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STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number:	205,410 (S0000)
Drug Name:	[redacted] (b) (4) ® (propranolol) 3.75 mg/mL, Oral Solution
Indication:	Proliferating Infantile Hemangioma (IH) requiring systemic therapy
Applicant:	Pierre Fabre Pharmaceuticals
Dates:	Date of Document: May 17, 2013 PDUFA Due Date: March 17, 2014
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Table of Contents

1. EXECUTIVE SUMMARY **3**

2. INTRODUCTION **3**

2.1 OVERVIEW 3
2.2 DATA SOURCES 4

3. STATISTICAL EVALUATION **4**

3.1 DATA AND ANALYSIS QUALITY 4
3.2 EVALUATION OF EFFICACY 4
3.2.1 Study Design and Endpoints 4
3.2.1.1 Study Objectives and Design 4
3.2.1.2 Study Endpoints 6
3.2.2 Statistical Methodologies 7
3.2.3 Patient Disposition, Demographic and Baseline Characteristics 10
3.2.4 Efficacy Results and Conclusions 15
3.2.4.1 Sponsor's Results for Primary Efficacy Endpoint 15
3.2.4.2 Sponsor's Results for Other Secondary Efficacy Endpoint 15
3.2.4.3 Sponsor's Sensitivity and Adjusted Analyses for the Primary Endpoint 16
3.2.4.4 Sponsor's Conclusion 19
3.2.4.5 Statistical Reviewer's Findings and Comments 19
3.3 EVALUATION OF SAFETY 24

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS **25**

4.1 GENDER, RACE AND AGE 25
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS 26
4.2.1 IH Location and Randomization Ratio 26
4.2.2 Region 27

5. SUMMARY AND CONCLUSIONS **28**

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE 28
5.2 CONCLUSIONS AND RECOMMENDATIONS 29

6. APPENDIX: SPONSOR'S SENSITIVITY ANALYSES PER FDA'S REQUEST **30**

Reference ID: 3433600

1. EXECUTIVE SUMMARY

Study V00400 SB 201 appeared to support the propranolol's efficacy for both 3 mg and 1 mg 6 months regimens. However, there were differential dropout rates between the placebo and the study doses and between different regions/countries (most placebo dropouts were from Western Europe and France). While it can be argued that a much higher dropout rate in the placebo group might lend an additional assurance for propranolol's efficacy, that the placebo group had a much higher dropout rate and dropped out early and most placebo dropouts took propranolol as the prohibited medications after dropping out might have yielded a bias in favor of propranolol. Hence the strength of evidence for the propranolol efficacy is probably overstated by the nominal p-value based on a number of the reviewer's sensitivity analyses.

2. INTRODUCTION

2.1 OVERVIEW

This NDA submission included efficacy data for two studies in treating patients with proliferating infantile hemangiomas (IH) requiring systemic therapy; one was a pivotal Phase II/III Study V00400 SB 201 (referred as Study 201 in this review) and the other one was the Phase I PK Study 102, which was an open-label, single-arm, repeat-dose Phase I PK study. Study 201 was a randomized, placebo controlled, multi-dose, multi-center, adaptive phase II/III study in infants with proliferating IH requiring systemic therapy to compare four regimens of propranolol (1 or 3 mg/kg/day for 3 or 6 months) to placebo. This review is devoted to Study 201.

According to the sponsor, the design of Study 201 was finalized in line with recommendations made by both the FDA and the EMA, after extensive parallel scientific advice discussion (a Special Protocol Assessment (SPA) in the US and a Pediatric Investigation Plan (PIP) in Europe). The claimed efficacy of propranolol in the treatment of IH requiring systemic therapy is based on the results of the pivotal Study 201.

In this submission, the analyses of all the efficacy assessment for Study 102 were descriptive. For Study 201, the Phase II/III adaptive design was based on benefit and risk assessment to identify one or two suitable propranolol regimens at an interim analysis and to investigate the efficacy of the chosen regimen(s) compared to placebo after all patients had completed Week 24 or had been prematurely withdrawn from study treatment (primary analysis). The primary endpoint was complete or nearly complete resolution of target IH at Week 24.

Reference ID: 3433600

For Study 201, the interim analysis was conducted on the 188 Intent-to-Treat (ITT) Stage I patients. The efficacy results clearly favored the 3 mg/kg/day 6 months regimen, with 62.8% (27 patients) presenting complete or nearly complete resolution vs. 8.0% (2 patients) in the placebo 6 months regimen, 9.8% in the 1 mg/kg/day 3 months regimen, 37.5% in the 1 mg/kg/day 6 months regimen, and 7.7% in the 3 mg/kg/day 3 months regimen (See Table 6 on Page 15) and it was confirmed by the full primary analysis based on both stages.

2.2 DATA SOURCES

The sponsor's original submission including data files and clinical study reports are stored in the following link: \\Cdsesub1\evsprod\NDA205410. During the review cycle, we have asked the sponsor some clarifying questions regarding the study design and conduct. We also have asked the sponsor to perform some related analyses by including the overrun patients. The submission is stored in the following link: \\Cdsesub1\evsprod\NDA205410\0007.

3. STATISTICAL EVALUATION

3.1 DATA AND ANALYSIS QUALITY

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

3.2 EVALUATION OF EFFICACY

The following study description is mostly extracted from the sponsor's clinical study report. Any discrepancy identified between the sponsor's clinical study report and protocol is discussed in the section of statistical reviewer's findings.

3.2.1 Study Design and Endpoints

Study Title: A randomized, controlled, multi-dose, multicenter, adaptive phase II/III study in infants with proliferating infantile hemangiomas requiring systemic therapy to compare four regimens of propranolol (1 or 3 mg/kg/day for 3 or 6 months) to placebo (double blind)

3.2.1.1 Study Objectives and Design

The main purpose of this study was to evaluate the efficacy of propranolol versus placebo in treating infants with proliferating IH requiring systemic therapy.

Each patient was treated with the assigned study treatment until W24 (or premature discontinuation), then followed-up until W96, without receiving the study drug. The primary statistical analysis was planned on the W24 results. The current report covers only the methods and results of the first 24 weeks period. The objectives of this first study part were the following:

Reference ID: 3433600

Primary 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).

Safety Objectives

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.

The study was a randomized, double-blind, placebo controlled, multi-dose, multicenter, adaptive phase II/III study in infants with proliferating infantile hemangiomas requiring systemic therapy.

After eligibility checking and informed consent signature by the parent(s) or legal guardian, patients were randomized in a 2:2:2:2:1 ratio to receive respectively: one of four regimens of propranolol (regimen 1: ***1 mg/kg/day for 3 months***, regimen 2: ***1 mg/kg/day for 6 months***, regimen 3: ***3 mg/kg/day for 3 months***, regimen 4: ***3 mg/kg/day for 6 months***) or ***placebo***. The randomization was stratified by age and IH localization (Note that the 2:2:2:2:1 randomization ratio and IH localization stratum were added following protocol amendment PA02, introducing the extension of the study to non-facial hemangiomas and replaced the initial randomization ratio of 1:1:1:1:1 and continent stratum).

Propranolol dosing (1 or 3 mg/kg/day for 3 or 6 months) included a titration phase.

The study protocol was designed to ensure double-blind conditions at randomization and throughout the treatment period:

- Randomization was managed by an independent randomization team and centralized via an IVRS,
- Patients assigned to one of the two 3 months treatment duration regimens received placebo for the last 3 months of treatment,
- A dummy titration was used for patients assigned to placebo or a 1 mg/kg/day propranolol regimen.

The parent's complete participation up to W24 comprised 11 scheduled visits:

- A screening visit (when possible, the screening visit could be done on the same day as the baseline visit),
- 10 visits during the 24-week study treatment period, starting on baseline visit (Day [D]0, 0 to 14 days after the screening visit, then D7, D14, D21, Week[W]5, W12, W16, W20 and W24, end of study treatment: EOT),

Reference ID: 3433600

In the case of a worsening of IH during the study treatment period for which the investigator considered it was necessary for the Patient's well-being to administer a new treatment of his/her choice, the study treatment was permanently discontinued.

Adaptive Design

The adaptive design of this phase II/III study was organized in two stages:

- Stage 1, corresponded to the phase II part, comparing the four propranolol regimens to placebo,
- Stage 2, corresponded to the phase III part, comparing the single or two selected propranolol regimen(s) to placebo.

