Pierre Fabre Dermatologie
Represented by: Institut de Recherche Pierre Fabre
45, Place Abel Gance
F-92100 Boulogne

1. TITLE PAGE

CLINICAL STUDY REPORT

EFFICACY AND SAFETY OF HEMANGIOL® SOLUTION IN THE TREATMENT OF HIGH RISK INFANTILE HAEMANGIOMA.

Investigational product:	Hemangiol® 3.75 mg/mL oral solution, propranolol hydrochloride
Study design:	Multinational single-arm study
EudraCT number:	2014-005555-80
Protocol number:	V00400 SB 3 02
Phase of development:	III
Date of first enrolment:	29 June 2015
Date of last completed:	21 February 2017
Coordinating Investigator:	**Prof. Eulalia BASELGA, MD** Hospital de la Santa Creu i Sant Pau, Department of Dermatology Mas Casanova 90, 08041 BARCELONA – Spain Phone: +34 93 553 70 07
Sponsor Representative for study report:	**Karim KEDDAD, MD, PhD** (Head of Medical Unit) Institut de Recherche Pierre Fabre, Centre de R&D Pierre Fabre BP 13562, 3 avenue Hubert Curien, 31035 TOULOUSE – France Phone: +33 (0)5 34 50 61 69

Date of report: 10th August 2017

Study performed in compliance with Good Clinical Practice.

2. SYNOPSIS

Name of Company: Pierre Fabre Médicament	**Individual Study Table**	**(For National Authority Use Only)**
Name of finished product: Hemangiol®	**Referring to Module 5 of the Dossier**	
Name of active substance *(or ingredient)***: Propanolol**	**Vol.: .....Page: .....**	

Title of study:	Efficacy and safety of Hemangiol® solution in the treatment of high risk infantile haemangioma.	
Coordinating Investigator:	**Prof. Eulalia BASELGA, MD** Hospital de la Santa Creu I Sant Pau Department of Dermatology Mas Casanova 90 08041 BARCELONA - Spain	
Investigators	Ten investigators in 10 recruiting centres; 6 investigators/recruiting centres in Spain and 4 in Poland. All Investigators were academic paediatricians and/or dermatologists.	
Study centres:	A total of 10 sites were initiated, all were active (i.e. had at least one screened patient).	
Publication (reference):	Not written to date.	
Studied period *(years, months …)***:** **(date of first enrolment)** **(date of last completed)**	20 months: **First patient in**: 29 June 2015 **Last patient out**: 21 February 2017	**Phase of development:** **III**
Objectives:	**Primary objective**: To document the efficacy of Hemangiol® administered during at least 6 months and up to a maximum of 12 months of age in infants with high risk infantile haemangioma (IH). **Secondary objectives**: To document: • The safety of Hemangiol®, • The persistence of IH response up to 3 months after treatment interruption, • The efficacy of Hemangiol® re-administered during up to 6 months in case of haemangioma success regression and need of treatment re-initiation based on Investigator's judgment, • The impact of Hemangiol® on family burden and quality of life (QoL) linked to the IH.	
Methodology:	Multicentre, European, single-arm study in patients suffering from high risk infantile haemangioma in proliferative phase. Three periods were planned in the study after the enrolment visit (V1): • Initial treatment period (all patients) of 6 months minimum (9 visits planned: V2 to V10) until 12 months of age maximum including a 2-week up-titration period (V2-V4), • Follow-up (FU) period (all patients) of 3 months without treatment (visits FU1 and FU2), • Re-treatment period up to 6 months maximum (patients in success regression during FU for whom a re-initiation of treatment was deemed necessary by the Investigator).	
Number of patients (planned and analysed):	45 patients were planned to be enrolled. 45 were included in the study. All these 45 patients were treated and analysed.	

Name of Company: Pierre Fabre Médicament	Individual Study Table Referring to Module 5 of the Dossier Vol.: .....Page:	(For National Authority Use Only)
Name of finished product: Hemangiol®		
Name of active substance *(or ingredient)*: **Propanolol**		

Diagnosis and main criteria for inclusion:

Inclusion criteria:

- Aged 35-150 days old inclusive, also patient born prematurely but of his/her term equivalent age at inclusion (corrected age),
- High risk IH in proliferative phase (target haemangioma):
  - Life-threatening IH,
  - Peri-orbital, nasal, labial, laryngo-tracheal, limb joints IHs with functional impact or at risk of functional impact,
  - Disfiguring IH (IH > 5 cm, glabella location, nasal location, philtrum location, central chin location, central cheek location, labial IH with mouth deformities),
  - Ulcerated IH not responding to simple wound care measures, located anywhere on the body,
- Compliant with ethical and legal requirements.

