20 February 2014
EMA/CHMP/8171/2014
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

HEMANGIOL

International non-proprietary name: propranolol

Procedure No: EMEA/H/C/002621/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Product information

Name of the medicinal product:	HEMANGIOL
Applicant:	PIERRE FABRE DERMATOLOGIE Les Cauquillous 81506 LAVAUR FRANCE
Active substance:	PROPRANOLOL HYDROCHLORIDE
International Nonproprietary Name/Common Name:	PROPRANOLOL
Pharmaco-therapeutic group (ATC Code):	(C07)
Therapeutic indication:	HEMANGIOL is indicated in the treatment of proliferating infantile haemangioma requiring systemic therapy: • Life- or function-threatening haemangioma, • Ulcerated haemangioma with pain and/or lack of response to simple wound care measures, • Haemangioma with a risk of permanent scars or disfigurement. It is to be initiated in infants aged 5 weeks to 5 months (see section 4.2).
Pharmaceutical form:	Oral solution
Strength:	3.75 mg/ml
Route of administration:	Oral use
Packaging:	bottle (glass)
Package size:	1 bottle

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List of abbreviations

AE	Adverse Event
ATU	Autorisation temporaire d'utilisation (temporary authorization for use)
AUC	Area under the plasma concentration time curve
BID	Bis in die (Latin: twice a day)
Bpm	beats per minute
CEP	Certificate of Suitability of the EP
CL/F	Clearance of drug from plasma after oral administration
Cmax	Maximum plasma drug concentration
CS	Clinically significant
CSR	Clinical study report
CUP	Compassionate use program
DBP	Diastolic blood pressure
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IH	Infantile haemangioma
ITT	Intent-to-treat
LLOQ	Low limit of quantification
MA	Material Attribute
MAA	Marketing Authorisation Application
NCA	Non Compartmental Analysis
PCS	Potentially clinically significant
PDCO	Paediatric Committee (of the EMA)
Ph.Eur.	European Pharmacopoeia

PHACE (syndrome) Posterior fossa brain anomalies, haemangioma, arterial anomalies and cardiac defects and coarctation of the aorta, eye abnormalities and sternal abnormalities or ventral developmental defects

PIP	Paediatric investigation plan
PK	Pharmacokinetic(s)

PM	poor metabolisers
QbD	Quality by Design
QT	Interval from the start of the Q-wave to the end of the T-wave
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SPA	Special Protocol Assessment
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TE SAE	Treatment-emergent serious adverse event
T1/2	Terminal elimination half-life
URTI	upper respiratory tract viral infection
VAS	Visual analogue scale
VEGF	vascular endothelial growth factor
vs.	versus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant PIERRE FABRE DERMATOLOGIE submitted on 6 March 2013 an application for a Paediatric Use Marketing Authorisation in accordance with Article 30 of Regulation (EC) No 1901/2006, to the European Medicines Agency (EMA) for Hemangiol, through the centralised procedure under Article 31 of Regulation (EC) No 1901/2006. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 July 2011.

The applicant applied for the following indication:

Treatment of proliferating infantile haemangioma requiring systemic therapy. It is to be initiated in infants aged 5 weeks to 5 months.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that propranolol was considered to be a known active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 30 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0004/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0004/2013 was completed.

The PDCO issued an opinion on compliance for the PIP P/0004/2013.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's requests for consideration

New active Substance status

Not applicable

Scientific Advice

The applicant received Scientific Advice from the CHMP on 19 February 2009. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

A new application was filed in the following countries: Australia, Canada, Switzerland and United States of America.

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturers responsible for batch release

Farmea
10, rue Bouché Thomas
ZAC d'Orgemont
F-49000 Angers
France

Pierre Fabre Medicament Production – Chateaurenard
Site Simaphac, Zone Industrielle de Chateaurenard
45220 Chateaurenard
France

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Joseph Emmerich Co-Rapporteur: Greg Markey

- The application was received by the EMA on 6 March 2013.
- The procedure started on 27 March 2013.

- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 June 2013 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 June 2013 (Annex 2).
- During the meeting on 25 July 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant (Annex 4).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 October 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 22 November 2013 (Annex 5).
- The Rapporteurs circulated the Updated Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 12 December 2013 (Annex 6).
- During the CHMP meeting on 19 December 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant (Annex 7).
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 January 2014.
- During the meeting on 20 February 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Hemangiol.

2. Scientific discussion

2.1. Introduction

Problem statement

Infantile haemangioma (IH) are benign vascular tumours of childhood, characterised by endothelial cell proliferation. They occur in 3% to 10% of the population. Generally, these lesions are not detectable at birth but appear during the first 4 to 6 weeks of life. IHs exhibit a characteristic evolution with early rapid growth (proliferation) followed by a stabilisation period and a slow spontaneous involution. Known risk factors for the development of IH are: female gender (female to male ratio of 2.4:1), Caucasian ethnicity, low birth weight (especially <1500 g), and products of multiple gestations.

Whilst most IH exhibit an uncomplicated clinical course, some are associated with complications that can be life-threatening (e.g. respiratory failure in airway IH, congestive heart failure in liver IH) or function-threatening. If left untreated, they can leave permanent sequelae which may trigger psychological morbidity. Although most are not worrisome, around 12% of IHs are significantly complex, requiring referral to specialists for consideration of treatment.

IH 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. Currently, the first line treatment is corticosteroids (only authorised in France and Germany for severe cases), interferon alpha (IFN alpha) and vincristine are also used off-label as second line treatment.

About the product

Hemangiol is an oral solution of propranolol, a non-selective beta-adrenergic receptor blocking agent. When access to beta-receptor sites is blocked by propranolol, the chronotropic, inotropic, and vasodilatator responses to beta-adrenergic stimulation are decreased proportionately. Consequently, propranolol is mainly proposed as antihypertensive treatment in humans. Propranolol has been used since 1960's in adults for cardiovascular therapies and is commonly prescribed in several clinical situations, including control of hypertension, management of angina, prophylaxis of migraine, management of essential tremor, management of anxiety, adjunctive management of thyrotoxicosis, and prophylaxis of upper gastro-intestinal bleeding in patients with portal hypertension and oesophageal varices. In children, specific dosing recommendations have been established and its clinical use is accepted in several situations such as hypertension, arrhythmias, tetralogy of Fallot spells, hypertrophic myocardiopathy, and thyrotoxicosis.

Propranolol is a well-known drug for which capsule and tablet formulations are approved in both the European Union (EU) and the United States (US) for use in adults. Since 2000, an oral solution (Syprol) was registered in the United Kingdom for the use in children for the treatment of arrhythmia, phaechromocytoma, thyrotoxicosis, migraine, and tetralogy of Fallot.

The use of propranolol in the treatment of IH began after the publication by *Leauté-Labrèze et al* in 2008, who discovered by chance the potential effect of this substance on IH: propranolol was administered to a child with a nasal capillary haemangioma (stabilised on corticosteroid) to treat an obstructive hypertrophic myocardiopathy; after treatment initiation haemangioma changed from intense red to purple, and it softened, and improvement was observed with no regrowth after corticosteroid discontinuation.

The global clinical development plan for propranolol was designed and performed in line with recommendations made by both the European Medicines Agency (EMA) and the Food and Drug Administration (FDA), and comprises three clinical trials, including two Phase I PK studies and a pivotal Phase II/III study. In addition, at the request of the French Competent Authority (Agence Nationale de Sécurité du Médicament et des Produits de Santé [ANSM]), Study V00400 SB 301 was conducted to allow the continued use of propranolol in patients who had participated in a previous clinical trial, and for whom the investigator judged it clinically appropriate to continue treatment with oral propranolol. A Compassionate Use Program (CUP) is on-going in France. The first nominative authorisation (i.e. on a named patient basis) was approved on 13 Apr 2010 and was modified to a cohort authorisation in July 2012. Within the remit of the CUP, propranolol is prescribed to infants with proliferating high risk IH who could not be included in one of the ongoing clinical studies. In addition a CUP has been ongoing in Switzerland since February 2011.

The development programme/compliance with CHMP guidance/scientific advice

Scientific advice was obtained from the EMA on 19 February 2009 (EMEA/H/SA/1222/1/2008/PED/III).

The design for pivotal Study 201 was established in line with recommendations made by both the EMA and FDA during a Parallel Scientific Advice meeting. The study design was then discussed through a Special Protocol Assessment in the United States (US) and a paediatric investigation plan (PIP) in Europe.

It was stated in the parallel advice EMA/FDA meeting minutes that the presence of a placebo control in the phase II/III pivotal study did not allow, for ethical reasons, the inclusion of high risk IH: life- or function-threatening and ulcerated IH [with pain and lack of response to simple wound care measures]. The FDA stated that the inclusion of IH patients of moderate severity would not preclude approval in patients with more severe lesions.

The p-value for the Phase II/III pivotal study was adjusted to 0.005 in the statistical analysis plan, following advice from the FDA (letter dated 02 October 2009) that a single study with a robust p-value (<0.01) may be sufficient to allow approval based on a single trial.

However, in order to provide supportive data on the efficacy of oral propranolol in high risk IH cases, selected studies investigating the treatment of high risk IH with oral propranolol reported in the literature have been included in the analysis of efficacy. In addition, some efficacy data are available for high risk IH cases in the CUP in terms of discontinuation of treatment due to good efficacy and follow-up data collected post-hoc for a subgroup of patients.

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

The safety analysis submitted is composed of data from more than 2451 patients treated with propranolol from the following sources:

1. Frequency of adverse events (AEs) from the pooled database (Studies 201 and 102): 424 patients with IH treated with propranolol for up to 24 weeks.
2. Cumulative safety analysis from the CUP in France (660 patients) including non-serious reported adverse drug reactions (ADRs).
3. Presentation of all serious adverse events (SAEs) from Studies 201, 102, 301 and from the CUP.
4. Literature review of 60 scientific publications (involving 1367 patients with IH treated with propranolol) of which individual case reports have been extracted from 39 publications (involving 623 patients with IH treated with propranolol) and reported in a narrative form.

The PIP was approved by the Paediatric Committee of the EMA on 27 October 2010 and followed by 4 amendments. The following completed studies were checked for compliance: quality measures, V00400 SB 101 2A, V00400 SB 201, Pharmacokinetic study in paediatric population. The PDCO adopted on 8 February 2013 an opinion confirming the compliance of all studies in the agreed paediatric investigation plan as set out in the Agency's Decision (P/0004/2013) of 21 January 2013.

General comments on compliance with GMP, GLP, GCP

GMP: CHMP has been assured that acceptable standards of GMP are in place for these product types at the sites responsible for the manufacture and packaging of this product. Suitable manufacturing licences are provided from the finished product manufacturing sites.

No need for specific drug product inspection has been identified.

GLP: The non-clinical studies presented are updated published articles. Many of the studies, especially in toxicology, are old and were not conducted according to GLP standards. The single new toxicology study in juvenile rats has been conducted with Hemangiol in compliance with GLP. There is a deviation in the acceptable criteria of Quality Controls for the dosage of the cardiac biomarkers (in the range 50-150% instead of 75-125%). Information on the use of computer systems has been provided

GCP: all clinical studies were conducted in accordance with regulatory requirements, with the principles of the Declaration of Helsinki in effect at the time and following Good Clinical Practice.

A routine GCP inspection has been conducted for the pivotal clinical trial (study V00400 SB 201)

Type of application and other comments on the submitted dossier

- Legal basis

This is a complete independent Marketing Authorisation Application (MAA) for a known active substance, propranolol that has been filed by the Applicant in accordance with Article 8(3) of Directive 2001/83/EC. This is a , as Paediatric Use Marketing Authorisation (PUMA) as per Article 31 of Regulation (EC) No 1901/2006.

- Accelerated procedure

The Applicant submitted on 07 February 2013 a request for accelerated assessment pursuant to Article 14 (9) of Regulation (EC) No 726/2004. Based on the submitted data, the CHMP considered that the Applicant does not fulfil the requirements and did not recommend the granting of an accelerated assessment procedure.

The applicant claimed the approval for the following indication:

HEMANGIOL 3.75 mg/mL, oral solution is indicated in the treatment of proliferating infantile haemangioma requiring systemic therapy.

It is to be initiated in infants aged 5 weeks to 5 months.

The final indication following CHMP review of this application is:

HEMANGIOL is indicated in the treatment of proliferating infantile haemangioma requiring systemic therapy:

- Life- or function-threatening haemangioma,

- Ulcerated haemangioma with pain and/or lack of response to simple wound care measures,

- Haemangioma with a risk of permanent scars or disfigurement.

It is to be initiated in infants aged 5 weeks to 5 months (see section 4.2).

2.2. Quality aspects

2.2.1. Introduction

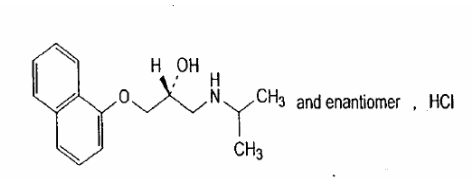
Hemangiol is presented as an oral solution containing propranolol in the form of hydrochloride salt, as the active substance. Each ml of the solution contains 3.75 mg of propranolol.

Other ingredients used in the formulation are hydroxyethylcellulose, saccharin sodium, strawberry flavour (contains propylene glycol), vanilla flavour (contains propylene glycol), citric acid and purified water.

The solution is packed in an amber-glass bottle fitted with a low density polyethylene (LDPE) insert and a child resistant polypropylene (PP) screw cap, provided with a polypropylene (PP) oral syringe graduated in mg of propranolol.

2.2.2. Active Substance

Propranolol (as propranolol hydrochloride) is chemically designated as (2RS)-1-[(1-methylethyl)amino]-3-(naphthalen-1-yloxy)propan-2-ol hydrochloride and has the following structure:



It is a white to off-white powder, soluble in water and alcohol, slightly soluble in chloroform, practically insoluble in ether. The substance melts between 163°C and 166°C. It is produced as racemic mixture of R and S enantiomers.

As there is a monograph of propranolol hydrochloride in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for propranolol hydrochloride which has been provided within the current Marketing Authorisation Application.

Manufacture

Propranolol hydrochloride is well known active substance, described in the Ph. Eur. The chemistry, manufacturing and control information on propranolol hydrochloride has been evaluated by the European Directorate for the Quality of Medicines (EDQM) and a CEP has been issued. A copy of the CEP has been provided. In addition the holder of the certificate has declared the absence of use of materials of human or animal origin in the manufacturing process of propranolol hydrochloride.

Specification

The drug substance complies with the Ph. Eur. monograph specifications. No additional tests, apart those listed in the Ph. Eur. monograph were required by the CEP. It has been confirmed that only impurities listed in the monograph may be present in the active substance and no additional impurity is specified in the CEP from the manufacturer. 2-propanol is declared in the CEP as the solvent used in the last steps of the synthesis and controlled by an appropriate limit. Analytical procedures for control of the active substance are the same as the one described in the Ph. Eur. monograph.

Batch analysis data of the three batches of propranolol hydrochloride were provided. The results were within the specification limits, consistent from batch to batch and demonstrated compliance with the Ph. Eur. monograph for this substance.

Stability

The retest period and type of the container for storing the substance are also included in the certificate.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The objective of the product development was to obtain an oral solution with a concentration of the active substance of 3.75mg/ml, specially designed for administration to paediatric population.

The development of the formulation is well described. The applicant has adopted a systematic risk based approach in optimising the product attributes to meet the target quality profile. In accordance with ICH Q8 (R2) the following steps were followed:

- definition of the Quality Target Product Profile (QTPP) as it relates to quality, safety and efficacy,
- identification of potential Critical Quality Attributes (CQAs) of the finished product, so that those product characteristics having an impact on product quality can be studied and controlled
- determination of critical quality attributes of the active substance and selection of the appropriate excipients to deliver finished product of the desired quality,
- selection of an appropriate manufacturing process,
- definition of a control strategy to guarantee the quality of the finished product.

Taste was considered an important finished product characteristic in view of the target population, which includes infants. Therefore formulation development focused on the excipients selection (texturing agent, pH adjustment agent, sweetening agent, preservative) and the flavouring of the product as propranolol is a bitter active substance. The choice and role of each excipient was appropriately justified. There are no novel excipients or excipient of human or animal origin used in the formulation. All excipients are compendial substances and comply with relevant Ph. Eur. monographs, except for the flavours. The flavours are food grade according to Regulation (EC) No 1334/2008, have an approved regulatory status and are considered GRAS (Generally Recognized as

Safe). Flavours are solubilised in propylene glycol. The percentage of propylene glycol which is brought by the strawberry and vanilla flavours is equal to 0.26% (m/V). Taking into account the maximal daily dose of 3 mg/kg and the concentration of the solution of 3.75 mg/ml, the maximal daily volume of the oral solution is 0.8 ml/kg which represents a maximal intake of propylene glycol at level 2.08 mg/kg/day. This is in accordance with the reflection paper: "Formulations of choice for the paediatric population" where it is recommended that "products containing high levels of propylene glycol should not be administered to paediatric patients below the age of 4 years".

An evaluation of the taste masking efficiency of the bitterness of propranolol was performed by the methodology of the electronic tongue. The results demonstrated around ≈80% masking effect compared to the reference in water. It addition, it has been confirmed that neither signals of poor acceptability nor premature treatment discontinuation were observed for reasons of taste during clinical studies. Furthermore the applicant clarified that the acceptability (including palatability) assessments cannot be added to any on-going study, since the treatment period is completed. However, the collection of such data will be considered in future clinical studies.

The use of preservative was found to be unnecessary. Microbiological studies performed on the formulation with and without preservative allowed the removal of the sodium propionate (used in clinical trial formulations) from the commercial formulation due to the concentration of propranolol in the formula and the antimicrobial properties of propranolol.

According to the SmPC section 4.2, the product may be diluted in a small quantity of milk, apple or orange juice. Compatibility studies were performed with the finished product diluted in the milk and in the juice to support the claim.

The product is presented with a measuring device (oral syringe). Justification of the choice of the measuring device has been provided. Graduation scale has been validated with the finished product. Dosing accuracy and precision over the graduation range have also been demonstrated.

Adventitious agents

None of the excipients used for Hemangiol are of animal or human origin.

Manufacture of the Product

The manufacturing process is standard. The product is manufactured by dissolving the components sequentially, followed by clarification, filling and capping. The process was subject to a risk assessment and the manufacturing steps considered to impact critical quality attributes were evaluated. For each manufacturing step, the in-process controls are defined to monitor the compliance of the process.

Suitable batch analysis data was provided on five batches of the product manufactured in the proposed commercial scale. The results indicated that the manufacturing process was reproducible and provides product that complies with the in-process and finished product specifications.

The process validation studies will be conducted on 3 production-scale batches at each of the proposed manufacturing sites. A satisfactory commercial scale validation scheme has been presented. This approach is acceptable as the manufacturing process is standard.

Product Specification

The product specification is conventional and includes tests for organoleptic characteristics (colour, clarity and odour), identification of the active substance by retention time and UV-spectrum, microbial contamination, pH, deliverable volume, purity (degradation products by HPLC) and content of the active substances (HPLC). The release and shelf-life specifications are identical with the exception of the pH limit.

The specification has been established based on development history, manufacturing history and on the results from the on-going ICH stability programme. Analytical methods and proposed acceptance criteria were established in accordance with the guidance ICH Q6A “Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances”. Analytical methods were adequately validated.

Batch analysis data have been provided on five commercial scale batches from the proposed commercial manufacturing sites, demonstrating compliance with the proposed release specification. It has been demonstrated that the finished product specification is suitable to control the quality of the product.

Stability of the Product

Stability data on five commercial scale batches, manufactured at the proposed manufacturing sites and scales were provided. The conditions used in the stability studies are in accordance with the ICH stability guideline. Data on up to 24 months of long term (25°C/60% RH) and intermediate (30°C/75% RH) and 6 months of accelerated (40°C/75% RH) storage conditions were provided. Samples were tested for organoleptic characteristics, pH, degradation products, microbial purity, assay, efficacy of preservation. The analytical procedures used were stability indicating and these were the same analytical methods as used for release of the finished product.

Stability testing included also forced degradation study. The product was exposed to elevated temperatures (heat stress), freezing and cooling (refrigerator conditions). In addition a photostability study was performed in accordance with ICHQ1B. Freezing of the bottle and its contents resulted in breakage. It has been concluded that the finished product cannot be stored in the freezer and a specific labelling recommendation “Do not freeze” was included in the product information. No physical, organoleptic or chemical changes were noted during the storage in refrigerator. It has been concluded that storage of the finished product in refrigerator is allowed.

Furthermore, an appropriate in-use testing has been carried out to demonstrate that the product could be used for 2 months after opening without special storage conditions. Since stability studies are on-going the applicant was not able to provide results from the in-use testing at the end of shelf-life. As the microbiological quality of the product was studied under simulated in-use conditions at release and during stability at different check points, sufficient evidence was gathered to support the extrapolation of the in-use stability at the end of shelf-life. Nevertheless the applicant was recommended to perform the in-use stability study at the end of shelf-life of the finished product. In addition, the applicant was recommended to confirm the efficacy of antimicrobial preservation (Ph. Eur. 5.1.3) under simulated in-use conditions at the end of shelf-life of the finished product. The applicant agreed with both recommendations from the Committee.