3.2.1.2 Study Endpoints

Primary Efficacy Criterion: success/failure based on the centralized independent assessment of photographs:

The primary efficacy criterion is the evolution of target IH from baseline to W24. The binary primary endpoint (success/failure) was 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 is defined as a centralized assessment of complete/nearly complete resolution of the target IH at W24 compared to baseline, where nearly complete resolution is defined as a minimal degree of telangiectasis, erythema, skin thickening, soft tissue swelling and/or distortion of anatomical landmarks.

Secondary Efficacy Endpoint: success/failure based on the on-site investigator's assessment:

The secondary efficacy criterion is success/failure (binary endpoint) based on the investigator on-site 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 analyzed in the present report.

Other Secondary and Exploratory Efficacy Endpoints Based on Centralized Assessments of the Target IH:

- Endpoints based on the independent blinded Type 1 assessments of complete/nearly complete resolution:
  - Success/failure (binary endpoint) at W12, W36 and W48 compared to baseline, where treatment success is defined as for the primary efficacy endpoint
  - Time to first sustained complete/nearly complete resolution (W12, W24, W36 or W48 compared to baseline)

Reference ID: 3433600

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

  - Categorical endpoints for target IH evolution (3-point scale: improvement, stabilization, worsening) between paired patient-visits (W5, W8, W12, W16, W20 or W24 compared to baseline, W5, W8, W12, W16 or W20, respectively). A global improvement was also computed on the W5-W24 period (Yes/No), e.g. a binary endpoint of improvement between at least one pair of visits, without any assessments of worsening between the paired visits versus failure to improve (worsening between at least one pair of visits or stabilization between all paired visits). The treatment failure definition ensured that a worsening of IH between for example W12 and W24 could be detected even if the IH was still in an improved state at W24 compared to baseline
  - Time to first sustained improvement (first improvement after which there was no worsening) of the target IH based on Type 2 centralized qualitative assessments (see Section 8.1.3) of paired patient-visits (W5, W8, W12, W16, W20 or W24 compared to baseline, W5, W8, W12, W16 or W20, respectively);

- Endpoints based on centralized quantitative assessments (Haeghen et al 2006):
  - Continuous and categorical endpoints (change in size and color of target IH) at W12 and
  - W24 compared to baseline

3.2.2 Statistical Methodologies

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 (i.e., IDMC) 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. A futility criterion was also included in the case that none of the four regimens was identified as potentially efficacious for further investigations in Stage 2 of the study.

Based on their review, the IDMC members had to recommend the Sponsor whether to continue the study with one or two propranolol regimen(s), to stop the study for futility or safety purpose or to increase the study sample size. The IDMC members ensured that their

Reference ID: 3433600

recommendations did not unblind the study. In the case where the Sponsor decided to continue the study, the independent statistician had to communicate to the independent randomization team which regimen(s) was (were) to be carried forward.

Note that recruitment was to continue to the five treatment arms in a 2:2:2:2:1 ratio after the first 40:20 (propranolol:placebo) patients had been randomized per arm and until the single or two propranolol regimens had been selected or the study terminated prematurely. Assuming that the study was not discontinued at the interim analysis, any patients recruited prior to the interim analysis decision to one of the treatment arms considered for the efficacy analysis of Stage 2 of the study (placebo and the chosen regimen[s] of propranolol) was to be included in the primary analysis of efficacy.

All the patients recruited in the study Stage 1 were to be followed up as per the protocol, even if they were assigned to one of the propranolol regimens not considered for the efficacy analysis of Stage 2 of the study. Data from the latter patients were not included in the primary analysis of efficacy.

Primary Analysis

The primary efficacy analysis compared the complete/nearly complete recovery rate issued from centralized assessment at Week 24 on the selected regimen of propranolol to placebo on the ITT data set. The objective was to test the superiority of the selected regimen using the methodology described by Posch et al (**Posch *et al* 2005**), for an adaptive confirmatory design with a single selection at an interim analysis. This methodology guarantees that the family-wise type I error rate is maintained at the nominal level of 0.005.

On stage 1 patients, the 4 individual p-values for the 4 regimens (*versus* placebo) were computed using one sided Z-test for proportions with pooled variance estimates.

On stage 2 patients, the individual p-value (named q) for the selected regimen (*versus* placebo) was computed using one sided Z-test for proportions with pooled variance estimates.

Then, on the stage 1 patients, for each of the 8 intersection hypotheses containing $H_{0,sel}$ (null hypothesis for the selected regimen), a p-value adjusted was determined in using Simes' procedure.

Finally, for each of the 8 intersection hypotheses, a combination p-value was computed by weighted inverse normal combination function:

$$C(p,q) = 1 - \left[w_1\Phi^{-1}(1-p) + w_2\Phi^{-1}(1-q)\right],$$

Reference ID: 3433600

with p = adjusted p-value of the concerning intersection hypothesis for stage 1 patients, q = p-value of the selected regimen determined for stage 2 patients, positive weights w_1, w_2 defined by $w_1^2 = n_{1p}/n_{1p} + n_{2p}$ and $w_2^2 = n_{2p}/n_{1p} + n_{2p}$.

In this study, n_{1p} (number of patients on placebo at stage 1) is equal to 18 and n_{2p} (number of patients on placebo at stage 2) is equal to 27.

The null hypothesis $H_0 = H_{0,Sel}$ is rejected if the combination p-values for the 8 intersection hypotheses that contain $H_{0,Sel}$ are all lower than or equal to α =0.005. The overall p-value for the combination test is the maximum of all 8 combination p-values as illustrated in Posch *et al* (**2005**).

Due to the nature of this study (an adaptive confirmatory design) all efficacy tests of the Primary Week 24 analysis were one-sided with a nominal level of α=0.005. None of the secondary efficacy endpoints analyzed in the Primary Week 24 analysis were planned to be part of the overall type I error control and are then considered as exploratory only, except for the key secondary efficacy endpoint (success/failure based on the investigator's on-site qualitative assessment of complete resolution of the target IH at W48) The key secondary efficacy endpoint that was part of the overall Type I error control, is not analyzed in the Primary Week 24 analysis. The level of two-sided tests used for safety was 0.05.
All statistical analyses were unadjusted except otherwise specified.

Sensitivity and Adjusted Analyses for the Primary Endpoint

- A sensitivity analysis of the primary endpoint was carried out on the per-protocol (PP) data set, based on the same principles as for the primary analysis, to evaluate the robustness of the results.
- In the case of premature treatment discontinuation not due to treatment intolerance and if the closest centralized assessment (Type 2) from the end of treatment did not confirm a stabilization or a worsening of the target IH, 50% of the patients concerned in each treatment group were selected at random and their complete or nearly complete recovery at W24 was redefined as a success. A sensitivity analysis of the redefined primary endpoint was carried out on the ITT data set, based on the same principles as for the primary analysis.
- An analysis of the primary endpoint (on ITT and PP data sets) using an extension of the combination test for logistic regression. The logistic regression model was adjusted for the stratification factors and randomization ratio.

Reference ID: 3433600

Other Secondary and Exploratory Efficacy Endpoints

Other secondary and exploratory efficacy endpoints were analyzed on the ITT data set. All endpoints were analyzed descriptively and, where applicable, inferential analyses were performed using the same principles as those described for the primary endpoint. Standard procedures (for example, Kaplan Meier analyses for time-to-event endpoints) were also used to analyze the endpoints. All efficacy endpoints were described by treatment group on the ITT data set with overrun.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

According to sponsor, 512 patients were screened to enter the study and the parent(s) or guardian of two patients refused their child's participation so did not sign the informed consent form. Among the 510 patients, 460 were randomized and 50 were screen failures. Among the 460 randomized patients, 4 were not treated; 2 because of patient(s)'/guardian's decision and 1 because no units of the assigned treatment were available on site. Overall 63 patients were randomized under protocol version 4, according to the 1:1:1:1 randomization ratio and 397 under version 5, 6, or 7 according to the 1:2:2:2:2 randomization ratio.