Non-inclusion criteria:

- Medically unstable health status that may have interfered with his/her ability to complete the study, especially acute broncho-pulmonary abnormality,
- Presence of one of more of the following medical conditions:
  - Congenital haemangioma, Kasabach-Merritt syndrome, PHACE syndrome, hepatic haemangioma,
  - Asthma, history of bronchospasm,
  - At risk of hypoglycaemia according to the medical file of the patient,
  - Phaeochromocytoma,
  - Hypotension (systolic blood pressure/diastolic blood pressure [SBP/DBP] < 65/45 mmHg for age 35-90 days, < 70/50 mmHg for age 91-150 days, < 80/55 mmHg for age > 150 days [for chronological ages]), second or third degree heart block, cardiogenic shock, bradycardia (heart rate [HR] < 100 bpm for age 35-90 days, < 90 bpm for age 91-150 days, < 80 bpm for age > 150 days), severe peripheral arterial circulatory disturbances, Raynaud's phenomenon, disease of the sinus note (including sinoatrial block), uncontrolled heart failure, Prinzmetal's angina,
  - Hepatic and/or renal impairment,
  - Psoriasis,
- Kalaemia > 5.0 mmol/L (only measured for patients presenting an IH with largest diameter of ulcerated area ≥ 3 cm),
- Patient's target haemangioma treated by LASER therapy within the past month,
- The patient (and/or the mother if she is breastfeeding the patient) had received at least one of the following prohibited medications within 14 days before the first study drug administration: corticosteroids by systemic, intra-lesional or topical route, imiquimod, vincristine, interferon alpha, propranolol or other beta-blockers, cardiovascular treatments, drugs inducing orthostatic hypotension, non-steroid anti-inflammatory drugs (NSAIDs) at anti-inflammatory dose, enzyme inducers, hypoglycaemic agents or drugs able to induce hypoglycaemia, lipid lowering agents, halogenated anaesthetic agents, lidocaine,
- Hypersensitivity to any study drug ingredient or any beta-blocker, medical history of anaphylactic reaction.

Name of Company: Pierre Fabre Médicament	Individual Study Table Referring to Module 5 of the Dossier Vol.: .....Page:	(For National Authority Use Only)
Name of finished product: Hemangiol®		
Name of active substance *(or ingredient)*: **Propanolol**		

Test product,	Hemangiol® (propranolol) 3.75 mg/mL solution.
Dose,	Dose titration during the initial and re-treatment periods: • 1 mg/kg/day, from Day (D) 1 to D7 of each treatment period, • 2 mg/kg/day, from D8 to D14 of each treatment period, • 3 mg/kg/day, from D15 up to the end of each treatment period. Maintenance dose: 3 mg/kg/day.
Mode of administration,	Orally, twice daily (morning and late afternoon) during or straight after a feed.
Batch numbers:	Hemangiol®: CL0088: Exp March 2018 and CL0106 Exp March 2019 5mL Syringes: 14-1466/00 Exp Oct 2017, 14-1468/00 Exp Jan 2018
Other product	Not applicable.
Duration of treatment:	6 to 17 months: • Initial treatment period: 6 to 11 months, • Re-treatment period: 0 to 6 months.
Reference therapy	Not applicable.
Criteria for evaluation:	**Efficacy** **Primary criterion**: Number of patients achieving success at the end of the initial treatment period confirmed by the Investigator (reported as Yes/No) based on the following: • Resolution: Disappearance of the target IH even with the persistence of a minimal degree of telangiectasias, erythema, skin thickening, soft tissue swelling and/or a minimal palpable component, whatever the presence of sequelae, • Absence of functional impact linked to the target IH: Absence of ulceration, feeding difficulties, torticollis, cartilage distortion or destruction, airway involvement visual compromise and pain, as judged by the Investigator. **Secondary criteria:** • Number of patients achieving success (Yes/No), defined in the same way as the primary criterion: - After 6 months of treatment, - At each visit. • Time (days) to first sustained success (defined in the same way as the primary criterion) from D1 up to the end of the study, • Evolution of target IH on a 3-point scale (improvement, stabilisation, worsening) compared to the baseline evaluation,