The overall stability data for Hemangiol oral solution proved that the product is stable under tested conditions. The results generated during the stability studies support the proposed shelf-life and storage conditions as defined in the SmPC.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The quality of Hemangiol oral solution has been adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted in support of the marketing authorisation application.

The quality of the active substance (propranolol hydrochloride) is assured by a European Certificate of Suitability of the Monograph of the European Pharmacopoeia (CEP).

The pharmaceutical development of the finished product has been satisfactorily described. The excipients are well established compendial substances and used in acceptable quantities. Their function has been satisfactorily described. Formulation development was focussed on producing a dosage form with appropriate dosing flexibility for administration of the product to young children. Aspects relating to the acceptability and palatability of the formulation were appropriately addressed during development.

The method of manufacture is considered standard and has been satisfactorily described, including in-process tests. The data shows consistent manufacture and is considered sufficient for this manufacturing process. A satisfactory validation protocol has been provided.

The proposed specifications were justified based on the batch and stability results, and are in general adequate for assuring the product quality and therefore were accepted.

The stability program is considered satisfactory. The batches placed on stability are considered representative of the product to be marketed. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory manner. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

2.2.6. Recommendations for future quality development

In the context of the obligation of the applicants to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- To perform the in-use stability study at the end of shelf-life of the finished product (36 months).

- To perform the test of efficacy of antimicrobial preservation (Ph. Eur. 5.1.3) under simulated in-use conditions at the end of shelf-life of the finished product (36 months).

2.3. Non-clinical aspects

2.3.1. Introduction

Propranolol is a well-known product with a long-term experience in clinical use, for more than 40 years in adults but also in children. Therefore, the use of the new oral liquid formulation of propranolol hydrochloride in infants, Hemangiol, is supported by a review of updated published non clinical studies in adult and juvenile animals. Moreover, the applicant conducted a GLP toxicity study in juvenile rats with an oral administration of the new formulation.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Some *in vivo* experimental models of haemangioma were established to study the pathogenesis of haemangioma. These animal models generally corresponded to human haemangioma tissue implanted into immunodeficient mice.

However, the applicant did not perform any pharmacodynamic studies in these models to support a proof-of-concept for the treatment of IH with propranolol due to:

- technical difficulties: these models are difficult to establish, need a lot of experience and are only proposed in few research universities in US or China and have not been validated so far by pharmacological interventions;

- the availability, at the start of development, of numerous published clinical data reporting successful treatment of IH with propranolol.

The pathogenesis of infantile haemangioma remains poorly understood; the neovascularisation and angiogenesis are probably involved. The potential mechanisms of action of propranolol described in the literature in proliferating IH could include:

1. a local haemodynamic effect (vasoconstriction and decrease of IH lesion perfusion)
2. an antiangiogenic effect (decrease expression of VEGF and bFGF by blocking the mitogen activated protein kinase (MAPK) and Raf activation or the Hypoxia Inducible Factor (HIF) pathway.
3. an aptotosis triggering effect on capillary endothelial cells.

The mechanism of action of propranolol in IH was investigated using experimental models and this is summarised thereafter in the Table 1.

Table 1: Pharmacology studies with propranolol in some models of haemangioma

Species / Strain	Method of Admin.	Organ Systems Evaluated	Doses and Duration	Noteworthy Findings	Reference
Fresh tissue of haemangioma	Oral	Endothelial Nitric Oxyd Synthase (eNOS)	-	Propranolol reduced the expression of eNOS	DAI et al., 2012
Haemangioma endothelial cells	*In vitro*	Angiogenesis	0.3 – 300µM 4 days	Propranolol decreased VEGF, VEGF-R1 and VEGF-R2 production, cell proliferation and tubulogenesis.	CHIM et al., 2012
Haemangioma endothelial cells	*In vitro*	Angiogenesis	25 – 100µM 24h	Propranolol decreased VEGF production, cell proliferation and tubulogenesis, and increased apoptosis via caspase activation.	JI et al., 2012

Secondary pharmacodynamic studies

The main pharmacological effect of propranolol not related to its desired therapeutic target and submitted by the applicant in the IH is the hypoglycaemic effect (see Table 2).

In fasted rats, an intraperitoneal injection of insulin produced a moderate hypoglycaemic effect, which was significantly enhanced by the SC administration of propranolol. However, propranolol did not alter blood sugar levels when tested alone. According to the authors, propranolol, by β-adrenergic blockade, may interfere with glycogenolytic and lipolytic actions of catecholamine liberated in response to hypoglycaemia, thereby counteracting normal homeostatic mechanisms involved in returning blood sugar to normal levels. Another possibility is that propranolol released endogenous insulin as shown in isolated perfused rat pancreas, whereby propranolol could act synergistically with insulin at its site of action to promote increased glucose uptake by muscles.

Moreover, the effects of propranolol were consistent with antagonism of the beta-adrenergic effect of circulating adrenaline.

Table 2: Secondary pharmacodynamics studies with propranolol

Species/ Strain	Method of Admin.	Organ Systems Evaluated	Doses and Duration	Noteworthy Findings	Reference
Rats / Harlan	Subcutaneous	Blood glucose	20 mg/kg Single administration	Propranolol alone did not alter blood sugar level Propranolol significantly enhanced ($p<0.05$) the insulin-induced hypoglycaemia	BROWN & RIGGILO, 1968
rabbits / Dutch rabbits	Injection into the marginal ear vein	Blood glucose	1.0 mg/kg/h	Normal rabbits : propranolol induced a slight hypoglycaemia Hypoglycaemic rabbits :propranolol potentiated the hypoglycaemic effect of insulin	CALVEY & SUMMERIL, 1968

Safety pharmacology programme

The hERG test is positive but there is a safety margin of 534 for infants at 3 mg/kg/d of propranolol. There is no effect of the propranolol on the QTc *in vivo*[1]. At toxic doses, propranolol may cause bronchospasm, and induce increased airway resistance, especially in asthmatic patients[2]. There are no effects on nervous central system detected in the juvenile toxicity study with propranolol.

Pharmacodynamic drug interactions

No additional pharmacodynamic drug interaction studies in animals were considered necessary. In the absence of specific drug interaction studies in children, the drug interactions with propranolol are those known in adults and described in details in the SmPC of the product.

2.3.3. Pharmacokinetics

The applicant reviewed published data in relation to the pharmacokinetics (PK) of propranolol. However most of the studies were performed in mature animals. In addition, the Applicant conducted a toxicity study in juvenile rats in which toxicokinetic evaluation was performed.

The non-clinical PK data from the literature indicate that propranolol is rapidly and almost completely absorbed after oral administration in animal (adult rat, dog and monkey and juvenile rat between PND4 and PND21) and in human. The absolute bioavailability is weak, 8 to 25% in rat, 27 % in dog and 3 % in monkey due to an extensive first pass metabolism by the liver. Peak plasma concentration is reached about 1 hour after dosing and is independent of the administered dose.

High concentrations of drug-related radioactivity were found in the lungs, and relatively high concentrations were also found in the brain, the liver and the kidneys. After administration of ^{14}C-propranolol at 1mg/kg per os in dogs, about 2 µg/g in lung, 0.40 µg/g in brain and kidney, 0.70 µg/g in liver of ^{14}C-propranolol found 1 hour after dose. This radioactivity became negligible after 8h post dose. This distribution profile is in agreement with the distribution characteristics of a lipophilic drug. The binding of propranolol to plasma proteins is 92.2% in rat, 96.6% in dog, 99.2% in monkey, and is 93.9% in human.

[1] Love J.N. The effect of propranolol intoxication on QTc interval in a canine model. J Emerg Med 1998 16(1) 1-4.
[2] Goodman&Gildman's. Propranolol. 11th edition 2006.

From the literature, in vitro data in S9 fraction of rats and human liver microsomes, as well as in vivo data in rats indicate that propranolol is extensively metabolized through three primary routes: ring hydroxylation, side-chain oxidation and direct glucuronidation. In vivo studies show some interspecies differences in propranolol metabolism. In the rat, ring hydroxylation is predominant, while side-chain oxidation is predominant in the dog. In both species a majority of propranolol metabolites are recovered in urine as glucuronides. In human, it was estimated that these routes of metabolism accounted for 42%, 41% and 17% of the total metabolism, respectively. Moreover, the 4-hydroxy-propranolol active metabolite was quantified, its plasma exposure accounting for less than 7% of the parent drug exposure.

In vitro studies indicate that the ring hydroxylation is catalysed mainly by CYP2D6. The side-chain oxidation is mediated by CYP1A2 and to some extent by CYP2D6. Propranolol is a substrate of CYP2C19, with a negligible contribution to the side-chain oxidation.

Data from the literature indicate that the excretion route and rate of propranolol are similar in non-clinical species and in human. A majority of a propranolol dose is excreted in urine within 24 hours after oral administration, mostly as metabolites. The urinary excretion of propranolol is around 68%, 80% and 70% in rat, dog and monkey, respectively, and 90% in human.

In vitro data from the literature indicate that P-glycoprotein (P-gp) is not a major determinant of propranolol disposition and that propranolol has a limited potential to be an inhibitor of the P-gp.

In vitro investigations on cytochromes P-450 (CYP) evidenced a potential for propranolol to be a weak inhibitor of CYP1A2 and moderate inhibitor of CYP2D6. This CYP2D6 inhibition potential has no consequences on in vivo drug-drug interactions, propranolol is not mentioned as a CYP2D6 inhibitor in different health authorities' drug-drug interaction database (e.g. FDA drug development and drug interaction: table of substrates, inhibitors and inducers).

2.3.4. Toxicology

Single dose toxicity

Acute toxicity of propranolol is poorly documented in animals, lethal doses 50 (LD50) are only reported in mice by several routes of administration: oral (565 mg/kg), IV (22-35 mg/kg), and IP (107 mg/kg).

At toxic doses, propranolol may cause bronchospasm, and induce increased airway resistance, especially in asthmatic patients. The primary cause of death related to propranolol administration at toxic doses in the spontaneously breathing rat, is respiratory failure followed by cardiovascular failure. Thus, the central and not the peripheral beta-blocker activity seems to be the most important factor for inducing death[3].

[3] TOET A.E., VAN DE KUIL A., et al. Toxic doses of rac-, (-)-(S)- and (+)-(R)-propranolol in rats and rabbits. Chirality 1996 8 411-7

Repeat dose toxicity

Very few repeat-dose toxicity studies conducted with propranolol were identified in the literature. These studies were carried out only in rodents, more than 20 years ago. These studies were not GLP compliant. No plasma exposure to propranolol was available under the experimental conditions of these studies.

Table 3: Repeated-dose toxicity studies by oral administration of propranolol HCl

Species/strain	Method of administration	Duration of dosing	Doses (mg/kg/d)	Noteworthy findings	Nature of data
Mice CD-1 ICR Swiss	Oral route (in the diet)	78 weeks	100	No deaths, body weight significantly but slightly lower Greater incidence of hunched mice No histopathological findings	WEIKEL J.H., 1979
Rats Long Evans	Oral (in the diet)	78 weeks	37.5	No differences with the control group concerning mortality, body weight, food consumption and hematology data	WEIKEL J.H., 1979
Wistar male rats	Oral (drinking water)	10 days	40-50	Reduction of the body weight gain, reversible (40% less water intake during treatment)	ERDTSIECK-ERNSTE E.B., 1993

A juvenile toxicity study was conducted in support of this application and further described below (see other toxicity studies).

Genotoxicity

The applicant detailed the published genotoxicity data with propranolol. The Ames tests were negative with doses of propranolol up to 1000 µg/plate**.** In vitro genotoxicity studies carried out in rats and humans hepatocytes and in Chinese hamster V79 cells showed negative results on cytotoxicity test and DNA fragmentation assay**.** Propranolol did not cause DNA damage, whatever the tested concentration**.** Propranolol up to 37.25 mg/kg did not induce a significant increase in polychromatic erythrocytes carrying micronuclei compared to control ($p<0.001$) and did not induce significant chromosomal aberrations in spermatocytes at all doses up to 111.75 mg/kg. Based on overall available published data, there was no evidence of propranolol genotoxicity.

Table 4: Overview of the published genotoxicity studies with propranolol

Type of Test	Species/strain	Doses (mg/kg)	Results	Nature of data
Ames test, gene mutation in bacteria i*n vitro*	*S.typhimurium* (TA98, TA100, TA1535, TA1537)	1 to 1000 µg/plate, with or without metabolic activation	No mutagenic effect of propranolol	Published scientific literature (CCRIS, 2006)
Gene mutation in mammalian cells i*n vitro*	rat and human hepatocytes/ Chinese hamster V79 cells	0.03, 0.1, 0.3, 3.0 mM	No DNA fragmentation and no or minimal DNA repair synthesis after 20 h of exposure to propranolol (0.1 mM) in both species	ROBBIANO L., 1991
DNA fragmentation assay i*n vitro*	DNA-strand breaking effect, isolated nuclei of rat liver	10, 20, 30, 35 mmol/L	Dose dependent DNA fragmentation (single-strand damage)	PRESTA et al., 1983
DNA fragmentation assay i*n vitro*	DNA-strand breaking effect, human fibroblasts	<65 µg/mL	No strand breakage	HUSSAIN et al., 1988
Micronucleus test, chromosomal aberrations i*n vivo*	Rat hepatocytes	75 mg/kg IP single administration	No mutagenic effect of propranolol	PRESTA et al., 1983
Chromosomal aberrations test i*n vivo*	bone narrow cells in Swiss albinos mice	0, 37.25, 74.5 or 111.75 mg/kg IP bw2 days	No mutagenic effect of propranolol	ARUNA & KRISHNAMURTHY, 1986
Micronucleus assay i*n vivo*	Somatic and germ cells of Swiss albinos mice	37.25; 74.5; 111.75 mg/kg IP in two divided doses at 24 hour-interval	From 74.5, increase in micronuclei in erythrocytes without effect on the ration PCE/NCE and no significant chromosomal aberrations in germ cells	ARUNA and KRISHNAMURTHY, 1986

Carcinogenicity

No carcinogenic effect of propranolol was reported in the literature. In dietary administration studies in which mice and rats were treated with propranolol hydrochloride for up to 18 months at doses of up to 150 mg/kg/day, there was no evidence of drug-related tumorigenesis.

Reproduction Toxicity

The targeted patient population is a paediatric population. The evaluation of the reproductive and developmental toxicity of propranolol was thus limited to its potential effects both on male and female fertilities when given in adult animals and on postnatal development when given in juvenile animals.

Propranolol demonstrated some effects on male and female fertility *in vitro* and *in vivo* in the rat. Propranolol at equivalent human therapeutic doses might induce hazardous effects on male fertility following repeated administration in rats but these effects were always reversible as they returned to normal values after discontinuation of treatment.

Toxicokinetic data

Toxicokinetic assessment was performed within the pivotal juvenile toxicity study described below (see other toxicity studies).

Local Tolerance

No local tolerance study was conducted which is acceptable given the clinical experience with propranolol.

Other toxicity studies

A GLP compliant toxicity study conducted in juvenile rats by the applicant showed that propranolol given orally up to 40 mg/kg/d, between PND 4 to 21 did not induce treatment-related effects on reproductive parameters and reproductive development, developmental parameters and neurologic development. Thus, the NOAEL was considered to be 40 mg/kg/day (representing an AUC of 1051 h•ng/ml in females and 2516 h.ng/ml in males) for these endpoints leading to a safety margin of 1.2 in females and of 2.9 in males. Nevertheless, mortality (4 pups out of a total of 64 in the main group) was observed at 40 mg/kg/day but the relationship to propranolol administration could not be established. For that reason, the NOAEL for juvenile toxicity was considered to be 20 mg/kg/day (representing an AUC0-24h of 262 and 2211 h•ng/mL in male and female rats, respectively) resulting in the absence of sufficient exposure margins to clinical exposure (AUC0-24h of 860 h•ng/mL).

In published studies in juvenile animals, propranolol administration induced a deficit in body weight and body weight gain but this was always reversible at cessation of treatment. Retarded growth rate following chronic oral propranolol administration to growing rats was independent of changes in plasma growth hormone and hypothalamic somatostatin concentration.

2.3.5. Ecotoxicity / environmental risk assessment

Table 5: Summary of main study results

Substance (propranolol / Hemangiol)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}		Between -0.41 and 3.65 (literature)	below action limit
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**

PECsurfacewater, default PECsurfacewater, refined	0.21 (Fpen 0.01) 0.00130 (Fpen 0.00635%)	µg/L ng/L µg/L	> 0.01µg/L threshold (for default value) < 0.01µg/L threshold (for refined value) Not PBT
Other concerns (e.g. chemical class)			No

The values $\log_{Kow}$ are variable according the references provided and were not determined experimentally. As propranolol hydrochloride is an ionisable compound, an ion-corrected $\log_{Dow}$ and $\log_{Kow}$ was calculated to be 0.68 ± 0.01 or 3.45 ± 0.01, respectively, below the action limit of 4.5. As a result testing for persistence, bioaccumulation and toxicity is not required.

The propranolol hydrochloride $PEC_{SURFACEWATER}$ value is below the action limit of 0.01 µg/L with the use of a refined F_{pen} based estimation for the prevalence of the treated haemangioma of 12 %. The applicant follows the recommendations of the guideline and determines an acceptable PEC_{sw}. A phase II assessment is therefore not needed.

2.3.6. Discussion on non-clinical aspects

No new studies of acute and chronic systemic toxicity, genotoxicity, carcinogenicity or reprotoxicity were performed. The published toxicological data are sufficient and scientifically relevant for the development of Hemangiol. The main effects reported after repeated administration of propranolol in adult and juvenile rats were a transient decrease in body weight associated with a transient decrease in organ weight. These effects were completely reversible when treatment was discontinued.

No genotoxic potential of propranolol was evidenced in the review of literature.

Long-term carcinogenicity studies, carried out in mice and rats treated with propranolol (up to 150 mg/kg/day for 18 month) showed no evidence of drug-related tumorigenesis. Moreover, there is no signal from clinical safety data and the duration of treatment in infants (6 months) is short.

Propranolol demonstrated some effects on male and female fertility in vitro and in vivo in the rat. Propranolol at equivalent human therapeutic doses might induce hazardous effects on male fertility following repeated administration in rats but these effects were always reversible as they returned to normal values after discontinuation of treatment. Moreover, no reproductive effect was observed in the GLP juvenile toxicity study and despite the long-term in clinical use for cardiovascular diseases, none side effects have been reported about fertility of children treated by propranolol. A risk for the environment is not expected.

In the published data, a higher rate of mortality was always reported at dose levels higher than 50 mg/kg/day in juvenile rats. Because of the absence of specific propranolol related clinical signs of toxicity or macroscopic lesions in animals which died following propranolol administration, a robust relationship between mortality and propranolol administration on the basis of these experimental parameters, remain difficult to establish.

Consequently, the relationship between mortality and propranolol administration in juvenile rats at dose levels lower than 50 mg/kg/day appears unlikely. Moreover, propranolol has been widely prescribed in the paediatric population for more than 40 years, either for cardiovascular disease or

infantile haemangioma, and no signal concerning a potential relationship between treatment and any major safety concerns was reported in the literature. Only one fatal case was reported with propranolol in the treatment of infantile haemangioma, which was attributed to acute renal failure following diarrhoea. Then, the relevance of the uncertain treatment-related mortality seen at the highest dose in juvenile rats appears to be of little relevance for the paediatric population.

2.3.7. Conclusion on the non-clinical aspects

This non-clinical development is acceptable and in accordance with the "Guideline on the non-clinical documentation for mixed marketing authorisation applications" CPMP/SWP/799/95 dated April 2006. The pharmacologic, pharmacokinetic, and toxicological characteristics of propranolol are well characterised.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 6: Summarises the clinical studies conducted for this marketing authorisation application.

