Pierre Fabre Dermatologie
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1. TITLE PAGE

CLINICAL STUDY REPORT

A RANDOMISED, DOUBLE BLIND, CONTROLLED, MULTICENTRE STUDY IN INFANTS WITH INFANTILE HEMANGIOMA TO COMPARE PROPRANOLOL GEL TO PLACEBO.

Investigational product:	V0400GL (propranolol 1% gel)
Study Design:	Randomised, double blind, placebo controlled, multicentre study
EudraCT number:	**2011-003144-50**
Protocol number:	V00400 GL 2 01 1A
Phase of development:	Phase IIa
Date of first enrolment:	February 10, 2012
Date of last completed:	May 09, 2013
Coordinating Investigator:	Christine Léauté-Labrèze, MD CHU de Bordeaux Hospital, F-33000 BORDEAUX Phone: +33 (0)5 56 79 59 42
Sponsor Representative for Study Report:	Head of Therapeutic Area: Alain Delarue, MD, IRPF 3 avenue Hubert Curien, F-31100 TOULOUSE Phone: +33 (0)5 34 50 61 88

Date of report: **November 10, 2013**

Study performed in compliance with Good Clinical Practice.

2. SYNOPSIS

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

Title of study:	**A randomised, double blind, controlled, multicentre study in infants with infantile hemangioma to compare propranolol gel to placebo.**	
Coordinating Investigator:	Dr Christine Léauté-Labrèze, MD CHU de Bordeaux Hospital, F-33000 BORDEAUX	
Investigators:	44 recruiting investigators (mainly paediatricians and/or dermatologists): 26 in France, 15 in Spain and 3 in Poland.	
Study centres:	17 active sites involved in the management of infantile hemangiomas in 3 European countries: France (9 sites), Spain (5 sites) and Poland (3 sites)	
Publication (reference):	Not written to date	
Studied period:: **Date of first enrolment** **Date of last completed**	12 weeks of treatment and 12 weeks of post treatment follow-up per patient. First patient in = February 10, 2012 Last patient out = May 09, 2013	**Phase of development:** IIa
Objectives:	Primary objective: To assess the efficacy of a propranolol 1% gel (as named V0400GL) in terms of complete/nearly complete resolution of the IH at W12 compared to baseline. Secondary objectives: - To assess V0400GL efficacy in terms of complete/nearly complete resolution of the IH at W4, W8 and W24 compared to baseline. - To evaluate the parent(s) or guardian(s) on-site qualitative assessments. - To assess the persistence of efficacy 12 weeks after the end of treatment. - To assess the safety profile and the local tolerance of the V0400GL.	
Methodology:	This was a prospective, multicentre, international, randomised, double-blind placebo-controlled proof of concept study in two parallel groups: V0400GL applied topically twice daily (maximum 150 mg of gel per application) placebo gel applied topically twice daily (maximum 150 mg of gel per application) Patients were randomized to receive V0400GL or placebo in a 1:1 ratio, with stratification by age (35 to 90 days and 91 to 150 days). Patients were treated daily for 12 weeks (from D0 to visit W12) and then followed up for a further 12 weeks (up to visit W24). If study treatment was discontinued, the patient was followed up to W24 if possible. Patients attended the clinic at Screening, and then during the treatment period on Day 0 (D0, baseline), W2, W4, W8 and W12 (end of treatment [EOT]). After a 3-month off-treatment follow-up period, patients attended the clinic at W24 for the end of study (EOS) visit.	
Number of patients (planned and analysed):	It was planned to recruit 80 patients (40 per treatment group, randomised in a 1:1 ratio). 82 patients were screened and 81 patients were randomised, treated and analysed: 41 patients in the placebo group and 40 patients in the V0400GL group.	
Diagnosis and main criteria for inclusion:	Patients with only one proliferating IH with largest diameter $\geq$ 1cm and $\leq$ 5 cm present anywhere on the body except on the head, the neck, the hands and on the diaper area, and aged between 35 to 150 days old inclusive, at inclusion.	