Name of Company: Pierre Fabre Médicament	Individual Study Table	(For National Authority Use Only)
Name of finished product: **Hemangiol®**	**Referring to Module 5 of the Dossier**	
Name of active substance *(or ingredient)***:** **Propanolol**	**Vol.: .....Page: .....**	

Criteria for evaluation (cont'd):

- Time (days) to the first sustained improvement (defined as first visit where improvement was obtained and maintained at each scheduled subsequent visit) from D1 up to the end of the initial treatment period:
  - Compared to the previous visit;
  - Compared to baseline.
- Number of patients re-initiating treatment ("re-initiation"/"no re-initiation of treatment"), defined as a patient who restarted study treatment at the re-initiation visit (R)1 or a patient who received other treatment for IH,
- Change in size of target IH from baseline at each post-baseline visit (largest diameter of the superficial component, deep component, ulcerated area),
- Investigator's qualitative assessment of IH characteristics at each post-baseline visit:
  - Colour intensity on a 5-point scale (barely perceptible to bright red),
  - Tenseness on a 3-point scale (soft, firm, not appreciable),
  - Superficial component on a 4-point scale (flat to marked elevation),
  - Deep component on a 3-point scale (none, possible/definite presence),
  - Distortion of anatomical landmarks on a 3-point scale (none to marked).
- Investigator's assessment of the functional impact of the target IH at each post-baseline visit (using the Hemangioma Severity and Hemangioma Dynamic Complication Scales [HSS and HDCS]):
  - Ulceration on a 5-point scale,
  - Feeding difficulties on a 4-point scale,
  - Torticollis on a 4-point scale,
  - Cartilage distortion or destruction on a 4-point scale,
  - Airway involvement on a 6-point scale,
  - Visual compromise on a 6-point scale,
  - Pain on a 5-point scale.

<u>Quality of Life</u>

- Short Form-36 (SF-36) questionnaire by one of the parent during visits (V1,V5, V7 and end of each study period):
  - Score for the following 8 scales: physical functioning; role limitations because of physical problems. bodily pain, general health perceptions, energy/vitality, social functioning, role limitations due to emotional problems and mental health,
  - Scales scores then used to calculate two summary measures of physical and mental health.
- Haemangioma family burden (HFB) by self-administered questionnaire (V1 and end of each study period):
  - Score for the following 5 dimensions of life: family life, relationship and work, emotions/feelings, psychological and disease management (Module 1),
  - Score for the impact of the disease (Module 2),
  - Module 1 and 2 were then used to calculate a total HFB score.

<u>Safety</u>

Continuous assessment of number and type of adverse event (AEs),

- Global physical examination at each visit (Investigator rated assessments as normal/abnormal not clinically significant/abnormal clinically significant),
- Vital signs (height, weight, blood pressure [BP], HR) measured at each visit.

Name of Company: Pierre Fabre Médicament	Individual Study Table	(For National Authority Use Only)
Name of finished product: **Hemangiol®**	**Referring to Module 5 of the Dossier**	
Name of active substance *(or ingredient)***:** **Propanolol**	**Vol.: .....Page: .....**	

Statistical methods:

Sample size

The sample size was evaluated at 45 patients based on:

- A success rate of 60% at the end of treatment,
- α risk of 5% in two sided conditions,
- A confidence interval (CI) half-width calculated with the Jeffreys method of 15%, meaning that the lower limit of the CI would be above 45%, far from a rate of resolution without treatment (31% of complete resolution at a median age of 4 years.
- A drop-out rate of 10%.

Analysis sets

The following analysis sets were defined:

- The **Included Set**, all patients included at the Inclusion visit (V2/D1),
- The **Full Analysis Set (FAS)**, all patients who received at least one dose of the study treatment. This data set was used to perform analyses of safety and efficacy.

  Six subsets of **FAS** were analysed:
  - Achieved success at the end of the initial treatment period (primary endpoint),
  - Improved (compared to baseline) at the end of the initial treatment period,
  - With only the initial treatment period,
  - Completed the initial treatment period (i.e. no premature study withdrawal before the end of the initial treatment period),
  - Were in the follow-up period,
  - Required re-treatment.
- The **Per Protocol (PP) Set**, was the subset of the FAS composed of all patients without any major protocol deviation or other source of bias for primary criterion analyses,

Analysis of efficacy

All statistical results are descriptive (number, percentage and 95% CI), no statistical tests were performed.