Type of study Study Identifier	Objectives of the study	Study design and Type of Control	Test Products; Dosage Regimen; Route of Administration	Number of Subjects Analysed	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
V00400 SB 1 01 2A: **Evaluation of PK parameters of a new propranolol hydrochloride formulation (oral solution) compared to the reference propranolol hydrochloride formulation (tablet)**	Main objective: To evaluate the PK parameters of a new propranolol hydrochloride formulation (oral solution) compared to the reference propranolol hydrochloride formulation (tablet) after a single oral dose in 12 healthy subjects. Secondary objectives: To document the clinical and biological tolerability of the 2 propranolol hydrochloride formulations after single oral administration in 12 healthy subjects.	A single-centre, randomised, open-label, single dose, 2-period crossover study.	*Test product*: propranolol HCl oral solution (5 mg/mL, expressed as base). *Dose*: single administration of a dose of 80 mg propranolol (16 mL of solution). *Administration*: oral, at around 8 a.m. after an overnight fast of at least 10 hours. *Test product*: propranolol HCl tablet of 40 mg (corresponding to 35.09 mg base). *Dose*: single administration of 2 tablets (corresponding to 70.18 mg propranolol base). *Administration*: oral, at around 8 a.m. after an overnight fast of at least 10 hours.	12	Healthy adult subjects (18 to 45 years).	Two single administrations with a wash-out interval of at least 3 days.	Complete; Full
PK **V00400 SB 1 02:** **A multicentre, open-label, repeated-dose, PK study of propranolol in infants treated for proliferating infantile haemangiomas (IHs) requiring systemic therapy**	Primary objective: To characterise the PK of propranolol at steady-state in infants during a treatment for proliferating IH requiring systemic therapy. Secondary objectives: To characterise the PK of a propranolol metabolite (4-OH-propranolol). To assess the efficacy of propranolol on the evolution of the target IH over 12 weeks. To document the safety profile of propranolol in the treatment of IH.	An open-label, multicentre, repeated-dose study. Infants were stratified to 2 groups according to their age at inclusion, which defined the timing of their PK assessment at steady-state: Group 1: aged from 35 to 90 days inclusive at inclusion; PK assessment after 4 weeks of treatment. Group 2: aged from 91 to 150 days inclusive at inclusion; PK assessment after 12 weeks of treatment.	*Test product:* propranolol oral solution 3.75 mg/mL. *Dose*: 3 mg/kg/day (at the end of titration). *Titration procedure*: D0 1 mg/kg/day. D7 increase to 2 mg/kg/day. D14 increase to 3 mg/kg/day. *Administration*: oral, twice daily (morning and late afternoon).	23 randomised and treated (10 in Group 1, 13 in Group 2).	Infants with proliferating IHs requiring systemic therapy (aged 35 to 150 days at inclusion).	12 weeks.	Complete; Full
Population PK **PK V0400 1 01:**	- To describe the PK of propranolol in infants, - To evaluate the between subjects	See Study V00400 SB 1 02	See Study V00400 SB 1 02	From the 23 infants treated, propranolol plasma	Infants with proliferating IHs requiring systemic therapy	12 weeks.	Complete; Full

A multicentre, open-label, repeated-dose, pharmacokinetic study of propranolol in infants treated for proliferating infantile haemangioma (IHs) requiring systemic therapy: population pharmacokinetic analysis	variability and to understand the source of this subjects variability.			concentrations from 22 infants were used for the PPK analysis. (10 in Group 1 and 12 in Group 2)	(aged 35 to 150 days at inclusion).		
Efficacy / Safety **V00400 SB 2 01:** **A randomized, controlled, multidose, multicentre, adaptive phase II/III study in infants with proliferating infantile haemangioma requiring systemic therapy to compare four regimens of propranolol (1 or 3 mg/kg/day for 3 or 6 months) to placebo (double blind)** ***Primary Analysis up to Week 24***	The objectives of the first 24 weeks (6 months) period were: Primary objectives: To identify the appropriate dose and duration of propranolol treatment, and to demonstrate its superiority over placebo based on the complete/nearly complete resolution of the target IH at Week 24 (6 months). Secondary objective: To document the safety profile of the four regimens of propranolol in the treatment of IH in infants aged 1 to 5 months (35 to 150 days) at inclusion.	Randomized, placebo-controlled, 2-stage, 5-arm (Stage 1) then 2-arm (Stage 2), adaptive Phase II/III design, stratified by age and IH localization with treatment regimen selection at the end of the first stage.	*Tests products*: placebo or propranolol oral solution: 1.25, 2.50 or 3.75 mg/mL. *Dose*: 1 or 3 mg/kg/day (at the end of titration). *Titration procedure*: D0 1 mg/kg/day D7 increase to 2 mg/kg/day (for the 3 mg/kg/day arms) D14 increase to 3 mg/kg/day (for the 3 mg/kg/day arms) Dummy titration was used for the placebo and propranolol 1 mg/kg/day arms. *Stage 1*: 5 treatment arms: - 6 months placebo - 3 months propranolol 1 mg/kg/day followed by 3 months placebo - 6 months propranolol 1 mg/kg/day - 3 months propranolol 3 mg/kg/day followed by 3 months placebo - 6 months propranolol 3 mg/kg/day *Stage 2*: 2 treatment arms: - 3 mg/kg/day 6 months (best regimen of propranolol from	456 randomised and treated patients (pts) (including 188 pts in stage 1, 88 pts in stage 2 and 180 overrun* pts): - 6 months placebo: 55 pts including 25 pts in stage 1 and 30 pts in stage 2) - Propranolol 1 mg/kg/day 3 months: 98 pts (including 41 pts in stage 1 and 57 overrun* pts) - Propranolol 1 mg/kg/day 6 months: 102 pts (including 40 pts in stage 1 and 62 overrun* pts) - Propranolol 3 mg/kg/day 3 months: 100 pts including 39 pts in stage 1 and 61 overrun* pts) - Propranolol 3	Infants with proliferating IHs requiring systemic therapy (aged 35 to 150 days).	3 months of propranolol followed by 3 months of placebo, or 6 months of propranolol or placebo.	Complete; Full *Primary Analysis up to Week 24*

			Stage 1), and - placebo (2:1 ratio). Mode of administration: oral twice daily (0.4 mL/kg; morning and late afternoon around meal intake).	mg/kg/day 6 months: 101 pts (including 43 pts in stage 1 and 58 pts in stage 2) * Overrun= patients of Stage 2 randomized in the unselected propranolol regimen arms.			
Efficacy / Safety **V00400 SB 3 01:** **A multicentre, open-label study of propranolol in infants with proliferating infantile haemangioma requiring systemic therapy** ***"Ongoing study"***	The objective of this study is to allow the use of propranolol with adequate conditions of administration and follow up infants judged as requiring this systemic treatment after participation to a previous trial. As requested in such conditions, the safety profile (included any potential long term impact) and the effect on the resolution of target proliferating infantile haemangioma will be documented.	Multicentre, uncontrolled, open-label study.	**Test product**: propranolol oral solution **Dose:** 2 or 3 mg/kg/day according to individual tolerability profile and Investigator's judgement **Titration procedure:** D0 1 mg/kg/day D7 increase to 2 mg/kg/day D14 increase to 3 mg/kg/day (if judged necessary by the investigator) **Administration:** oral twice daily (morning and late afternoon around meal intake).	Number of patients not predictable, (but cannot be above the total number of patients previously included in the concerned studies). Estimated maximum number of patients: around 100 patients Currently 11 infants are randomised and treated.	Infants with proliferating IHs requiring systemic therapy (having been treated and completed study V00400SB102 or study V00400SB201)	Up to 6 months	Ongoing study

The applicant claimed the approval for the following indication:

HEMANGIOL 3.75 mg/mL, oral solution is indicated in the treatment of proliferating infantile haemangioma requiring systemic therapy.

It is to be initiated in infants aged 5 weeks to 5 months.

The final indication following CHMP review of this application is:

HEMANGIOL is indicated in the treatment of proliferating infantile haemangioma requiring systemic therapy:

- *Life- or function-threatening haemangioma,*
- *Ulcerated haemangioma with pain and/or lack of response to simple wound care measures,*
- *Haemangioma with a risk of permanent scars or disfigurement.*

It is to be initiated in infants aged 5 weeks to 5 months (see section 4.2).

2.4.2. Pharmacokinetics

Propranolol is a well-known and already approved medicinal product in the EU. It has been used for many years in adults for cardiovascular indications. Its pharmacokinetic characteristics have been extensively documented in adults and its main PK features in adult patients elucidated. However, data in infants are very limited.

Hemangiol is an oral solution containing 4.28 mg/ml of propranolol as hydrochloride salt (corresponding to 3.75 mg/ml propranolol base). The intended dose is 1.5 mg/kg body weight bid. This solution appears to be suitable for administration in infants weighing up to 12.5 kg. At the claimed dose (1.5 mg*2/kg), the intake volume is less than 5 ml. The applicant submitted a PIP intended to guarantee adequate and relevant development of Hemangiol in the treatment of IH, which was approved by the Paediatric Committee of the EMA on 27 Oct 2010 and followed by 4 amendments leading to the final PIP decision P/0004/2013.

Propranolol pharmacokinetic characteristics have been extensively documented in adults. Its main PK features in adult patients are summarised below.

In addition, in order to assess the biopharmaceutical performances of the paediatric oral solution comparatively to a current EU marketed propranolol tablet formulation and the characterisation of propranolol PK properties in the target population i.e. in infants with IH, the applicant performed two PK studies. One conducted in adult healthy volunteers and the second in paediatric patients.

The analytical techniques employed in the study are adequately validated. Their performances are suitable for the planned investigations.

Standard methods were used for pharmacokinetic and statistical analyses.

Absorption

The applicant has presented clinical pharmacokinetic data of absorption from propranolol published data. Propranolol is almost completely absorbed after oral administration. However, it undergoes high first-pass metabolism by the liver and on average only about 25% of propranolol reaches the systemic circulation. Maximum plasma drug concentrations (Cmax) occur approximately 1 to 2 hours after an oral dose. Administration of protein-rich foods increases the bioavailability of propranolol by about 50% with no change in time of maximal plasma concentration (T_{max}). Propranolol is a substrate for the intestinal efflux transporter, P-glycoprotein (P-gp). However, studies suggest that P-gp is not dose-limiting for intestinal absorption of propranolol in the usual therapeutic dose range.

Distribution

The Applicant has presented clinical pharmacokinetic data of distribution from published data. Approximately 90% of circulating propranolol is bound to plasma proteins. Propranolol is a racemic mixture, the (S-) and (R-)enantiomers being preferentially bound to α1-glycoprotein (α1-GP) and albumin (HSA), respectively. The volume of distribution of propranolol is approximately 4 L/kg. Propranolol crosses the blood-brain barrier.

A comparative bioavailability study in adult healthy volunteers showed that the relative bioavailability of the solution (5 mg/mL) is approximately 20% higher than that observed with the tablets.

The study has been conducted under fasting conditions, while the oral solution will be used under fed conditions. The applicant brought literature data suggesting that food intake would not influence propranolol bioavailability. Section 4.2 of the SmPC has been updated to reflect the use of propranolol as instructed in the pivotal clinical study.

Elimination

The Applicant has presented clinical pharmacokinetic data on elimination and metabolism based on published data. Propranolol is extensively metabolized through three primary routes: ring hydroxylation (mainly 4-hydroxylation), side-chain oxidation, and direct glucuronidation. It has been estimated that these routes of metabolism accounted for 42%, 41%, and 17% of the total metabolism, respectively, but with considerable variability between individuals. The four major final metabolites are propranolol glucuronide, naphthyloxylactic acid, glucuronic acid, and sulfate conjugates of 4-hydroxy propranolol. The T1/2 of propranolol ranges from 3 to 6 hours. Propranolol is excreted as metabolites in urines, less than 1% of a dose being excreted as unchanged drug in the urine[4].

Dose proportionality and time dependencies

Propranolol is a class I compound almost completely absorbed after oral administration and having demonstrated a linear pharmacokinetics.

Special populations

Paediatric population: The pharmacokinetics of propranolol has been evaluated at steady-state in 23 IH infants receiving a 3 mg/kg (propranolol base) bid. The included patients have been stratified in two groups: Group 1 from 35 to 90 days-old, and Group 2 from 91 to 150 days-old at inclusion. The data collected has been analysed following two approaches: a classical non Compartmental Analysis (NCA) and a model based approach (population-PK).

- From the NCA analysis, the following findings have been reported: In both groups, the peak concentration was reached 2 hours after dosing, with a mean maximum plasma drug concentration (Cmax) of about 79 ng/mL. These values are comparable to those published in the literature for infants suffering from cardiovascular diseases. The corresponding plasma exposures (area under the plasma concentration time curve; AUC0-12 were 541 and 430 h*ng/mL in Groups 1 and 2, respectively. The total plasma clearance of propranolol was 2.7 and 3.3 L/h/kg in Groups 1 and 2, respectively. These values evidenced that once corrected for weight, primary pharmacokinetic parameters such as clearance (CL/F) determined in infants are similar to those published in the literature for propranolol in adults (ranging from 2.1 to 5.2 L/h/kg according to the study). These data indicate that CL/F is a very consistent parameter for propranolol across age. However, considering that the PK profiles have been established in limited number of patients (respectively

[4] NACE G.S., WOOD A.J. Pharmacokinetics of long acting propranolol. Implications for therapeutic use. Clin Pharmacokinet 1987 13(1) 51-64

8 and 11 in each age group) only on the basis of six plasma samples (0, 1, 2, 4, 6 and 9 hours after dosing). Therefore, the estimation of PK parameters could not be accurate and thus should be handled cautiously.

- A population pharmacokinetic model using a body weight function on plasma clearance was established. This model adequately predicted the pharmacokinetics of propranolol in infants, and confirmed that the dose expressed as mg/kg should be used without further dose adaptation by range of age. Furthermore, this model was applied to estimate the impact on the maximum plasma concentration of the interval between the two intakes in the day, and documented that the maximum concentration is marginally affected when comparing a 9- or 12-hour dosing interval.

Gender: It has been proposed that the clearance of propranolol in men is dependent on circulating concentrations of testosterone. In women, none of the metabolic clearances for propranolol showed any significant association with either oestradiol or testosterone[5].

Race: *Sowinski et al [199*6][6] investigated the pharmacokinetics of propranolol in African-American in comparison to Caucasian subjects. The clearance of (R)- and (S)-propranolol were about 76% and 53% higher in African-Americans than in Caucasians, respectively. Chinese subjects had a greater proportion of unbound propranolol in plasma compared to Caucasians (18% to 45% higher), which was associated with a lower plasma concentration of α 1-GP[7].

Renal Impairment: *Bianchetti et al, [1976]*[8] investigated the pharmacokinetics of propranolol in patients with chronic renal failure and patients on regular dialysis, in comparison to healthy subjects. The C_{max} of propranolol in the chronic renal failure group was 3- and 6-fold higher than those observed in the dialysis patients and in the healthy subjects, respectively. Propranolol plasma clearance was also reduced in the patients with chronic renal failure. Chronic renal failure has been associated with a decrease in drug metabolism via down-regulation of hepatic cytochrom P450 activity resulting in a lower "first-pass" clearance[9].

Hepatic Impairment: Propranolol is extensively metabolized by the liver. *Wood et al,* [1978][10] investigated the pharmacokinetics of propranolol in patients with liver cirrhosis in comparison to healthy subjects. The steady-state unbound concentration of propranolol in patients with cirrhosis was 3-fold higher than in healthy subjects. In cirrhotic patients, the $T_{1/2}$ increased to 11 hours compared to 4 hours in healthy subjects.

Genetic Polymorphism: In CYP2D6 poor metabolisers (PM), no difference in terms of oral clearance or T1/2 of propranolol was observed when compared to CYP2D6 extensive metabolizers (EM). Nevertheless, in the CYP2D6 PM population, the partial clearance of 4-OH propranolol was significantly lower, and the partial clearance of naphthyloxyactic acid was significantly higher than in the CTP2D6 EM population.

[5] WALLE T., FAGAN T.C., et al. Stimulatory as well as inhibitory effects of ethinyloestradiol on the metabolic clearances of propranolol in young women. Br J Clin Pharmacol 1996 41 305-9
[6] SOWINSKI K.M., LIMA J.J., et al. Racial differences in propranolol enantiomer kinetics following simultaneous i.v. and oral administration. Br J Clin Pharmacol 1996 42 339-46
[7] ZHOU H.H., ADEDOYIN A., et al. Differences in plasma binding of drugs between caucasians and chinese subjects. Clin Pharmacol Ther 1990 48(1) 10-7
[8] BIANCHETTI G., GRAZIANI G., et al. Pharmacokinetics and effects of propranolol in terminal uraemic patients and in patients undergoing regular dialysis treatment. Clin Pharmacokinet 1976 1(5) 373-84
[9] WOOD A.J.J., VESTAL R.E., et al. Propranolol disposition in renal failure. Br J Clin Pharmac 1980 10 561-6
[10] WOOD A.J.J., KORNHAUSER D.M., et al. The influence of cirrrhosis on steady-state blood concentrations of unbound propranolol after oral administration. Clin Pharmacokin 1978 3 478-87

Pharmacokinetic interaction studies

The Applicant did not perform any drug interaction studies in the target population. The same drug interactions than for adults have been included in section 4.5 of the SmPC which is considered acceptable.

In vitro studies indicated that the aromatic hydroxylation of propranolol is catalysed mainly by CYP2D6. The side-chain oxidation of propranolol was mainly mediated by CYP1A2 and to some extent by CYP2D6. The ring hydroxylation of propranolol was mediated almost exclusively by CYP2D6. The contribution of CYP2C19 to side-chain oxidation was negligible[11]. Because the metabolism of propranolol involves multiple CYP isoenzymes (CYP2D6, 1A2, 2C19), co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition) of one or more of these pathways may lead to clinically relevant drug interactions.

Combinations should not only consider infants given any other medicinal products but also infants breastfed by mothers taking any other medicinal products. In this case, the need of stopping breast-feeding should be discussed.

2.4.3. Pharmacodynamics

No specific pharmacodynamic studies have been submitted with this application.

Mechanism of action

Currently, the pathogenesis of IH remains poorly understood. Potential mechanisms of action of propranolol claimed by the Applicant for treatment of proliferating IH are the following, there are based on bibliographic references:

A *local hemodynamic effect*: vasoconstriction, which is a classical consequence of beta-adrenergic blockade and decrease of IH lesion perfusion;

An *anti-angiogenic effect* characterized by a decrease of the proliferation of vascular endothelial cells, a reduction of the neovascularization and formation of vascular tubules, and a reduction of the secretion of Matrix Metalloproteinase 9 which is crucial for endothelial cell migration. Several hypotheses for the molecular mechanism of action are yet to be elucidated;

An *apoptosis-triggering effect* on capillary endothelial cells. Beyond this effect, beta-2 adrenoceptors are expressed on the capillary endothelial cells, their activation promotes the vascular endothelial growth factor and basic fibroblast growth factor signalling pathways and the resulting proangiogenesis/proliferation; their blockade by propranolol can inhibit capillary endothelial cell proliferation.

The proposed target of propranolol is illustrated in Figure 1.

[11] YOSHIMOTO K., ECHIZEN H., et al. Identification of human CYP isoforms involved in the metabolism of propranolol enantiomers – Ndesisopropylation is mediated mainly by CYP1A2. Br J Clin Pharmac 1995 39 421-31

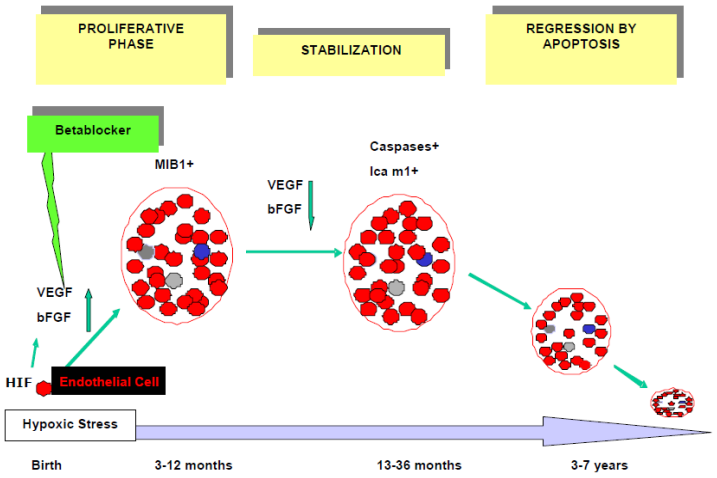


Figure 1: Potential Mechanism of Action of Propranolol in the Treatment of Infantile Haemangioma

Source: From LÉAUTÉ-LABRÈZE and TAÏEB, 2008.

bFGF: basic fibroblast growth factor; Caspases: cysteine-aspartic proteases; HIF: hypoxia inducible factor; VEGF: vascular endothelial growth factor.

2.4.4. Discussion and conclusions on clinical pharmacology

The applicant has not performed specific studies on absorption, distribution, elimination or interactions; clinical pharmacokinetic data from the literature were presented instead. This is acceptable since the pharmacokinetic characteristics are well described in the literature. Additional clinical PK studies are not considered necessary.

In order to assess the biopharmaceutical performances of the paediatric oral solution comparatively to a current EU marketed propranolol tablet formulation and the characterisation of propranolol PK properties in the target population i.e. in infants with IH, the applicant performed two PK studies. One conducted in adult healthy volunteers and the second in paediatric patients. Bioavailability of the oral solution compared to the reference tables has also been established in 12 adults showing that the extent of absorption was 20% higher for the solution compared with the tablet formulation. The PK profile in children has been characterised in a PK study in 23 infants. Propranolol is metabolised in the liver and excreted by the kidneys.

There is no data in children in cases of renal or hepatic impairment, therefore the use of propranolol is not recommended in these cases (this has been reflected in sections 4.2 and 4.4 of the SmPC).

The mechanism of action remains poorly understood and based on published hypothesis. The applicant has not performed any study to further clarify this mechanism.

2.5. Clinical efficacy

The propranolol clinical program in proliferating IH consists in one pivotal phase II/III study (V00400 SB201), one PK phase I study (V00400SB102), a compassionate use program and literature review.

The first claimed indication, *proliferating IH requiring systemic therapy*, is wider than the population included in the clinical pivotal trial V00400SB201. The efficacy of propranolol in high-risk patients (i.e. life and function-threatening or severe ulcerated IH) is only based on data from PK Study 102, a compassionate use program and on publications.