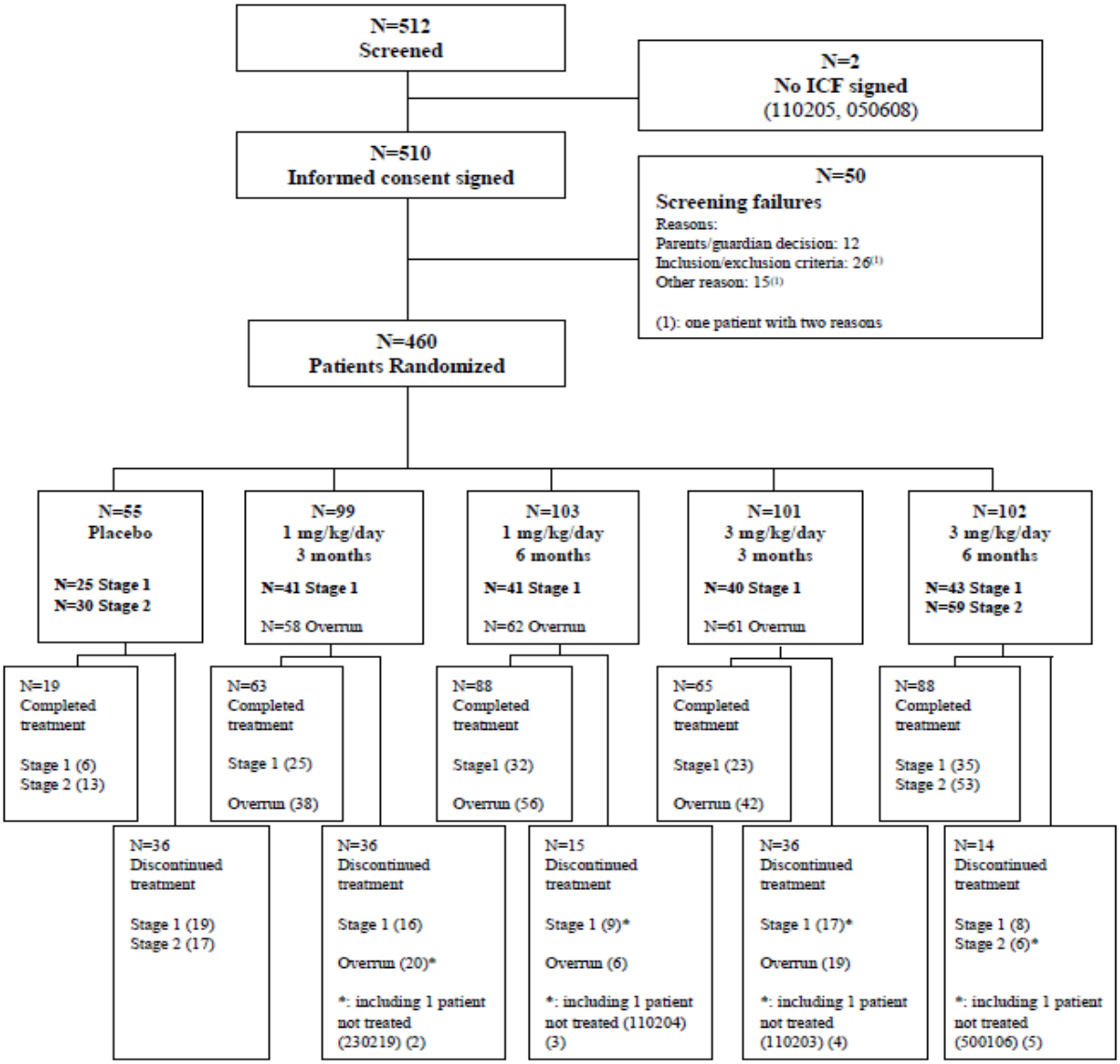
The 190 first randomized patients entered the stage 1 of the study, among which 188 were treated: 25 in the placebo arm, 41 in the 1 mg/kg/day 3 months arm, 40 in the 1 mg/kg/day 6 months arm, 39 in the 3 mg/kg/day 3 months arm and 43 in the 3 mg/kg/day 6 months arm. The interim analysis was conducted on these 188 patients' data and the IDMC recommendation was to continue the trial, with a single active arm (that was shown to be the 3 mg/kg/day 6 months arm after the unblinding for the primary W24 analysis) and the placebo arm, without sample size adjustment or protocol amendment.

In the meantime, accrual in the study had continued and the planned sample size had been reached. Consequently, as stated in the protocol, patients randomized after stage 1 in one of the three arms not selected for stage 2 (1 mg/kg/day 3 months, 1 mg/kg/day 6 months and 3 mg/kg/day 3 months) were not taken into account for the efficacy analyses (respectively 57, 62 and 61 patients). These patients are called "overrun" patients in the remainder of the report. The detailed patient disposition is shown in Figure 1. The sponsor's dropout reasons for early treatment discontinuation for all randomized patients are listed in Table 1 and those for only patients who were in the planned adaptive design are shown in Tables 2 and 3. Patients' baseline demographic characteristics for the safety data set and for the adaptive designed data set are shown in Tables 4 and 5.

Reviewer's Note: According to Tables 4 and 5, it appears that patients are well balanced in two treatment arms in terms of their baseline covariates such as age and weight. Nevertheless, we noted that in the placebo group, much higher percent of patients were white and from Western Europe, in particular the country of France comparing with others.

Reference ID: 3433600

Figure 1 Disposition of Patients – All patients



4 patients did not receive any medication:

Reasons:

(2) 230219 (1mg/d 3 m): no treatment available: Immediate treatment needed but bottles of study treatment leaking and no other treatment available at the pharmacy

(3) 110204 (1mg/d 6 m): parents decision

(4) 110203 (3mg/d 3 m): parents decision

(5) 500106 (3mg/d 6 m): no treatment available: Assigned treatment not available on site

Source: Sponsor's Figure 6 of CSR

Reference ID: 3433600

Table 1 Sponsor's Summary of Reasons for Early Treatment Discontinuation for All Randomized Patients in Study 201

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

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

Source: Sponsor's Table 9 of CSR

Table 2 Sponsor's Summary of Reasons for Early Treatment Discontinuation for ITT Data Set at Stage I in Study 201

Reasons for treatment discontinuation	Placebo (N = 25)	V0400SB 1 mg/kg/day 3mths (N = 41)	V0400SB 1 mg/kg/day 6mths (N = 41)	V0400SB 3 mg/kg/day 3mths (N = 40)	V0400SB 3 mg/kg/day 6mths (N = 43)	Total (N = 190)
Erroneous inclusion according to the protocol	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Treatment intolerance	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Treatment inefficacy	16 (64.0%)	14 (34.1%)	4 (9.8%)	13 (32.5%)	6 (14.0%)	53 (27.9%)
Safety reason not linked to the protocol therapy	1 (4.0%)	1 (2.4%)	1 (2.4%)	1 (2.5%)	0 (0.0%)	4 (2.1%)
Patient's parent(s) or guardian(s) decision	4 (16.0%)	3 (7.3%)	4 (9.8%)	6 (15.0%)	2 (4.7%)	19 (10.0%)
Other	0 (0.0%)	2 (4.9%)	0 (0.0%)	0 (0.0%)	1 (2.3%)	3 (1.6%)
Overall	19 (76.0%)	16 (39.0%)	9 (22.0%)	17 (42.5%)	8 (18.6%)	69 (36.3%)

Source: Sponsor's Table 44 of CSR

Table 3 Sponsor's Summary of Reasons for Early Treatment Discontinuation for Adaptively Designed Data Set at Stage II in Study 201

Reasons for treatment discontinuation	Placebo (N = 30)	V0400SB 3 mg/kg/day 6mths (N = 59)	Total (N = 89)
Erroneous inclusion according to the protocol	0 (0.0%)	0 (0.0%)	0 (0.0%)
Treatment intolerance	0 (0.0%)	0 (0.0%)	0 (0.0%)
Treatment inefficacy	16 (53.3%)	3 (5.1%)	19 (21.3%)
Safety reason not linked to the protocol therapy	1 (3.3%)	1 (1.7%)	2 (2.2%)
Patient's parent(s) or guardian(s) decision	3 (10.0%)	2 (3.4%)	5 (5.6%)
Other	1 (3.3%)	1 (1.7%)	2 (2.2%)
Overall	17 (56.7%)	6 (10.2%)	23 (25.8%)

Source: Sponsor's Table 45 of CSR

Reference ID: 3433600

Table 4 Sponsor's Summary of Demographic Characteristics for Safety Data Set for Study 201

