designated as either a treatment success or failure, as part of the binary primary outcome.

In the Investigators' assessment of complete/ near complete resolution at W24, patients were classified as "missing data" if they had no W24 efficacy assessments due to premature discontinuation. This analysis fails to take into account the high rate of discontinuations in the placebo group due to inefficacy of placebo. By classifying these patients as "missing data" rather than "treatment failures", the Investigators' assessment of complete/ near complete resolution

overestimates the success rate of placebo (2 successes out of 19 evaluable patients gives a success rate of 10.5%).

In order to account for the discontinuations in the placebo group, and to better compare the primary centralised analysis with the Investigators' assessment, we have performed a post-hoc analysis, where the Investigators' assessment at W24 was transformed into a binary outcome using the same approach used for the centralised analysis. Failure was attributed if the Investigators evaluation at W24 was not a "complete or nearly complete response", if the patient discontinued treatment prematurely, or if the patient took additional treatment for IH before W24. These data were then analysed using the same statistical methods as the primary analysis.

Table 40 presents the results of this new analysis, alongside a recap of results from the primary centralized assessment and the original Investigators' assessment of complete/near complete resolution. Transformation of the Investigators' assessment into the binary success/failure outcome reduced success rate in the placebo group to 3.6%, from the original artificially inflated success rate of 10.5%. In this transformed binary analysis of Investigators' assessment, the rate of treatment success with propranolol was still much higher in the centralised assessment (60.4%) than with the transformed binary analysis of Investigators' assessment (22.8%). However, by transforming the Investigators' assessment into a binary outcome, the treatment effect with propranolol became statistically significantly higher than placebo (p=0.004), supporting the primary efficacy analysis

Table 40: Complete/near complete resolution at week 24 (Primary centralised reading, Investigators' assessment and Investigators' assessment transformed into binary outcome)

	Complete/near complete Resolution at Week 24					
	Primary centralised reading		Investigators' assessment		Investigators' Assessment (transformed into binary outcome)	
	Placebo	V0400SB 3mg/kg/day 6mths	Placebo	V0400SB 3mg/kg/day 6mths	Placebo	V0400SB 3mg/kg/day 6mths
	n=55	n=101	n=55	n=101	n=55	n=101
n/missing	55 / 0	101 / 0	19 / 36	90 / 11	55/0	101/0
Yes	2 (3.6%)	61 (60.4%)	2 (10.5%)	24 (26.7%)	2 (3.6%)	23 (22.8%)
No	53 (96.4%)	40 (39.6%)	17 (89.5%)	66 (73.3%)	53 (96.4%)	78 (77.2%)
Combination test	p<.0001		p=0.4419		p = 0.004	

Source: CSR Table 18, CSR Table 138, new analysis: UNPL_INVEST_Response_ANA_Unadj.RTF

12.3.1.1.7. Convergence between outcomes

In Study 201, a blinded centralised assessment of efficacy was chosen as the primary efficacy criterion for the reasons outlined above. The divergence between the centralised assessment and the Investigators' onsite assessment of success was unexpected and was the only instance of divergence between outcomes. Possible reasons for this divergence include Investigator heterogeneity and subjectivity (56 sites in 16 countries), overly high expectations of success, parental pressure and overly stringent application of the criteria of success.

In this section:

- the divergence between the centralised and Investigators' assessment of complete/near complete resolution is analysed, showing that the difference arises solely from diverging evaluation of success in the propranolol group,
- the consistency in time to first sustained improvement between the centralised, Investigators' and parents' assessments is demonstrated,
- the consistency in time to first worsening between the centralised and Investigators' assessments is demonstrated.

Convergence of complete/ near complete resolution:

[Data is presented on] the numbers of patients who had convergent and divergent treatment success at W24 for the centralised reading and the Investigators' assessment (transformed into binary outcome). Interestingly, the centralised and Investigators' assessment was fully convergent for the outcome of treatment failure, both in the placebo and propranolol groups. The difference between the centralised and Investigators' assessments arose solely from divergent evaluations of success in the propranolol group. This suggests that the centralised and Investigators' assessment of treatment failure was consistent, but that the Investigators applied a more stringent and subjective interpretation of treatment success compared to the centralised assessment. It was to avoid such subjectivity that the centralised assessment was chosen as the primary efficacy outcome.

A post-hoc subgroup analysis of the centralised primary efficacy endpoint was performed on the subgroup of patients with convergent responses between the centralised and Investigators' assessments of success. In this analysis, a significantly higher ($p<0.001$) success rate was observed with propranolol (36.5%) than with placebo (3.6%).

Qualitative assessment of IH evolution on a 3-point scale (improvement, worsening, and stabilisation) was evaluated by centralised assessment, Investigators' onsite assessment and parents' assessment. Each analysis compared each scheduled post-baseline visit with the previous scheduled visit.

Convergence of sustained improvement:

Qualitative assessment of IH evolution on a 3-point scale (improvement, worsening, and stabilisation) was evaluated by centralised assessment, Investigators' onsite assessment and parents' assessment. Each analysis compared each scheduled post-baseline visit with the previous scheduled visit.

Sustained improvement was defined as the first improvement after which there was no worsening. Table 41 shows the Kaplan-Meyer rate of first sustained improvement at each time point from W5 to W24 for the centralised assessment, the Investigators' assessment and the parents' assessment. In each assessment, propranolol was significantly more effective than placebo ($p<0.001$). The Kaplan-Meyer rate of first sustained improvement with propranolol was comparable between the centralised assessment, the Investigators' assessment and the parents' assessment at each time point and at W24 (W24 data: 79.5%, 82.5%, and 85.6%, respectively).

Of note, placebo Kaplan-Meyer rates were markedly higher in the Investigators' and parents' assessments than with the centralised assessment. This is more in line with the usual situation where placebo success rates are higher with subjective measurements than with centralised measurements.

Table 41: Time to first sustained improvement (ITT population)

Time to first sustained improvement of target IH up to W24	Centralized qualitative assessment:		Investigators' on site assessment		Parents' on site assessment	
	Placebo (N = 55)	V0400SB 3 mg/kg/day 6mths (N = 101)	Placebo (N = 55)	V0400SB 3 mg/kg/day 6mths (N = 101)	Placebo (N = 55)	V0400SB 3 mg/kg/day 6mths (N = 101)
	N n (KM rate)*					
Day 0 (Baseline)	55 0 (0.0%)	101 0 (0.0%)	55 0 (0.0%)	101 0 (0.0%)	55 0 (0.0%)	101 0 (0.0%)
Week 5*	37 2 (5.4%)	99 72 (72.7%)	27 10 (20.1%)	29 68 (70.9%)	28 10 (19.9%)	32 64 (67.4%)
Week 8	26 3 (9.0%)	26 73 (73.8%)	17 11 (24.8%)	26 70 (73.1%)	18 11 (24.4%)	29 66 (69.7%)
Week 12	21 3 (9.0%)	25 74 (74.8%)	12 11 (24.8%)	24 72 (75.4%)	13 11 (24.4%)	27 68 (71.9%)
Week 16	19 3 (9.0%)	22 75 (76.0%)	10 12 (32.4%)	20 73 (76.6%)	11 14 (45.0%)	23 70 (74.4%)
Week 20	17 3 (9.0%)	16 76 (77.5%)	7 12 (32.4%)	14 75 (80.0%)	6 14 (45.0%)	16 74 (80.8%)
Week 24	16 3 (9.0%)	11 77 (79.5%)	6 12 (32.4%)	8 76 (82.5%)	5 14 (45.0%)	8 76 (85.6%)
P	<0.0001		<0.0001		<0.0001	

Source: CSR Tables 126, 155 and 159

N = number of patients at risk. n = cumulative number of events KM rate = Kaplan-Meier cumulative incidence estimates
*In the centralised assessment, W5 is compared with baseline (previous visit). In the Investigators' assessment, W5 is compared with D21 (previous visit).

Convergence of time to first worsening

Qualitative assessment of IH evolution on a 3-point scale (improvement, worsening, and stabilisation) was evaluated by centralised and Investigators' onsite assessment.

Worsening was evaluated as part of the qualitative assessment of IH evolution on a 3-point scale (improvement, worsening, and stabilisation). A post-hoc analysis was performed to evaluate the time to first worsening from the time of randomisation.

Survival analysis showed that the time to first worsening was notably shorter with placebo than with propranolol and that this result was strongly convergent between the primary centralised assessment and the Investigators' assessment (Table 42 Figure 6 and Figure 7).

By W5, KM rates showed that first worsening had been experienced by >50% of patients in each placebo group and less than 10% in each propranolol group. This pattern continued throughout the study, with comparable results between the centralised and Investigators' assessment throughout the study. At W24, both analyses converged to demonstrate notably more patients with IH worsening in the placebo group (KM rates: 69.1% and 75.9% in the centralised and Investigators' assessments, respectively) than in the propranolol group (KM rates: 19.9% and 26.3%, respectively).

Table 42: Time to first worsening from randomisation to Week 24 (centralised and Investigators' assessment)

	Centralised qualitative assessment		Investigator assessment	
	Placebo n=55 N n (KM rate)*	V0400SB 3mg/kg/day 6mths n=101 N n (KM rate)*	Placebo n=55 N n (KM rate)*	V0400SB 3mg/kg/day 6mths n=101 N n (KM rate)*
Day 0 (Baseline)	55 0 (0.0%)	101 0 (0.0%)	55 0 (0.0%)	101 1 (1.0%)
Week 5	37 31 (56.4%)	99 4 (4.0%)	32 34 (62.9%)	98 6 (6.0%)
Week 8	24 36 (65.5%)	97 5 (5.0%)	20 38 (70.3%)	94 8 (8.0%)
Week 12	19 36 (65.5%)	96 8 (7.9%)	16 38 (70.3%)	91 14 (14.0%)
Week 16	19 38 (69.1%)	92 13 (12.9%)	16 41 (75.9%)	85 19 (19.1%)
Week 20	17 38 (69.1%)	87 18 (17.9%)	13 41 (75.9%)	79 25 (25.2%)
Week 24	17 38 (69.1%)	82 20 (19.9%)	13 41 (75.9%)	73 26 (26.3%)

* N = number of patients at risk. n = cumulative number of events. KM rate = Kaplan-Meier cumulative incidence estimates

Figure 6: Time to first worsening (centralised assessment)