As a consequence, the Applicant proposed a more specific indication:

"HEMANGIOL is indicated in the treatment of proliferating infantile haemangioma requiring systemic therapy:

- Life-or function-threatening haemangioma,

- Ulcerated haemangioma with pain and/or lack of response to simple wound care measures,

- Haemangioma with a risk of permanent scars or disfigurement.

It is to be initiated in infants aged 5 weeks to 5 months (see section 4.2)".

A summary of all sub-categories of the target population is presented in Table 7.

Table 7: Data Sources Presented in this Submission 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	**X**	**X**	**X** (life-threatening excluded)	
2	IH in certain anatomical locations that often leave permanent scars or deformity, especially the nose, lip, ear, and glabellar area.			**X**	**X**	**X**
3	Large facial IH, especially those with a prominent dermal component (more likely to leave permanent scarring).			**X**	**X**	**X**
4	Smaller haemangioma in exposed areas, such as the face and hands, may be considered for treatment with modalities unlikely to cause scarring or significant side effects.			**X**	**X**	**X** (>1.5 cm)
5	- Ulceration		**X**	**X**	**X**	**X**
	- Severe ulcerated IH (whatever the localization) with pain and/or lack of response to simple wound care measures.1	High risk	**X**	**X**	**X**	
6	Pedunculated haemangioma (likely to leave significant fibrofatty tissue after involution).			**X**	**X**	**X**
7	IH with a potential risk of disfigurement			**X**	**X**	**X**

CUP: compassionate use program; IH: infantile haemangioma.
1. Only certain high risk cases of ulceration were not included in Study 201, according to the definition provided (Study 201 non-inclusion criterion).

2.5.1. Dose response study(ies)

No dedicated dose-response study has been performed for this application. The proposed regimen was extensively discussed with the EMA during the paediatric investigation plan, based on published data in the target indication and on the experience of propranolol in the paediatric population for cardiologic indications. Based on the available data and the already known safety profile of propranolol, 2 dosages (1mg/kg/day and 3mg/kg/day divided in 2 intakes) and 2 durations of treatment (3 or 6 months) were chosen.

The dose has been expressed in propranolol base in line with EU guidelines whereas the dose is expressed in propranolol hydrochloride in the SmPC of the already authorised medicinal products in Europe. In order to avoid the risk of confusion, clarifications have been added to the product information.

2.5.2. Main study

Study V00400SB201

A randomized, controlled, multidose, multicentre, adaptive phase II/III study in infants with proliferating infantile haemangioma requiring systemic therapy to compare 4 regimens of propranolol (1 or 3 mg/kg/day for 3 or 6 months) to placebo (double blind).

Methods

Study Participants

Inclusion criteria

A patient was considered eligible if he/she met all of the following criteria:

1. Written informed consent(s) for study participation and the use of the patient's images had been obtained according to national regulations from the Patient's parent(s) or guardian(s) prior to performing any study procedures,
2. The Patient was 35 to 150 days old, inclusive, at inclusion (D0),
3. A proliferating IH (target haemangioma) 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,
4. If required by national regulations, the Patient was registered with a social security or health insurance system and/or his/her parent(s) or legal guardian(s) was (were) registered with a social security or health insurance system.

Non-inclusion criteria

1. The Patient had a medically unstable health status that might interfere with his/her ability to complete the study,

2. The Patient presented with one or more of the following medical conditions: Congenital haemangioma; Kasabach-Merritt syndrome; bronchial asthma; bronchospasm; hypoglycaemia (< 40 mg/dl or at risk); untreated phaeochromocytoma; hypotension (< 50/30 mmHg); second or third degree heart block; cardiogenic shock; metabolic acidosis; bradycardia (< 80 bpm); severe peripheral arterial circulatory disturbances; Raynaud's phenomenon; sick sinus syndrome; uncontrolled heart failure or Prinzmetal's angina; documented PHACES syndrome with central nervous system involvement,

3. The Patient (and/or mother if she was breastfeeding the Patient) had received at least one of the following prohibited medications within the 14 days preceding randomization:

4. Anaesthetic agents, lidocaïne (the exclusion period was shortened to 48 hours, if anaesthesia had been performed for diagnosis investigation e.g. MRI…)

5. Cardiovascular treatments: anti-arrhythmic, calcium channel blockers, ACE inhibitors, inotropic agents, vasodilators (hydralazine hydrochloride…), clonidine…

6. Hypoglycaemic agents or drugs able to induce hypoglycaemia,

7. Inducers of hepatic drug metabolism or substrates or inhibitors of CYP2D6, CYP1A2,CYP2C19,

8. Anti-ulcer drugs (cimetidine, ranitidine, proton pump inhibitors other than omeprazole and lanzoprazole),

9. Metoclopramide, Non-steroid anti-inflammatory drugs (NSAIDs) at anti-inflammatory dose, Sympathomimetic agents and parenteral adrenaline, Benzodiazepines, Neuroleptic drugs (chlorpromazine, sultopride hydrochloride…), Other drugs: triptans, ergotamine, theophylline, warfarin, thyroxine, floctafenine,

10. The Patient had previously been administered at least one of the following prohibited medications: systemic (oral, intra-venous or intra-muscular), intra-lesional or topical corticosteroids, imiquimod, vincristine, alfa-interferon, propranolol or other beta-blockers,

11. The Patient had previously been treated for IH, including any surgical and/or medical procedures (e.g. laser therapy),

12. A systemic corticosteroid treatment was the most advisable therapy for the Patient in the opinion of the Investigator (for Czech Republic),

13. The Patient's mother had been breastfeeding the Patient while she was also being treated with beta-blockers (including propranolol) or, she had been breastfeeding the Patient within the 14 days preceding randomization while she was also being treated with systemic (oral, intra-venous or intra-muscular) corticosteroids, vincristine or Alfa interferon,

14. The Patient was known to have a hypersensitivity to propranolol and/or any other beta-blockers,

15. The Patient had previously experienced an anaphylactic reaction,

16. One or more of the following types of IH were present:

- Life-threatening IH,

- Function-threatening IH (e.g. those causing impairment of vision, or respiratory compromise caused by airway lesions),

- Ulcerated IH (whatever the localization) with pain and lack of response to simple wound care measures,

17. Diagnosis of the Patient's soft tissue tumor as IH was not clinically certain, particularly in the case of sub-dermal lesions,

18. The Patient was born prematurely and had not yet reached his/her term-equivalent age(e.g. an infant born 2 months prematurely cannot be included before the age of 2 months),

19. The Patient had a LVEF (left ventricular systolic function) ≤ 40% and/or cardiomyopathy and/or hereditary arrhythmia disorder,

20. The Patient was participating in another clinical study or lived in the same household as an infant already participating in this study,

21. The Patient's parent(s) or guardian(s) could not be contacted by telephone in case of emergency.

Treatments

Patients received in double-blind conditions study treatment with an oral solution of either:

- Propranolol 1 mg/kg/day 3 months (regimen 1)
- Propranolol 1 mg/kg/day 6 months (regimen 2),
- Propranolol 3 mg/kg/day 3 months (regimen 3)
- Propranolol 3 mg/kg/day 6 months (regimen 4)
- Placebo for 6 months

The treatment duration was 6 months (24 weeks): 3 months (12 weeks) of propranolol followed by 3 months (12 weeks) of placebo or 6 months of propranolol or placebo.

The 3 mg/kg/day dose (regimens 3 and 4) was titrated using 1 mg/kg/day increments during the first 3 weeks.

Consequently, to maintain the double-blind conditions on placebo and all propranolol arms throughout the treatment period, patients assigned to one of the two 3 months treatment duration regimens have received placebo for the last 3 months of treatment and dummy titration was used for patients assigned to placebo or a 1 mg/kg/day propranolol regimen.

Study treatment was administered to patients orally, twice daily (morning and late afternoon).

Objectives

The primary objectives of this study were to identify the appropriate dose and duration of propranolol treatment, and to demonstrate its superiority over placebo based on the complete/nearly complete resolution of the target IH at Week 24 (W24). The study had also a safety objective, to document the safety profile of the four regimens of propranolol in the treatment of IH in infants aged 1 to 5 months (35 to 150 days) at inclusion.

Outcomes/endpoints

Primary endpoint

The primary outcome assessed the evolution of target IH from baseline to W24 evaluated based on the intra-patient blinded centralized independent qualitative assessments (Type 1) of W24 photographs of the target IH compared to baseline. A treatment success was defined as a centralized assessment of complete/nearly complete resolution of the target IH at W24 compared to

baseline. 'Nearly complete resolution' was defined as: a minimal degree of telangiectasia, erythema, skin thickening, soft tissue swelling, and/or distortion of anatomic landmarks.

Due to the lack of guideline, the primary outcome was discussed and established following scientific advices/discussions with the regulatory agencies. Both qualitative and quantitative assessments are needed to correctly assess the effect of treatment. A centralized blinded evaluation of standardized photographs has been performed to ensure the robustness of this criterion. However, the assessment is not considered as fully blinded as readers known which photographs corresponded to baseline condition. The acquisition method procedure for photographs and the evaluation were extensively detailed in the protocol. The training of the photographer, the procedure of acquisition, the quality control check and the blinded assessment are considered to allow an independent and reproducible assessment of the primary outcome.

Secondary endpoint: success/failure (binary endpoint) based on the investigator onsite qualitative assessment of complete resolution of the target IH at W48, where a treatment success is defined as complete resolution of the target IH without sequelae or with minimal sequelae at W48. This (post-W24) endpoint is not analysed in the present report.

Other secondary endpoints:

Centralised assessments of the target IH:

1. Endpoints based on the independent blinded assessments of complete/nearly complete resolution (Type 1):

Success/failure at W12 compared to baseline, where treatment success was defined as for the primary efficacy endpoint

Time to first sustained complete/nearly complete resolution (W12, W24 compared to baseline)

2. Endpoints based on the independent blinded 3-point scale assessments of IH evolution (Type 2: improvement, stabilization or worsening 2):

Categorical endpoints for target IH evolution between paired patient-visits (W5, W8, W12, W16, W20 or W24 compared to baseline, W5, W8, W12, W16 or W20, respectively). A global improvement was also computed on the W5-W24 period (Yes/No).

Time to first sustained improvement (first improvement after which there is no worsening)

3. Endpoints based on centralized quantitative assessments:

Continuous and categorical endpoints (change in size and colour of target IH) at W12 and W24 compared to baseline

Investigator on-site qualitative assessments at each scheduled post-baseline visit compared to baseline:

- Categorical endpoints for complete/nearly complete resolution of target IH,

  Nearly complete resolution was defined as a minimal degree of telangiectasia, erythema, skin thickening, soft tissue swelling or 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 telangiectasia, macular discolouration 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
- Time to first sustained complete resolution without sequelae or with minimal sequelae

Investigator on-site qualitative assessments of paired consecutive patient-visits:

- Categorical endpoints for target IH evolution (3-point scale: improvement, stabilization, worsening)
- Time to first sustained improvement (first improvement after which there is no worsening)

Parent(s) or guardian(s) on-site qualitative assessments at each scheduled post-baseline visit compared to the previous scheduled visit

- Categorical endpoints for target IH evolution (3-point scale: improvement, stabilization, worsening)
- Time to first sustained improvement (first improvement after which there is no worsening)

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 nontarget facial IH and non-facial IH at each scheduled post-baseline visit (3-point scale: no sequelae; minimal sequelae; marked sequelae)
- Categorical endpoints based on whether or not invasive procedures were carried out during the study on the target/non-target facial/non-facial IH.

Sample size

The appropriate sample size has been calculated to achieve adequate power (>90%) for an overall one-sided type I error rate of α=0.005 to test for superiority of the selected regimen(s) of propranolol versus placebo under the different scenarios investigated.

Randomisation

Randomisation was managed by an independent randomization team and centralized via an IVRS. Stratified block randomization in a 2:1 ratio (each propranolol regimen: placebo) was used in both stages of the study.

Blinding (masking)

A number of measures were taken to maintain the blinding in the double-blind study:

The placebo oral solution and the active solutions were identical in terms of colour, viscosity, odour and volume to be administered. The investigator in charge of the clinical assessment of haemangioma was not involved in the electrocardiogram (ECG) assessment during the study treatment period, since bradycardia is an easy observable effect of beta-blockers. ECG data were maintained blinded. For the primary criterion assessment, pairs of photographs per patient were centrally assessed by two independent readers who were blinded to the treatment arms.

The interim analysis was conducted by an Independent Statistician and reviewed by the Independent Data Monitoring Committee.

Statistical methods

Interim analysis

In order 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, an interim analysis was carried out at the end of Stage 1 after the first 40:20 (propranolol: placebo) patients per treatment arm had completed their visit W24 or been prematurely withdrawn from the study treatment. This analysis was performed by an independent statistician and reviewed by an independent data monitoring committee to avoid unblinding of the study personnel (investigational sites, Sponsor and Sub-contractor project team). Efficacy was evaluated based on intra-patient blinded centralized independent qualitative assessments of the target IH photographs.

Primary analysis

The analysis of all data of the study until W24/EOT referred as the primary analysis was carried out after all patients randomized in the study had completed their visit W24 or been prematurely withdrawn from the study treatment. A one-sided significance level of 0.005 was chosen for this single pivotal phase III study. The p-values from the first and second stages of the study were combined using the weighted inverse normal combination function. Simes' method was used to define an adjusted first stage p-value ensuring the type I error rate control.

The primary efficacy analysis data set was the *intention-to-treat (ITT) data set*: all randomized patients in Stage 1 and all the patients in Stage 2 randomized to placebo or the selected regimen of propranolol and having received at least one dose of study therapy (or in the case of uncertainty). The wording "or in the case of uncertainty" need to be clarified. This is the primary efficacy analysis data set.

Results

Participant flow

A total of 460 patients were randomized to treatment, of whom 456 received at least one dose of study treatment. The first 190 randomized patients having either completed the 24-week study

treatment period or been prematurely withdrawn from study treatment entered the Stage 1 of the study, of whom 188 were treated.

The number of patients lost to follow-up is low (11/460) and similar in the 5 treatments arms. However, early treatment discontinuations were frequent (29.8%) and unbalanced with 36 of 55 patients (65.5%) in the placebo arm and 14 of 102 patients (13.7%) in the propranolol 3mg/kg/day 6 months arm. The main reason (22.4%) was due to treatment inefficacy judged by the investigator (defined as a “worse state compared to the previous visit”), followed by parental decision (8.5%); safety reason only represented 1.7% of cases. The rate of treatment inefficacy was particularly high, 58.2%, in the placebo arm in which treatment discontinuation occurred since the first weeks of treatments. In the 2 regimens 3 months of propranolol followed by 3 months of placebo, the same observation can be made with a rate of discontinuation for inefficacy of 30.3% in the 1mg/kg/day arm and 24.8% in the 3 mg/kg/day arm. A change in KM curve was also observed after 90 days, the rate of discontinuations increasing when infants were switched to placebo.

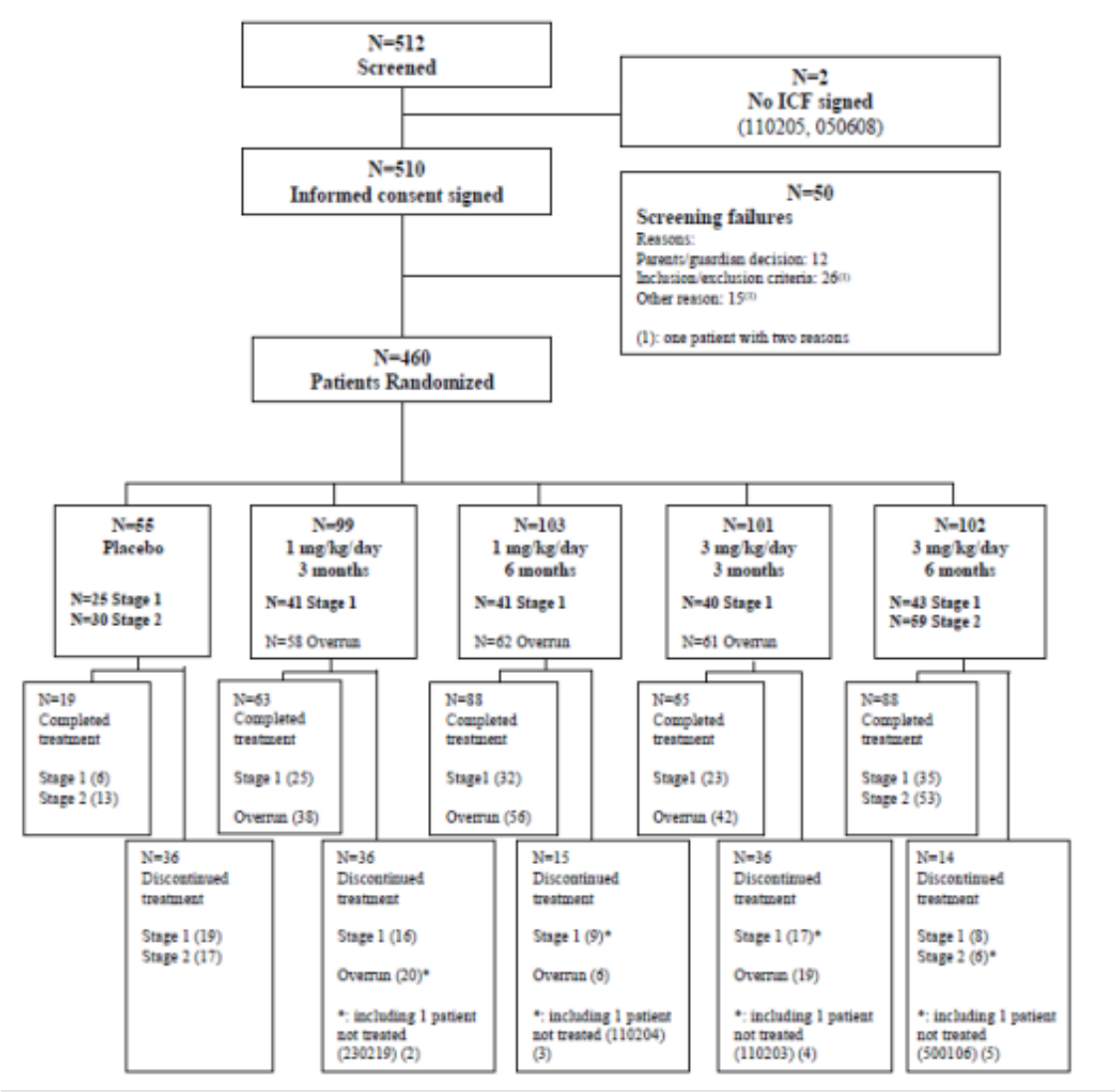


Figure 2: Disposition of patients - All patients

Recruitment

The first patient was enrolled 24th February 2010 and the last completed visit (W24) date was 8th May 2012.

Conduct of the study

The study was conducted in 56 recruiting (i.e. having screened at least one patient) investigating centres from 16 countries (Australia, Canada, Czech Republic, France, Germany, Hungary, Italy, Lithuania, Mexico, New Zealand, Peru, Poland, Romania, Russian Federation, Spain and the United States of America [USA]). The original protocol was dated 25th June 2009.

There were 18 study amendments. Eight protocols and six amendments (excluding a local amendment) were introduced. Versions 4 to 7 were used during the recruitment period, and the 8th protocol version (dated 19 March 2012) was circulated even after the end of the inclusion (since the

first enrolment date was February 24, 2010 and the last W24 visit completed date was May 8, 2012). The primary W24 analysis database was unlocked twice.