Characteristics	Placebo (N=55)	V0400SB 1 mg/kg/day 3mths (N=98)	V0400SB 1 mg/kg/day 6 mths (N=102)	V0400SB 3 mg/kg/day 3mths (N=100)	V0400SB 3 mg/kg/day 6 mths (N=101)	Total (N=456)
Gender, n (%)						
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 (days), mean (SD)	103.9 (30)	103.6 (33.1)	102.7 (30.1)	107.5 (30.1)	101.6 (31)	103.9 (31)
Age, n (%)						
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%)	62 (62.7%)	64 (64.0%)	64 (63.4%)	289 (63.4%)
IH site, n (%)						
Facial	40 (72.7%)	71 (72.4%)	72 (70.6%)	64 (64.0%)	71 (70.3%)	318 (69.7%)
Non-Facial	15 (27.3%)	27 (27.6%)	30 (29.4%)	36 (36.0%)	30 (29.7%)	138 (30.3%)
Weight at Birth (kg), 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)
Race and Ethnicity						
White	46 (83.7%)	79 (80.6%)	79 (77.5%)	82 (82%)	82 (81.2%)	368 (80.7%)
Black	0 (0%)	1 (1%)	0 (0%)	2 (2%)	0 (0%)	3 (0.7%)
Asian	1 (1.8%)	1 (1%)	3 (2.9%)	2 (2%)	0 (0%)	7 (1.5%)
Others	8 (14.5%)	17 (17.3%)	20 (19.6%)	14 (14%)	19 (18.8)	78 (17)
Continent						
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%)
Country						
France	21 (38.2%)	25 (25.5%)	18 (17.6%)	22 (22.0%)	28 (27.7%)	114 (25%)
Germany	8 (14.5%)	17 (17.3%)	9 (8.8%)	17 (17.0%)	9 (8.9%)	60 (13.2%)
Spain	5 (9.1%)	9 (9.2%)	14 (13.7%)	17 (17.0%)	14 (13.9%)	59 (12.9%)
USA	6 (10.9%)	13 (13.3%)	13 (12.7%)	11 (11.0%)	10 (9.9%)	53 (11.6%)
Peru	1 (1.8%)	5 (5.1%)	9 (8.8%)	8 (8.0%)	12 (11.9%)	35 (7.7%)
Australia	1 (1.8%)	5 (5.1%)	14 (13.7%)	5 (5.0%)	7 (6.9%)	32 (7.0%)
Poland	4 (7.3%)	4 (4.1%)	6 (5.9%)	8 (8.0%)	4 (4.0%)	26 (5.7%)
Canada	2 (3.6%)	5 (5.1%)	6 (5.9%)	3 (3.0%)	2 (2.0%)	18 (3.9%)
Lithuania	1 (1.8%)	7 (7.1%)	4 (3.9%)	1 (1.0%)	5 (5.0%)	18 (3.9%)
Hungary	1 (1.8%)	2 (2.0%)	4 (3.9%)	2 (2.0%)	2 (2.0%)	11 (2.4%)
Czech Republic	2 (3.6%)	1 (1.0%)	3 (2.9%)	1 (1.0%)	1 (1.0%)	8 (1.8%)
Romania	2 (3.6%)	2 (2.0%)	1 (1.0%)	0 (0%)	2 (2.0%)	7 (1.5%)
Mexico	0 (0%)	2 (2.0%)	0 (0%)	3 (3.0%)	0 (0%)	5 (1.1%)
New-Zealand	0 (0%)	0 (0%)	1 (1%)	1 (1.0%)	3 (3%)	5 (1.1%)
Russia	0 (0%)	1 (1.0%)	0 (0%)	1 (1.0%)	1 (1%)	3 (0.7%)
Italy	1 (1.8%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	2 (0.4%)

Source: Sponsor's Table 58 of CSR

Reference ID: 3433600

Table 5 Sponsor's Summary of Demographic Characteristics for Adaptively Designed Data Set for Study 201

Characteristics	Placebo (N=55)	V0400SB 1 mg/kg/day 3mths (N=41)	V0400SB 1 mg/kg/day 6 mths (N=40)	V0400SB 3 mg/kg/day 3mths (N=39)	V0400SB 3 mg/kg/day 6 mths (N=101)	Total (N=276)
Gender, n (%)						
Male	17 (30.9%)	15 (36.6%)	11 (27.5%)	9 (23.1%)	31 (30.7%)	83 (30.1%)
Female	38 (69.1%)	26 (63.4%)	29 (72.5%)	30 (76.9%)	70 (69.3%)	193 (69.9%)
Age (days), mean (SD)	103.9 (31.1)	102.9 (30)	102.1 (29.3)	106.1 (33.6)	101.6 (31)	103 (30.8)
Age, n (%)						
35-90 days	20 (36.4%)	16 (39%)	16 (40%)	15 (38.5%)	37 (36.6%)	104 (37.7%)
>90 days	35 (63.6%)	25 (61%)	24 (60%)	24 (61.5%)	64 (63.4%)	172 (62.3%)
IH site, n (%)						
Facial	40 (72.7%)	33 (80.5%)	33 (82.5%)	29 (74.4%)	71 (70.3%)	206 (74.6%)
Non-Facial	15 (27.3%)	8 (19.5%)	7 (17.5%)	10 (25.6%)	30 (29.7%)	70 (25.4%)
Weight at Birth (kg), mean (SD)	2.93 (0.79)	3.02 (0.67)	3.11 (0.78)	2.92 (0.67)	3.06 (0.77)	3.02 (0.74)
Race and Ethnicity						
White	46 (83.7%)	36 (87.8%)	33 (82.5%)	37 (94.9%)	82 (81.2%)	234 (84.8%)
Black	0 (0%)	1 (1%)	0 (0%)	1 (2.6%)	0 (0%)	1 (0.4%)
Asian	1 (1.8%)	0 (0%)	1 (2.5%)	0 (0%)	0 (0%)	2 (0.7%)
Others	8 (14.5%)	5 (12.2%)	6 (15.0%)	1 (2.6%)	19 (18.8%)	39 (14%)
Continent						
USA-Canada	8 (14.5%)	12 (29.3%)	9 (22.5%)	8 (20.5%)	12 (11.9%)	49 (17.8%)
Other America	1 (1.8%)	0 (7.1%)	0 (0%)	0 (0%)	12 (11.9%)	13 (4.7%)
Western Europe	35 (63.6%)	23 (56.1%)	25 (62.5%)	28 (71.8%)	52 (51.5%)	163 (59.1%)
Other Europe	10 (18.2%)	6 (14.6%)	6 (15.0%)	2 (5.1%)	15 (14.9%)	39(14.1%)
Oceania	1 (1.8%)	0 (0%)	0 (0%)	1 (2.6%)	10 (9.9%)	12 (4.3%)
Country						
France	21 (38.2%)	11 (26.8%)	12 (30%)	11 (28.2%)	28 (27.7%)	83 (30.1%)
Germany	8 (14.5%)	10 (24.4%)	6 (15%)	11 (28.2%)	9 (8.9%)	44 (15.9%)
Spain	5 (9.1%)	2 (4.9%)	7 (17.5%)	6 (15.4%)	14 (13.9%)	34 (12.3%)
USA	6 (10.9%)	9 (22%)	7 (17.5%)	6 (15.4%)	10 (9.9%)	38 (13.8%)
Peru	1 (1.8%)	0 (0%)	0 (0%)	0 (0%)	12 (11.9%)	13 (4.7%)
Australia	1 (1.8%)	0 (0%)	0 (0%)	1 (2.6%)	7 (6.9%)	9 (3.3%)
Poland	4 (7.3%)	1 (2.4%)	5 (12.5%)	2 (5.1%)	4 (4.0%)	16 (5.8%)
Canada	2 (3.6%)	3 (7.3%)	2 (5.0%)	2 (5.1%)	2 (2.0%)	11 (4.0%)
Lithuania	1 (1.8%)	3 (7.3%)	1 (2.5%)	0 (0%)	5 (5.0%)	10 (3.6%)
Hungary	1 (1.8%)	2 (4.9%)	0 (0%)	0 (0%)	2 (2.0%)	5 (1.8%)
Czech Republic	2 (3.6%)	0 (0%)	0 (0%)	0(0%)	1 (1.0%)	3 (1.1%)
Romania	2 (3.6%)	0 (0%)	0(0%)	0 (0%)	2 (2.0%)	4 (1.4%)
Mexico	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
New-Zealand	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (3%)	3(1.1%)
Russia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (0.4%)
Italy	1 (1.8%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	2 (0.7%)

Source: Sponsor's Table 57 of CSR

Reference ID: 3433600

3.2.4 Efficacy Results and Conclusions

3.2.4.1 Sponsor's Results for Primary Efficacy Endpoint

The sponsor's analysis results for the primary efficacy endpoint are presented in Table 6. According to the sponsor, "Overall, 2 patients (3.6%) in the placebo arm and 61 patients (60.4%) in the active dose arm (3 mg/kg/day 6 months) presented complete or nearly complete resolution of their IH at week 24, according to the centralized reading of the photographs. The combined p-value (<0.0001) shows that the difference was statistically significant at the 0.005 level. The results are consistent between the two stages: the two successes in the placebo group were seen in stage 1 patients, with no success in stage 2; the success rates in the active arm were similar between the two stages: 62.8% (27 patients out of 43) for stage 1 and 58.6% (34 patients out of 58) for stage 2 as were the absolute differences between the two arms (54.8% for stage 1 and 58.6% for stage 2)."