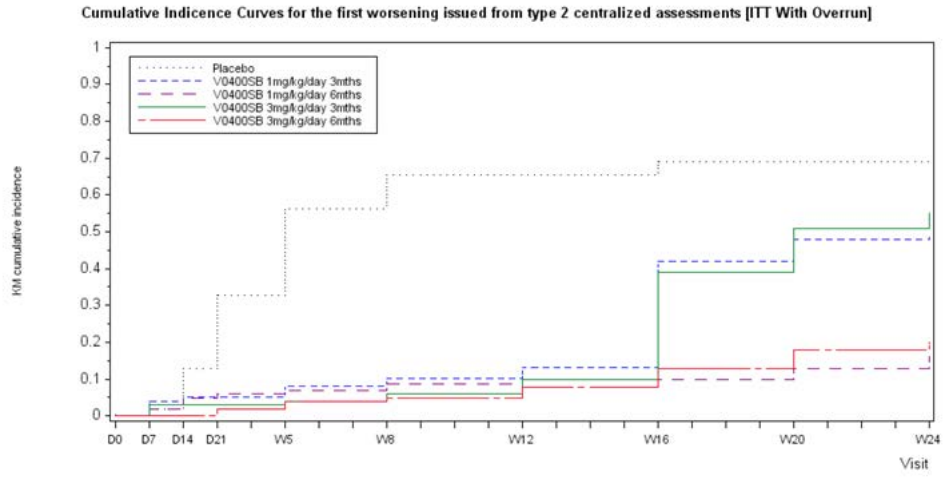
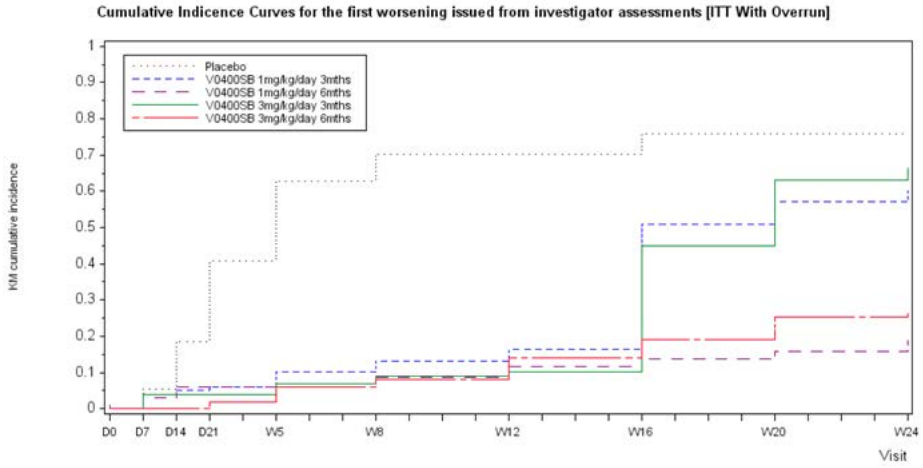


Figure 7: Time to first worsening (Investigators' assessment, ITT population)



12.3.1.1.8. Conclusions

The primary centralised efficacy endpoint was designed, developed and validated to be stringent, robust and reproducible. Investigators were trained and validated in photograph acquisition and the centralised readers were trained, validated and monitored, ensuring robustness and reproducibility.

The consistency of results of the centralised primary variable across the analysis populations (ITT population: 60.4%, PP population: 60.2% and sensitivity analysis: 61.4%) reinforces the robustness of the primary evaluation method and does not suggest bias in the evaluation of photographs.

The divergence between the rates of complete/ near complete resolution at W24 between centralised and Investigators arose exclusively from differences in treatment success in the propranolol group. There was no divergence in the judgment of treatment failures.

Other secondary criteria had strong convergence between the centralised assessment and on-site qualitative assessments. The time to first sustained improvement was strongly consistent between the centralised, Investigators' and parents' assessment. Similarly, the time to first worsening was strongly consistent between the centralised and Investigators' assessment.

In conclusion, and based on both the primary efficacy criterion and the secondary criteria, the efficacy of propranolol has been adequately demonstrated without any doubts as to the validity of the primary assessments performed.

12.3.1.2. Clinical evaluator's comment

The sponsor's detailed response to the question has been provided in full as the efficacy of Hemangiol for the proposed indication hinges on the interpretation of the data summarised in the response.

The sponsor's response indicates that the photographic criteria used to define complete or nearly complete resolution of IH at Week 24 were not validated by comparison with the actual physical appearance of the lesion as assessed by clinical examination undertaken by physicians experienced in the assessment and management of IH. Therefore, the centralized (photograph) assessment of outcome should be considered to be a non-validated surrogate measure of the outcome of interest, which is considered to be complete/nearly complete resolution of the IH following treatment assessed by "in vivo" clinical examination.

There is no doubt that the results of the primary efficacy endpoint analysis of complete/nearly complete resolution of target IH at Week 24, based on centralized comparative assessment of the Baseline and Week 24 photographs, are statistically robust. However, the sponsor claims that the results are also clinically robust based on the endpoint of change in lesion as assessed photographically by two experienced physicians. The sponsor justifies the use of the photographs to assess clinical change in IH following treatment on the basis that interpretation can be centralized and standardized resulting in minimization of bias. However, it is considered that assessment of change in the IH following treatment based on physical examination of the lesion by experienced physicians is a more clinically relevant method of assessing progress than photographic evidence.

The primary endpoint analysis showed that the complete/nearly complete resolution rate at Week 24 of the target IH in the ITT data set was statistically significantly higher in the propranolol group (3 mg/kg/day for 6 months) than in the placebo group: 60.4% (61/101) vs 3.6% (2/55), respectively; $p < 0.0001$. The results of the analyses of the primary outcome endpoint in the PP data set and the sensitivity analyses in the ITT data set (planned and unplanned) also showed that the complete/nearly complete response rates in the propranolol group were statistically significantly higher than in the placebo group. The placebo response rates in the planned and unplanned sensitivity analyses were markedly higher than the placebo response rates in the ITT and PP sets, while the propranolol response rates remained consistent in the four analyses (see Table 38 above). This appears to be a function of the methods used in sensitivity analyses, which resulted in inflating the placebo response rate, given that nearly all patients in the placebo group in the primary analysis were non-responders. In addition to the PP and sensitivity analyses, the subgroup analyses of the primary endpoint also support the primary efficacy analysis.

The results of the primary analysis based on centralized assessment of photographic progression of the target IH at Week 24 are inconsistent with the protocol specified secondary analysis based on investigator assessment of treatment outcome. In the prespecified investigator assessment, the complete/nearly complete resolution rate at Week 24 of the target IH was 10.5% (2/19) compared with 26.7% (24/90) in the propranolol group, p=0.4419. The sponsor considers that the reason for this discrepancy "is most likely attributable to subjectivity in the definition of complete/near complete resolution which may be influenced by differences in training, standard treatment used in the centres and expectations (of Investigators and parents)". The sponsor rejects the possibility that the difference is due to bias in the centralized photographic assessment and refers to the evidence supporting the validity of the assessment procedure. However, review of the evidence provided by the sponsor is considered to show that centralized assessment has "internal validity", but no evidence has been provided that the method accurately reflects the progression of IH detectable by physical examination by experienced physicians (i.e., "external validity").

The investigator assessment of complete/nearly complete resolution was undertaken on a different patient population from that used for the centralized photographic assessment. The sponsor considered that the investigator assessment resulted in an overestimation of the Week 24 complete/nearly complete success rate in the placebo group due to the large number of patients in this group discontinuing for lack of efficacy being classified as "missing data" rather than as "treatment failures". Consequently, the sponsor undertook a post hoc analysis where the investigator assessment at Week 24 was transformed into a binary outcome using the same approach to categorization of patients as the primary analysis. In this post hoc analysis, patients were considered to be "treatment failures" if the investigator assessment at Week 24 was not a "complete or nearly complete response", if the patient discontinued treatment prematurely, or if the patient took additional treatment for IH before W24. These data were then analysed using the same statistical methods as the primary analysis.

The results of the post hoc analysis showed that there was a statistically significant difference in the success rate between the placebo and propranolol groups at Week 24 (3.6% [2/55] vs 22.8% [23/101; p=0.004). In the post hoc analysis, while the complete/nearly complete resolution success rate in the placebo group was identical to that in the primary efficacy analysis (3.6%), the success rate in the propranolol 3 mg/kg/day group remained strikingly lower than in the primary analysis (22.8% vs 60.4%, respectively).

The sponsor undertook a comparison between the patients who had convergent or divergent treatment outcomes (success vs failure) at Week 24 for the primary centralized assessment and post hoc investigator assessment. This comparison found that, while both assessments were fully convergent for the outcome of "treatment failure" in both the placebo and propranolol groups, the assessments were markedly divergent for the outcome of "treatment success" in the propranolol group. The sponsor states that the results suggest "that the centralised and Investigators' assessment of treatment failure was consistent, but that the Investigators applied a more stringent and subjective interpretation of treatment success compared to the centralised assessment. It was to avoid such subjectivity that the centralised assessment was chosen as the primary efficacy outcome". However, another reason might be that centralized assessment of IH progression based on photographic changes is not a particularly reliable measure of progression assessed by physical examination by experienced physicians. Furthermore, no data were presented establishing that assessments were subjectively different among investigators. Therefore, the sponsor's contention that the investigators applied a more stringent and subjective interpretation of treatment success compared with the centralized assessors is considered to be speculative.

The results of the KM assessment of time to first improvement in IH evolution on a qualitative 3-point scale (improvement, worsening, or stabilization) showed that analyses for the propranolol group converged at Week 24 for centralized, investigator on-site and parent-on-site assessments (KM rates: 79.5%, 82.5% and 85.6%, respectively). However, analyses were non-convergent for the placebo group at Week 24 with the KM rates being markedly lower for centralized assessment compared with both investigator on-site and patient on-site assessments (KM rates: 9.0%, 32.4%, and 45.0%, respectively). In each of the three assessment groups, the difference between placebo and propranolol were statistically significant.

The results of the post hoc KM assessment of time to first worsening (improvement, worsening, or stabilization) showed that at Week 24 both centralized and investigator on-site assessments converged, and showed notably more patients with IH worsening in the placebo group (KM rate: 69.1% and 75.9%, respectively) than in the propranolol group (KM rates: 19.9% vs 26.3%, respectively).

In conclusion, it is considered that the marked inconsistency in the complete/nearly complete resolution rate in the propranolol group between the primary centralized assessment (60.4% [61/101]) and both the protocol specified investigator's assessment (26.7% [24/101]), and the post hoc investigator's assessment (22.8% [23/101]) in the pivotal study raises doubts about

the efficacy of propranolol for the proposed usage. While propranolol might be an effective treatment for IH it is considered that the pivotal study has not unequivocally demonstrated that this is the case.

12.3.2. Question 2

Please provide the number of patients with complete resolution and the number of patients with nearly complete resolution contributing to the total number of patients with complete/nearly complete resolution for the primary efficacy endpoint analysis in the pivotal study (i.e. 61 patients on propranolol 3 mg/kg/day 6 months, 2 patients on placebo).

12.3.2.1. Sponsor's Response (complete)

The primary efficacy endpoint of Study 201 was based on individual clinical success, being defined as "complete/ nearly complete resolution of the target IH at W24", where nearly complete resolution was defined as "a minimal degree of telangiectasias, erythema, skin thickening, soft tissue swelling, and/or distortion of anatomic landmarks".