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Test product, **Dose,** **Mode of administration,** **Batch number:**	V0400GL 10mg/g gel Sufficient quantity to ensure adequate hemangioma coverage with a maximum quantity of 150 mg/application. Topical administration twice daily. Batch CLP093A (expiry 03/2013) Batch CLP095A (expiry 07/2013)
Duration of treatment:	12 weeks
Reference therapy, **Dose,** **Mode of administration,** **Batch number:**	Placebo 10mg/g gel Sufficient quantity to ensure adequate hemangioma coverage with a maximum quantity of 150 mg/application. Topical administration twice daily. Batch CLP092A (expiry 03/2013) Batch CLP094A (expiry 07/2013)
Criteria for evaluation: **Efficacy:**	*Primary efficacy criterion:* The primary efficacy criterion was the evolution of IH from baseline to W12. The binary primary endpoint (success/failure) was evaluated based on the intra-patient blinded centralised independent qualitative assessments of W12 photographs of the IH compared to baseline. A treatment success was defined as a centralised assessment of complete/nearly complete resolution of the IH at W12 compared to baseline, where nearly complete resolution was defined as a minimal degree of telangiectasis, erythema, skin thickening, soft tissue swelling and/or distortion of anatomical landmarks. *Secondary efficacy criteria:* • Centralised assessments of complete/nearly complete resolution of the IH at W4, W8 and W24 compared to baseline. • Investigator on-site qualitative assessments o At each scheduled post-baseline visit compared to baseline categorical endpoints for complete/nearly complete resolution o At week 4, week 8, week 12 and week 24 compared to baseline categorical endpoints for IH evolution (4-points scale: complete resolution, improvement, stabilisation, worsening) o At each scheduled post-baseline visit compared to the previous schedule visit, categorical endpoints for IH evolution (4-points scale: complete resolution, improvement, stabilisation, worsening) • Parent(s) or guardian(s) on-site qualitative assessments at each scheduled post-baseline visit compared to the previous scheduled visit o Categorical endpoints for IH evolution (4-points scale: complete resolution, improvement, stabilisation, worsening) ***Persistence of efficacy criteria:*** • Persistence of complete/nearly complete resolution of the IH at W24 compared to W12 based on centralised assessments. • Investigator qualitative assessments by categorical endpoints for hemangioma evolution (4-points scale: complete resolution, improvement, stabilisation, worsening) at Week 24 (3 months after end of treatment). ***Safety criteria:*** • Adverse events • Vital signs: heart rate, blood pressure, respiratory rate, • Physical findings: height, weight, head circumference, temperature, pulmonary auscultation, liver palpation, global physical examination.

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Statistical methods:

The main objective of the study was to assess the efficacy of V0400GL topical treatment versus placebo in infants with localized uncomplicated proliferating IH.

Only the primary analysis of the primary efficacy criterion, on which is based the sample size justification, could lead to a causal interpretation. All other statistical results were to be regarded as descriptive.

The statistical significance level of the various two sided tests of all analyses was 5%.

Data sets analysed:

- The full analysis set (FAS) corresponded to all randomised patients having received at least one dose of the study treatment. This data set was used to perform analyses of Efficacy (including the primary analysis) and Safety.
- The Per Protocol (PP) Set corresponded to FAS patients without any major protocol deviation or other source of bias for primary criterion analyses and characterised by a minimal treatment exposure of 28 days (4 weeks) and primary efficacy criterion available. This data set was used to perform the supportive analysis of the primary analysis.
- The Persistence Analysis Set (PAS) corresponded to FAS patients with a follow-up period, excluding patients having received a non authorised medication for IH between W12 and W24 visits identified by the Validation Committee. This data set was used to perform the analyses of persistence of efficacy criteria.