Table 6 Sponsor's Primary Analysis Results: Complete or Nearly Complete Resolution at Week 24, central reading – ITT data set for Study 201

Primary Endpoint	Placebo	V0400SB 1mg/kg/day 3 months	V0400SB 1mg/kg/day 6 months	V0400SB 3mg/kg/day 3 months	V0400SB 3mg/kg/day 6 months
Stage 1	(N=25)	(N=41)	(N=40)	(N=39)	(N=43)
Yes	2 (8.0%)	4 (9.8%)	15 (37.5%)	3 (7.7%)	27 (62.8%)
No	23 (92.0%)	37 (90.2%)	25 (62.5%)	36 (92.3%)	16 (37.2%)
P-value vs. Placebo*		0.41	0.004	0.52	<0.0001
Stage 2	(N=30)				(N=58)
Yes	0 (0.0%)				34 (58.6%)
No	30 (100%)				24 (41.4%)
P-value vs. Placebo					<0.0001
Overall/combined	(N=55)				(N=101)
Yes	2 (3.6%)				61 (60.4%)
No	53 (96.4%)				40 (39.6%)
P-value vs. Placebo					<0.0001

Source: Sponsor's Tables 17 and 18 of CSR
*The sponsor's reported p-values are one-sided.

3.2.4.2 Sponsor's Results for Other Secondary Efficacy Endpoint

The sponsor's analysis results for other secondary efficacy endpoints are presented in Table 7. As shown from the table, patients' improvement on centralized assessment occurred early in the 3mg/kg/day 6 months arm during treatment, with 88% improvement (and 1% worsening) at W5 vs. 5.4% (and 10.8% worsening) in the placebo arm. Sustained improvement (i.e., maintained at each subsequent visit) occurred early in the 3 mg/kg/day 6 months arm, with 72.7% of the patients showing sustained improvement at W5.

Reference ID: 3433600

Similar results on improvement (data not shown in this review) and time to first sustained improvement of the IH were observed for on-site investigators' and parents'/guardians' assessment. The observed difference between the results of the primary endpoint from central readers' and investigators' assessments could be explained by non-comparable assessment conditions.

A significantly greater reduction in target IH surface and target IH color was achieved in the 3mg/kg/day & 6 months arm. A greater reduction in the maximal diameter was also observed, but it was not statistically different from the reduction in the placebo arm.

Table 7 Sponsor's Analysis Results for Secondary Efficacy Endpoints for Study 201

Secondary Efficacy Endpoints	Placebo (N=55)	V0400SB 3 mg/kg/day 6 months (N=101)	p-value
Change in surface area at W24 compared to baseline (cm^2) 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 (NS)
Change in color at W24 compared to baseline (dE*2000) Mean (SD)	-0.054 (4.824)	-7.369 (7.43)	<0.0001
Centralized qualitative assessment			
Improvement at W5 (i.e., 3-point evolution of target IH)	5.4%	88%	
Worsening at W5	10.8%	1%	
First sustained improvement at W5, KM rate*	5.4%	72.7%	<0.0001†
First sustained improvement at W24, KM rate*	9.0%	79.5%	
Investigator's on site assessment			
Complete or nearly complete resolution of target IH at W24 (compared to baseline)	10.5%	26.7%	0.4419 (NS)
First sustained improvement at W5, KM rate*	20.1%	70.9%	
First sustained improvement at W24, KM rate*	32.4%	82.5%	<0.0001‡
Parents' on site assessment			
First sustained improvement at W5, KM rate*	19.9%	67.4%	
First sustained improvement at W24, KM rate*	45.0%	85.6%	<0.0001‡

Note: **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. NS=Non statistically significant*

Source: Sponsor's Table shown in synopsis and Table 118 (for improvement by centralized qualitative assessment) of CSR

3.2.4.3 Sponsor's Sensitivity and Adjusted Analyses for the Primary Endpoint

The results of the sponsor's sensitivity analysis and the adjusted analyses by age, IH site and randomization ratio on the primary endpoint for the Per-Protocol (PP) data set are presented in Tables 8 to 11. The sponsor stated that "similar results as those of the ITT data set are observed for the PP data set: a significant (p<0.0001) adjusted treatment effect in favor of the active group; a higher observed success rate in younger patients (65.7%; 23/35) than in older patients (56.9%; 33/58) but with similar placebo corrected effects (60.1% in the younger patients and 56.9% in the older patients); similar response rates in the two IH localization strata; a higher observed success rate with the 1:1 randomization ratio, likely explained by random variations and the small number of subjects (90.0%: 10 patients, 9 success with the 1:1 ratio versus 56.6%; 47 successes in 83 patients with the 2:1 ratio)."

Reference ID: 3433600

Table 8 Sponsor's Primary Endpoint Adjusted Analysis – PP Data Set for Study 201

Primary Endpoint	Placebo (N=53)	V0400SB 3mg/kg/day 6 months (N=93)	P-value
Stage 1			
Yes	1 (4.3%)	23 (63.9%)	<0.0001
No	22 (95.7%)	13 (36.1%)	
Stage 2			
Yes	0 (0%)	33 (57.9%)	<0.0001
No	30 (100%)	24 (42.1%)	
Overall/combined			
Yes	1 (1.9%)	56 (60.2%)	<0.0001
No	52 (98.1%)	37 (39.8%)	

Source: Sponsor's Table 104 of CSR

Table 9 Sponsor's Analysis Results for Primary Efficacy Endpoint Stratified by Age Groups for PP Data Set for Study 201

Primary Endpoint	Placebo (N=53)	V0400SB 3mg/kg/day 6 months (N=93)
Age 35 to 90 days		
Stage 1		
Yes	1 (14.3%)	11 (73.3%)
No	6 (85.7%)	4 (26.7%)
Stage 2		
Yes	0 (0.0%)	12 (60%)
No	11 (100%)	8 (40%)
Overall/combined		
Yes	1 (5.6%)	23 (65.7%)
No	17 (94.4%)	12 (34.3%)
Age > 3 months		
Stage 1		
Yes	0 (0%)	12 (57.1%)
No	16 (100%)	9 (42.9%)
Stage 2		
Yes	0 (0.0%)	21 (56.8%)
No	19 (100%)	16 (43.2%)
Overall/combined		
Yes	0 (0%)	33 (56.9%)
No	35 (100%)	25 (43.1%)

Source: Sponsor's Table 100 of CSR

Table 10 Sponsor's Analysis Results for Primary Efficacy Endpoint Stratified by IH Site for PP Data Set for Study 201

Primary Endpoint	Placebo (N=53)	V0400SB 3mg/kg/day 6 months (N=93)
Facial IH		
Stage 1		
Yes	1 (5.3%)	20 (66.7%)
No	18 (94.7%)	10 (33.3%)
Stage 2		
Yes	0 (0.0%)	20 (55.6%)
No	19 (100%)	16 (44.4%)
Overall/combined		
Yes	1 (2.6%)	40 (60.6%)
No	37 (97.4%)	26 (39.4%)

Reference ID: 3433600

Primary Endpoint	Placebo (N=53)	V0400SB 3mg/kg/day 6 months (N=93)
Non Facial IH		
Stage 1		
Yes	0 (0%)	3 (50.0%)
No	4 (100%)	3 (50.0%)
Stage 2		
Yes	0 (0.0%)	13 (61.9%)
No	11 (100%)	8 (38.1%)
Overall/combined		
Yes	0 (0%)	16 (59.3%)
No	15 (100%)	11 (40.7%)

Source: Sponsor's Table 102 of CSR

Table 11 Sponsor's Analysis Results for Primary Efficacy Endpoint by Randomization Version for PP Data Set for Study 201

Primary Endpoint	Placebo (N=53)	V0400SB 3mg/kg/day 6 months (N=93)
Randomization ratio 1:1		
Stage 1		
Yes	1 (10%)	9 (90%)
No	9 (90%)	1 (10%)
Stage 2		
Yes		
No		
Overall/combined		
Yes	1 (10%)	9 (90%)
No	9 (90%)	1 (10%)
Randomization ratio 2:1		
Stage 1		
Yes	0 (0%)	14 (53.8%)
No	13 (100%)	12 (46.2%)
Stage 2		
Yes	0 (0.0%)	33 (57.9%)
No	30 (100%)	24 (42.1%)
Overall/combined		
Yes	0 (0%)	47 (56.6%)
No	43 (100%)	36 (43.4%)

Source: Sponsor's Table 103 of CSR

As mentioned in Section 3.2.2, the sponsor conducted another sensitivity analysis for the primary endpoint using the centralized Type 2 assessment. Their results are presented in the following Table 12. As observed from the table, the rates of complete or nearly complete resolutions with this alternative definition are 27.3% (15 out of 55 patients) in the placebo and 61.4% (62 out of 101 patients) in the active treatment arm, with a statistically significant difference ($p<0.0001$).