Central readers were not instructed to separate in their assessments complete response and nearly complete response, but only to conclude as to ""complete/ nearly complete resolution of the target IH at W24": yes or no.

As defined in the study protocol, the primary endpoint was a binary endpoint "success/failure" based on this assessment. Therefore the primary endpoint was not a composite endpoint comprising addition of separate results for complete resolution and nearly complete resolution. Separate results for complete resolution and nearly complete resolution for the centralised analysis of efficacy were not performed and are not available.

12.3.2.2. Clinical evaluator's comment

The sponsor's response is satisfactory.

12.3.3. Question 3

The inclusion criteria for the pivotal study included a proliferating IH (target hemangioma) "requiring systemic therapy". Were investigators instructed to document their reasons for considering that an individual patient's IH required systemic therapy? If so, what were these reasons?

12.3.3.1. Sponsor's response (complete)

Investigators were not instructed to document their reasons for considering that an individual patient's IH required systemic therapy.

However, since the publication of Frieden in 1997 when the efficacy of propranolol had not yet been discovered (Frieden et al. 1997), there was a global consensus of which IH should require systemic therapy. An enlargement of this definition, established after the discovery of propranolol's efficacy, was to include IH with a potential risk of disfigurement (not restricted to facial or exposed areas) (Drolet et al. 2013).

Table 43 below shows which patients could have been included by investigators. The following patients were not included in the pivotal phase II/III study 201 for ethical reasons due to the placebo arm:

- Life- and function-threatening IH (e.g. those causing impairment of vision, respiratory compromise caused by airway lesions, congestive heart failure, hepatic involvement).
- Severe ulcerated IH (whatever the localization) with pain and/or lack of response to simple wound care measures.

Table 43: Data sources presented in the dossier in relation to the Overall Target Indication

	Target Indication for Treatment	Risk Stratification	Submission Study Category			
			CUP	Publications	102	201
1	Life- and function-threatening IH (e.g. those causing impairment of vision, respiratory compromise caused by airway lesions, congestive heart failure, hepatic involvement).	High risk	✓	✓	✓ (life-threatening excluded)	
2	IH in certain anatomical locations that often leave permanent scars or deformity, especially the nose, lip, ear, and glabellar area.			✓	✓	✓
3	Large facial IH, especially those with a prominent dermal component (more likely to leave permanent scarring).			✓	✓	✓
4	Smaller hemangiomas in exposed areas, such as the face and hands, may be considered for treatment with modalities unlikely to cause scarring or significant side effects.			✓	✓	✓ (>1.5 cm)
5	Ulceration			✓	✓	✓
	Severe ulcerated IH (whatever the localization) with pain and/or lack of response to simple wound care measures.[1]	High risk	✓	✓	✓	
6	Pedunculated hemangiomas (likely to leave significant fibrofatty tissue after involution).			✓	✓	✓
7	IH with a potential risk of disfigurement			✓	✓	✓

CUP: compassionate use program; IH: infantile hemangioma.

1. Only certain high risk cases of ulceration were not included in Study 201, according to the definition provided (Study 201 non-inclusion criterion).

12.3.3.2. Clinical evaluator's comment

The sponsor's response is satisfactory.

12.3.4. Question 4

Does the sponsor have any information on the outcome of the IHs (e.g., spontaneous regression) in the patients in the placebo arm in the pivotal study who withdrew prematurely due lack of efficacy (32/55; 58.2%)? If not, does the sponsor intend to obtain this information and, if so, over what time-period will such information be collected?

12.3.4.1. Sponsor's response (abridged/edited)

Most of the patients in the placebo arm withdrew prematurely (36/55 [65.5%]). The main reason was treatment inefficacy, particularly in the placebo arm where 32/55 (58.2%) discontinued prematurely treatment for inefficacy.

When patients did not have a premature End of Study (EOS), follow up information was available. Among the 36 patients with premature EOT in the placebo arm, 14 have continued the follow-up period. All of them have been treated with oral off-label propranolol or other beta-blocker.

This makes it impossible to evaluate the spontaneous regression when stopping the placebo treatment. As a consequence, the natural evolution of IH with no active treatment may only be documented in the patients having been randomised to placebo and having completed the 6 month study period. Since a large proportion of patients did not complete the study because of lack of efficacy, the use of the completers to assess natural evolution of IH overestimates the proportion of spontaneous regression. Despite this limitation the rate of success on placebo remains very low.

12.3.4.2. Clinical evaluator's comment

The sponsor's response is acceptable. No reliable estimate of spontaneous regression in the placebo group can be obtained from this study.

12.3.5. Question 5

In the pivotal study (CSR) is stated that the centralized readers evaluated the overall quality of the photographs for each combined image evaluation on a three-level scale: unevaluable; poor; good. What was the outcome of this quality assessment?

12.3.5.1. Sponsor's response (complete)

No patient had photographs that could not be assessable. Quality of photographs was judged as Poor in only 2.5%, never jeopardizing the assessment by central readers. For all other patients, quality of photographs was judged as Good.

12.3.5.2. Clinical Evaluator's Comment

The sponsor's response is satisfactory.

12.3.6. Question 6

Please provide an explanation why three of the four "Independent advisory board" members were study investigators, and therefore not independent?

12.3.6.1. Sponsor's Response (Complete)

Two boards/committees were involved in the study V00400 SB 201:

- the Independent Data Monitoring Committee (IDMC)
- the Expert advisory board

IDMC:

The aim of the IDMC was to safeguard the interests of the study participants, investigators and the sponsor; to assess the appropriateness of the required study sample size; to assess the safety and efficacy of the study's interventions; to monitor the overall conduct of the study; and to protect its validity and credibility.

The voting members were chosen due to their experience in clinical trials methodology and/or the disease area:

[Information redacted]

Following the interim analysis of the data (190 first randomized patients) and the review of initial study hypotheses, the committee chairman has recommended in writing to the sponsor that a regimen of propranolol should be carried forward to the phase III stage of the study. Any safety concerns were also raised in the recommendation letter.

None of the IDMC members were study investigators.

Expert advisory board:

As mentioned in the [dossier] CTD Module 2.5, at the time of initiation of the development of V0400SB, the only guidelines available for the treatment of IH were presented in the Guidelines of Care for Hemangiomas of Infancy (Frieden et al 1997), published before the discovery of

propranolol in the treatment of IH. Therefore there were no current uniform guidelines regarding the ideal propranolol dosing regimen, treatment duration, or monitoring periods, and thus off-label treatment has largely been based on investigators' experience and information available in the literature. In addition, there were no official, validated assessments or tools for the measurement of IH evolution/resolution.

For these reasons Pierre Fabre worked very closely with both the regulatory agencies and experts in the field throughout the clinical development program.

It was similarly mentioned in the CTD Module 2.7.3 there were no official, validated assessments or tools for the measurement of IH improvement/resolution. For this reason Pierre Fabre worked very closely with both the regulatory agencies and experts in the field to ensure as far as possible that the efficacy assessments and endpoints in Study 201 reflected faithfully a true change in IH presentation, and that the resulting data would be accurate and of a high quality.

Pierre Fabre worked in association with an external IH expert advisory board (four members, three of whom were study investigators) to clearly define *'nearly complete resolution' as: a minimal degree of telangiectasias, erythema, skin thickening, soft tissue swelling, and/or distortion of anatomic landmarks.'* This efficacy criterion is more stringent than most efficacy criteria reported in the publications, a key point that should be taken into account in order to avoid any biased interpretation when performing historical comparisons.

The same was described in the study protocol:

"In order to obtain additional recent data more specific to this study population, the sponsor has worked with several of the US and European sites to be involved in the study, who are currently using off-label propranolol. At the time that this protocol is written, many of the sites only have a limited number of patients who have been treated with propranolol and followed up for at least 24 weeks after starting the treatment, but all of the feedback suggests that similar results are being observed across all sites."

The sponsor has also worked more closely with an external IH expert advisory board (4 members:

[Information redacted]

Thus, at no time it was expected that the four experts remained independent. Their contribution was to help the Sponsor to (re)define a primary endpoint fulfilling the Agencies' expectations but also corresponding to the medical practice and to the profile and evolution of HIs.

Therefore, these 4 IH experts have brought their large medical practice in IH and their growing experience in treating IH with oral propranolol to help the Sponsor to define an appropriate primary endpoint, and to estimate the percentage of treatment success in order to perform the sample size calculation.

Other than this initial contribution to the definition of the primary criterion, before the study start, the experts had no other impact on the study design, conduct or interpretation. The

inclusion of the clinical centres of 3 of these experts as investigating centres came as a second step, and their contribution as investigators was exactly similar to that of all other centres

12.3.6.2. Clinical evaluator's comment

The sponsor's comments are noted.

12.3.7. Question 7

Were the independent observers assessed for red-green colour blindness?

12.3.7.1. Sponsor's response (abridged/edited)

The two centralized assessors were not assessed for green-red colour blindness before the study. However, they have confirmed that they do not have problems of colour vision.

12.3.7.2. Clinical evaluator's comment

The sponsor's response is satisfactory. The sponsor provided a statement from the two centralized assessors indicating that they have normal colour vision.

12.3.8. Questions 8 and 9

How was the IH deep component (non-visible) assessed for response?

How did the independent observers determine a change in: deep component, skin thickening, tenseness and soft tissue swelling from photographs?

12.3.8.1. Sponsor's response (complete/edited)

The two centralized photographs have précised how they assessed the IH deep component (non visible) and changes in deep component, skin thickening, tenseness and soft tissue swelling from photographs:

"In the absence of 3D imaging, volume changes were indirectly assessed using orthogonal (side-on and front-on) views, and, whenever possible, by comparison with anatomic landmarks of the healthy opposite site of the body and face or with contralateral extremity in case of limb involvement. A deep component was defined as visible swelling (lump) without overlying visible superficial vascular component. Presence of skin thickening and soft tissue swelling was diagnosed on deformation of anatomical landmarks or asymmetry with contralateral structures. Tenseness was not a primary criteria but was considered present when the superficial component was shiny (from camera flash reflectance) with a bright red hue".

12.3.8.2. Clinical evaluator's comment

The sponsor's response is noted. However, it is considered that 2-D photographic interpretation of deep component, skin thickening, tenseness and soft tissue swelling associated with IH cannot satisfactorily replace physical examination of the lesion by experienced physicians.

12.3.9. Question 10

Why was the glucose level of 40mg/dl (2.2 mmol/l) used as the cut off to describe hypoglycaemia and not 2.6 mmol/l as is standard in clinical practice?