Primary criterion

The primary efficacy criterion was binary (success/failure). Success was defined as the following occurring by the end of the initial treatment period:

- Resolution of the target IH *AND* the absence of functional impact linked to the target IH.

Failure was defined as the following occurring before the end of the initial treatment period:

- Premature study withdrawal for inefficacy or safety reason with a related AE leading to definitive study drug discontinuation before the end of the initial treatment period *OR r*eceiving prohibited treatments for the target IH in the usual conditions (appropriate formulation, dose and treatment duration) used to treat IH.

Statistical methods (cont'd):

Primary analysis

Descriptive analysis of success at the end of the initial treatment period was performed on the FAS, using last observation carried forward (LOCF) imputation (excluding baseline value) for missing data.

Supportive analysis

The same analysis as the primary analysis was performed on the PP set.

Sensitivity analysis

The same analysis as the primary analysis was performed on 1) the FAS, without imputation for missing data and 2) the subset of patients in the FAS who completed the initial treatment period (i.e. no premature study withdrawal before the end of the initial treatment period).

Secondary criteria

- Success at 6 months: descriptive analyses of success at V10 performed on the FAS using 1) LOCF imputation (excluding baseline value) for missing data and 2) without imputation for missing data,
- Success at each visit: descriptive analysis at each visit during:
  - The initial treatment period performed on the FAS,
  - The follow-up period performed on 1) the subset of the FAS who were in success at the end of the initial treatment period and 2) according to initial treatment duration (i.e. stopped after 6 months basic treatment/continued treatment after 6 months),
  - The re-treatment period performed on the subset of the FAS who required re-treatment,
- Time to first sustained success from D1 up to end of study compared to baseline and time to first sustained improvement compared to baseline/previous visit: Kaplan-Meier cumulative incidence estimates and associated curves were provided at each time point for the subset of patients who only participated in the initial treatment period and for the subset who required re-treatment,
- Evolution of target IH on a 3-point scale: qualitative description at each visit during the initial treatment period performed on the FAS, during the follow-up period performed on the subset of the FAS who were in improvement at the end of the initial treatment period and during the re-treatment period performed on the subset of the FAS who required re-treatment,
- Time to first sustained improvement compared to baseline and compared to previous visit: the same analyses as the time to first success were performed,
- Re-initiation of treatment: descriptive analyses performed on the subset of the FAS who were in success at the end of the initial treatment period and according to initial treatment duration (i.e. stopped after the basic 6 months treatment/continued treatment after 6 months),
- Size, other qualitative assessments and functional impact of target IH: change from baseline, descriptive analyses at each visit performed on the FAS.

Statistical methods (cont'd):

Quality of life assessment

- SF-36: 8 scales scores were derived and used to calculate 2 summary measures of physical and mental health. Descriptive statistics were performed by visit and at the end of the initial treatment period on the FAS,
- HFB questionnaire: scores were derived for the 5 dimensions of life and a 6th score for impact. A total score was calculated from these. The scores were normalised yielding a score between 0 and 100. Descriptive statistics were performed by visit and at the end of the initial treatment period on the FAS.

Analysis of safety

Descriptive statistics were performed on the FAS.

- AEs (emergent/non-emergent),
- Height, weight,
- Vital signs: analysis relative to normal ranges.

Post-hoc analyses

- Efficacy: Time to sustained success from D1 up to the end of follow-up on all FAS patients: patients with re-treatment were considered as 'no sustained success',
- Safety: Number of patients with change from baseline in HR ≤ -30 bpm **or** an HR value < lower limit of normal range (LLN).

Summary - Conclusions:

In total, 45 patients were enrolled and received the study treatment. Forty-three patients (95.6%) completed the study. Of these, all completed the initial treatment period, 34 patients (75.6%) entered the follow-up phase. 8 patients (17.8%) entered the re-treatment period.

Demographic characteristics met the expected population profile. Overall, there were more females (73.3%) than males (26.7%) and the mean (standard deviation [SD]) chronological age at study intake was 91.9 (37.7) days. Mean (SD) weight at birth was 3.2 (0.7) kg and breastfeeding was ongoing at enrolment for more than half of the patients (55.6%).

As per the inclusion criteria, a few high risk IHs were considered life-threatening, most IHs had a functional impact or risk thereof on the patient (64.4%) and most were considered disfiguring (60.0%). Ulcerated IHs were reported in 6 patients (13.3%).