Primary efficacy analysis:

The primary efficacy criterion is the evolution of target IH from baseline to W12 (success/failure) based on the intra-patient blinded centralised independent qualitative assessments of W12 photographs of the IH compared to baseline.

Patients who discontinued prematurely treatment period for inefficacy or safety reason with a related AE leading to definitive study drug discontinuation (noted “treatment intolerance” in the CRF reasons for early treatment stop) between week 4 and week 12 visits were classified as failures. "A related AE" is an AE with a relationship to the study drug other than “Not suspected”. Patients who discontinued prematurely treatment period for other reason were evaluated based on the intra-patient blinded centralised independent qualitative assessments of W12 photographs of the IH compared to baseline. For patients without post-baseline evaluation based on the intra-patient blinded centralised independent qualitative assessments of W12 photographs of the IH compared to baseline, the primary efficacy criterion was considered as missing in the statistical analysis. For patients having taken non-allowed concomitant treatment before week 12 visit, the Validation Committee decided whether they were classified as failures.

- The proportion of patients with treatment success (complete/ nearly complete resolution) was analysed on the FAS at W12 using a logistic regression model with age stratum, binary variable associated to superficial / non superficial type at baseline and treatment group as factors with LOCF imputation (excluding baseline value) for missing data. Odds ratios (OR) and the corresponding 95% confidence intervals were provided as a measure of the treatment effect.
- A supportive analysis was performed on the PP Set.
- Two sensitivity analyses were performed on the FAS.

The proportion of successes on the primary criterion was also analysed using the logistic regression model with only age stratum, and treatment group as factors, with LOCF imputation for missing data. The Odds Ratio and the corresponding 95% confidence interval were provided as a measure of the treatment effect.

The primary analysis on the FAS was repeated without LOCF imputation for missing data. For patients who discontinued prematurely the study drug before Week 12, primary efficacy criterion was considered as missing in this analysis.

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Statistical methods:

Secondary efficacy criteria:

All the secondary efficacy criteria were analysed on the FAS, except persistence of efficacy criteria that were analysed on the PAS. Descriptive statistics were provided for all criteria, by treatment group and assessment time.

Investigators on-site qualitative assessments:

- *Success** (complete/nearly complete resolution) and *IH evolution* (4-points scale: complete resolution, improvement, stabilisation, worsening) compared to baseline and to the previous scheduled visit, were compared between treatment groups at W12 using the logistic regression model with age stratum, binary variable associated to superficial / non superficial type at baseline and treatment group as factors with LOCF imputation (excluding baseline value) for missing data.

*Classifications as failures on primary criterion (for patients having taken non-allowed concomitant treatment before week 12 visit identified by the Validation Committee or patients who discontinued prematurely treatment period for inefficacy or safety reason with a related AE leading to definitive study drug discontinuation) were also applied for Investigator qualitative assessments on resolution of IH compared to baseline (success/failure) at Week 12.

*Glo*bal improvement (yes/no) over W2-W12 period was compared between treatment groups using logistic regression model with age stratum, binary variable associated to superficial / non superficial type at baseline and treatment group as factors. Yes was assigned if at least one improvement and no worsening had been assessed. Otherwise no was assigned. No was also assigned if the patient prematurely discontinued treatment or took a prohibited treatment.

- *Time to first sustained improvement (first improvement after which there was no worsening) up to W12 compared each visit with the previous visit up to W12 and was described using Kaplan Meier survival curves, by treatment group.*

Parent(s) or guardian(s) on-site qualitative assessments

IH evolution analysed as described for investigators assessment (above)

Time to first sustained improvement analysed as described for investigators assessment (above)

Persistence of Efficacy (analysed on PAS)

- Investigator qualitative assessments (4-points scale: complete resolution, improvement, stabilisation, worsening) for hemangioma evolution at Week 24/EOS compared to Week 12/EOT were compared between treatment groups visit using logistic regression model with age stratum, binary variable associated to superficial / non superficial type at baseline and treatment group as factors with LOCF imputation (excluding baseline value) for missing data.
- Rate of successes and persistent successes at Week 24/EOS were also analysed based on the centralised independent qualitative assessments in the same way of the primary analysis of the primary efficacy criterion.