Reference ID: 3433600

Table 12 Sponsor's Sensitivity Analysis Results for Study 201

Primary Endpoint	Placebo (N=55)	V0400SB 3mg/kg/day 6 months (N=101)	P-value
Stage 1			
Yes	9 (36%)	28 (65.1%)	0.01
No	16 (64%)	15 (34.9%)	
Stage 2			
Yes	6 (20%)	34 (58.6%)	0.0003
No	24 (80%)	24 (41.4%)	
Overall/combined			
Yes	15 (27.3%)	62 (61.4%)	<0.0001
No	40 (72.7%)	39 (38.6%)	

Source: Sponsor's Table 105 of CSR

3.2.4.4 Sponsor's Conclusion

This double-blind clinical study compared four regimens of propranolol (1 and 3 mg/kg/day for 3 or 6 months each) to placebo for 6 months in the treatment of proliferating IH requiring systemic therapy in infants (aged 1-5 months at initiation), using an objective primary efficacy endpoint based on blinded centralized photographic assessment. Propranolol, administered at the doses of 1 and 3 mg/kg/day (twice daily) for up to 3 or 6 months showed a satisfactory safety profile, and at the dose of 3 mg/kg/day for 6 months, demonstrated a highly significant efficacy level. These results support the dose regimen of 3 mg/kg/day for 6 months in the treatment of proliferating IH requiring systemic therapy.

3.2.4.5 Statistical Reviewer's Findings and Comments

1. (Alternative Trial Designs) Although Study 201 was originally planned by an adaptive design, before the interim analysis (IA) was performed at the end of Stage 1 and the IDMC meeting took place on January 06, 2012 for the IA results, the sponsor had already recruited all of the needed patients in a conventional trial setting and randomized those patients to all five treatment groups.

   Now that most patients were indeed continued to the end of Stage 2 and completed the study, this trial probably should not be treated and analyzed as an adaptive design trial, rather, it should be a conventional five arms parallel trial with an unblinded interim analysis. Therefore, we asked the sponsor to perform some exploratory analyses for the primary efficacy endpoint. The sponsor's analysis results are presented in Tables 13 and 14.

   The statistical reviewer had confirmed the sponsor's analysis results. As seen from the two tables, no efficacy was demonstrated for either 1mg/kg/day or 3 mg/kg/day of propranolol in 3 months regimen but the efficacy was demonstrated for both doses in 6 months regimens with very small p-values. Furthermore, now that the response rate between the two regimens in 6 months do not seem to differ much, during the review cycle, we asked the sponsor to provide the rationale for the selection of the 3 mg/kg/day × 6months dose regimen. The sponsor calculated the Jeffrey's 95% confidence intervals of response rates for both 6 months regimens and the test for the interaction of dose by stage. With the confidence intervals overlapping and

Reference ID: 3433600

the p-value of 0.1065 for the interaction, they stated that 'it is not possible to conclude a difference between doses varying between stages and therefore that response rates evaluated in the Pooled ITT with overrun analysis are not questionable as a global estimation of the treatment effect. The detailed explanation and analysis are stored in the 0007 submission.

Table 13 Sponsor's Primary Efficacy Endpoint Results for Pooled ITT with Overrun Population – Conventional Parallel Design

Primary Endpoint (Centralized-Complete/ nearly complete resolution at Week 24)	Placebo (N=55)	V0400SB 1 mg/kg/day 3 months (N=98)	V0400SB 1 mg/kg/day 6 months (N=102)	V0400SB 3 mg/kg/day 3 months (N=100)	V0400SB 3 mg/kg/day 6 months (N=101)
No Yes	53 (96.4%) 2 (3.6%)	90 (91.8%) 8 (8.2%)	52 (51.0%) 50 (49.0%)	88 (88.0%) 12 (12.0%)	40 (39.6%) 61 (60.4%)
P-value*		1.0	<0.0001	0.5614	<0.0001

* p-value were obtained by two sided Fisher's exact test after Bonferroni adjustment
Source: Sponsor's Table 1 of efficacy-information-amendment.pdf:2 from 007 Submission

Table 14 Sponsor's Primary Efficacy Endpoint Results for Pooled ITT with Overrun Population–Group Sequential Design

Propranolol Regimen	Look	Information Fraction	Nominal critical point		Test Statistics	Decision
			Reject H0	Accept H0		
1 mg/kg/day 3 months	Interim	0.448	4.684	0.420	0.211	Should have stopped for futility
	Final	1.022	3.023	3.023	1.059	Non-Significant
1 mg/kg/day 6 months	Interim	0.434	4.760	0.325	2.395	Continue (NS)
	Final	1.046	3.023	3.023	4.334	Significant
3 mg/kg/day 3 months	Interim	0.428	4.799	0.277	-0.045	Should have stopped for futility
	Final	1.035	3.023	3.023	1.640	Non-Significant
3 mg/kg/day 6 months	Interim	0.454	4.647	0.466	3.698	Continue (NS)
	Final	1.040	3.023	3.023	4.942	Significant

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

2. (Differential Dropouts) In Study V00400 SB 201, dropout rate by treatment group for all randomized patients and those at Stage 1 and Stage 2 have been shown in Tables 1, 2 and 3, respectively. When focusing on the comparison between the group of propranolol 3mg/kg/day in 6 months and placebo, we noted that there were more dropouts in the placebo group (dropout rate of 66%) than in the group propranolol 3mg/kg/day x 6 months (dropout rate of 13.7%). The placebo's dropout rate is even higher when we consider Stage 1 only (76% vs. 18.6%).

Table 15 presents this statistical reviewer's exploration on dropout rates by study visit and by treatment group. It is worth noting that the placebo patients also dropped out very early. This finding of high dropout rates in placebo and 3 months' regimens of propranolol may suggest lack of efficacy with these treatment arms. However, patients were supposedly to be blinded with the assigned treatments given. Since the primary endpoint only captured good response from patients who did not drop out, when a lot of placebo patients dropped out, there may be a concern that the final analysis comparing the response rate between the drug groups and placebo might exaggerate the true treatment effects.

Reference ID: 3433600

Table 15 Dropout Rates by Visit and by Treatment arm for Study 201

	Placebo (N=55)	V0400SB 1 mg/kg/day 3 months (N=98)	V0400SB 1 mg/kg/day 6 months (N=102)	V0400SB 3 mg/kg/day 3 months (N=100)	V0400SB 3 mg/kg/day 6 months (N=101)
Day 7	1 (0.02)	1 (0.01)	3 (0.03)	1 (0.01)	0 (0)
Day 14	6 (0.11)	1 (0.01)	1 (0.01)	0 (0)	0 (0)
Day 21	**11 (0.2)**	0 (0)	1 (0.01)	0 (0)	1 (0.01)
Week 5	**11 (0.2)**	3 (0.03)	1 (0.01)	1 (0.01)	1 (0.01)
Week 8	2 (0.04)	3 (0.03)	3 (0.03)	3 (0.03)	0 (0)
Week 12	3 (0.05)	1 (0.01)	1 (0.01)	1 (0.01)	2 (0.02)
Week 16	1 (0.02)	**17 (0.17)**	1 (0.01)	**16 (0.16)**	4 (0.04)
Week 20	1 (0.02)	8 (0.08)	1 (0.01)	8 (0.08)	3 (0.03)
Week 24 (Completers)	19 (0.35)	63 (0.64)	90 (0.88)	68 (0.68)	90 (0.90)

Source: statistical reviewer's calculation based on investigator's n site assessment data

3. (Blind Broken?) As stated earlier, the primary endpoint captured only good response from patients who responded to the treatments and did not drop out of the study. That is, all of the dropouts were treated as failures. To examine the possibility that the blind is broken, the statistical reviewer further studied the distribution of placebo patients and those dropouts.