12.3.9.1. Sponsor's response (complete)

As shown in [the dossier and Table 5, above] the glucose level of 40mg/dl (2.2 mmol/l) was defined as the point for intervention, but not used as the cut off to describe hypoglycaemia (lower than one of the accepted normal range value for blood glucose). Interventions were defined as follows:

- to not start the study treatment
- to permanently discontinue the study treatment
- and in all cases to monitor patients until resolution

12.3.9.2. Clinical evaluator's comment

The sponsor's response is noted. In Australian paediatric practice, hypoglycaemia is commonly defined as blood glucose level < 2.2 mmol (capillary or whole blood) or < 2.6 mmol/L (plasma or serum), and it is likely that treatment would be initiated at these levels (see Paediatrics Manual, The Children's Hospital at Westmead Handbook, Second Edition, Kilham et al).

12.3.10. Question 11

What are the results of the Kappa statistic for intra- and inter-observer error as described in the method section?

12.3.10.1. Sponsor's response (abridged)

All photos have reached an agreement between readers, either during reading sessions or by adjudication. The Kappa for intra-observer errors for all Type 1 central readings on photographs were 0.72 for reader 1 (Pierre Souteyrand) and 0.80 for reader 2 (Pierre Vabres).

12.3.10.2. Clinical evaluator's comment

The sponsor response is satisfactory. The sponsor provided a tabulated list of the Kappa for inter-observer error for all Type 1 central readings.

12.4. Safety

12.4.1. Question 1

Please provide a tabulated summary of patients in the pooled safety population with temporary treatment discontinuations by treatment group (i.e., all placebo [n=236], all 1 mg/kg/day [n=200], all 3 mg/kg/day [n=224], and all propranolol [n=424]). The table should summarize the data in the same manner as the data for TEAEs resulting in permanent treatment discontinuation summarized in the ISS/SCS ([dossier] table 23). In addition, please provide information on the mean duration (and range) of the total temporary treatment discontinuations for each of the treatment groups.

12.4.1.1. Sponsor's response (abridged)

In all, 53 patients had a temporary treatment discontinuation. These are presented by treatment group (i.e., all placebo [n=236], all 1 mg/kg/day [n=200], all 3 mg/kg/day [n=224], and all propranolol [n=424]).

12.4.1.2. Clinical evaluator's comment

The sponsor provided the requested tables. The sponsor stated that a total of 53 patients had a temporary treatment discontinuation due to TEAEs. This number is incorrect as it refers to the total number of patients in the combined propranolol groups (i.e., excludes patients in the all placebo group). The total number of patients with a temporary treatment discontinuation due to TEAEs was 63 (10 [4.2%] in the all placebo group and 53 [12.5%]) in the all propranolol group.

Temporary treatment discontinuations due to TEAEs occurred notably more commonly in the all propranolol 3 mg/kg/day group than in the all placebo group (15.2% [34/244] vs 4.2% [10/236], respectively). TEAEs resulting in temporary treatment discontinuation reported in ≥

1% of patients in the all placebo or all propranolol 3 mg/kg/day groups, and in descending order of frequency in the propranolol group vs the placebo group were: bronchitis (3.1% vs 0.8%); gastroenteritis (3.1% vs 0.4%); bronchiolitis (2.2% vs 2.1%); vomiting (2.2% vs 0%); and pyrexia (1.3% vs 0%). The only TEAE resulting in temporary treatment discontinuation reported more frequently in the all placebo group than in the all propranolol 3 mg/kg/day group was febrile infection (0.4% vs 0%, respectively).

12.4.2. Question 2

Please provide the proportion of patients in the pivotal study (201) and the pooled safety population with HR values less than 80 bmp in each treatment arm during the course of treatment, and indicate the number (and percentage) of these events occurring during and after the titration period. The proposed Hemangiol PI recommends that specialist advice be sought for patients with bradycardia (HR < 80 bpm). Please explain why the cutoff figure of 80 bpm was chosen as the point for intervention.

12.4.2.1. Sponsor's response (abridged/edited)

As shown [in the dossier, see also Table 5 above] Heart rate of 60 bpm was defined as the point for intervention, but not used as the cut off to describe bradycardia (lower than one of the accepted normal range value for heart rate).

Interventions were defined as follows:

- to not start the study treatment
- to permanently discontinue the study treatment
- and in all cases to monitor patients until resolution

For the purposes of the dossier, FDA requested to consider a threshold of 80 bpm as a point for definition of bradycardia.

Proportion of patients with HR values less than 80 bpm during the course of treatment, and during and after the titration period are presented for the pivotal study (201) by treatment regimen group (safety population).

Table 44: Heart rate values < 80 bpm in study 201.

	Placebo 6mths n=55	V0400SB 1mg/kg/day 3mths n=98	V0400SB 1mg/kg/day 6mths n=102	V0400SB 3mg/kg/day 3mths n=123	V0400SB 3mg/kg/day 6mths n=101
1: At least one HR <80 bpm during treatment period	3 (5.5 %)	7 (7.1 %)	6 (5.9 %)	18 (14.6 %)	15 (14.9 %)
2: At least one HR <80 bpm during up-titration period	3 (5.5 %)	4 (4.1 %)	2 (2.0 %)	11 (8.9 %)	9 (8.9 %)
3: At least one HR <80 bpm after up-titration period	-	5 (5.1 %)	5 (4.9 %)	7 (5.7 %)	12 (11.9 %)

12.4.2.2. Clinical evaluator's comment

The sponsor's response is satisfactory. The response included a set of 4 tables similar to the one provided above, but including data from the total safety population in addition to data from the pivotal study (201). However, the headings of two tables appear to be associated with the wrong data sets. In any event, the data provided for the pivotal study (201) for the safety included above indicate that by Month 6, 14.9% of patients in the propranolol 3 mg/kg/day group had experienced at least one episode of bradycardia (HR < 80 bpm) compared with 5.5% of patients in the placebo group. In addition, bradycardia occurred notably more commonly in the 3 mg/kg/day group during up-titration than in the placebo group. There was also a dose response relationship between bradycardia and propranolol. In the pooled safety population, the proportion of patients experiencing at least one episode of bradycardia (HR < 80 bpm) in the treatment period in the placebo, all propranolol 1 mg/kg/day, and all propranolol 3

mg/kg/day groups was 2.5% (6/236), 6.5% (13/200), and 14.3% (32/224), respectively. The pattern for bradycardia in the pooled safety population was similar to that observed in the pivotal study (201). Overall, the results indicate that bradycardia (HR < 80 bpm) occurred relatively frequently with the propranolol 3 mg/kg/day treatment region and notably more commonly than with placebo.

12.4.3. Questions 3 and 4

Please provide the number and percentage of patients with first, second, and third degree heart block identified by routine ECG monitoring in the safety population in the first 4 hours following the first dose (D0) and following dose increase in the titration period (D7, and D14).

Please provide the number and percentage of patients with first, second, and third degree heart block identified by routine ECG monitoring in the safety population during the course of the study.

12.4.3.1. Sponsor's response (complete)

No patient presented a third degree atrio-ventricular block.

One patient (study 201, 1 mg/kg/day) presented a second degree atrio-ventricular block Mobitz I diagnosed in the 240 minutes post-first dose ECG on D0. The event was of mild intensity and led to definitive discontinuation of the study drug. The event considered as a SAE lasted less than 1 day and recovered without corrective treatment. On the basis of Holter investigation findings, a preexisting cardiologic disease was considered probable.

First degree atrio-ventricular block have been evaluated by PR interval values > 160 ms. Number and percentage of patients with PR values higher than 160 ms during the course of treatment, during and after the titration period for the pooled safety population are presented by treatment arm regimen group in Table 45 and by dose of V0400SB or placebo in Table 46.

Table 45: PR interval > 160 ms in the pooled safety population, by treatment regimen

	Placebo 6mths n=55	V0400SB 1mg/kg/day 3mths n=98	V0400SB 1mg/kg/day 6mths n=102	V0400SB 3mg/kg/day 3mths n=123	V0400SB 3mg/kg/day 6mths n=101
1: At least one PR >160 msec during treatment period	1 (1.8 %)	-	-	5 (4.1 %)	3 (3.0 %)
2: At least one PR >160 msec during up-titration period	1 (1.8 %)	-	-	5 (4.1 %)	2 (2.0 %)
3: At least one PR >160 msec after up-titration period	-	-	-	1 (0.8 %)	1 (1.0 %)

Table 46: PR interval > 160 ms in the pooled safety population, by dose of V0400 SB or placebo

	All Placebo n=236	All V0400SB 1mg/kg/day n=200	All V0400SB 3mg/kg/day n=224	All V0400SB n=424
1: At least one PR >160 msec during treatment period	2 (0.8 %)	-	8 (3.6 %)	8 (1.9 %)
2: At least one PR >160 msec during up-titration period	1 (0.4 %)	-	7 (3.1 %)	7 (1.7 %)
3: At least one PR >160 msec after up-titration period	1 (0.4 %)	-	1 (0.4 %)	1 (0.2 %)

12.4.3.2. Clinical evaluator's comment

The sponsor's response is satisfactory.

12.4.4. Question 5

Were any patients permanently or temporarily discontinued from treatment due to abnormalities detected by routine ECG monitoring in the clinical development program. If so, please provide information on these patients.

12.4.4.1. Sponsor's response (abridged/edited)

Patients who permanently discontinued from treatment due to abnormalities detected by routine ECG monitoring are presented below:

- A Patient (1 mg/kg/d) presented a QT interval prolonged at ECG D7 T60 minutes, of moderate intensity (QTc = 443ms), recovered without corrective treatment at ECG performed 28 days later
- A Patient (1 mg/kg/d) presented a second degree atrio-ventricular block Mobitz I diagnosed in the 240 minutes post-first dose ECG on D0. The event was of mild intensity. The event considered as a SAE lasted less than 1 day and recovered without corrective treatment. On the basis of Holter investigation findings, a pre-existing cardiologic disease was considered probable.
- A Patient (3 mg/kg/d) premature baby with very low birth weight presented at D7 with bradycardia of moderate intensity (HR<100 bpm during hospitalisation for moderate enterocolitis. The event considered as a SAE recovered in 3 days with a corrective treatment (caffeine 0.2 mL IV). Enterocolitis was treated appropriately with antibiotics and symptomatic treatments.

No patient presented a temporary treatment discontinuation due to abnormalities detected by routine ECG monitoring.

12.4.4.2. Clinical evaluator's comment

The sponsor's response is satisfactory.

12.4.5. Question 6

In the clinical development program, how many patients had routine echocardiography undertaken before treatment with propranolol was initiated and confirm that only one patient was excluded from treatment because of detected abnormalities.

12.4.5.1. Sponsor's response (complete)

In the clinical development program, an echocardiography was performed as planned as per protocols in 516 patients. It was not performed in 17 screened but not randomised patients.

The Applicant confirms that this echocardiography led to the non inclusion of one single patient on the basis of a questionable intracardiac mass, of undocumented clinical relevance.