Patients who discontinued prematurely follow-up period for inefficacy or safety reason (with a related AE) between week 12 and week 24 visits were classified as failures for persistence analysis.

Safety Analysis

The safety analysis (extent of exposure, AEs, tolerability, vital signs, global physical examination and concomitant treatments) was performed on the FAS, as descriptive summary statistics by treatment group and by period (treatment period and follow-up period).

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Summary - Conclusions:

Study Patients

Of the 82 patients were screened, 81 (98.8%) were selected and were randomised to receive treatment. The one screened patient who was not selected was excluded because she met one non inclusion criteria. Overall, 10 patients withdrew prematurely: 6 in the placebo group and 4 in the V0400GL group before the end of treatment at W12.

The numbers of completers were:

- 12 week treatment period: 34 (85.0%) in the placebo group and 37 (90.2%) in the V0400GL group.
- 24 week entire study: 30 (75.0%) in the placebo group and 35 (85.4%) in the V0400GL group

Major protocol deviations were reported for 7 (17.5%) of patients with placebo and 3 (7.3%) of patients with V0400GL.

Therefore the following data sets were analysed:

	Placebo n=40		**V0400 GL 01A n=41**		**Total n=81**	
Full Analysis Set (FAS)	40	(100.0%)	41	(100.0%)	81	(100.0%)
Per Protocol Set (PP Set)	33	(82.5%)	38	(92.7%)	71	(87.7%)
Persistence Analysis Set (PAS)	32	(80.0%)	35	(85.4%)	67	(82.7%)

Demographics were generally comparable between the two groups. Overall there was a notably higher proportion of females (71.6%) versus males (28.4%) (which reflects the demographics of IH in the general population). However, there were differences in IH baseline characteristics.

Regarding IH baseline characteristics, the incidence of superficial IH was markedly higher in the placebo group (80.0%) than in the V0400GL group (36.6%). In addition, compared to the placebo group, lesions in the V0400GL group tended to be more red in colour intensity and to be more elevated. Given the topical application of study drug, these differences could have an impact of efficacy assessment and could disadvantage the active treatment.

Efficacy results

The primary efficacy criterion (complete/ nearly complete resolution of the target IH at W12) demonstrated a significant (p=0.018) effect of V0400GL, with success reported for 6 patients (14.6%) of patients in the V0400GL group versus 1 patient (2.6%) of patients in the placebo group. There was no effect of age stratum on treatment success (p=0.79) but IH type (superficial or not) had a significant effect on the analysis (p=0.027). This result should however, be interpreted with caution since randomisation was not stratified on IH type and there is a strong imbalance in the baseline incidence of superficial IH between treatment groups. Furthermore, the number of patients is very limited for some subgroups.

	Placebo n=40		**V0400 GL 01A n=41**	
Missing	2		-	
Evolution of IH from baseline to W12*				
Failure	37	(97.4%)	35	(85.4%)
Success	1	(2.6%)	6	(14.6%)
Model Evolution of IH*=Age stratum+IH Type+Treatment**				
Test for Treatment effect, p= 0.018				
Test for Age stratum effect, p= 0.79				
Test for IH Type** effect, p= 0.027				
Odds Ratio Estimate for Treatment effect			15.33	
[OR 95% CI]			[1.59; 147.57]	

The primary results were confirmed by supportive analysis on the PP set (p=0.024) and by subgroup analysis on the subgroup of patients with superficial IH at D0 (p=0.021). Sensitivity analyses supported these results.