   As shown in Table 4, 64% of the placebo patients were from Western Europe, where only 50% of the propranolol arms are from that region (i.e., Western Europe). In particular, France had the largest number of placebo patients (38%) among all countries. We also noted that based on Table 4, the overall placebo patients were 12% (i.e.,55/456) of all patients in the study. Nevertheless, both Western Europe and other Europe had most placebo patients of 14% (i.e., 45/308) and noticeably France had 18% (i.e., 21/114) placebo patients. On the other hand, we noted that Western Europe had the highest placebo dropouts, where 86% (i.e.,18/21) of placebo patients in France dropped out. Table 16 shows dropout rates and also placebo patients' dropout rates in different regions (i.e., continents).

Table 16 Dropout Rate by Continent in Study 201

	North America (N=71)	Other America (N=40)	W. Europe (N=235)	Other Europe (N=73)	Oceania (N=37)
n (%) of total dropouts	25 (35.2%)	2 (5%)	91 (38.7%)	7 (9.6%)	8 (21.6%)
n (%) of placebo dropouts	5/8 (62.5%)	0/1 (0%)	26/35 (74.3%)	4/10 (40%)	1/1 (100%)

Source: Statistical Reviewer's Calculation

Because of the finding of the differential dropouts, during the review cycle, we asked the sponsor to perform some exploratory analyses of the primary efficacy endpoint by region for the pooled (with overrun) population of patients using (i) ITT data set and (ii) per protocol data set. In the sponsor's response, they emphasized that 'Stratification was performed on patients' age and on IH location. No stratification was performed on center, nor on country. Therefore, the differences for number of randomized patients to placebo group between countries can be partially explained by the different randomization ratio V0400SB:Placebo, further to protocol version n°5: Western European and Northern American countries started to recruit patients earlier than other countries, based on protocol version n°4, and the first period of patients were

Reference ID: 3433600

randomized in these countries with a randomization ratio 1:1:1:1:1, further to protocol version n°5, patients were recruited exclusively with a randomization ratio 2:2:2:2:1. This change in ratio was more impactful in those countries having started the latest."

Table 17 presents the sponsor's analysis results on the primary endpoint by different study periods when the randomization ratio was changed. The sponsor emphasized: "The observed success rate in the 3mg/kg/day 6 month regimen was slightly higher with the initial randomization ratio (1:1:1:1:1) with 10 out of 13 patients (76.9%) showing complete or nearly complete resolution than with the 2:2:2:2:1 ratio (success: 51/88: 58.0%)(Table 3), but this small difference is likely to be explained by random variation and the small number of patients randomized with the 1:1:1:1:1 scheme ". Nonetheless, this reviewer noted that there were two responders observed out of 12 placebo patients in the first period but no responder out of 43 placebo patients in the 2nd period.

Table 17 Primary Efficacy Analysis (complete/near complete resolution at W24), by randomization ratio for Study 201

Primary endpoint Complete or nearly complete resolution of target IH at week 24		
	Placebo (N = 55)	V0400SB 3 mg/kg/day 6mths (N = 101)
Randomization ratio 1:1:1:1:1		
n/missing	12 / 0	13 / 0
Yes	2 (16.7%)	10 (76.9%)
No	10 (83.3%)	3 (23.1%)
Randomization ratio 2:2:2:21		
n/missing	43 / 0	88 / 0
Yes	0 (0.0%)	51 (58.0%)
No	43 (100%)	37 (42.0%)
Overall/combined		
n/missing	55 / 0	101 / 0
Yes	2 (3.6%)	61 (60.4%)
No	53 (96.4%)	40 (39.6%)
Logistic regression analysis		p<.0001

Source: Sponsor's Tables 99 and 100 of CSR

Furthermore, the statistical reviewer noted that more placebo patients took prohibited IH medication(s) (most of them after dropping out) and the prohibited IH medication they mostly took was the study drug, propranolol. For placebo dropouts, the mean number of days from randomization to when they took prohibited IH medication(s) was only 42 days, comparing with the other treatment dropouts taking prohibited medication, which were all more than 110 days. The following Table 18 shows the statistical reviewer's calculated percent of patients who took the prohibited IH medications throughout of the study (including follow-up) and the mean days (and s.d.) that patients who started prohibited IH medications for those dropouts.

Reference ID: 3433600

Table 18 Information for Patients who took prohibited IH medications for Study 201

	Placebo (N=55)	V0400SB 1 mg/kg/day 3 months (N=98)	V0400SB 1 mg/kg/day 6 months (N=102)	V0400SB 3 mg/kg/day 3 months (N=100)	V0400SB 3 mg/kg/day 6 months (N=101)
n (%)	25 (45%)	33 (33%)	22 (22%)	28 (28%)	13 (13%)
mean days (s.d.)*	42 (40.4)	123 (46.7)	119 (68.3)	124 (37.1)	119 (47.9)

Source: Statistical reviewer's calculation
* The recorded are mean days of starting IH medications after randomization for dropouts.

4. (Sensitivity Analyses) Comparing with two responders in the placebo group (one started to show complete or nearly complete resolution of target IH at Week 12 and the other one at Week 16), the action of discontinuing patients' participation in the trial mostly based on parents' or investigators' decision might yield a bias in favor of propranolol, particularly simply assuming dropouts were failures. The statistical reviewer performed the following sensitivity analyses. In all treatment arms, for each visit, the statistical reviewer assumed that patients who left the study after some visit were all responders and conducted the analyses using the same statistical method for the primary analysis. For example, a patient who stayed till Week 8 but dropped out afterwards was treated as a responder for the Week 8 analysis.

   Note that Study V00400SB 201 was only designed to have the patient's investigator on-site visit assessments in comparing with their baseline values collected, the statistical reviewer's sensitivity analyses shown in Table 19 was performed based on this assessment. .

Table 19 Statistical Reviewer's Sensitivity Analyses for Study 201

Designated day or week to become responders n (%), p-value*	Placebo (N=55)	V0400SB 1 mg/kg/day 3 months (N=98)	V0400SB 1 mg/kg/day 6 months (N=102)	V0400SB 3 mg/kg/day 3 months (N=100)	V0400SB 3 mg/kg/day 6 months (N=101)
Day 14	37 (67.3%)	35 (36.1%) worse	29 (28.4%) worse	35 (35.7%) worse	35 (34.7%) worse
Day 21	31 (56.4%)	34 (35.1%) worse	28 (27.5%) worse	35 (35.7%) worse	35 (34.7%) worse
Week 5	20 (36.4%)	34 (35.1%) worse	27 (26.5%) worse	35 (35.7%) worse	34 (33.7%) worse
Week 8	9 (16.4%)	31 (32%) p = 0.039	26 (25.5%) p = 0.19	34 (35%) p = 0.019	33 (33%) p = 0.028
Week 12	7 (12.7%)	28 (29%) p = 0.025	23 (23%) p = 0.135	31 (32%) p = 0.011	33 (33%) p = 0.006
Week 16	4 (7.3%)	27 (28%) p = 0.003	22 (22%) p = 0.022	30 (31%) p = 0.001	31 (30.7%) p = 0.001
Week 20	3 (5%)	10 (10%) p = 0.31	21 (21%) p = 0.01	14 (14%) p = 0.10	27 (27%) p = 0.001

Note: The reported p-values were two sided and calculated based on the primary analysis method.

The analyses in Table 19 seem to suggest that there seems to have a nontrivial impact of assuming dropouts were failures on the p-values. If we assume all patients who dropped out after Week 8 were responders, then the p-values in favor of propranolol do not achieve

Reference ID: 3433600

<0.00125. Note that this is a single trial using a soft endpoint, so an alpha threshold should be less than 0.00125.

One could argue that this assumption of making all dropouts after Week 8 as responders may be too strong. Thus, additional sensitivity analyses by giving each dropout patient a probability of being a responder were conducted and displayed in Table 20. It can be seen that assigning those patients who dropped out after Week 8 to have a 50% chance to be a responder, , the p-value for the comparison between Propranolol 3 mg/kg/day of 6 month regimen and placebo was at the level of 0.02.