12.4.6. Clinical evaluator's comment

The sponsor's response is satisfactory.

12.4.7. Question 7

In the ISS/SCS (CTD 2.7.4), patients with at least one TEAE occurring on the days of dose increase are presented by pooled dose of V0400SB or placebo for D1 in [the dossier] table 2.7.4.2.29b ([dossier] section 5.3.5.3 – Vol. 1), for D7 in table 2.7.4.2.30b (section 5.3.5.3 – Vol. 1) and for D14 in table 2.7.4.2.31b (section 5.3.5.3 – Vol. 1). The summary states that on D1, D7 and D14, no TEAEs were experienced in the pooled placebo group. However, this statement appears to be inconsistent with the tables referred to in the summary which suggest that 4, 2, and 5 patients in the placebo group experienced adverse events on D0, D7, and D14, respectively. Please comment on this apparent discrepancy.

12.4.7.1. Sponsor's response (complete)

The Applicant agrees that there is an apparent discrepancy. In fact, none of TEAEs that appeared during the up-titration at D0, D7 and D14 had an incidence > 1% in the Placebo group. The text should be corrected as follows: "Patients with at least one TEAE occurring on the days of dose increase are presented by pooled dose of V0400SB or placebo for D1 in [dossier] table 2.7.4.2.29b ([dossier] section 5.3.5.3 - ISS tables), for D7 in table 2.7.4.2.30b ([dossier] section 5.3.5.3 – ISS tables) and for D14 in table 2.7.4.2.31b (section 5.3.5.3 – ISS tables).

Considering TEAEs experienced by at least 1% of patients on D1, D7 and D14 in any pooled dose group, none was of such incidence in the pooled placebo group and the maximum was 2.7%:

- D1: diarrhoea, peripheral coldness, somnolence, decreased appetite, vomiting and hypersomnia
- D7: diarrhoea, pyrexia, eczema, nightmare, peripheral coldness
- D14: hypersomnia.

12.4.7.2. Clinical evaluator's comment

The sponsor's response is satisfactory.

12.4.8. Question 8

Please describe the types of vaccination reaction for both the treatment and placebo groups, and explain why the treatment group had such a high rate of reported adverse events?

12.4.8.1. Sponsor's response (abridged/edited)

Investigators were not requested to classify the types of vaccination reactions. However, [the CSR] mentions the reported term by the investigator for the following Preferred Terms: IMMUNISATION REACTION, IRRITABILITY POSTVACCINAL, VACCINATION COMPLICATION, VACCINATION SITE PAIN, VACCINATION SITE REACTION.

Vaccination complications occurred in 1.3% of patients in the pooled placebo group, 7.5% in the pooled 1 mg/kg/day group, 8.5% in the pooled 3 mg/kg/day group and 8.0% in the pooled all V0400SB group. However the difference in vaccination complications between V0400SB and placebo did not persist if when corrected for the different rates of vaccination in the two groups.

Data is presented, for the first 3 months of treatment, for patients who were vaccinated (prior/concomitant medication beginning with the ATC2 code "J07") and the number of patients with a vaccination complication. In total, vaccinations were received by 23 patients in the pooled all placebo group and 234 in the pooled all V0400SB group, while vaccination complication was reported for 3 patients in the pooled all placebo group and 32 in the pooled all V0400SB group. The rate of vaccination complications frequency divided by vaccination frequency was similar with placebo and V0400SB: 13% in the pooled placebo group and 13.7% in the pooled all V0400SB group.

Of note, some patients who had a vaccination complication were not recorded as having received a vaccination. Therefore it is probable that the number of vaccinations has been under-reported and therefore the observed ratio of vaccination complications per vaccinations may be overestimated.

WHO vaccination protocols recommends vaccination between the ages of 3 and 6 months, with a booster shot one year later. This could also explain the low number of TEAEs of vaccination complication after the age of 6 months of age, and correspondingly, after the first 3 months of treatment (given that the age at inclusion was between 35 and 150 days).

12.4.8.2. Clinical evaluator's comment

The sponsor's response is satisfactory.

12.4.9. Question 9

Did any of the Subjects treated with propranolol who did not achieve a treatment response have their lesions biopsied to confirm the diagnosis? Other conditions such as haemangioendothelioma may visually appear like an IH but are frequently propranolol insensitive and many require chemotherapy, or other treatments, to achieve resolution.

12.4.9.1. Sponsor's response (complete)

Diagnosis of Infantile Hemangioma is based on clinical features and does not require biopsy. No patient had a biopsy of the lesion to confirm the diagnosis of Infantile Hemangioma.

12.4.9.2. Clinical evaluator's comment

The sponsor's response is satisfactory.

12.4.10. Question 10

What were the diagnoses for [3 patients with alkaline phosphatase of 4843 IU/l, 2207 IU/L and 937 IU/l, respectively]?

12.4.10.1. Sponsor's response (abridged/edited)

As displayed below, no diagnosis has been reported for these cases. However, according to investigators, hyperphosphatasemia were transient, asymptomatic (less than 3 months) and completely recovered:

[Information redacted]

The chronology is not suggestive of a causal relationship between elevated ALP and propranolol. Actually, in [two] patients, elevated ALP was reported at W24, 3 months after the end of study treatment. Furthermore, in [one] patient, ALP value, already elevated at screening, has decreased over time under study treatment without any corrective medication. An alternative cause for these transient hyperphosphatasemia could be Transient hyperphosphatasemia of infancy and early childhood (THI).

12.4.10.2. Clinical evaluator's comment

The sponsor's response is satisfactory.

12.4.11. Question 11

What was the cause of the two episodes of cytolytic hepatitis in a patient?

12.4.11.1. Sponsor's response (abridged/edited)

[The] Patient is a female randomized in the V0400 treatment arm (3 mg/kg/day).

[Information redacted]

Hepatotoxicity has not been identified as a potential risk with propranolol, and there is no exclusion criteria defined in the protocol concerning hepatic enzymes abnormalities. Laboratory tests including dosing of plasmatic hepatic enzymes were scheduled at screening, W12 and W24. Hepatic cytolysis, which was already present at baseline in [the] patient, decreased over time and resolved while the patient was under treatment. No causes have been reported by the investigator. However cases of CMV induced hepatitis have been reported in immunocompetent host and CMV infection can provide a possible cause for the hepatic cytolysis at baseline.

12.4.11.2. Clinical evaluator's comment

The sponsor's response is satisfactory.

12.4.12. Question 12

What was the cause of the persistent thrombocytosis and neutropaenia seen in a patient? Why was this not considered an adverse event?

12.4.12.1. Sponsor's response (complete)

Thrombocytosis (796 G/L) and neutropenia (0.49 G/L) observed at W12 were considered by the investigator as Clinically Significant. However, the same was already observed at Screening lab tests. Therefore, it has been notified as a Medical History. As there was no increase in severity during the study, it was not notified as an adverse Event.

12.4.12.2. Clinical evaluator's comment

The sponsor's response is satisfactory.

12.4.13. Question 13

How many premature infants were in the treatment and placebo groups? Did all premature infants that received propranolol commence after 5 weeks of age?

12.4.13.1. Sponsor's response (complete)

In total, 26.2% of patients included in the clinical trials of Hemangiol were born prematurely. A slightly higher incidence of prematurity was observed in the placebo regimen (34.5%) compared to the V0400SB regimens (21.6% in the 1 mg/kg/day 3 months regimen, 27.5% in the 1 mg/kg/day 6 months regimen, 26.8% in the 3 mg/kg/day 3 months regimen and 23.8% in the 3 mg/kg/day 6 months regimen).

As a reminder, in order to be included into the study, all patients had to have reached a corrected age of at least 35 days (5 weeks).

12.4.13.2. Clinical evaluator's comment

The sponsor's response is satisfactory.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

Following evaluation of the sponsor's Response to questions, the second round assessment of the benefits of Hemangiol remains largely unchanged from the first round assessment. While it is possible that Hemangiol might provide a benefit to infants aged from 30 to 150 days with proliferating IH requiring systemic therapy, it is considered that this has not been unequivocally demonstrated in the pivotal study (V00400 SB 2 01).

In the pivotal study, the proportion of infants aged from 30 to 150 days achieving complete/nearly complete resolution of proliferating IH requiring systemic therapy at Week 24 was markedly higher in the propranolol 3 mg/kg/day x 6 months arm than in the placebo arm, based on centralized (blinded) reading of patient photographs in the ITT data set (60.4%, 61/101, vs 3.6%, 2/55, respectively, p<0.0001). The absolute difference between the active and placebo treatment arms (56.8%) indicates that approximately 2 patients need to be treated with propranolol 3 mg/kg/day x 6 months arm in order for 1 of them to show a complete or nearly complete resolution in their IH at Week 24 based on photographic data (i.e., number needed to treat [NNT] = 2). However, the results for the primary efficacy analysis for complete/nearly complete resolution of IH at Week 24 were strikingly inconsistent with the results for this outcome based on investigator on-site assessment in the propranolol 3 mg/kg/day x 6 months and placebo arms (26.7%, 24/90, vs 10.5%, 2/19, respectively, p=0.4419).

In its Response, the sponsor argues that the discrepancy between the results of the primary and secondary assessments of complete/nearly complete resolution of the target IH at Week 24 was most likely attributable to subjective differences among investigators in the interpretation of complete/nearly complete resolution. Furthermore, the sponsor considered that the differences in interpretation of the outcome "may be influenced by differences in training, standard treatment used in the centres, and expectations (on Investigator's and parents)". The sponsor stated that it adopted centralized assessment of outcome based on standardized interpretation of photographic evidence by trained observers because of the potential for subjective interpretation resulting from clinical determination of complete/nearly complete resolution by individual investigators.

The sponsor rejects the possibility that the difference in outcome between the primary and secondary analyses was due to bias in the centralized assessment (photographs) procedure. However, no validation of treatment outcomes based on the centralized assessment (photographs) procedure with treatment outcomes based on clinical examination undertaken by experienced physicians was undertaken. The sponsor considers that such validation is unnecessary given the methods used to develop and apply the centralized assessment (photographs) procedure and the robustness of the statistical analyses of the outcome (i.e., strongly positive results favouring propranolol compared with placebo in the primary analysis in the ITT data supported by analysis in the PP data set and two sensitivity analyses [one planned, one unplanned]). However, it is considered that, while the sponsor has demonstrated the "internal validity" of the centralized assessment (photographs) procedure, no evidence has been provided demonstrating that the procedure reliably predicts treatment outcomes determined from clinical examination by experienced physicians (i.e., "external validity"). It is considered that the results of physical assessment of treatment outcome in children with progressive IH by experienced physicians should be the "gold standard" against which all surrogate assessments, such as centralized assessment based on photographic appearance of the lesion, should be validated.