IH characteristics at baseline met the expected population profile. Most patients had a localised (focal) IH (62.2%), whereas the remaining patients had multifocal (17.8%), segmental (4.4%) and IHs of indeterminate subtype (15.6%). In relation to the depth of affected vessel, most IHs were of a mixed (superficial and deep) subtype (82.2%). The majority of patients had IHs of the facial and neck area.

Efficacy results:

Primary criterion

The primary efficacy criterion was treatment success at the end of the initial treatment period (Yes/No). Success was determined by the Investigator and was evaluated based on the resolution of the target IH and the absence of functional impact linked to the target IH. A total of 34 patients (75.6%) achieved success at the end of the initial treatment period. The results of the supportive and sensitivity analyses confirmed the results of the primary analysis and demonstrated their robustness.

Name of Company: Pierre Fabre Médicament	Individual Study Table	(For National Authority Use Only)
Name of finished product: **Hemangiol®**	**Referring to Module 5 of the Dossier**	
Name of active substance *(or ingredient)***:** **Propanolol**	**Vol.: .....Page: .....**	

Efficacy results (Cont'd):

Secondary criteria

Success at 6 months and at each visit

The secondary efficacy criteria of success at 6 months and success at each visit demonstrated that treatment success became more apparent after 6 months of treatment, when 21 patients (46.7%) achieved treatment success. Continuation of treatment beyond 6 months up to success or a maximum of 12 months of age, a further 13 patients achieved success totalling 34 patients (75.6%) at the end of the initial treatment period.

Patients who achieved success during the initial treatment period were followed-up for 3 months without any treatment to monitor if success was maintained or if success regression occurred. At the end of the 3-month follow-up period, 23 out of the 34 patients (67.6%) had maintained success while 11 patients (32.4%) had success regression. Success was maintained in 13 out of the 21 patients (61.9%) treated for the basic 6 month period and in 10 out of the 13 patients (76.9%) who continued treatment after 6 months up to success (before 12 months of age).

Re-treatment

Of the patients who achieved success at the end of the initial treatment period, the majority of patients were judged by the Investigators as not requiring re-treatment (26 patients, 76.5%). Only 8 patients (23.5%) re-initiated treatment, (5 patients who had only the basic 6 month treatment and 3 patients who had continued treatment until success or up to 6 months of age). At the end of the 6 month retreatment period, 7 out of the 8 patients (87.5%) achieved treatment success.

Time to sustained success and sustained improvement

Median time to first sustained success was 246.0 days (min, max; 64.0, 307.0 days) in patients who participated in the initial treatment period. In these patients, the median time to first sustained improvement compared to previous visit was 15.0 days (min, max; 7.0, 276.0 days) and the median time to first sustained improvement compared to baseline was 8.0 days (min, max; 7.0, 85.0 days).

Three-point evolution

The 3-point evolution of the target IH assessment demonstrated that most or all patients had an improvement (as opposed to stabilisation or worsening) from baseline (97.8% at the end of the initial treatment period). This was maintained during the follow-up period (94.1% at the end of the follow-up period). Of the patients who required re-treatment, most or all had an improvement from baseline at each visit (100% at the end of the re-initiation period).

Size of target IH

The mean size of the superficial (-1.82 cm) and deep component (- 2.88 cm) steadily decreased at each visit during the initial basic 6 months treatment. Patients who then continued treatment after 6 months had a decrease in size from baseline of (-1.28 cm) for the superficial component and (-1.91 cm) for the deep component. During the follow-up period, the decrease achieved in the basic treatment period was maintained for the superficial component (-1.83 cm) and was further decreased for the deep component (-3.08 cm). For re-treated patients, at the start of the re-treatment period, the size of the superficial component was still noticeably decreased (-2.63 cm) from baseline but the deep component had returned to a size similar to that seen at baseline (-1.70 cm). However, both components steadily decreased in size from baseline with re-treatment. The mean ulcerated area (in those who had ulcerated IHs) steadily decreased in size from baseline until there was no ulcerated area apparent at month 3 and thereafter. This was maintained during the follow-up period.

Qualitative assessment of target IH

The colour intensity, tenseness, elevation of the superficial component, deep component of the target IH and the distortion of local anatomical landmarks all tended to steadily lessen with treatment. This was maintained during the follow-up period.

Functional impact of target IH

Ulceration, feeding difficulties, torticollis, cartilage distortion or destruction, airway involvement, visual compromise and pain related to the target IH all tended to steadily lessen with treatment. These favourable changes were generally maintained during the follow-up period where no treatment was given.