Baseline data

Table 8: Demographic characteristics - Safety data set

Characteristics	Placebo (N = 55)	V0400SB 1mg/kg/day 3mths (N = 98)	V0400SB 1mg/kg/day 6mths (N = 102)	V0400SB 3mg/kg/day 3mths (N = 100)	V0400SB 3mg/kg/day 6mths (N = 101)	Total (N = 456)
Gender						
N/Missing	55/0	98/0	102/0	100/0	101/0	456/0
Male	17 (30.9%)	30 (30.6%)	32 (31.4%)	21 (21.0%)	31 (30.7%)	131 (28.7%)
Female	38 (69.1%)	68 (69.4%)	70 (68.6%)	79 (79.0%)	70 (69.3%)	325 (71.3%)
Age at randomisation						
N/Missing	55/0	98/0	102/0	100/0	101/0	456/0
Mean (SD)	103.91 (31.06)	103.58 (33.07)	102.65 (30.12)	107.53 (30.14)	101.63 (31.00)	103.85 (31.02)
Q1 Q2 Q3	78.00 108.00 135.00	75.00 102.00 136.00	78.00 98.50 133.00	84.00 107.50 135.50	78.00 102.00 130.00	79.00 103.00 134.00
min max	37 151	37 150	42 149	49 150	35 152	35 152
Age group at randomisation						
N/Missing	55/0	98/0	102/0	100/0	101/0	456/0
35 - 90 days	20 (36.4%)	36 (36.7%)	38 (37.3%)	36 (36.0%)	37 (36.6%)	167 (36.6%)
> 90 days	35 (63.6%)	62 (63.3%)	64 (62.7%)	64 (64.0%)	64 (63.4%)	289 (63.4%)
Age at baseline						
N/Missing	55/0	98/0	102/0	100/0	101/0	456/0
Mean (SD)	103.93 (31.04)	103.70 (33.20)	102.72 (30.24)	107.54 (30.13)	101.66 (30.95)	103.90 (31.06)
Q1 Q2 Q3	78.00 108.00 135.00	75.00 102.00 137.00	78.00 98.50 133.00	84.00 107.50 135.50	78.00 102.00 130.00	79.00 103.00 134.00
min max	37 151	37 154	42 156	49 150	35 152	35 156
Age group at baseline						
N/Missing	55/0	98/0	102/0	100/0	101/0	456/0
35 - 90 days	20 (36.4%)	36 (36.7%)	38 (37.3%)	36 (36.0%)	37 (36.6%)	167 (36.6%)
> 90 days	35 (63.6%)	62 (63.3%)	64 (62.7%)	64 (64.0%)	64 (63.4%)	289 (63.4%)
Patient born prematurely						
N/Missing	55/0	97/1	102/0	100/0	101/0	455/1
Yes, more than 2 months premature	3 (5.5%)	1 (1.0%)	2 (2.0%)	2 (2.0%)	4 (4.0%)	12 (2.6%)
Yes, 1 to 2 months premature	6 (10.9%)	12 (12.4%)	9 (8.8%)	11 (11.0%)	9 (8.9%)	47 (10.3%)
Yes, 0 to 1 month premature	10 (18.2%)	8 (8.2%)	17 (16.7%)	17 (17.0%)	11 (10.9%)	63 (13.8%)
No	36 (65.5%)	76 (78.4%)	74 (72.5%)	70 (70.0%)	77 (76.2%)	333 (73.2%)
Weight at birth (kg)						
N/Missing	55/0	98/0	101/1	100/0	100/1	454/2
Mean (SD)	2.93 (0.79)	3.02 (0.68)	3.02 (0.77)	2.97 (0.73)	3.06 (0.77)	3.01 (0.74)
Q1 Q2 Q3	2.49 3.08 3.45	2.61 3.14 3.55	2.55 3.12 3.56	2.66 3.10 3.50	2.69 3.16 3.57	2.60 3.14 3.51
min max	0.89 4.39	0.70 4.29	0.80 4.74	0.75 4.63	0.71 5.38	0.70 5.38

Continent						
N/Missing	55/0	98/0	102/0	100/0	101/0	456/0
USA-Canada	8 (14.5%)	18 (18.4%)	19 (18.6%)	14 (14.0%)	12 (11.9%)	71 (15.6%)
Other America	1 (1.8%)	7 (7.1%)	9 (8.8%)	11 (11.0%)	12 (11.9%)	40 (8.8%)
Western Europe	35 (63.6%)	51 (52.0%)	41 (40.2%)	56 (56.0%)	52 (51.5%)	235 (51.5%)
Other Europe	10 (18.2%)	17 (17.3%)	18 (17.6%)	13 (13.0%)	15 (14.9%)	73 (16.0%)
Oceania	1 (1.8%)	5 (5.1%)	15 (14.7%)	6 (6.0%)	10 (9.9%)	37 (8.1%)

Numbers analysed

The primary efficacy analysis ITT data set (all patients randomized in Stage 1 and all patients in Stage 2 in the selected regimens without overrun) comprised 55 patients in the placebo 6 months regimen and 101 patients in the 3 mg/kg/day 6 months regimen and is presented in Table 9.

Table 9: Number of patients in key data sets analysed - randomized patients

	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)
Randomized	55	99	103	101	102	460
W24 completers	19	63	88	65	88	323
Safety (all patients treated = ITT with overrun)	55	98	102	100	101	456
Efficacy Stage 1+Stage 2-without overrun (primary W24 analysis)						
Intent-to-treat (ITT)	**55***	41	40	39	**101***	276
Per-protocol (PP)	53	38	38	37	93	259
Stage 1 (IDMC analysis)						
ITT Stage 1	25	41	40	39	43	188
Stage 2						
Overrun treated patients	0	57	62	61	0	180

Source: Section 5.3.5.1, Study V00400 SB 2 01, Figure 6 and Table 11.
IDMC: independent data monitoring committee; ITT: intent-to-treat; PP: per-protocol.
** Note that these two arms were the only arms compared together for the primary efficacy analysis.*

Outcomes and estimation

Interim analysis

One hundred and ninety patients were randomized into Stage 1 of the study. The interim analysis was conducted on the 188 ITT Stage 1 treated patients. Results are summarised in **Table 10**.

Table 10: Interim analysis results: complete or nearly complete resolution at week 24, central reading - ITT data set-Stage 1

	Placebo (N 25)	V0400SB 1 mg/kg/day 3mths (N = 41)		V0400SB 1 mg/kg/day 6mths (N = 40)		V0400SB 3 mg/kg/day 3mths (N = 39)		V0400SB 3 mg/kg/day 6mths (N = 43)	
Primary endpoint: Complete or nearly complete resolution of target IH at week 24									
			Pvalue *vs.* placebo		Pvalue *vs.* placebo		Pvalue *vs.* placebo		Pvalue *vs.* placebo
n/missing	25 / 0	41 / 0		40 / 0		39 / 0		43 / 0	
Yes	2 (8.0%)	4 (9.8%)	0.4049	15 (37.5%)	0.0042	3 (7.7%)	0.5178	27 (62.8%)	<.0001
No	23 (92.0%)	37 (90.2%)		25 (62.5%)		36 (92.3%)		16 (37.2%)	
Source: Section 5.3.5.1 Study V00400 SB 2 01, Table 17.									

The interim analysis conducted to choose the best regimen of propranolol (dosage and duration) for the treatment of proliferating IH, showed that the primary outcome, "complete or nearly complete resolution", was obtained in less than 10% of patients for the placebo, the 1 mg/kg/day 3 months and the 3 mg/kg/day 3 months regimens. It was 37.5% in the 1 mg/kg/day 6 months regimen. The best results were obtained in the 3 mg/kg/day 6 months regimen with 62.8% of patients reaching the outcome. Thus, this regimen was recommended by the IDMC.

Primary efficacy analysis (W24)

The results of the primary analysis, complete or nearly complete resolution of target IH at week 24, are presented in Table 11.

Table 11: Primary analysis results: Complete or nearly complete resolution at week 24, central reading - ITT data set

	Placebo (N = 55)	V0400SB 3 mg/kg/day 6mths (N = 101)	Pvalue
Primary endpoint: Complete or nearly complete resolution of target IH at week 24			
Stage 1			
n/missing	25 / 0	43 / 0	<.0001
Yes	2 (8.0%)	27 (62.8%)	
No	23 (92.0%)	16 (37.2%)	
Stage 2			
n/missing	30 / 0	58 / 0	<.0001
Yes	0 (0.0%)	34 (58.6%)	
No	30 (100%)	24 (41.4%)	
Overall/combined			
n/missing	55 / 0	101 / 0	<.0001
Yes	2 (3.6%)	61 (60.4%)	
No	53 (96.4%)	40 (39.6%)	

The primary endpoint, "complete or nearly complete resolution of IH at week 24", showed a statistical significant difference in favour of the 3 mg/kg/day 6 months compared to placebo. The combined p-value (<0.0001) showed that the difference was statistically significant at the 0.005 level. An important difference was observed in the response to treatment between propranolol and placebo: 60.4% versus 3.6%. Moreover, results were concordant between the two stages of the study. Propranolol demonstrated a significant clinical efficacy of treatment on proliferating IH in the

included population. When results were adjusted by age, localisation or randomisation, they were similar in each category.

The photographs were assessed by two readers (three readers until September 2011), discrepancies between their assessment were observed for 50 cases at W24. Of them, 28 were finally considered as complete/nearly completed resolution and 22 as failure. A significant number of patients received propranolol after they experienced a premature end of study treatment which was mainly related to treatment lack of efficacy. After EOT, the exposure to propranolol was particularly significant in the placebo arm (45.5% exposure, vs 30.6% and 10.9% in the other arms). The protocol planned that these patients were considered as “failure” in ITT data set considered for the statistical analysis for the primary outcome. Thus, the result of the centralised qualitative assessment of these patients was arbitrarily considered “negative” without any real assessment and did not take into account the possibility of spontaneous IH resolution (seen in 2 patients from a total of 24 whom remained in the placebo arm until W24).

Of the patients who discontinued treatment prematurely, follow-up up to W24 was completed for 14/36 patients in the placebo group, these 14 patients received at least one IH treatment between early discontinuation and W24. In the propranolol 3 mg/kg/day group, of the patients who discontinued treatment prematurely, follow-up up to W24 was completed for 8/14 patients, with 5/8 received at least one treatment for IH between early discontinuation and W24.

Other secondary outcomes

Table 12: Secondary Efficacy Endpoints for the Primary Analysis - ITT data set

Secondary Efficacy Endpoints	Placebo (N = 55)	V0400SB 3 mg/kg/day 6mths (N = 101)	
Centralized quantitative assessments			
Change in surface area at W24 compared to baseline (cm^2)			p-value
Mean (SD)	0.464 (1.804)	-1.207 (2.439)	0.0093
Change in maximal diameter at W24 compared to baseline (cm)			
Mean, SD	-0.028 (0.743)	-0.179 (0.731)	0.4127
Change in color at W24 compared to baseline (dE*2000)			
Mean, SD	-0.054 (4.824)	-7.369 (7.430)	<.0001
Centralized qualitative assessment			
Sustained improvement at W5			
KM rate*	5.4%	72.7%	
Sustained improvement at W24			
KM rate*	9.0%	79.5%	<.0001†
Investigator's on site assessment			
Complete or nearly complete resolution of target IH at W24 compared to baseline			
Yes	10.5%	26.7%	0.4419
Sustained improvement at W5			
KM rate*	20.1%	70.9%	
Sustained improvement at W24			
KM rate*	32.4%	82.5%	<.0001‡
Parents' on site assessment			
Sustained improvement at W5			
KM rate*	19.9%	67.4%	
Sustained improvement at W24			
KM rate*	45.0%	85.6%	<.0001‡

Source: Section 5.3.5.1, Study V00400 SB 2 01, Synopsis.

** KM rate = Kaplan-Meier cumulative incidence estimate*

† calculated on time to first sustained improvement assessed at D0, W5, W8, W12, W16, W20, W24

.‡ calculated on time to first sustained improvement assessed at D0, D7, D14, D21, W5, W8, W12, W16, W20, W24.

Evolution of IH over time

In the placebo arm, improvement was seldom observed and about 11% worsening was observed at the two first comparisons (W5 versus baseline and W8 versus W5). The evolution was clearly different in the 3 mg/kg/day 6 months group, with early improvement in a vast majority of the patients.

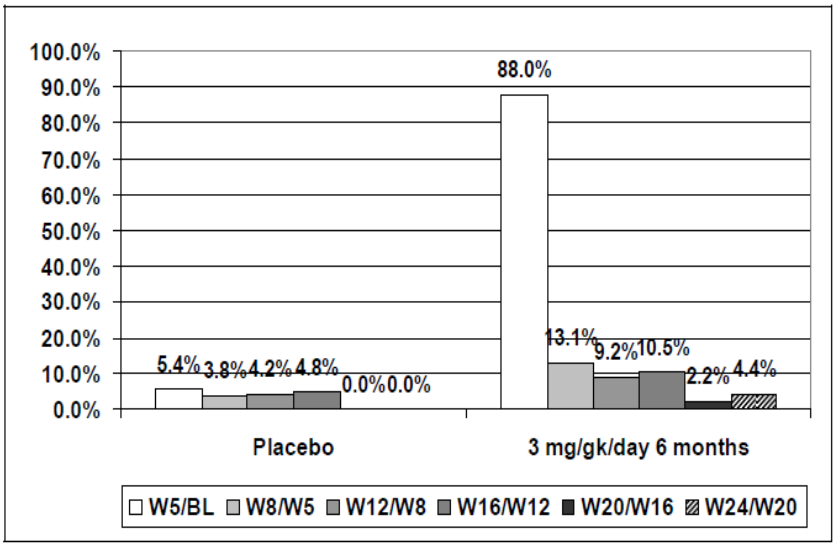


Figure 3: 3-point evolution of IH over time – Proportion of improvement – ITT data set

Investigator's on site qualitative assessment

IH complete/nearly complete resolution at each visit

An important discrepancy was observed between the centralised and the investigators assessment for the outcome "complete/near complete response between baseline and W24". According to the centralised reading, the response rate was 3.6% in the placebo arm vs 60.4% in the 3 mg/kg/day 6 months arm, whereas when considering the investigator judgement they were respectively 10.5% and 26.7%. The applicant considers such differences were justified by the fact that the investigators' assessment of the same criterion was 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 based on a direct visual examination of the patient at W24 with the W0 pictures and medial data available at the investigator site.

Table 13: Consistency between centralised and investigator assessments of complete/nearly complete resolution

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

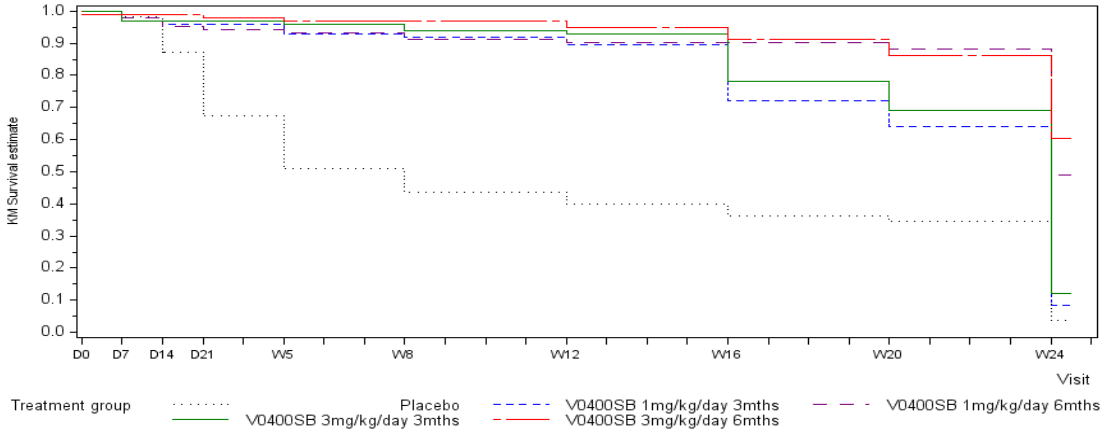
According to the applicant, the difference between the centralised assessment and the investigator onsite assessment can be explained by the missing data that are handled differently. So a new analysis performed on the investigators' assessment transformed into binary outcome and using the same statistical methods as the primary analysis is provided (a difference was observed in favour of the 3 mg/kg/day arm but the percentage of patients with complete/nearly complete

resolution of IH 22.8% was still lower than for the centralised assessment 60.4%). However to be convincing, different analyses handling missing data under various assumptions should have been provided. Furthermore, discrepancies were observed even between centralised readers.

Ancillary analyses

Sustainability of Treatment Effect and Regrowth

In relation to persistence of efficacy, overall, the earliest treatment failures were seen in the placebo 6 months regimen and passing 50% treatment failure by Week 5. This was followed by the 3-month propranolol treatment regimens, with the first notable increase in treatment failures at Week 16 (after the transfer to placebo for 3 months, at Week 12). The lowest proportion of treatment failures were seen in the 6 month propranolol treatment regimens, less than 10% of patients in the 3 mg/kg/day 6 months regimen had failed treatment by Week 16, just over 10% by Week 20, and approximately 40% had failed treatment by Week 24.



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

Figure 4: Survival curves for time to failure (ITT with overrun)

Table 14: Time to treatment failure (ITT with overrun)

	Placebo n=55 N n (KM rate)*	V0400SB 1mg/kg/day 3mths n=98 N n (KM rate)*	V0400SB 1mg/kg/day 6mths n=102 N n (KM rate)*	V0400SB 3mg/kg/day 3mths n=100 N n (KM rate)*	V0400SB 3mg/kg/day 6mths n=101 N n (KM rate)*
Time to failure					
Day 0 (Baseline)	55 0 (100.0%)	98 1 (99.0%)	102 0 (100.0%)	100 0 (100.0%)	101 1 (99.0%)
Day 7	55 1 (98.2%)	97 4 (95.9%)	102 2 (98.0%)	100 3 (97.0%)	100 1 (99.0%)
Day 14	54 7 (87.3%)	94 5 (94.9%)	100 5 (95.1%)	97 3 (97.0%)	100 1 (99.0%)
Day 21	48 18 (67.3%)	93 5 (94.9%)	97 6 (94.1%)	97 3 (97.0%)	100 2 (98.0%)
Week 5	37 27 (50.9%)	93 8 (91.8%)	96 7 (93.1%)	97 4 (96.0%)	99 3 (97.0%)
Week 8	28 31 (43.6%)	90 9 (90.8%)	95 9 (91.2%)	96 6 (94.0%)	98 3 (97.0%)
Week 12	24 33 (40.0%)	89 11 (88.8%)	93 10 (90.2%)	94 7 (93.0%)	98 5 (95.0%)
Week 16	22 35 (36.4%)	87 28 (71.4%)	92 10 (90.2%)	93 22 (78.0%)	96 9 (91.1%)
Week 20	20 36 (34.5%)	70 36 (63.3%)	92 12 (88.2%)	78 31 (69.0%)	92 14 (86.1%)
Week 24	19 53 (3.6%)	62 90 (8.2%)	90 52 (49.0%)	69 88 (12.0%)	87 40 (60.4%)

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

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

On the further 72 weeks open label period of the pivotal study that is still ongoing, complete or nearly complete resolution criterion used for the demonstration of efficacy during the double-blind part of the study is still maintained at Week 48 in 54.2% of patients having been treated with propranolol 1 mg/kg./day for 6 months and 59.8% of patients having been treated with propranolol 3 mg/kg./day for 6 months. , only about 11% of patients of the 3 mg/kg/day 6 months regimen required the re-introduction of a systemic treatment.

Table 15: Patients IH response after week 24, initial treatment regimen - Patients having completed the initial 24-week 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	
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

Table 16: Patients receiving further systemic treatment after week 24, by initial treatment regimen - Patients having completed the initial 24-week 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

Isolated cases of regrowth of IH have been reported in the literature, after definitive discontinuation of propranolol treatment following an initial successful response. Based on the submitted data (pivotal Study 201, CUP and publications), the risk of IH regrowth after the end of treatment does not seem negligible (around 14%). In the pivotal trial, among the patients who have completed the 24 week period (n=323), 25 patients have been retreated by propranolol or other beta-blocker. Several hypotheses have been put forward: the duration of treatment, the age at initiation and/or at the end of treatment, the size or the morphology of the haemangioma, but currently no formal conclusions can be raised.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 17: Summary of Efficacy for trial V00400 SB 201

Title: A randomized, controlled, multidose, multicentre, adaptive phase II/III study in infants with proliferating infantile haemangioma requiring systemic therapy to compare four regimens of propranolol (1 or 3 mg/kg/day for 3 or 6 months) to placebo (double blind)			
Study identifier	V00400 SB 201		
Design	Phase II/III, randomised, double-blinded, placebo-controlled, adaptive two stage design		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks not applicable 72 weeks
Hypothesis	Superiority		
Treatments groups	Placebo		Placebo bid. 6 months, n=55
	V0400SB 1mg/kg/day 3mths		Propranolol 1mg/kg bid 3 months + placebo bid 3 months, n=41
	V0400SB 1mg/kg/day 6mths		Propranolol 1mg/kg bid 6 months, n=40
	V0400SB 3mg/kg/day 3mths		Propranolol 3mg/kg bid 3 months + placebo bid 3 months, n=39
	V0400SB 3mg/kg/day 6mths		Propranolol 3mg/kg bid 6 months, n=101
Endpoints and definitions	Primary endpoint	Complete or nearly complete resolution at week 24	Central reading of photographs by two independent trained readers
	Secondary endpoint	Success/failure at W48	Investigator on-site assessment of complete resolution of target IH / Not available
	Secondary other: endpoint	Surface area W24	Change in surface area at W24 compared to baseline (cm^2) Centralised quantitative assessment
		Maximal diameter W24	Change in maximal diameter at W24 compared to baseline (cm) Centralised quantitative assessment
		Change colour W24	Change in colour at W24 compared to baseline (dE*2000) Centralised quantitative assessment
		Sustained improvement at W24	Centralised qualitative assessment
		Complete or nearly complete resolution at week 24	Investigator's on site assessment
		Sustained improvement at W24	Investigator's on site assessment
		Sustained improvement at W24	Parents' on site assessment
Database lock	28 September 2012		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	**Placebo**	**3 mg/kg/day 6 months**
	Number of subject	55	101
	Complete or nearly complete resolution at week 24 centralised / Yes (%)	**2 (3.6%)**	**61 (60.4%)**
	P-value	**0.0001**	
	Change in surface area at W24 compared to baseline (cm^2) Mean (SD)	0.464 (1.804)	-1.207 (2.439)
	P-value	0.0093	
	Change in maximal diameter at W24 compared to baseline (cm) Mean (SD)	-0.028 (0.743)	-0.179 (0.731)
	P-value	0.4127	
	Change in color at W24 compared to baseline (dE*2000) Mean (SD)	-0.054 (4.824)	-7.369 (7.430)
	P-value	<.0001	
	Complete or nearly complete resolution at W24 investigators Yes (%)	2 (10.5%)	24 (26.7%)
	P-value	0.4419	
	Sustained improvement at W24 centralised / KM rate	9.0%	79.5%
	P-value	<0.001	
	Sustained improvement at W24 investigator / KM rate	32.4%	82.5%
	P-value	<0.001	
	Sustained improvement at W24 parent / KM rate	45.0%	85.6%
	P-value	<0.001	

Supportive studies

Study V00400SB102: A Phase I multicentre, open-label, repeated-dose, pharmacokinetic study of propranolol in infants treated for proliferating infantile haemangioma (IHs) requiring systemic therapy.