The sponsor also argues that the methodology used to classify patients in the placebo group who discontinued due to lack of efficacy in the prespecified secondary analysis of investigator assessed complete/nearly complete resolution resulted in an overestimation of success at Week 24 in this group. The "overestimation" was due to the large number of patients in the placebo group who discontinued because of lack of efficacy being classified as "missing data" rather than as "treatment failures". In order to address this matter, the Response included a post hoc analysis in which the Week 24 investigator assessment was transformed into a binary outcome (treatment success vs treatment failure) with missing data, premature discontinuations, and additional IH treatments being handled as treatment failures (i.e., same approach used for the primary analysis). In this post hoc analysis, complete/nearly complete resolution at Week 24 investigator assessment (treatment success) in the propranolol 3 mg/kg/day x 6 months arm was statistically significantly greater than in the placebo arm (22.8% [23/101] vs 3.6% [23/101], respectively, p = 0.004). The complete/nearly complete resolution rate in the placebo

arm in the post hoc analysis of investigator assessment was identical to the corresponding rate in the placebo arm in the primary analysis of centralized (photography) assessment (3.6%), but the rates for this outcome in the propranolol 3 mg/kg/day x 6 months arms remained strikingly discordant between the primary and post hoc analyses (60.4% vs 22.8%, respectively).

The sponsor stated that the result of the post hoc analysis suggest "that the centralised and Investigators' assessment of treatment failure was consistent, but that the Investigators applied a more stringent and subjective interpretation of treatment success compared to the centralised assessment. It was to avoid such subjectivity that the centralised assessment was chosen as the primary efficacy outcome". However, the difference between assessment methods might be that centralized assessment of IH progression based on photographic changes is not a particularly reliable measure of progression compared with physical examination by experienced physicians. Furthermore, no data were presented establishing that assessments were subjectively different among investigators. Therefore, the sponsor's contention that the investigators applied a more stringent and subjective interpretation of treatment success compared with the centralized assessors is considered to be speculative.

The marked difference between the complete/nearly complete resolution rate at Week 24 observed following treatment with the propranolol 3 mg/kg/day x 6 months regimen between the primary centralized (photography) assessment (60.4% [61/101]) and the prespecified investigator (26.7% [24/101]) and post hoc investigator (22.8% [23/101]) assessments cannot be discounted. It is considered that the striking lack of consistency between the centralized (photography) and investigator on-site assessments of complete/nearly complete resolution of progressive IH at Week 24 following propranolol 3 mg/kg/day x 6 months in the pivotal study raises doubts about the benefits of this treatment for this condition.

The efficacy endpoints in the pivotal study relating to qualitative improvement in the appearance of the IH based on a 3-point scale (improvement, worsening or stabilization) are considered to be exploratory. The prespecified KM analysis of time to first sustained improvement after which there was no worsening at each time point through to and including Week 24 showed that the proportion of patients achieving this endpoint (KM estimates) was notably higher (nominal $p<0.001$) in the propranolol 3 mg/kg/day x 6 months arm than in the placebo arm for the centralized, investigator on-site and parent on-site assessments. There was convergence between the three assessment methods for the propranolol 3 mg/kg/day x 6 months arm, but not for the placebo arm where the proportion of patients achieving sustained improvement at each time point through to and including Week 24 was notably lower with the centralized assessment than with the investigator and parent on-site assessments. The post hoc survival analysis of time to first worsening from randomization showed that time to first worsening through to Week 24 was notably shorter with placebo than with propranolol 3 mg/kg/day x 6 months arm, and that this result was convergent for the centralized and investigator on-site assessments. Overall, the qualitative improvements in IH data through to Week 24 suggest that propranolol 3 mg/kg/day x 6 months might be more effective than placebo, but these data are considered to be exploratory rather than definitive.

In the pivotal study, improvement in the surface area, maximal diameter and colour of the IH from baseline to Week 12 and Week 24 were observed in the propranolol 3 mg/kg/day x 6 months arm compared with placebo. Global improvement (yes/no) from baseline between Week 5 and Week 24 was notably greater in the propranolol 3 mg/kg/day x 6 months arm than in the placebo arm (73.0%, 73 patients, vs 5.5%, 3 patients, nominal $p<0.0001$), based on central assessment in the ITT population.

With respect to treatment-emergent IH complications reported in the pivotal study in the ITT population in the placebo and 3 mg/kg/day x 6 months arms: treatment-emergent IH functional impairment was reported in 2 patients in the placebo arm, both of whom prematurely withdrew from treatment, and no patients in the active 3 mg/kg/day x 6 months arm; treatment-emergent IH ulceration was reported in 2 patients in the placebo arm, both of whom prematurely

withdrew from treatment due to inefficacy, and in 4 patients in the active 3 mg/kg/day x 6 months arm (2 patients resolved while on treatment, 2 led to premature withdrawal from treatment due to inefficacy); and treatment-emergent IH bleeding/haemorrhaging was reported in 1 patient in the placebo arm resulting in premature withdrawal from treatment due to inefficacy, and 1 patient in the active 3mg/kg/day x 6 months arm that resolved while on treatment. Overall, IH complications in the pivotal study were infrequent and confirm that the IHs in this study were low-risk.

There are no confirmatory data in the submission demonstrating that propranolol 3 mg/kg/day for 6 months can satisfactorily maintain efficacy following cessation of therapy. The submission included preliminary data from the pivotal study on patients who entered a 72-week open-label extension phase after completing the 24-week double-blind treatment period. Of the patients in the 3 mg/kg/day x 6 months arm who entered the extension phase, 59.8% (49/82) were reported with complete/near complete resolution of IH at Week 48 (based on centralized assessment of photographic data) compared with 31.6% (6/19) in the placebo arm. The preliminary results showed that complete/nearly complete resolution at Week 24 can be maintained through to Week 48 in patients in the propranolol 3 mg/kg/day x 6 months arm (60.4%, 61/100 and 58.8%, 49/82, respectively), while the percentage of patients with complete/nearly complete resolution actually increased from Week 24 to Week 48 in the placebo arm (3.6%, 2/55 to 31.6%, 6/19). The preliminary data also showed that 11.4% (10/88) of patients in the propranolol 3 mg/kg/day x 6 months arm required retreatment of IH with propranolol starting more than 7 days after the end of treatment, but before week 48, compared with 5.3% (1/19) of patients in the placebo arm. There are no data in the submission on the spontaneous regression rate in patients in the placebo arm.

The efficacy data relating to treatment of IH with propranolol from the CUP are entirely observational, while the efficacy data from the sponsor's review of the scientific literature are primarily observational. The primarily observational data from these two sources suggest that treatment with propranolol can improve IH in children treated with propranolol.

13.2. Second round assessment of risks

Following evaluation of the sponsor's Response, the second round assessment of the risks of Hemangiol remains largely unchanged from the first round assessment.

There is a notably increased risk of adverse events associated with propranolol compared with placebo for the treatment of IH. Some of these risks, while occurring infrequently, are particularly clinically significant (i.e., bronchospasm, hypotension, bradycardia, hypoglycaemia, and AV conduction disorders). The risks of treatment with propranolol can be mitigated by careful patient selection based on history (including family history) and clinical examination undertaken prior to treatment, careful monitoring of heart rate, blood pressure, and possibly ECG over at least the first 4 hours following the initial dose and subsequent dose increases, and prompt recognition of adverse events occurring while on treatment followed by permanent treatment discontinuation, temporary treatment discontinuation and/or symptomatic treatment as appropriate.

The risks of propranolol in adults are well known as the drug has been in clinical use for at least the last 40 years. While the drug has been used less extensively in children than in adults, there is no reason to expect that the safety profile will differ in the two populations. Overall, the risks of treatment observed in infants were consistent with the known safety profile of propranolol and generated no new safety signals.

The most clinically important identified risks with propranolol in infants include bronchospasm and bronchial hype-reactivity reactions, bradycardia, intensification of AV block, hypotension, and hypoglycaemia including related seizures. In order to mitigate the risks of propranolol in infants the proposed Hemangiol PI recommends that treatment with HI should be initiated by

physician's with expertise in treatment of the condition, and in a controlled setting having facilities to manage adverse events requiring urgent treatment should they arise. This is considered to be a prudent recommendation, and should apply not only to the day of initiation of treatment, but also to the days of dose increase.

The most frequently reported important identified risks in the safety population were bronchospasm and bronchial hyper-reactivity. These risks were reported in 20.3% (86/424) of propranolol treated patients in the safety population. Of the 86 patients experiencing this bronchial reactions, 11 (2.6%) had TEAEs grouped under the term bronchospasm, 29 (6.8%) had TEAEs grouped under the term bronchiolitis, and 46 (10.8%) had TEAEs grouped under the term bronchitis. In the CUP, 2.4% (16/660) patients experience these reactions.

The important identified risk of hypotension (TEAE) was reported in 1.2% (5/424) of propranolol treated patients in the safety population (all considered by the investigator to be possibly related to treatment). In the pivotal study, BP values below the normal range were frequently observed in the active treatment arms and in the placebo arm, and reductions in DBP were reported more commonly than reductions in SPB. In the pivotal study, almost all very low SBP/DBP potentially clinically significant values (< 50/30 mmHg) occurred during the titration period, and were low DBP values rather than low SBP values. Over D7-1h to D14-4h of the titration period, the proportion of patients in the pivotal study with very low potentially clinically significant SBP/DBP values was similar in the grouped 3 mg/kg/day and placebo regimens (14.4%, 29/201, 52 events vs 14.5% 8/55, 12 events, respectively), and lowest in the grouped 1 mg/kg/day regimen (7.0%, 14/200; 20 events). The proportion of patients with very low PCSVs SBP/DBP decreased after the titration period in each of the treatment arms. In the CUP, hypotension was reported in 0.3% (2/660) of patients.

The important identified risk of bradycardia (TEAE) was reported in 0.5% (2/424) of propranolol treated patients in the safety population. In the safety population, both cases were from the pivotal study and both resulted in permanent treatment discontinuation. In the pivotal study, low HR potentially clinically significant values (< 60 bpm) occurred infrequently in all treatment arms with the rates being 1.8% (1/55), 1.0% (1/98), 1.0% (1/102), 0% (0/100) and 5.0% (5/101) in the placebo, 1 mg/kg/day x 3 months, 1 mg/day/kg x 6 months, 3 mg/kg/day x 3 months, and 3 mg/kg/day x 6 months arms, respectively. In the CUP, hypotension was reported in 0.3% (2/660) of patients.

However, when bradycardia was defined as HR < 80 bpm, rather than < 60 bpm (the point for intervention), a notably greater proportion of subjects in the propranolol 3 mg/kg/day x 6 month arm experienced this event at least once during the pivotal study (safety population) than in the placebo arm (14.9% [15/101] vs 5.5% [3/55], respectively). Overall, in the pivotal study, at least one HR < 80 bpm event was experienced in the placebo, 1 mg/day/kg x 3 months, 1 mg/kg/day x 6 months, 3 mg/kg/day x 3 months and 3 mg/kg/day x 6 months with frequencies of 5.5%, 7.1%, 5.9%, 14.6% and 14.9%.