Secondary Efficacy Criteria

- The investigators assessment of global improvement demonstrated a significant treatment effect with V0400GL at W12 compared to W2 (68.3% of improvement versus 42.1% in the placebo group; p=0.033). V0400GL exerted a statistically significant treatment effect (p=0.026) with global improvement of IH from W2 to W12 reported for 65.9% of patients with V0400GL versus 45.9% of patients with placebo.
- The time to first sustained improvement (based on investigators assessments) was significantly shorter in the V0400GL group, with sustained improvement seen from W2 (p=0.026)
- The parents assessment of improvement did not demonstrate a significant treatment effect for V0400GL (p=0.43).

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Secondary Efficacy Criteria (cont'd)

- Persistence of treatment effect was evaluated at W24, after a 3 month off-treatment period. Treatment success at W24 was reported for over 2-fold more patients in the V0400GL group (17.6%) compared to the placebo group (6.9%), but this did not translate into a significant treatment effect (p=0.63).

Safety results

Overall, the safety profile was acceptable with no new safety signals detected.

- Mean exposure was similar between treatment groups
- There were no deaths in the study. Five SAEs were experienced by 4 patients (gastroenteritis/placebo-treatment period; viral infection and bronchitis/V0400-treatment period, RSV bronchiolitis and rotavirus infection/V0400-follow-up period). All patients recovered and no SAE was considered related to study drug.
- The majority of patients in each group had at least one TEAE, with a slightly higher incidence in the V0400GL group (78.0%) versus the placebo group (72.5%)
- In general, TEAEs were more common during the treatment period than during follow-up, and were slightly more frequent with V0400GL than with placebo in each study period. During the treatment period the incidence of TEAEs was 67.5% in the placebo group and 75.6% in the V0400GL group.
- TEAEs that were notably more common with V0400GL than placebo (>5% difference) were pyrexia, teething, condition aggravated and conjunctivitis in the treatment period and rhinorrheoa in the follow-up period
- The PT condition aggravated was more frequent with V0400GL (4 patients comprising 3 verbatim terms of ulcerated IH and 1 of redness of IH skin) than with placebo (1 patient with a verbatim term of ulcerated IH). All TEAEs of condition ulcerated occurred during the treatment period. All these TEAEs resolved during the study except one IH ulceration.
- Since study drug was applied topically, the SOC Skin and subcutaneous disorders was analysed. TEAEs in this SOC were more common in the treatment period than during follow-up, with a higher frequency in the V0400GL group. Pigmentation disorder and pruritis occurred exclusively with V0400GL and were each reported by 2 patients during the treatment period and 1 patient during follow-up. All these TEAEs resolved during the study.
- The maximum intensity of TEAEs was mild or moderate for all TEAEs during the treatment period.
- Five patients had TEAEs considered by the investigator as related to the study treatment: 1 patient in the placebo group (restlessness and nervousness) and 4 patients in the V0400GL group (condition aggravated, insomnia, folliculitis). None of these events were reported as serious or severe in intensity, all occurred in the treatment period, and all resolved during the study.
- Two patients had TEAEs leading to definitive study drug discontinuation in the V0400GL group. Both had condition aggravated in the context of IH ulceration and both occurred in the treatment period; one had not resolved at the end of the study.
- Local tolerability was good for the majority (at least 82.9%) of patients in each treatment group at each visit
- Analysis of vital signs and physical examination did not uncover any safety concerns. The incidence of bradycardia was similar between treatment groups.

Conclusion:

This study in 81 patients, demonstrated the efficacy and the safety of a topical propranolol 1% gel (V0400GL) despite the imbalance in IH characteristics between groups which potentially disadvantaged the active treatment.

Improvement of IH was observed during the treatment course with V0400GL but resolution of IH remains limited over the 12 weeks active treatment period (14.6%).

Even if conclusions should be drawn with care, IH resolution appeared better in superficial IH (5/15 patients).

V0400GL has a good safety profile, with a good local and systemic tolerability.

Date of report: November 10, 2013