There was a higher proportion of female patients than male in both groups (17/23 [73.9%] overall were female). The patients were stratified into treatment groups by age and, as a result, the mean age for patients in Group 1 was 69.7 days (ranging from 50 to 89 days) and in Group 2 was 128.2 days (ranging from 91 to 152 days). Mean weight, height, and head circumference were similarly

higher in Group 2 than Group 1. At baseline there were no major IH complications and no cardiac complications. Resolution of the target IH was seen as early as Day 28 and by Day 84, 36.4% of patients (8/22) had resolution of their target IH. In addition, complications of IH disappeared over time, confirming the regression of the IH.

Compassionate use program: the CUP conducted in France has included 922 patients, between 13 Apr 2010 and 12 April 2013. The objective was not to assess the efficacy of propranolol oral solution. The recruited population included more severe patients than the main clinical study 201. The dose and the titration phase are similar than in this study but the treatment duration is not limited to 6 months (mean duration = 7.1 months, calculated based on 313 patients who discontinued treatment). The mean age at inclusion, i.e. 5.7 months, was also higher than in the clinical study (around 3.5 months), which a very important range from 1 days to 6.2 years. "Efficacy" data have been provided for 313 patients (34%) for whom the main reason for discontinuation (83.7 %) is a good efficacy. Among the 262 patients who stopped treatment for good efficacy, a reintroduction has been necessary for 4 patients more than 2 months after discontinuation, one of them needing a second reintroduction. Among the 262 patients who stopped treatment for good efficacy 154 were reported as complete/almost complete recovered.

Literature review: The demonstration of clinical efficacy of propranolol in the treatment of proliferating IH requiring systemic treatment for severe cases (life- and function-threatening, severe ulcerated) is based on this literature review.

A literature review has been performed of all articles published in this field since the first discovery of the efficacy of propranolol for the treatment of IH by Leauté-Labrèze in 2008. Seventy one (71) key publications (studies and cases reported) have been selected to present a critical analysis of the efficacy of oral propranolol in cases of IH requiring systemic therapy. It represented 364 patients. This literature review has provided data of propranolol efficacy in treating high-risk IH, focusing on ulcerated IH, ocular IH, airway IH, hepatic IH and PHACES:

- Ocular IH: 3 prospective interventional studies (n=22 patients with ocular IH treated with propranolol), 17 case series (n=127), 6 individual case reports (n=6).

- Ulcerated IH: 3 prospective interventional studies (n=12 patients with ulcerated IH treated with propranolol), 7 case series, including 4 case series that only evaluated ulcerated IH and 3 case series that included ulcerated IH as part of a wider IH population (n=71 patients with ulcerated IH treated with propranolol), 4 individual case reports.

- Airway IH: 2 multicentre retrospective studies (n=19 patients with airway IH treated with propranolol), 10 case series (n=34 patients with airway IH treated with propranolol), 11 individual case reports.

- Hepatic IH: 2 case series (n=11 patients with hepatic IH treated with propranolol) and 9 individual case reports.

- PHACES: 4 case series (n=36 patients with PHACES treated with propranolol) and 1 individual case report.

2.5.3. Discussion on clinical efficacy

The current application is based on one pivotal clinical trial (study 201), one supportive PK trial (study 102), data from a compassionate use program and publications.

The applicant selected 3 mg/kg/day for the main efficacy studies based on the long experience in treatment for cardiological indications in children of the dose range 1-4 mg/kg/day with a well-known efficacy and safety profile. The applicant has also followed the advice of the FDA and EMA to study different doses (1 mg/kg/day and 3 mg/kg/day) and treatment duration (3 months and 6 months). Propranolol was administered always around meal time to avoid hypoglycaemia.

Design and conduct of clinical studies

The *pivotal Study 201* was a randomized, double-blind, controlled, multidose, multicentre, adaptive phase II/III study in infants with proliferating infantile haemangioma (IHs) requiring systemic therapy to compare 4 regimens of propranolol (1 or 3 mg/kg/day for 3 or 6 months) to placebo.

Treatments were adequate and the regimens used were in compliance with FDA and EMA advice.

Due to the adaptive design, the study was divided into two phases with an interim analysis conducted by an IDMC to select the dose to be pursued in the second phase. The rationale for the choice of one (3 mg/kg/day 6 months) of the two groups treated with propranolol was not clearly defined.

The primary endpoint assessed the evolution of the target IH from baseline to week 24, based of intra-patient blinded photographs judged by two independent readers. The chosen outcome was *complete/nearly complete resolution of the target IH at W24 compared to baseline.*

Moreover, a training of the photographers and detailed procedure for the acquisition, the quality control and the assessment have been elaborated to sustain the robustness and the reproducibility of the evaluation of this endpoint. The blinded assessment is particularly important in this target disease, due to the early claimed effect of propranolol on aspect and morphology of IH during the first hours of treatment and the fact that haemangioma can spontaneously reverse. However, considering that readers knew which photograph of the pairs was taken at baseline, the assessment was not fully blinded.

The secondary endpoint defined in the protocol was *success/failure* based on the investigator qualitative assessment on complete resolution at W48, this analyse was not submitted in the current application. A large number of other secondary endpoints were assessed by three ways: centralised assessment, investigator's on-site assessment and parental assessment.

The phase I *Study 102was submitted as a supportive study. It is a* multicentre, open-label, repeated-dose, pharmacokinetic study of propranolol in 23 infants treated for proliferating IHs requiring systemic therapy only studied the efficacy of propranolol has a secondary endpoint. Patients were treated in absence of comparator/placebo. No centralised assessment of efficacy endpoints was performed.

Efficacy data and additional analyses

Pivotal study 201

All baseline characteristics were well-balanced between both treatment groups.

For the primary efficacy endpoint in the 6-month regimen, the difference in response rate between Hemangiol and placebo was highly clinically and statistically significant. The efficacy results seem similar by age group and haemangioma localisation.

A significant number of patients received propranolol after they experienced a premature end of study treatment mainly related to lack of efficacy. After EOT, the exposure to propranolol was particularly significant in the placebo arm (45.5% exposure, vs 30.6% and 10.9% in the other arms). The protocol planned that these patients were considered as "failure" in ITT data set considered for the statistical analysis for the primary outcome. Thus, the result of the centralised qualitative assessment of these patients was arbitrarily considered "negative" without any real assessment and did not take into account the possibility of spontaneous IH resolution (seen in 2 patients from a total of 24 whom remained in the placebo arm until W24). The new analysis submitted by the Applicant, excluding all premature discontinuations, even if the results were in line with the primary analysis, is not sufficient to explore the impact of premature discontinuations. Thus, based on the overall data, it cannot be ruled out that the difference on efficacy observed in favour of propranolol 3mg/kg/day arm has been overestimated taking into account that the spontaneous resolution of the IH cannot be assessed.

A large number of secondary efficacy endpoints have been assessed by central reading, by investigators and by parents, they were globally in favour of propranolol efficacy for the treatment of IH.

Regarding the criterion of "complete or nearly complete resolution of target IH" an important discrepancy has been observed between central and investigator onsite assessment (consistent in 115 of 156 cases only). However, in view of the consistent result across efficacy endpoints this did not raise concerns.

Moreover in this pivotal trial, a low number of regrowth of IH was observed in the overall population. In the CUP, 4 cases of retreatment with propranolol have been documented. Based on study results and on publications (14% of patients with regrowth), the risk of IH regrowth after the end of treatment does not seem negligible. Several hypotheses have been put forward: the duration of treatment, the age at initiation and/or at the end of treatment, the size or the morphology of the haemangioma, but currently no formal conclusions can be made.

PK study 102 was submitted to further support the efficacy data. Some limitations have been identified to properly demonstrate the efficacy of propranolol in the target indication. A limited number of patients (n=23) were included; however the characteristic of patients were in line with those of the main clinical study, with the exception that more severe patients can be treated. The efficacy results of study 102 are considered supportive an in line with the efficacy results of the pivotal study.

Results in high risk patients from the *compassionate use program* were in line with those observed in the pivotal trial and supported the efficacy of propranolol in the treatment of high risk IH.

The *literature review* submitted by the applicant also supports the efficacy of propranolol in the target population. .

2.5.4. Conclusions on the clinical efficacy

The Applicant has investigated twice daily dosing of propranolol administered at daily doses of 1 and 3 mg/kg for up to 3 or 6 months in study V00400 SB 2 01. The results from this study provide evidence of efficacy for the dose of 3 mg/kg/day for 6 months. The target population has been redefined and the Applicant had performed further analysis of available data to sustain the extrapolation of the pivotal study results to the high risk patients.

2.6. Clinical safety

The primary safety analysis encompasses pooled data from the following two clinical studies, in the target population of infants with proliferating IHs requiring systemic therapy:

– Study 102, an open-label, repeated-dose study to determine the steady-state PK of propranolol in 23 infants.

– Study 201, a pivotal, adaptive Phase II/III, randomized, placebo-controlled clinical trial with four regimens of propranolol (final dose of 1 and 3 mg/kg/day, each for 3 or 6 months, following uptitration). In total, 456 received at least one dose of study treatment (401/propranolol and 55/placebo).

Additional safety analyses presented in this submission encompass data from the following sources:

– Study 301, an ongoing multicentre, open-label study of propranolol in infants with proliferating IH requiring systemic therapy, who had participated in Studies 102 or 201. At the cut-off date of 31 Dec 2012, 11 patients have been enrolled and 1 SAE has been notified.

– A compassionate use program (CUP) on-going in France and Switzerland. A total of 660 patients have been treated.

– Studies and individual case reports of patients with IH treated with oral propranolol presented in the scientific literature. For the evaluation of safety, a total of 1367 patients from 60 publications were considered.

However, the clinical safety dataset does not include the data from the follow-up phase of study 201 until week 96 and from the study 301, these data should be provided when available.

Patient exposure

The clinical studies 102 and 201 performed in infant patients were pooled in the global V00400SB safety database for the purpose of this submission. Overall, 479 patients in the pooled safety population were exposed to study drug (V0400SB or placebo): 23 patients in study 102 and 456 in study 201.

Table 18: Actual Exposure to Study Drug, Including Uptitration Doses (Safety Population)

Regimen Dose within regimen	Number of Patients	Duration of Exposure (days)		Patient-months
		Mean (SD)	Min /Median//Max	
Placebo for 6 months	**55**	**82.6 (67.3)**	**6 / 47.0 / 176**	**149.3**
V0400SB 1 mg/kg/day for 3 months then placebo for 3 months				
V0400SB 1 mg/kg/day	98	81.1 (21.0)	1 / 84.0 / 214	261.3
Placebo	88	68.6 (26.4)	6 / 84.0 / 91	198.3
V0400SB 1 mg/kg/day for 6 months	**102**	**156.9 (39.9)**	**7 / 168.0 / 220**	**525.9**
V0400SB 3 mg/kg/day for 3 months then placebo for 3 months				
V0400SB 1 mg/kg/day	123	7.5 (2.8)	6 / 7.0 / 28	30.4
V0400SB 2 mg/kg/day	120	7.0 (0.7)	3 / 7.0 / 9	27.4
V0400SB 3 mg/kg/day	119	69.6 (8.0)	21 / 70.0 / 98	272.0
Placebo	93	70.3 (23.8)	8 / 83.0 / 89	214.8
V0400SB 3 mg/kg/day for 6 months	**101**	**161.0 (26.6)**	**19 / 168.0 / 190**	**534.1**
V0400SB 1 mg/kg/day	101	7.2 (1.5)	6 / 7.0 / 21	24.0
V0400SB 2 mg/kg/day	101	7.1 (0.7)	5 / 7.0 / 10	23.5
V0400SB 3 mg/kg/day	101	146.7 (26.4)	7 / 154.0 / 176	486.8

Source: Table 2.7.4.1.2.1a, Table 2.7.4.1.2.2a (Section 5.3.5.3 - Vol. 1)

In patients with infantile haemangioma, the recommended dose of propranolol is 3 mg/kg/day divided in two intakes (with a titration phase) for 6 months. 220 patients were exposed to this dosage with a mean duration of 70 days for the 3 months regimen and of 147 days for the 6 months regimen. Thus, taking into account the titration phase, 88 patients were exposed to the claimed regimen. It can consider that the number of patients exposed to propranolol at the target dose and duration is low considering the potential target population (range mentioned in the RMP is 15000 to 45000 patients per year in Europe).

The mean duration of exposure in the 3 mg/kg/days 6 months regimen was 161.0 days (less than 6 months), with a range from 19 to 190 days. Moreover, it should be noted that the exposure to study drug was markedly lower with placebo than with propranolol in terms of number of patients and duration of treatment. Consequently, the comparison of the safety profile between placebo and propranolol is biased and should be interpreted with caution. Finally, propranolol has not been studied for duration of treatment beyond 6 months; thus, the safety profile of a long-term treatment in the claimed population has not been established.

Baseline characteristic

Regarding baseline demographic characteristics, no significant difference was detected between treatment groups by age, sex, race (majority of Caucasians), in the pooled safety data from studies 102 and 201. Mean weight at birth was 3.0 kg and most patients were female (71.4%). The target IH was more commonly facial (71.2%) than non-facial (28.8%). Regarding age, the mean age at randomization was 103.8 days, with 63.0% of patients aged 91-150 days at randomization and 37.0% aged 35-90 days at randomization. As a consequence, there are fewer safety data for the younger patients. Moreover, 26.2% of patients were born prematurely, with a slightly higher rate of prematurity in the placebo regimen (34.5%) compared to the propranolol arms (21.6-27.5%). Thus, the safety extrapolations need to be limited to the studied population only, particularly safety data on younger children (less than 35 days) or premature treated are missing, and this population should be included in potential off label use. Regarding the disease history, no significant differences were detected between treatment groups. The more frequent localisation is facial IH, this is also due to the original protocol which only included initially facial IH, other locations were

authorised later. Moreover, no major difference has been observed between arms on medical history or on concomitant disease.

The most used concomitant medications during the clinical trials were vitamins and vaccines, which can be considered as common talking into, account the target population of infants between 5 weeks and 1 year.

Adverse events

The Table summarises the adverse events pooled by dose of V0400SB, all V0400SB or all placebo, whatever the regimen.

Table 19: Summary of Adverse Events (Updated Table 24 of the CSR)

	Placebo (N = 55)	V0400SB 1mg/kg/day 3mths (N = 98)	V0400SB 1mg/kg/day 6mths (N = 102)	V0400SB 3mg/kg/day 3mths (N = 100)	V0400SB 3mg/kg/day 6mths (N = 101)
Patients with at least one AE	43 (78.2%)	90 (91.8%)	91 (89.2%)	91 (91.0%)	97 (96.0%)
Patients with at least one TEAE	42 (76.4%)	89 (90.8%)	91 (89.2%)	91 (91.0%)	97 (96.0%)
Patients with one TEAE	14 (25.5%)	15 (15.3%)	16 (15.7%)	10 (10.0%)	15 (14.9%)
Patients with two TEAEs	8 (14.5%)	10 (10.2%)	6 (5.9%)	8 (8.0%)	13 (12.9%)
Patients with more than two TEAEs	20 (36.4%)	64 (65.3%)	69 (67.6%)	73 (73.0%)	69 (68.3%)
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%)	46 (46.9%)	37 (36.3%)	37 (37.0%)	36 (35.6%)
Patients with at least one Serious AE	3 (5.5%)	6 (6.1%)	3 (2.9%)	9 (9.0%)	6 (5.9%)
Occurence of TEAEs	148	545	514	494	543
Occurence of AEs leading to definitive study drug discontinuation	7	4	2	10	3
Occurence of related TEAEs	31	157	91	76	78
Occurence of serious AEs	3	6	5	13	7

The SOCs with the highest frequencies were infections and infestations (56.8%), gastrointestinal disorders (50.2%), and general disorders and administration site conditions (29.5%). It should also be noted that more than 20% of patients exposed to propranolol have psychiatric disorders, skin and soft tissue disorders and respiratory disorders.

Table 20: Number of Patients with at Least one TEAE, by MedDRA System Organ Class (SOC) by dose of V0400SB or placebo whatever the regimen and on all patients treated by V0400SB whatever the dose [Safety set]

System Organ Class	All Placebo n=236	All V0400SB 1mg/kg/day n=200	All V0400SB 3mg/kg/day n=224	All V0400SB n=424
INFECTIONS AND INFESTATIONS	99 (41.9 %)	113 (56.5 %)	128 (57.1 %)	241 (56.8 %)
GASTROINTESTINAL DISORDERS	49 (20.8 %)	97 (48.5 %)	116 (51.8 %)	213 (50.2 %)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	32 (13.6 %)	61 (30.5 %)	64 (28.6 %)	125 (29.5 %)
PSYCHIATRIC DISORDERS	19 (8.1 %)	50 (25.0 %)	47 (21.0 %)	97 (22.9 %)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	18 (7.6 %)	43 (21.5 %)	44 (19.6 %)	87 (20.5 %)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	28 (11.9 %)	38 (19.0 %)	48 (21.4 %)	86 (20.3 %)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	6 (2.5 %)	20 (10.0 %)	18 (8.0 %)	38 (9.0 %)
VASCULAR DISORDERS	3 (1.3 %)	19 (9.5 %)	19 (8.5 %)	38 (9.0 %)
NERVOUS SYSTEM DISORDERS	5 (2.1 %)	21 (10.5 %)	13 (5.8 %)	34 (8.0 %)
EYE DISORDERS	6 (2.5 %)	15 (7.5 %)	18 (8.0 %)	33 (7.8 %)
INVESTIGATIONS	7 (3.0 %)	14 (7.0 %)	16 (7.1 %)	30 (7.1 %)
METABOLISM AND NUTRITION DISORDERS	4 (1.7 %)	12 (6.0 %)	11 (4.9 %)	23 (5.4 %)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	-	8 (4.0 %)	6 (2.7 %)	14 (3.3 %)
CARDIAC DISORDERS	-	3 (1.5 %)	3 (1.3 %)	6 (1.4 %)
SURGICAL AND MEDICAL PROCEDURES	1 (0.4 %)	4 (2.0 %)	-	4 (0.9 %)
IMMUNE SYSTEM DISORDERS	-	1 (0.5 %)	2 (0.9 %)	3 (0.7 %)
EAR AND LABYRINTH DISORDERS	2 (0.8 %)	1 (0.5 %)	1 (0.4 %)	2 (0.5 %)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	-	1 (0.5 %)	1 (0.4 %)	2 (0.5 %)
RENAL AND URINARY DISORDERS	-	1 (0.5 %)	1 (0.4 %)	2 (0.5 %)
HEPATOBILIARY DISORDERS	-	-	1 (0.4 %)	1 (0.2 %)
SOCIAL CIRCUMSTANCES	-	1 (0.5 %)	-	1 (0.2 %)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	2 (0.8 %)	-	-	-

Related TEAEs

As expected, the percentage of patients with at least 1 related TEAE was notably higher in each pooled V0400SB group (37.5% in the pooled V0400SB 1 mg/kg/day group and 35.3% in the V0400SB 3 mg/kg/day group) than in the pooled placebo group (14.8%). They are representative of class-effect events with beta-blockers; the most common related TEAEs were: peripheral coldness, diarrhoea, sleep disorder, middle insomnia, and nightmare. The incidence in this young population is low and no dose-response effect was observed between low and high dose of propranolol.