The important identified risk of hypoglycaemia (TEAE) was reported in 0.5% (2/424) of propranolol treated patients in the pooled safety population. In the pooled safety population, both events (2.5 mmol/L and 2.9 mmol/L, detected by pin-prick) occurred in the titration period and both events resolved spontaneously. One of the events was preceded by 2 to 3 days of gastroenteritis (vomiting, diarrhoea, poor feeding), but propranolol dosing was not stopped. Routine blood biochemistry during the treatment period (venous blood) revealed 2 patients with critical blood glucose values (< 2.6 mmol/L) during the titration period, with levels returning to normal while on propranolol, and 2 patients with isolated critical values at Week 24 (1, 0.4%, in the all pooled placebo group [n=256] and 1, 0.2%, in the all propranolol group [n=424] of the pooled safety population). In the CUP, hypoglycaemia was reported in 0.6% (4/660) of patients.

The important identified risk of intensification of AV block (TEAE) was reported in 1 (0.2%) of 424 propranolol treated patients. This event occurred almost immediately after the first dose (0.5 mg/kg) of propranolol and was considered by the sponsor to be possibly related to treatment, although there is some evidence that the event might have been related to a pre-existing cardiac disorder. In the CUP, complete AV block associated with acute heart failure resulting in death occurred in 1 (0.15%) of 660 patients. The events were not considered by the sponsor to be related to the study drug due to the presence of confounding factors. Of note, in the pivotal study right-bundle branch block was reported in 2 propranolol treated patients as a TEAE, and QT prolongation was reported in 3 patients as a TEAE.

There were no reports of AV block being detected by routine, repeat ECG monitoring in the clinical trial program. The sponsor proposes that routine ECG not be undertaken before initiation of treatment. The sponsor states that in the clinical development program, ECG before initiation of treatment did not identify a single condition likely to interfere with tolerability to propranolol, while echocardiography before the initiation of treatment resulted in the non-inclusion of 1 patient on the basis of a questionable intra-cardiac mass of doubtful clinical relevance.

In the pivotal study, a total of 9 patients experienced one PR > 160 msec event (1.8% [1/55] of patients in the placebo arm, 4.1% [51/123] of patients in the 3 mg/kg/day x 3 months arm, and 3.0% [3/101] of patients in the 3 mg/kg/day x 6 months arm]. One patient in the 1 mg/kg/day x 3 months arm experienced second degree AV block (Mobitz I), and no patients experienced third degree AV block.

The risk of experiencing at least one TEAE was greater in patients treated with propranolol compared with placebo. In the pooled safety population, TEAEs were reported in 65.3% (154/236) of patients in the all placebo group and 86.8% (368/424) of patients in the all propranolol group, with no marked difference between the all 1 mg/kg/day and all 3 mg/kg/day groups (84.5%, 169/200 vs 88.8%, 199/224, respectively). In the pooled safety population, TEAEs reported in at least 10% of patients in the all propranolol group (n=424) vs the all placebo group (n=236) were (in descending order of frequency): nasopharyngitis (23.6% vs 15.3%); pyrexia (21.2% vs 7.2%); diarrhoea (18.9% vs 3.4%); teething (15.3% vs 9.3%); cough (11.8% vs 7.2%); vomiting (10.6% vs 3.4%); and URTI (10.1% vs 7.6%).

In the pivotal study, TEAEs reported in at least 5% of patients in the propranolol 3 mg/kg/day x 6 months arm (n=101) vs the placebo arm (n=55) were (in descending order of frequency): nasopharyngitis (33.7% vs 18.2%); diarrhoea (27.7% vs 7.3%); pyrexia (26.7% vs 9.1%); teething (20.8% vs 10.9%); bronchitis (16.8% vs 1.8%); URTI (13.9% vs 7.3%); vomiting (12.9% vs 5.5%); cough (11.9% vs 7.3%); gastroenteritis (10.9% vs 3.6%); peripheral coldness (9.9% vs 1.8%); bronchiolitis (8.9% vs 5.5%); dermatitis diaper (8.9% vs 3.6%); toothache (8.9% vs 3.6%); conjunctivitis (7.9% vs 3.6%); vaccination complication (7.9% vs 3.6%); sleep disorder (6.9% vs 1.8%); middle insomnia (5.0% vs 5.5%); nightmare (5.0% vs 1.8%); and rash (5.0% vs 1.8%).

In the pivotal study, clinically significant TEAEs defined as occurring in least 2% of patients in the 3 mg/kg/day x 6 months arm (n=101) and with at least a 3-fold higher incidence than in the placebo arm (n=55) were: diarrhoea (27.7% vs 7.3%); bronchitis (16.8% vs 1.8%); gastroenteritis (10.9% vs 3.6%); peripheral coldness (9.9% vs 1.8%); sleep disorder (6.9% vs 1.8%); ear infection (4.0% vs 0%); pharyngitis (3.0% vs 0%); viral infection (3.0% vs 0%); GORD (3.0% vs 0%); and AST increased (3.0% vs 0%). In the pivotal study, the majority of TEAEs in the treatment arms were reported to be mild or moderate in intensity, to have occurred before or at Week 12, and to have resolved by Week 24.

The risk of experiencing a treatment-related TEAE was greater in patients treated with propranolol compared with placebo. In the pooled safety population, the percentage of patients with a least one treatment-related TEAE in the all placebo group was 36.3% (154/424)

compared with 14.8% (35/236) in the all placebo group. In the pivotal study, 34.7% (5/101) of patients in the 3 mg/kg/day x 6 months arm experienced at least one TEAE compared with 29.1% (16/55) of patients in the placebo arm. Treatment-related TEAEs reported in ≥ 2% of patients in the 3 mg/kg/day arm (n=101) and/or the placebo arm (n=55) were: peripheral coldness (8.9% vs 0%); diarrhoea (7.9% vs 3.6%); sleep disorder (6.9% vs 1.8%); nightmare (5.0% vs 1.8%); middle insomnia (4.0% vs 5.5%,); vomiting (3.0%, vs 1.8%); AST increased (3.0% vs 0%); insomnia (3.0% vs 5.5%); rash (2.0% vs 0%); blood potassium increased (2.0% vs 0%), and frequent bowel motions (1.0% vs 3.6%). Only three of these events (middle insomnia, insomnia, frequent bowel motions) occurred more commonly in the placebo arm than in the propranolol 3 mg/mg/kg/day x 6 months arm.

There were no deaths reported in the pooled safety population. However, there was 1 death reported in a propranolol treated patient in the CUP due to complete AV block and acute cardiac failure (mentioned above). In the pivotal study, the risk of experiencing a SAE was similar in the propranolol 3 mg/kg/day x 6 months and placebo arms (5.9%, 6/101, 7 events vs 5.5%, 3/55, 3 events, respectively). Of the total number of SAEs reported in the pivotal study (33 events), 26 events occurred in 401 patients while on propranolol (i.e., 0.06 events per patient), and 7 events occurred in 236 while on placebo (i.e., 0.03 events per patient).

Of the SAEs reported in the pivotal study, 5 were assessed as related to the study drug by the investigator and/or the sponsor: 1x condition aggravated in 1 patient in the placebo arm; 1x AV block second degree Mobitz 1 type in the active treatment phase in the 1 mg/kg/day x 6 months arm; 1x obstructive bronchitis in the active treatment phase in the 3 mg/kg/day x 3 months arm; 1x condition aggravated (ulceration of IH) in the active treatment phase in the 3 mg/kg/day x 3 months arm; and 1x bradycardia in the active treatment phase in the 3 mg/kg/day x 3 months arm. The only one of the events not categorized as a sudden unexpected serious adverse reaction (SUSAR) was bradycardia. Preliminary data from the post-week 24 extension to the pivotal study raises no additional concerns relating to SAEs.

Permanent treatment discontinuation due to TEAEs occurred more commonly in patients treated with placebo than patients treated with propranolol. In the pivotal study, permanent treatment discontinuations due to TEAEs were reported in 10.9% (6/55) of patients in the placebo arm and 4.0% (16/401) of patients in the combined propranolol arms. In the pooled safety population, 4.7% (11/236) of patients in the all placebo group had at least one TEAE resulting in permanent treatment discontinuation compared with 2.6% (11/424) of patients in the all propranolol group. The only TEAEs resulting in permanent treatment discontinuation in ≥ 2 patients in the pooled safety population all occurred in the all placebo group (n=236) and were condition aggravated (3, 1.3%), drug ineffective (2, 0.8%) and bronchiolitis (2, 0.8%).

In the pooled safety population, the risk of temporary treatment discontinuations due to TEAEs was notably higher in patients in the all 3 mg/kg/day propranolol group than in the all placebo group (15.2% [34/224]] vs 4.2% [10/236], respectively). TEAEs resulting in temporary treatment discontinuation reported in ≥ 1% of patients in the all placebo or all propranolol 3 mg/kg/day groups, and in descending order of frequency in the propranolol group vs the placebo group were: bronchitis (3.1% vs 0.8%); gastroenteritis (3.1% vs 0.4%); bronchiolitis (2.2% vs 2.1%); vomiting (2.2% vs 0%); and pyrexia (1.3% vs 0%). The only TEAE resulting in temporary treatment discontinuation reported more frequently in the all placebo group than in the all propranolol 3 mg/kg/day group was febrile infection (0.4% vs 0%, respectively).

There were no data from the clinical studies of the risks of propranolol in infants with high-risk IH, but the CUP included patients with high-risk IH. There were no data in the clinical studies on the risks of concomitant use of propranolol and other drugs. Therefore, all the known risks of interactions between the propranolol and other drug should be considered to apply to the use of the drug for the treatment of infants with IH. There were no data on the treatment of infants with IH with concomitant hepatic, renal, cardiac and/or respiratory disease. Therefore, it is

considered that all infants with IH with these concomitant conditions should not be treated with propranolol.

13.3. Second round assessment of benefit-risk balance

Following consideration of the initial submission and the sponsor's Response to the first round clinical questions it is considered that the benefit-risk balance for propranolol at the proposed dose is unfavourable. The efficacy data from the pivotal study in patients aged 30 to 150 days with low risk progressive IH requiring treatment have not unequivocally demonstrated that propranolol administered at a dose of 3 mg/kg/day results in a clinically significant benefit of complete/nearly complete resolution of IH at Week 24 compared with placebo. However, the safety data from the pivotal study have demonstrated that the risks of treatment with propranolol 3 mg/kg/day for the proposed indication are greater than the risks of placebo.