Name of Company: Pierre Fabre Médicament	Individual Study Table	(For National Authority Use Only)
Name of finished product: **Hemangiol®**	**Referring to Module 5 of the Dossier**	
Name of active substance *(or ingredient)*: **Propanolol**	**Vol.: .....Page: .....**	

Quality of Life results:

Despite no or very marginal impact of the patient's IH at baseline on the QoL of parents, the mean of all the SF-36 scaled scores increased from baseline at almost all assessment timepoints. This general increase from baseline indicated that the impact of the patient's IH decreased in each of these areas with treatment. The summary scores demonstrated that the impact on mental and physical health generally decreased with treatment with an increase in mean score from baseline seen at most assessment time points especially for the mental component summary (mean increase of 3.2 at the end of the initial treatment, 2.76 at the end of follow-up). For the physical component summary, the change was 0.93 at the end of the initial treatment period and -0.09 at the end of the follow-up visit.

The mean of all 6-dimension scores and of the total score of the HFB questionnaire decreased from baseline at each assessment time point. This indicated a decrease in the burden perceived by the patients' parents or guardians following treatment despite no impact of their child's IH on their family life and relationship/work life at baseline (median=0) . The HFB median total score change was -8.85 at the end of the initial treatment period, and -7.10 at the end of follow-up, mainly due to the relevant decrease in the emotional and psychological dimensions of the burden (median change of -22.2 [-50%] at both time points for both dimensions).

Safety results:

The total mean (SD) extent of exposure of patients to study treatment was 251.3 (81.1) days, i.e. 8.3 months, which fell well within the planned treatment duration of a minimum of 6 months and a maximum of 17 months.

Overall, 36 patients of the FAS (80.0%) experienced at least 1 treatment-emergent AE (TEAE) with most patients (71.1%) experiencing at least 3 TEAEs. The most frequently reported TEAEs (i.e. in ≥ 15% of patients) were bronchitis, pyrexia, conjunctivitis, nasopharyngitis and upper respiratory tract infection, bradycardia and teething pain. All other TEAEs were reported with an incidence of < 15% of patients.

Almost all TEAEs were mild or moderate in intensity. Severe TEAEs were only experienced by 1 patient (hernia and laparoscopic surgery) during the treatment period and were not considered to be related to treatment.

Overall, 17 of the 45 patients included in the FAS (37.8%) experienced at least 1 related TEAE with the most frequently reported events (i.e. in ≥ 5% of patients) being bronchitis, bradycardia and infantile haemangioma. All other TEAEs were reported with an incidence of < 5% of patients. The majority of the related TEAEs occurred in the initial treatment period; 35.6% of patients in the FAS experienced at least 1 related TEAE, almost all were experienced before or at 6 months. The most frequently reported related TEAEs were bronchitis and bradycardia. During the re-treatment period, all 8 patients who required re-treatment experienced TEAEs, however, only 2 TEAEs were suspected to be related to study treatment; 1 event of upper respiratory tract infection and 1 event of infantile haemangioma.

There were no deaths or AEs leading to definitive treatment discontinuation reported in this study. Nine patients experienced 16 serious AEs (SAEs) (13 were treatment-emergent SAEs), none of which were suspected to be related to study treatment. All SAEs were resolved by the end of the study.

Only 1 patient had a significant reduction in HR from baseline (greater than 30 bpm *and* a HR value that was below the 80 bpm). This occurred during the follow-up period. During the initial treatment period, 4 patients had a reduction in HR from baseline that was greater than 30 bpm, however, the HR values remained above the 80 bpm. Only 1 patient had a low HR (70 – 80 bpm) which occurred during the initial treatment period and very low rate HR (<60 bpm) was recorded in no patient.

About half of the patients had no change in DBP or SBP relative to normal ranges.

Overall, no bradycardia reported during this study was associated with clinical symptoms.

Mean weight and height steadily increased at each assessment time point as expected of an infant population. The most common concomitant treatments in all periods were anti-infective agents.

Overall Conclusion:

Treatment with Hemangiol® for a duration of at least 6 months and up to 12 months of age is efficacious in the great majority of infants with high risk IH. The extension of the treatment beyond 6 months up to a maximum of 12 months of age clinically meaningfully increases the success rate. Efficacy is persistent in most subjects after 3 months without treatment. In subjects requiring re-initiation of treatment, Hemangiol® was also efficacious. Safety profile in this high risk haemangioma population was satisfactory with no unexpected signal.

Date of report:10th August 2017