Table 21: Related TEAEs, Occurring in at Least 2% of Patients in Either Dose of V0400SB, by Preferred Term and by Pooled Dose of Placebo or V0400SB (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
PERIPHERAL COLDNESS	-	16 (8.0%)	14 (6.3%)	30 (7.1%)
DIARRHEA	3 (1.3%)	9 (4.5%)	14 (6.3%)	23 (5.4%)
SLEEP DISORDER	2 (0.8%)	12 (6.0%)	9 (4.0%)	21 (5.0%)
MIDDLE INSOMNIA	4 (1.7%)	9 (4.5%)	11 (4.9%)	20 (4.7%)
NIGHTMARE	4 (1.7%)	4 (2.0%)	14 (6.3%)	18 (4.2%)
VOMITING	1 (0.4%)	6 (3.0%)	5 (2.2%)	11 (2.6%)
CONSTIPATION	1 (0.4%)	4 (2.0%)	6 (2.7%)	10 (2.4%)
DECREASED APPETITE	1 (0.4%)	4 (2.0%)	6 (2.7%)	10 (2.4%)
SOMNOLENCE	-	8 (4.0%)	2 (0.9%)	10 (2.4%)
RESTLESSNESS	2 (0.8%)	7 (3.5%)	2 (0.9%)	9 (2.1%)
HYPERSOMNIA	1 (0.4%)	6 (3.0%)	3 (1.3%)	9 (2.1%)
INSOMNIA	5 (2.1%)	2 (1.0%)	4 (1.8%)	6 (1.4%)
IRRITABILITY	1 (0.4%)	6 (3.0%)	-	6 (1.4%)

Most of the TEAEs which higher incidence with propranolol than with placebo integrated well known non-serious side effects of propranolol such as diarrhoea, vomiting, peripheral coldness, sleep disorder, middle insomnia, somnolence, restlessness, hypersomnia and agitation, as well as events frequently occurring in young infants such as constipation, vaccination complication, conjunctivitis, gastroenteritis, infantile colic, flatulence, influenza, viral infection, erythema, abdominal pain… The incidence in this young population is low and no dose-response effect was observed between low and high dose of propranolol.

The ADR table included in section 4.8 of the SmPC were included from the pooled safety database analysis without any threshold of frequency. The frequency calculation for inclusion in the SmPC table in Section 4.8 was based on the frequency of the adverse event (or grouped adverse events) reported whatever the Investigator causal assessment.

	Very Common	Common	Uncommon
Infections and infestations	Bronchitis (10.8%)	Bronchiolitis (6.8%)	
Metabolism and nutrition disorders		Decreased appetite (3.1%)	
Psychiatric disorders	Sleep disorder (16.7%)	Agitation (6.4%) Nightmares (4.2%) Irritability (3.3%)	
Nervous system disorders		Somnolence (2.8%)	
Cardiac disorders			AV block (0.2%)
Vascular disorders		Peripheral coldness (7.1%)	
Respiratory, thoracic and mediastinal disorders		Bronchospasm (2.6%)	
Gastrointestinal disorders	Diarrhoea (18.9%) Vomiting (10.6%)	Constipation (6.8%) Abdominal pain (5.9%)	

Skin and subcutaneous tissue disorders	Erythema (6.1%)	Urticaria (0.7%) Alopecia (0.5%)
Investigations	Decreased blood pressure (1.2%)	Decreased blood glucose (0.5%) Decreased heart rate (0.5%) Neutropenia (0.7%)

The majority of AE have mild to moderate intensity; the number of patients with severe adverse events both in placebo or treatments arms is low. The unknown outcomes were rare (only 8 patients in the safety database).

No difference was observed regarding the number of adverse events between the 2 categories of age (35-90 and 91-150 days), the prematurity, the sex or the IH localisation. However, premature born children should be considered as high-risk population regarding severe events.

Important identified risks with propranolol

Hypoglycaemia, bradycardia, hypotension, and bronchospasm are important identified risks known to occur with propranolol in infants. During the pivotal clinical trial (study 201), parents were provided a specific letter on safety monitoring during the treatment phase and were also advised on the management of hypoglycaemia, hypotension and bradycardia. Acute monitoring has been performed before treatment initiation and at each increase of dose. Warning and precaution for use have been included in the SmPC and PL, to give recommendations regarding the hours of administration and the monitoring of children.

Hypoglycaemia: the 2 reported cases of hypoglycaemia were of mild intensity without symptom. Moreover, the general context of gastroenteritis and vomiting for one patient can explain the occurrence of hypoglycaemia. Due to the low number of cases, it can be consider that the titration phase and the advices given to parents have been efficient. Hypoglycaemia is particularly a safety concern in infants born prematurely.

Bradycardia was reported in 1 patient during the uptitration period and 1 patient after uptitration. The 2 reported cases of bradycardia were of moderate intensity: one with clinical significance and one without symptom. Due to the low number of cases, it can also be considered that the titration phase and the acute monitoring (ECG monitoring at the first dose and at each dose increase, specialist advice in case of cardiac abnormalities) of patients during the administration have been efficient.

For HR values, on treatment a decrease around 8-10 bpm was observed in propranolol arm, not recovered in placebo arm. The decreased HR was maintained all along the study. No major effect on QT prolongation was observed during clinical trials. After the first intake and each dose increase, the effect of propranolol on heart rate should be carefully monitored, including blood pressure and heart rate at least hourly for at least 2 hours.

Hypotension was reported for 3 patients during the uptitration period and 3 patients after uptitration. Moreover, a decrease for diastolic and systolic blood pressure was observed during the titration phases both in placebo and propranolol groups. At expected this decrease was more marked in the propranolol arms due to its pharmacological properties. The changes for blood

pressure from baseline are quite stable during the treatment phase. The difficulty to properly monitored blood pressure in this young population is acknowledged, thus these results were quite difficult to interpret and no dose relationship can be fully demonstrated.

Four cases of *bronchospasm* have been reported in the safety database, equally shared between placebo and propranolol arm; they were of mild to moderate intensity and all patients recovered.

Serious adverse event / deaths / other significant events

There was no death in the pooled safety population.

In total, 36 SAEs were reported in 27 treated patients including 34 TE SAEs in 26 patients. The most common serious adverse events were: condition aggravated, drug ineffective and bronchiolitis (each reported in 3 patients), and bronchitis (2 patients). Regarding the intensity of SAE, 11 were considered as mild, 12 as moderate and 13 as severe. Four patients (all on V0400SB) had SAEs that were considered treatment-related by both the investigator and the Sponsor: bradycardia in the context of non-related enterocolitis, second degree AV block in a patient with a probable pre-existing cardiological disease, and aggravated condition (in 2 patients). In addition, one SAE of severe bronchitis was considered related by the Sponsor only. All related SAEs resolved with corrective treatment, except for AV block which spontaneously resolved.

Table 22: Treatment Emergent Serious Adverse Events, by Regimen (Pooled Safety Population)

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

Two deaths have been reported in the supportive data, one during the CUP and one in a publication:

- A 5-month infant, with biliary atresia and severe pulmonary arterial hypertension, had received propranolol for 13 days with good cardiovascular tolerance. She received five injections of lauromacrogol for sclerosis of oesophageal varices under general anaesthesia. Fifteen minutes after the last injection, she experienced an atrioventricular block grade 3, refractory to treatment,

followed by cardiac arrest and death of the infant in the following hours despite intensive resuscitations measures. Causality of V0400SB was considered doubtful considering the context of occurrence and very close monitoring since propranolol initiation (FR-2011-1487).

- One death was reported by *Metry et al 2013*. One patient with IH of the face, chest, back, neck, arm, hand, airway, and the gastro-intestinal tracts with PHACE syndrome was treated with oral propranolol 1 mg/kg/day in combination with corticosteroids at 2 mg/kg/day. Although IH response was considered excellent the patient experienced severe sleeping disturbances and worsening of peripheral arteriopathy with digital infarction leading to death after 16 months of propranolol treatment.

Laboratory findings

Glycaemia: Propranolol prevents the response of endogenous catecholamines to correct hypoglycaemia and also masks the adrenergic warning signs of hypoglycaemia, particularly tachycardia, palpitations and sweating. Therefore blood glucose levels were monitored. It should be noted that the majority of patients in each pooled dose group had no change in glycaemia category during the 4h post-dose period, and the predose value were similar at each up-titration phase. The number of patients with decreasing shift in glycaemia category was low (less than 15% in each groups) and similar in placebo or propranolol groups.

Other biochemistry parameters: the normal ranges for each biochemistry parameter were used to categorize patients as having low, normal or high values at each visit and the number of patients who had shifts in category from the baseline value. No change from baseline in category was the most common outcome for most biochemistry parameters. Several cases of high potassium values and blood potassium increase were observed in the safety database, this important risk should be further discussed.

Haematology: The known safety profile of propranolol did not show a deleterious impact on haematological parameters. The number of study drug related AEs is very low, thus no signal was detected

Neutropenia: a review of all grade 4 neutropenia has been performed. 9 cases have been identified. Out of the 9 cases of grade 4 neutropenia:

- 2 patients (520104 and 160210) had grade 4 neutropenia at screening (one in placebo and the other in the propranolol 1mg/kg/d group); the value was normalized at week 24 with no clinical signs of infection. Therefore it's unlikely that the study drug played any role on these cases.

- the other 7 patients (all of them in a propranolol treatment groups) had screening values from normal to grade 3 neutropenia, all of them presented worsening of the screening value up to grade 4 neutropenia during treatment and related mild infectious condition. Five out of the seven patients had the infectious condition during the propranolol treatment, one patient (050805) had the infectious condition during the 3 months placebo treatment but after 3 months of propranolol treatment, and one patient (810107) had the infectious condition after the end of 6 months propranolol treatment.

Vital signs

The 6 adverse events of hypotension on the pivotal study were all asymptomatic and were not serious or severe in intensity. Bradycardia was more common with the higher dose of V0400SB but overall numbers were too small to make meaningful comparisons. On ECG, the PR interval increased from the pre-dose values at +2h and +4h on each day of dose increase, with a greater increase observed with V0400SB than with placebo. The PR interval prolongation observed with V0400SB is in line with the known effects of propranolol as well as with the physiological increase with age TEAEs of QT prolongation were reported for 3 patients during uptitration and 1 patient after uptitration. These TEAEs were asymptomatic and were not serious. There were no relevant findings regarding respiratory rate, body temperature, or physical exam (height, weight, and head circumference).

Safety in special populations

By Age: IH growth mostly occurs before 5 months, therefore to target the proliferative phase of IH, patients in this study were aged 35-150 days at randomization. In addition, a previous study showed that 80% of the full IH size is reached during the early proliferative stage at a mean age of 3 months (i.e. 90 days). Therefore patients were stratified by at randomization into 2 age categories: 35-90 days and 91-150 days. No differences were observed in the occurrence of TEAEs of special interest (hypotension, bradycardia, bronchospasm and hypoglycaemia) between the two age categories, although low patient numbers did not allow for robust comparisons to be made. By Gender: No differences were observed in the occurrence of TEAEs of special interest (hypotension, bradycardia, bronchospasm and hypoglycaemia) between males and females, although low patient numbers did not allow for robust comparisons to be made. By IH Localization: Comparison of patients with facial and non-facial IH within each regimen for each demographic parameter showed variability, but no obvious patterns of differences. Overall, no meaningful differences in the safety profile arose upon an analysis of patient subgroups (age, sex, IH localization, prematurity, or birth weight) in comparison with the overall pooled population were found but premature patients are still considered as higher risk patients.

Withdrawal and Rebound: From the data provided, 11% of patients of the 3mg/kg/day 6 months regimen required reintroduction of a systemic treatment; However the real rebound effect will be more accurately assessed when the long term safety data post-treatment withdrawal up to Week 96 will be available in Q2 2014.

Safety related to drug-drug interactions and other interactions

Concomitant use of propranolol is not recommended with bradycardia –inducing calcium-channel blockers (diltiazem, verapamil, bepridil). Co-administration with propranolol can cause altered automaticity (excessive bradycardia, sinus arrest), sino-atrial and atrio-ventricular conduction disorders, and increased risk of ventricular arrhythmias (torsades de pointes) along with heart failure. This combination must only be administered under close clinical and ECG monitoring, particularly at the start of the treatment.

Caution should be exercised when proporanolol is administered in combination with cardiovascular medicinal products such as antiarrhythmics. Propafenone has negative inotropic and beta-blocking

properties that can be additive to those of propranolol, despite a reassuring study in healthy volunteers. The metabolism of propranolol is reduced by co-administration of quinidine, leading to a 2- to 3- fold increased blood concentration and greater degrees of clinical beta-blockade.

Amiodarone is an antiarrhythmic agent with negative chronotropic properties that may be additive to those seen with β-blockers such as propranolol. Automatism and conduction disorders are expected because of the suppression of sympathetic compensative mechanisms. The metabolism of intravenous lidocaine is inhibited by co-administration of propranolol, resulting in a 25% increase in lidocaine concentrations. Lidocaine toxicity (neurological and cardiac adverse events) has been reported following co-administration with propranolol.

Both digitalis glycosides and beta-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.

Caution should be exercised when patients receiving a beta blocker are administered a dihydropyridine. Both agents may induce hypotension, heart failure in patients whose cardiac function is partially controlled because of additive inotropic effects. Reduction of reflex sympathetic response involved when excessive distal vasodilatation.

When combined with beta-blockers, drugs that decrease arterial pressure (ACE Inhibitors, angiotensin II-receptors antagonists, diuretics, alpha-blockers whatever the indication, centrally-acting antihypertensives, reserpine, etc) can cause or major hypotension, notably orthostatic. With centrally-acting antihypertensives, beta-blockers may exacerbate the rebound hypertension after clonidine abrupt withdrawal, and propranolol should be stopped several days before discontinuing clonidine.

Patients with infantile haemangioma may be at increased risk if they have received or are concomitantly receiving treatment with corticosteroids because adrenal suppression may result in loss of the counterregulatory cortisol response and increase the risk of hypoglycaemia. This also applies when children are breastfed by mothers treated with corticosteroids in case of high dosage or prolonged treatment.

Non-steroidal anti-inflammatory drugs (NSAIDS) have been reported to blunt the antihypertensive effect of beta-blocking agents.

Drugs that induce postural hypotension (nitrates derivatives, type 5-phosphodiesterase inhibitors, tricyclic antidepressants, antipsychotics, dopaminergic agonists, levodopa, amifostine, baclofen…) may add their effects to that of betablockers.

Blood levels of propranolol may be decreased by co-administration of enzyme inducers like rifampicin or phenobarbital.

All beta-blocking agents can mask certain symptoms of hypoglycaemia: palpitations and tachycardia. Use of propranolol alongside hypoglycaemic therapy in diabetic patients should be with caution since it may prolong the hypoglycaemic response to insulin. In this case, inform the caregiver, and increase monitoring of blood glucose levels, particularly at the start of treatment.

Co-administration of cholestyramine or colestipol with propranolol resulted in up to 50% decrease in propranolol concentrations.

Halogenated anaesthetic agents may depress myocardial contractility and vascular compensating response when administered with propranolol. Beta stimulating agents may be used to counteract the beta-blockade.

Discontinuation due to adverse events

In total, in the pooled safety population, 26 TEAEs leading to definitive study drug discontinuation were reported for 22 patients. The percentage of patients reporting TEAEs leading to definitive study drug discontinuation was slightly higher in the pooled placebo group (4.7%) than in each pooled V0400SB group: 2.0% in the pooled V0400SB 1 mg/kg/day group and 3.1% in the pooled V0400SB 3 mg/kg/day group. No emergent preferred term was identified to induce treatment discontinuation, but in 5 cases, the drugs discontinuation was due to lack of efficacy (3 cases of condition aggravated, 2 drug ineffective), all in the placebo group

Post marketing experience

Not applicable

2.6.1. Discussion on clinical safety

In clinical trials for proliferating infantile haemangioma, the most frequently reported adverse drug reactions in infant treated with Hemangiol were sleep disorders, aggravated respiratory tract infections such as bronchitis and bronchiolitis associated with cough and fever, diarrhoea, and vomiting.

Globally, the most severe adverse reactions reported in the compassionate use program and in literature concerned hypoglycaemia (and related event like hypoglycaemic seizure) and aggravated respiratory tract infections with respiratory distress.

The 4 major identified risks of propranolol are hypoglycaemia, bradycardia, hypotension and bronchospasm. As a consequence, a number of precautions should be taken when children are treated with Hemangiol.

Prior to initiating propranolol therapy, a screening for the risks associated with propranolol use must be performed. An analysis of the medical history and a full clinical examination must be performed including heart rate, cardiac and pulmonary auscultation.

In case of suspected cardiac abnormality, a specialist advice must be sought before treatment initiation to determine any subjacent contra-indication.

In case of acute broncho-pulmonary abnormality, the initiation of the treatment should be postponed.

Propranolol, due to its pharmacological action, may cause or worsen bradycardia or blood pressure abnormalities. After the first intake and each dose increase, physicians are advised to monitor the clinical and heart rate, including blood pressure and heart rate must be performed at least hourly for at least 2 hours. In case of symptomatic bradycardia or bradycardia under 80 bpm, immediate specialist advice must be sought. In case of severe and/or symptomatic bradycardia or hypotension

occurring at any time during treatment, treatment must be discontinued and a specialist advice should be sought.

Propranolol prevents the response of endogenous catecholamines to correct hypoglycaemia. It masks the adrenergic warning signs of hypoglycaemia, particularly tachycardia, shakiness, anxiety and hunger. It can aggravate hypoglycaemia in children, especially in case of fasting, vomiting or overdose.

These hypoglycaemic episodes associated with the taking of propranolol may present exceptionally in the form of seizures and/or coma. As a consequence, if clinical signs of hypoglycaemia occur, it is necessary to make the child drink a sugary liquid solution and to temporarily stop the treatment. Appropriate monitoring of the child is required until symptoms disappear. In children with diabetes, blood glucose monitoring should be increased.

In the event of lower respiratory tract infection associated with dyspnoea and wheezing, treatment should be temporarily discontinued. The administration of beta2 agonists and inhaled corticosteroids is possible. The readministration of propranolol may be considered when the child has fully recovered; in case of reoccurrence, treatment should be permanently discontinued. In the event of isolated bronchospasm, treatment must be permanently discontinued.

Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure.

There are very limited safety data of propranolol in PHACE syndrome patients available. Propranolol may increase the risk of stroke in PHACE syndrome patients with severe cerebrovascular anomalies by dropping blood pressure and attenuating flow through occluded, narrow, or stenotic vessels.

Therefore, infants with large facial infantile haemangioma should be thoroughly investigated for potential arteriopathy associated with PHACE syndrome, with magnetic resonance angiography of the head and neck and cardiac imaging to include the aortic arch, prior to considering propranolol therapy.

Since propranolol passes through breast milk, mothers being treated with propranolol who breastfeed their infant should inform their health care professional.

Beta-blockers will result in an attenuation of reflex tachycardia and an increased risk of hypotension. It is necessary to alert the anaesthetist to the fact that the patient is being treated with beta-blockers. Therefore, when a patient is scheduled for surgery, beta-blocker therapy should be discontinued at least 48 hours prior to the procedure.

Cases of hyperkalaemia have been reported in patients with large ulcerated haemangioma. A monitoring of electrolyte should be performed in these patients.

No relevant difference was observed in the safety profile based on the age (35-90 days or 90-150 days), the prematurity, the sex or the IH localisation. However, as infants born prematurely are at higher risk of undesirable events, special care should be taken to them.

Discontinuation rate due to adverse events was low, 11 cases (4.7%) were reported in the placebo arm and 11 (2.6%) in the propranolol arm.

During the pivotal study (study 201), patients between 5 weeks and 5 months were monitored every 3-4 weeks and recalculation of the dose was performed according to body weight. The

applicant has presented calculations showing the difference between the actual dose received and the theoretical dose based on body weight with adjustments every month from W5 to W24 (as planned in the protocol). On average, patients were under-dosed by 6.66% with monthly adjustments as compared to 11.9% when adjustments are every 2 months (as proposed in the SmPC). The CHMP agrees with the applicant that underdosage of 6-7% will not have any impact on safety.

The complementary safety data from the CUP and scientific publications since 2008 are in line with the safety profile shown in the pivotal study and does not add any new safety signal.

The inspection of the pivotal trial showed that the AE section of the submitted CSR was incomplete; the Applicant has therefore submitted an update of the safety database. One hundred and sixty seven (167) diaries are still missing, but no new information impacting the benefit/risk profile can be expected. The new analysis performed by the Applicant leads to the inclusion of 126 AEs collected over the W0-W24/EOT period, which represented 5.4% of the total AEs reported (2298) in the study over this period. No new SAE or death has been added. Thus, this update did not modify the overall safety profile of propranolol in the claimed indication. The Applicant performed new analysis of the 9 reported cases of neutropenia and a literature review regarding this risk in the target population. No case has been identified in this review and no formal conclusion can be made: the unbalance of cases between groups can be explained by the lower duration of exposure in the placebo arm and these cases may be due to transient neutropenia following benign viral and/or bacterial childhood infections.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Propranolol is a well-known substance, used both in adults and children for many years. The overall safety profile of propranolol in patients with proliferating infantile haemangioma is considered acceptable on the basis of the data submitted. The update of the safety database after the issues which had arisen during the GCP inspection of the pivotal trial did not modify the overall safety profile in the target population. The safety profile in younger children or of long-term exposure beyond 6 months cannot be established at the present time. A close monitoring of identified risks (hypotension, bradycardia, hypoglycaemia and bronchospasm) at the initiation of treatment and at each dose increase, as well as throughout the treatment is essential; recommendations have been included in the product information.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considers that the pharmacovigilance system as described by the applicant fulfils the legislative requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

2.8. Risk Management Plan

The CHMP received the following PRAC advice on the submitted Risk Management Plan:

The PRAC considered that the risk management system version 1.0 is acceptable. In addition, minor revisions were recommended to be taken into account at the next RMP update. The PRAC advice is attached.