14. Second round recommendation regarding authorisation

Following consideration of the initial submission and the sponsor's Response to the first round clinical questions it is recommended that the application to register Hemangiol for the treatment of proliferating infantile hemangioma requiring systemic therapy **be rejected**. The reasons for this recommendation are as follows:

1. In the pivotal study, the marked benefit of treatment with propranolol 3 mg/kg/day x 6 months compared with placebo for the primary efficacy endpoint of complete/nearly complete resolution of IH at Week 24, based on blinded central assessment of photographs by 2 readers (60.4% vs 3.6%, respectively, p<0.0001), was not confirmed by blinded on-site assessment of this endpoint by investigators (26.7% vs 10.5%, respectively, p=0.4419). The difference in outcome between the two assessment methods is considered to be important, and the results of the on-site investigator assessment by physicians experienced in the management of IH cannot be dismissed. The inconsistency between the results for complete/nearly complete resolution of IH at Week 24 for the two assessment methods is considered to raise uncertainty about the true effect of propranolol compared with placebo for this outcome. Therefore, it is considered that the pivotal study has not satisfactorily established that treatment with propranolol 3 mg/kg/day x 6 months results in clinically significant complete/nearly complete resolution of IH at Week 24 compared with placebo.
2. In the pivotal study, a post hoc analysis of the investigator on-site assessment using the same methodology as that adopted for the primary efficacy endpoint showed a statistically greater rate of success (complete/nearly complete resolution) at Week 24 in the propranolol 3 mg/kg/day x 6 month arm compared with the placebo arm (22.8% vs 3.6%, respectively, p=0.004). However, while the success rates in the placebo group in the post hoc analysis and the primary analysis were identical (3.6%), the success rates in the propranolol 3 mg/kg/day x 6 month arm were markedly discordant (22.8% vs 60.4%, respectively). The success rate in the propranolol 3 mg/kg/day x 6 month arm in the post hoc analysis of the investigator on-site assessment is consistent with the prespecified secondary analysis of the investigator on-site assessment (22.8% and 26.7%, respectively). In both investigator-on-site assessments of the primary efficacy endpoint, the success rate in the propranolol 3 mg/kg/day x 6 month arm were markedly lower than that observed in the primary analysis, casting doubt on the reliability of centralized (photograph) assessment to accurately predict clinical outcomes.
3. In the pivotal study, there are data suggesting that propranolol 3 mg/kg/day x 6 months might improve the appearance of IH at Week 24 compared with placebo. However, the study was not designed to test the effect of propranolol on improvement, and all evidence

suggesting that the proposed dose provides a treatment benefit relating to improvement at Week 24 is exploratory rather than definitive.

4. There are no pivotal data indicating that treatment benefits observed at Week 24 can be maintained following cessation of treatment. The available data suggesting that this might be the case are preliminary and considered to be exploratory.

5. In the pivotal study, the risks of treatment with propranolol 3 mg/kg/day x 6 months for the proposed indication were notably greater than placebo. Therefore, in order for the benefit-risk balance to be favourable it is considered that treatment with propranolol 3 mg/kg/day x 6 months for the proposed indication must demonstrate unequivocal efficacy compared with placebo. For the reasons discussed above, it is considered that propranolol 3 mg/kg/day x 6 months has failed to demonstrate unequivocal efficacy compared with placebo. Consequently, the benefit-risk balance for propranolol 3 mg/kg/day x 6 months for the treatment of the proposed indication is unfavourable.

[**AusPAR note:** In the event the application was approved, the evaluator's recommendation regarding the *Indications* section of the PI was as follows:

It is recommended that wording of the indication be amended to read - *"treatment of low-risk, proliferating infantile hemangioma requiring systemic therapy in infants aged from 30 to 150 days"*. The pivotal study included only patients with low-risk IH, and patients with life-threatening HIs, function threatening IHs and complicated ulcerated IHs were specifically excluded from the study. Furthermore, in the pivotal study, on-site investigator assessment showed that complications arising from IHs were infrequent suggesting that the IHs were low risk. Therefore, it is considered that IHs should be specified in the indication as low-risk. There are no pivotal efficacy data in the submission in infants with high-risk IHs. The age of patients to be treated should be stated in the indication in order to draw attention to the fact that the pivotal study included only patients in this age range, and that there are no pivotal data on patients outside this age range.

Details of other recommended revisions to the PI are not included in this CER Extract]

15. References

Ahogo CK et al. Factors associated with the relapse of infantile hemangiomas in children treated with oral propranolol Br J Dermatol. 2013-0203.

Bagazgoitia L et al. Propranolol for infantile hemangiomas. Pediatr Dermatol 2011 Mar-Apr;28(2):108-14.

Bernabeu-Wittel J et al. Propranolol for the treatment of severe hemangiomas of infancy: results from a series of 28 patients. Actas Dermosifiliogr 2011 Sep;102(7):510-6.

Bertrand J et al. Propranolol versus prednisone in the treatment of infantile hemangiomas: a retrospective comparative study. Pediatr Dermatol. 2011 Nov-Dec;28(6):649-54.

Bertrand J et al. Propranolol in the treatment of problematic infantile hemangioma: review of 35 consecutive patients from a vascular anomalies clinic. J Cutan Med Surg. 2012 Mar-Apr;16(2):115-21.

Bowers RE et al. The natural history of the strawberry nevus. Archives of Dermatology. 1960;82:59-72.

Bruckner AL, Frieden IJ. Hemangiomas in Infancy. J Am Acad Dermatol. 2003;138:156-157.

Buckmiller L et al. Propranolol for infantile hemangiomas : early experience at a tertiary vascular anomalies center. Laryngoscope 2010 Apr;120(4):676-81.

Chen et al. Infantile hemangiomas: an update on pathogenesis and therapy. *Pediatrics* 2013; 131(1):99-108.

Chang LC et al. Growth characteristics of infantile hemangiomas: implications for management. Pediatrics. 2008 Aug;122(2):360-7

Dickson P et al. A prospective study of infantile haemangiomas with a focus on incidence and risk factors. Pediatric Dermatology. 2011;28(6):663-669.

Drolet BA et al. Infantile hemangiomas: an emerging health issue linked t an increased rate of low birth weight infants. J Pedaitr 2008; 153:7125-5.

Drolet BA et al. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. Pediatrics 2013 Jan;131(1):128-140

Frieden IJ et al. Guidelines of care for hemangiomas of infancy. J Am Acad Dermatol. 1997 Oct;37(4):631-7

Haider KM et al. Outpatient treatment of periocular infantile hemangiomas with oral propranolol J Am Assoc Ped Ophthalmo Strabismus 2010;14(3):251-6

Haggstrom AN et al. Patterns of infantile hemangiomas: new clues to hemangioma pathogenesis and embryonic facial development. Pediatrics. 2006 Mar;117(3):698-703.

Haggstrom et al. Prospective study of infantile hemangiomas: demographic, prenatal and perinatal characteristics. J Pediatr 2007;150:291-294.

Hermans DJ et al. Propranolol, a very promising treatment for ulceration in infantile hemangiomas: a study of 20 cases with matched historical controls. J Am Acad Dermatol. 2011;64(5):833-8

Hogeling M et al. A randomized controlled trial of propranolol for infantile hemangiomas. Pediatrics 2011;128(2):e259-e266.

Holmes WJM et al. Propranolol as first-line treatment for rapidly proliferating infantile haemangiomas. J Plast Reconstr Aesthet Surg. 2011;64(4):445-51.

Hoornweg MJ, et al. Prevalence and characteristics of haemangiomas in young children. Ned Tijdschr Geneeskd 2005;149(44) 2455-8

Kilcline C and Frieden IJ. Infantile hemangiomas: how common are they? A systematic review of the medical literature. Pediatr Dermatol. 2008; 25(2) 168-73.

Kopitar Z et al. Dose-dependent bioavailability of propranolol. International Journal of Clinical Pharmacology, Therapy and Toxicology 1986;24(6):319-22.

Leboulanger N et al. Propranolol in the therapeutic strategy of infantile laryngotracheal hemangioma : a preliminary retrospective study of French experience. Int J Pedia Otorhinolaryngol. 2010;74(11):1254-7.

Lister W. Natural history of Strawberry Naevi. Lancet 1938 1:1429

Paediatrics Manual. The Children's Hospital at Westmead Handbook (2nd Edition), 2009; Eds Kilham H, Alexander S, Wood N, Isaacs D.

Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, et al. Propranolol for severe hemangiomas of infancy. N Engl J Med. 2008 Jun 12;358(24):2649-51

Mackichan JJ et al. Dose-dependent disposition of oral propranolol in normal subjects. Biopharm Drug Dispos. 1980;1(4):159-66

Phillips RJ et al. Use of propranolol for treatment of infantile haemangiomas in an outpatient setting. J Paediatr Child Health. 2012 Oct;48(10):902-6

Ponce F, Williams L et al. Propranolol palliation of tetralogy of Fallot: experience with long-term drug treatment in pediatric patients. Pediatrics 1973; 52:100-8.

Posch M et al. Testing and estimation in flexible group sequential designs with adaptive treatment selection. Statist Med. 2005 Dec 30;24(24):3697-714.

Riopel DA and Walle T. Kinetics and clinical observations in cyanotic children on propranolol. Clin Pharmacol Ther 1980;28:743-50.

Routledge PA and Shand DG. Clinical Pharmacokinetics of Propranolol. Clinical Pharmacokinetics 1979;(4):73-90

Saint-Jean et al. Propranolol for treatment of ulcerated infantile hemangiomas. J Am Acad Dermatol. 2011 May;64(5):827-32

Sans V et al. Propranolol for severe infantile hemangiomas: follow-up report. Pediatrics 2009 Sep;124(3):e423-31.

Schiestl C et al. Efficacy and safety of propranolol as first-line treatment for infantile hemangiomas Eur J Pediatr. 2011 Apr;170(4):493-501.

Snir M et al. Refractive and structural changes in infantile periocular capillary haemangioma treated with propranolol Eye 2011 Dec;25(12):1627-34.

Storch CH and Hoeger PH. Propranolol for infantile haemangiomas: insights into the molecular mechanisms of action. Br J Dermatol. 2010 Aug;163(2):269-74

Sundine MJ and Wirth GA. Hemangiomas: an overview. Clinical Pediatrics. 2007 Apr;46(3):206-221

Talaat AA. Propranolol treatment of infantile hemangioma: clinical and radiologic evaluations J Pediatr Surg. 2012 Apr;47(4):707-14.

Vogelpoel H et al. Biowaiver monographs for immediate release solid oral dosage forms based on biopharmaceutics classification system (BCS) literature data: verapamil hydrochloride, propranolol hydrochloride, and atenolol. Association J Pharm Sci 2004; 93:1945-1956.

Walle T et al. Partial metabolic clearances as determinants of the oral bioavailability of propranolol. Br J Clin Pharmac 1986;22:317-23

Walle T et al. Pathway-selective sex differences in the metabolic clearance of propranolol in human subjects. Clin Pharmacol Ther 1989;46(3):257-63

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au