PRAC Advice

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

The applicant identified the following safety concerns in the RMP:

Table 23: Summary of the Safety Concerns

Important identified risks	▪ Bradycardia ▪ Prolonged atrio-ventricular conduction or intensification of an AV block ▪ Hypotension ▪ Hypoglycaemia and related seizure ▪ Bronchospasm and bronchial hyperreactivity reactions
Important potential risks	▪ Cerebrovascular complication in case of PHACE syndrome with SNC involvement ▪ Hyperkalaemia in case of large ulcerated IH ▪ Potential risk of administration error ▪ Drug interaction with anaesthetic agents
Missing information	▪ Off-label use ▪ Long-term effects **(including on growth)** ▪ Drug interaction through breast-feeding ▪ Dosing and treatment of premature infants before the corrected age of at least 35 days

Other identified risks (not considered as important according to the definition)	- Gastrointestinal disorders: diarrhoea - Neurological disorders: sleep disorders with nightmares - Psychiatric disorders: agitation, somnolence - Vascular disorders : peripheral coldness, Raynaud's syndrome - Agranulocytosis

Pharmacovigilance plans

Table 24: on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Drug utilisation study (3)	To assess the off-label use and measure effectiveness of risk minimisation measures	Off label use	Planned	Q2 2017 (final report)
V0400SB201 long term safety follow-up (3)	To investigate long term safety profile (including neurodevelopment assessment)	Long term safety	Started	Final study report planned Q2 2014

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

- **Risk minimisation measures**

Table 25: Summary of risk minimisation measures

<table>
<tr><th>Safety concerns</th><th>Routine risk minimisation measures</th><th>Additional risk minimisation measures</th></tr>
<tr><td colspan="3">Important identified risks</td></tr>
<tr><td>Bradycardia and intensification of AV block</td><td>
Proposed text in SmPC:

Section 4.3: Bradycardia below the following limits:
<table>
<tr><td>Age</td><td>0-3 months</td><td>3-6 months</td><td>6-12 months</td></tr>
<tr><td>Heart rate (beats/min)</td><td>100</td><td>90</td><td>80</td></tr>
</table>
Section 4.4: Propranolol, due to its pharmacological action, may cause or worsen bradycardia or blood pressure abnormalities. Bradycardia should be diagnosed if the heart rate declines by more than 30 bpm from baseline. Bradycardia is defined below the following limits:
<table>
<tr><td>Age</td><td>0-3 months</td><td>3-6 months</td><td>6-12 months</td></tr>
<tr><td>Heart rate (beats/min)</td><td>100</td><td>90</td><td>80</td></tr>
</table>
After the first intake and each dose increase, a clinical monitoring, including blood pressure and heart rate must be performed at least hourly for at least 2 hours. In case of symptomatic bradycardia or bradycardia under 80 bpm, immediate specialist advice must be sought.

In case of severe and/or symptomatic bradycardia or hypotension occurring at any time during treatment, treatment must be discontinued and a specialist advice should be sought.

Section 4.8: Bradycardia, Decreased heart rate

Proposed text in leaflet:

Do not give HEMANGIOL if your child has a slow heart rate for his/her age.

HEMANGIOL can decrease heart rate (bradycardia). This it why at treatment initiation and increases of dose, your child will be kept under close medical supervision over 2 hours after the intake for clinical and heart rate monitoring. Then, clinical examination of your child will be regularly performed during treatment with HEMANGIOL.

Call your doctor right away if your child has any signs such as
</td><td>Educational material for caregivers (only bradycardia)</td></tr>
</table>

<table>
<tr><td></td><td>fatigue, coldness, pallor, bluish-coloured skin, or fainting while taking HEMANGIOL.

In section Possible side effects

Bradycardia (abnormally low heart rate)

Other routine risk minimisation measures

- Prescription only medicine

- Initiation by physicians who have expertise in the diagnosis, treatment and management of infantile haemangioma in a controlled clinical setting where adequate facilities for handling of adverse events, including those requiring urgent measures, are available.</td><td></td></tr>
<tr><td>Hypotension</td><td>Proposed text in SmPC

• Section 4.3: Low blood pressure below the following limits:
<table><tr><td>Age</td><td>0-3 months</td><td>3-6 months</td><td>6-12 months</td></tr><tr><td>Blood pressure (mmHg)</td><td>65/45</td><td>70/50</td><td>80/55</td></tr></table>Section 4.4: Propranolol, due to its pharmacological action, may cause or worsen bradycardia or blood pressure abnormalities.

After the first intake and each dose increase, a clinical monitoring, including blood pressure and heart rate must be performed at least hourly for at least 2 hours. In case of symptomatic bradycardia or bradycardia under 80 bpm, immediate specialist advice must be sought.

In case of severe and/or symptomatic bradycardia or hypotension occurring at any time during treatment, treatment must be discontinued and a specialist advice should be sought.

Section 4.8: Hypotension, Decreased blood pressure

Proposed text in leaflet:

Do not give HEMANGIOL if your child has very low blood pressure.

HEMANGIOL can decrease blood pressure (hypotension). This is why at treatment initiation and increases of dose, your child will be kept under close medical supervision over 2 hours after the intake for clinical and heart rate monitoring. Then, clinical examination of your child will be regularly performed during treatment with HEMANGIOL.

Tell your doctor if your child has any signs such as fatigue, coldness,</td><td>Educational material for caregivers</td></tr>
</table>

	pallor, bluish-coloured skin, or fainting while taking HEMANGIOL In section Possible side effects - decrease in blood pressure. **Other routine risk minimisation measures** - Prescription only medicine - Initiation by physicians who have expertise in the diagnosis, treatment and management of infantile haemangioma in a controlled clinical setting where adequate facilities for handling of adverse events, including those requiring urgent measures, are available.	
Hypoglycaemia and related seizures	**Proposed text in SmPC:** **Section 4.2**: HEMANGIOL is to be taken during or right after a feeding to avoid the risk of hypoglycaemia. It should be administered directly into the child's mouth using a graduated oral syringe, calibrated in mg of propranolol, supplied with the oral solution bottle. If the child is not eating or is vomiting it is recommended to skip the dose. HEMANGIOL and the feed must be given by the same person in order to avoid the risk of hypoglycaemia. If different people are involved, good communication is essential in order to ensure the safety of the child. **Section 4.3:** Subjects prone to hypoglycaemia; Premature infants, for whom the corrected age of 5 weeks has not been reached **Section 4.4:** Propranolol prevents the response of endogenous catecholamines to correct hypoglycaemia. It masks the adrenergic warning signs of hypoglycaemia, particularly tachycardia, palpitations and sweating. It can aggravate hypoglycaemia in children, especially in case of fasting, vomiting or overdose. These hypoglycaemic episodes associated with the taking of propranolol may present exceptionally in the form of seizures and/or coma. If clinical signs of hypoglycaemia occur, it is necessary to make the child drink a sugary liquid solution and to temporarily stop the treatment. Appropriate monitoring of the child is required until symptoms disappear. In children with diabetes, blood glucose monitoring should be	*Educational material caregivers*

	increased. S**ection 4.8**: Hypoglycaemic seizure, Decreased blood glucose **Proposed text in leaflet:** In section what you need to know before your child receives HEMANGIOL Do not give HEMANGIOL if your child: • is born prematurely and he/she has not reached the corrected age of 5 weeks (the corrected age being calculated by substracting the number of weeks premature from the actual age). • weighs less than 2 kg. • is prone to low blood sugar level. In section Warning This medicine can mask the warning signs of hypoglycaemia (also known as low blood sugar level), especially if the baby is fasting, vomiting or in case of overdose. These signs may be: • Minor: pallor, tiredness, sweating, shakiness, palpitations, anxiety, hunger, difficulty waking up. • Major: excessive sleeping, difficulty to get a response, poor feeding, temperature decrease, convulsions (fits), brief pauses in breathing, loss of consciousness. To avoid risks of hypoglycaemia, your child must be fed regularly during treatment. If your child is not eating, develops another illness or is vomiting, it is recommended to skip the dose. Do not give HEMANGIOL to your child until he has been correctly fed again. If your child has any signs of hypoglycaemia while taking HEMANGIOL, administer if possible oral liquid containing sugar and, if symptoms persist, call your doctor right away or go directly to hospital In section How to give HEMANGIOL to your child. • The product is be taken during or right after a feeding • Feed your child regularly to avoid prolonged fast. • If your child is not eating or is vomiting it is recommended to skip the dose. • If your child spits up a dose or if you are uncertain whether they got it all of the medicine, do not give another dose, just wait	

	until the next scheduled dose. HEMANGIOL and the feeding must be given by the same person in order to avoid the risk of hypoglycaemia. If different persons are involved, communication should be strengthened. In section Possible side effects - decreased blood sugar - convulsions (fits) linked to hypoglycaemia (abnormally low blood sugar levels) **Other routine risk minimisation measures** - Prescription only medicine - Initiation by physicians who have expertise in the diagnosis, treatment and management of infantile haemangioma in a controlled clinical setting where adequate facilities for handling of adverse events, including those requiring urgent measures, are available.	
Bronchospasm and hyperreactivity reactions	**Proposed text in SmPC** **Section 4.3:** Asthma or history of bronchospasm **Section 4.4:** In the event of lower respiratory tract infection associated with dyspnoea and wheezing, treatment should be temporarily discontinued. The administration of beta2 agonists and inhaled corticosteroids is possible. The readministration of propranolol may be considered when the child has fully recovered; in case of reoccurrence, treatment should be permanently discontinued. In the event of isolated bronchospasm, treatment must be permanently discontinued. **Section 4.8:** Bronchospasm, bronchiolitis, bronchitis **Proposed text in leaflet:** Do not give HEMANGIOL If your child: - has asthma or history of breathing difficulties. In section Warning Risks of bronchospasm If after giving HEMANGIOL to your child you observe the following symptoms suggestive of a bronchospasm (temporary restriction of the bronchial tubes that leads to difficulty breathing): cough, quick or difficult breathing or wheezing, bluish-coloured skin: stop	Educational material for caregivers

	treatment and contact your doctor immediately. In section Possible side effects - bronchiolitis (inflammation of small bronchi with breathing difficulties and wheeze in the chest) associated with cough and fever, - bronchitis (inflammation of the bronchi), - bronchospasm (breathing difficulties) **Other routine risk minimisation measures** - Prescription only medicine - Initiation by physicians who have expertise in the diagnosis, treatment and management of infantile haemangioma in a controlled clinical setting where adequate facilities for handling of adverse events, including those requiring urgent measures, are available.	
Important potential risks		
Increased risk of arterial ischemic stroke in case of PHACE syndrome with CNS involvement	**Proposed text in SmPC** **Section 4.4**: Very limited safety data of propranolol in PHACE syndrome patients are available. Propranolol may increase the risk of stroke in PHACE syndrome patients with severe cerebrovascular anomalies by dropping blood pressure and attenuating flow through occluded, narrow, or stenotic vessels. Infants with large facial infantile hemangioma should be thoroughly investigated for potential arteriopathy associated with PHACE syndrome, with magnetic resonance angiography of the head and neck and cardiac imaging to include the aortic arch, prior to considering propranolol therapy. Specialized advice should be sought. **Other routine risk minimisation measures** - Prescription only medicine - Initiation by physicians who have expertise in the diagnosis, treatment and management of infantile haemangioma.	*Educational material for healthcare professionals*
Hyperkalaemia	**Proposed text in SmPC** **Section 4.4:** Hyperkaliemia cases have been reported in patients with large ulcerated hemangioma. A monitoring of electrolyte should be performed in these patients.	

	Section 4.8: Hyperkalaemia has been reported in the literature in few patients with large ulcerated haemangioma (see section 4.4).	
Potential risk of administration error	**- In section 4.2** Method of administration For oral use. HEMANGIOL is to be given during or right after a feed to avoid the risk of hypoglycaemia. It should be administered directly into the child's mouth using the graduated oral syringe, calibrated in mg of propranolol base, supplied with the oral solution bottle (see instructions for use in section 3 of the patient information leaflet). The bottle should not be shaken before use. If necessary, the medicinal product may be diluted in a small quantity of baby-milk or apple and/or orange age-adapted fruit juice. Don't put the medicine in the full bottle. The mixing may be done with one teaspoonful (approximately 5 mL) of milk for children weighing up to 5 kg, or with a tablespoonful (approximately 15 mL) of milk or fruit juice for children weighing more than 5 kg, delivered in a baby's bottle. The mixing should be used within 2 hours. HEMANGIOL and the feed must be given by the same person in order to avoid the risk of hypoglycaemia. If different people are involved, good communication is essential in order to ensure the safety of the child. **- In section 4.9** Support and treatment: place the patient on a cardiac monitor, monitor vital signs, mental status and blood glucose. Give intravenous fluids for hypotension and atropine for bradycardia. Glucagon then catecholamines should be considered if the patient does not respond appropriately to IV fluid. Isoproterenol and aminophylline may be used for bronchospasm. **Handling information detailed in the leaflet with schemes**	*Educational material for caregivers*
Drug interaction with anaesthetic agents	**Proposed text in SmPC** **Section 4.4:** General anaesthesia Beta-blockers will result in an attenuation of reflex tachycardia and an increased risk of hypotension. It is necessary to alert the anaesthetist to the fact that the patient is being treated with beta-blockers. When a patient is scheduled for surgery, beta-blocker therapy	None

	should be discontinued at least 48 hours prior to the procedure. **Section 4.5:** Halogenated Anesthetic Agents They may depress myocardial contractility and vascular compensating response when administered with propranolol. Beta stimulating agents may be used to counteract the beta-blockade.	
Missing information		
Potential off label use	**Proposed text in SmPC:** **Section 4.1:** HEMANGIOL is indicated in the treatment of proliferating infantile haemangioma requiring systemic therapy: • Life- or function-threatening haemangioma, • Ulcerated haemangioma with pain and/or lack of response to simple wound care measures, • Haemangioma with a risk of permanent scars or disfigurement. It is to be initiated in infants aged 5 weeks to 5 months (see sections 4.2 and 4.4). **Section 4.2:** Specific populations In the absence of clinical efficacy and safety data, HEMANGIOL should not be used in children aged below 5 weeks. There is no sufficient clinical efficacy and safety data to recommend HEMANGIOL initiation in children aged above 5 months. Infants with hepatic or renal impairment In the absence of data, administration of the product is not recommended to infants with hepatic or renal impairment (see section 4.4). **Other routine risk minimisation measures** - Prescription only medicine - Initiation by physicians who have expertise in the diagnosis, treatment and management of infantile haemangioma.	None
Long term effects (including on growth)	**Proposed text in SmPC:** **Section 4.2:** HEMANGIOL should be administered for a 6-month period.	None
Drug interaction through breastfeeding	**Proposed text in SmPC:** **Section 4.3:** Breastfed infants, if the mother is treated with medicines contraindicated with propranolol **Section 4.5:** In the absence of specific studies in children, the drug	None

	interactions with propranolol are those known in adults. Combinations should consider the 2 following situations (not mutually exclusive): - infants given any other drug, notably those mentioned below. - infants breastfed by mothers taking any other drug, notably those mentioned below. In this case, the need of stopping lactation should be discussed. A close clinical surveillance of any impaired tolerance of propranolol is requested. A mention *"This also applies when children are breastfed by mothers treated with..."* has been added when it applies to the drugs listed in section 4.5.	
Dosing and treatment of premature infants before the corrected of at least 35 days	**Proposed text in SmPC:** **Section 4.3:** Premature infants, for whom the corrected age of 5 weeks has not been reached *(the corrected age being calculated by subtracting the number of weeks of prematurity from the actual age)* **Section 4.4: Premature infants** Premature infants Patients born before term should not be treated before 5 weeks of corrected age.	None

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

The results of the pivotal phase 3 study showed compelling evidence of efficacy for the 3mg/kg/day dosing regimen administered for 6 months in the treatment of proliferating IH requiring systemic therapy. Two patients (3.6%) in the placebo 6 months regimen and 61 patients (60.4%) in the 3 mg/kg/day 6 months regimen presented complete or nearly complete resolution of their IH

between baseline and Week 24. The combined p-value (<0.0001) showed that the difference was highly statistically significant. The results on the secondary efficacy endpoints supported the primary endpoint from central readers, however placebo get better results on the investigator's and parents' on site assessment. The efficacy results seem similar by age group and haemangioma localization.

Uncertainty in the knowledge about the beneficial effects.

Uncertainty about long-term effect treatment

Uncertainties still remain on the real rebound rate. Preliminary data from the pivotal study shows that approximately 11% of the patients required reintroduction of systemic therapy after week 24; but data from the 96 weeks follow-up period is not yet available. The Applicant should provide the information about the clinical outcome of those who required reintroduction of systemic therapy and efficacy maintenance at week 96.

Risks

Unfavourable effects

Adverse events (and AE related to the study drug) were experienced by 65.3% of patients (14.8% related) in the pooled placebo group and 86.8% of patients (36.3% related) in the pooled all V0400SB group, with no difference between V0400SB dose groups. The most common adverse events considered as related to study drug were peripheral coldness, diarrhoea, sleep disorder, and nightmare, all of which are known side effects of propranolol. Most adverse events were of mild or moderate maximum intensity, with a first onset before or on the Week 12 visit and most patients recovered. No dose-dependence was seen for the most common adverse events except for diarrhoea and bronchitis.

Hypoglycaemia, bradycardia, hypotension, and bronchospasm are important identified risks known to occur with propranolol in infants and were reported in the pooled safety population hypoglycaemia (2 patients), bradycardia (2 patients), hypotension (total 6 patients including 1 on placebo) and bronchospasm (total 4 patients including 2 on placebo). In general, the SAEs reported in the pooled safety population corresponded to the known safety profile of propranolol; no new safety signals have been identified.

The GCP inspection of the pivotal trial highlighted that the safety profile of propranolol in the target population could be incomplete. As a consequence, the Applicant submitted an update of the safety database. Nine cases of neutropenia have been reported: the unbalance of cases between groups can be explained by the lower duration of exposure in the placebo arm and these cases may be due to transient neutropenia following benign viral and/or bacterial childhood infections. No formal conclusion can be made on the additional data. Thus, this information was included in the SmPC and the RMP.

Uncertainty in the knowledge about the unfavourable effects

Long-term effect beyond 6 months of treatment with propranolol treatment could not be assessed. This information will be provided in the context of study V0400SB201 long term safety follow-up and in a drug utilisation study (see section 2.8).

Benefit-risk balance

Importance of favourable and unfavourable effects

The effects of the treatment are clinically relevant as Hemangiol showed complete or nearly complete resolution of IH in more than 60 % of the patients.

The safety profile did not show new safety signals than those already known for propranolol and w2as overall acceptable, given the benefits observed.

Benefit-risk balance

The benefit-risk balance is considered as positive

Discussion on the benefit-risk balance

The efficacy of propranolol for the treatment of proliferating infantile haemangioma requiring systemic therapy: Life- or function-threatening haemangioma, ulcerated haemangioma with pain and/or lack of response to simple wound care measures, haemangioma with a risk of permanent scars or disfigurement, is supported by a single pivotal trial.

Propranolol, at the dosage of 3 mg/kg/day for 6 months, demonstrated a statistically significant effect on the complete/nearly complete resolution of target IH in the studied population. The safety profile of propranolol in the current submission is in line with the one's already known for this substance.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Hemangiol in the treatment of proliferating infantile haemangioma requiring systemic therapy:

- Life- or function-threatening haemangioma,

- Ulcerated haemangioma with pain and/or lack of response to simple wound care measures,

- Haemangioma with a risk of permanent scars or disfigurement.

It is to be initiated in infants aged 5 weeks to 5 months (see section 4.2).

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 8 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.>

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Applicant shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The MAH shall provide an educational pack for the proposed indication, targeting all caregivers who are expected to prepare and administer HEMANGIOL to children. This educational pack is aimed at increasing awareness about the potential risk of hypotension, bradycardia, and bronchospasm, after taking HEMANGIOL, and providing guidance on how to monitor/manage that risk.

It is also aimed to instruct caregivers to correctly feed the children during treatment in order to avoid the risk of hypoglycaemia.

The MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authority prior to distribution of the educational pack. The educational pack must be available for distribution prior to the launch of

the new indication (treatment of proliferating infantile haemangioma) in the Member State.

The educational materials for caregivers treating children with HEMANGIOL should include the following key safety elements:

- Information on the conditions for which HEMANGIOL should not be given
- Information on the correct procedure of product preparation and administration including:
  - Instructions on how to prepare the solution with HEMANGIOL
  - Advice on how to feed children during treatment
  - Information on how to detect and manage any sign of hypoglycaemia during treatment with HEMANGIOL
  - Instructions on when to discontinue the administration of HEMANGIOL
- The need to monitor and to contact the healthcare professionals if the following signs and symptoms occur after treatment:
  - For bradycardia and hypotension: fatigue, coldness, pallor, bluish-coloured skin, and fainting.
  - For hypoglycaemia: minor symptoms like pallor, tiredness, sweating, shakiness, palpitations, anxiety, hunger, difficulty waking up; major symptoms like excessive sleeping, difficulty to get a response, poor feeding, temperature decrease, convulsions (fits), brief pauses in breathing, loss of consciousness

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0004/2013 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.