Table 20 Statistical Reviewer's Further Sensitivity Analyses only for Week 8 for Study 201

Change of Dropouts after Week 8 Being Responders	Placebo (N=55)	V0400SB 1 mg/kg/day 3 months (N=98)	V0400SB 1 mg/kg/day 6 months (N=102)	V0400SB 3 mg/kg/day 3 months (N=100)	V0400SB 3 mg/kg/day 6 months (N=101)
0.8	8 (15%)	26 (26.8%) p=0.087	25 (24.5%) p=0.144	31 (31.6%) p=0.024	32 (31.7%) p=0.019
0.5	6 (10.9%)	16 (16.5%) p=0.359	23 (22.6%) p=0.073	22 (22.5%) p=0.086	27 (26.7%) p=0.021
0.3	5 (9.1%)	8 (8.3%) p=0.843	22 (21.6%) p=0.048	13 (13.3%) p=0.467	28 (27.7%) **p=0.006**
0.1	2 (3.6%)	8 (8.3%) p=0.277	20 (19.6%) **p=0.006**	7 (7.1%) p=0.392	25 (24.8%) **p=0.0008**

To deal with this issue of dropouts treated as failures, we have asked the sponsor to perform exploratory analysis: (i) determining patients' responder status by using 168-day (24 Weeks) as the cutoff, in particular for those patients who took concomitant medications (which could include some patients on placebo who had been discontinued before W24), i.e., completers, and (ii) considering those who dropped out before W24, not as failures but using an imputation method (e.g., multiple imputation method) to understand the noise associated with early discontinuation/failures from various causes. In all the sensitivity analyses, the sponsor had p-value <0.001. Thus, the sponsor concluded that "all planned and post-hoc sensitivity analyses do confirm the results of the primary analysis and the absence of any bias generated by the definition of early withdrawals as failures. These analyses were briefly described in Section 6 of Appendix. The details can be found under the link for 0007 submission.

3.3 EVALUATION OF SAFETY

The drug's safety is not evaluated in this review.

Reference ID: 3433600

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 GENDER, RACE AND AGE

The sponsor conducted adjusted analysis of the primary endpoint using an extension of the combination test for logistic regression and adjusting for the stratification factors (i.e., age and IH localization strata) and randomization ratio. They did not perform any subgroup analysis for gender and race for all randomized patients. Tables 21 to 23 present the statistical reviewer's calculation for the response rate for gender, race and age subgroups on the primary endpoint.

Table 21 Statistical Reviewer's Subgroup Analysis by Gender for all Randomized Patients

Primary Endpoint	Placebo	V0400SB 1 mg/kg/day 3 months	V0400SB 1 mg/kg/day 6 months	V0400SB 3 mg/kg/day 3 months	V0400SB 3 mg/kg/day 6 months
Male	N=17	N=30	N=32	N=21	N=31
Responder	1 (6%)	3 (10%)	14 (44%)	3 (14%)	21 (68%)
Non-Responder	16	27	18	18	10
Female	N=38	N=68	N=70	N=79	N=70
Responder	1 (3%)	5 (7%)	36 (51%)	9 (11%)	40 (57%)
Non-Responder	37	63	34	70	30

Table 22 Statistical Reviewer's Subgroup Analysis by Race for all Randomized Patients

Primary Endpoint	Placebo	V0400SB 1 mg/kg/day 3 months	V0400SB 1 mg/kg/day 6 months	V0400SB 3 mg/kg/day 3 months	V0400SB 3 mg/kg/day 6 months
American Indian/Alaska Native	N=0	N=0	N=4	N=2	N=9
Responder	0	0	4 (100%)	0	5 (56%)
Non-Responder	0	0	0	2	4
Asian	N=1	N=1	N=3	N=2	N=0
Responder	0	0	1	0	0
Non-Responder	1	1	2	2	0
Black/African American	N=0	N=1	N=0	N=2	N=0
Responder	0	0	0	0	0
Non-Responder	0	1	0	2	0
Native Hawaiian/Other Pacific Islander	N=0	N=0	N=0	N=0	N=1
Responder	0	0	0	0	0
Non-Responder	0	0	0	0	1
Other	N=8	N=17	N=16	N=12	N=9
Responder	0	0	6 (38%)	1	6 (67%)
Non-Responder	8	17	10	11	3
White	N=46	N=79	N=79	N=82	N=82
Responder	2 (4%)	8 (10%)	39 (49%)	11 (13%)	50 (61%)
Non-Responder	44	71	40	71	32

Reference ID: 3433600

Table 23 Statistical Reviewer's Subgroup Analysis by Age for all Randomized Patients

Primary Endpoint	Placebo	V0400SB 1 mg/kg/day 3 months	V0400SB 1 mg/kg/day 6 months	V0400SB 3 mg/kg/day 3 months	V0400SB 3 mg/kg/day 6 months
Age ≤ 90 days	N=20	N=36	N=38	N=36	N=37
Responder	2 (10%)	2 (5.6%)	21 (55.3%)	3 (8.3%)	25 (67.6%)
Non-Responder	18	34	17	33	12
Age > 90 days	N=35	N=62	N=64	N=64	N=64
Responder	0 (0%)	6 (9.7%)	29 (45.3%)	9 (14.1%)	36 (56.3%)
Non-Responder	35	56	35	55	28

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

The sponsor conducted an adjusted analysis of the primary endpoint using an extension of the combination test for logistic regression and adjusting for the stratification factors (i.e., age and IH location) and randomization ratio. Per our request, the sponsor also performed subgroup analysis for three regions (USA-Canada & Other America, Western Europe and Other Europe and Oceania).

4.2.1 IH Location and Randomization Ratio

The sponsor's adjusted analysis results are shown in Table 24.

Table 24 Sponsor's Adjusted Analysis by Age, IH Location and Randomization Ratio for ITT Population for Study 201

For Primary Endpoint	Placebo (N=55)	V0400SB 3 mg/kg/day 6 months (N=101)
Age 35-90 days		
Yes	2 (10.0%)	25 (67.6%)
No	18 (90.0%)	12 (32.4%)
Age > 90 days		
Yes	0 (0%)	36 (56.3%)
No	35 (100%)	28 (43.8%)
Facial IH		
Yes	2 (5.0%)	43 (60.6%)
No	38 (95.0%)	28 (39.4%)
Non Facial IH		
Yes	0 (0%)	18 (60.0%)
No	15 (100%)	12 (40.0%)
Randomization ratio 1:1		
Yes	2 (16.7%)	10 (76.9%)
No	10 (83.3%)	3 (23.1%)
Randomization ratio 2:1		
Yes	0 (0%)	51 (58%)
No	43 (100%)	37 (42%)
Overall/combined		
Yes	2 (3.6%)	61 (60.4%)
No	53 (96.4%)	40 (39.6%)
Logistic regression analysis		p<0.0001

Source: Sponsor's Table 20 of CSR

Reference ID: 3433600

Based on the results, the sponsor stated that "The p-value for the treatment effect obtained in this adjusted analysis is strongly significant (p<0.0001). In both arms, the observed success rates seem to be higher in the younger age (35-90 days) stratum: the two patients with complete or nearly complete resolution in the placebo group are in this stratum and the rates in the active group are 67.6% (25/37) for the younger patients *versus* 56.3% (36/64) for the older patients. Nevertheless, the placebo corrected effect of propranolol 3 mg/kg/day 6 months is similar between the two age strata: 57.6% in the younger patients and 56.3% in the older patients with no evidence of any treatment by age interaction. There is no evidence of any IH localization effect, the success rate are nearly identical between the two localization groups. The observed success rate in the active treatment arm is slightly higher with the initial randomization ratio (1:1) with 10 out of 13 patients (76.9%) showing complete or nearly complete resolution than with the 2:1 ratio (success: 51/88: 58.0%), but this small difference is likely to be explained by random variation and the small number of patients randomized with the 1:1 scheme and no conclusion can be drawn."

4.2.2 Region

Table 25 and Table 26 show the sponsor's analysis on the primary endpoint for three regions for all randomized patients (i.e., ITT with overrun data set) and the per-protocol (i.e., PP) data set. Based on the results, they stated the following:

"The results observed both with the ITT and the PP sets are coherent and confirm in all 3 regions the higher efficacy of the 3 mg/kg/day 6-month regimen. Placebo response being observed in only 2 patients in the ITT with overrun data set does not allow any between-regions comparison. The different proportions of patients receiving placebo in the 3 regions was neither planned nor known either by investigator or the sponsor or the central readers at any time during the study, and central reading was performed irrespective of the region.
In total no bias may be identified that would interfere with the assessment of efficacy due to different placebo proportions between the 3 regions."

Table 25 Sponsor's Subgroup Analysis Results by Region for All Randomized Patients

Primary Endpoint	Placebo (N=55)	V0400SB 1 mg/kg/day 3 months (N=98)	V0400SB 1 mg/kg/day 6 months (N=102)	V0400SB 3 mg/kg/day 3 months (N=100)	V0400SB 3 mg/kg/day 6 months (N=101)
USA-Canada & Other America	N=9	N=25	N=28	N=25	N=24
Responder	1 (11.%)	2 (8%)	12 (43%)	0 (0%)	14 (58%)
Non-Responder	8	23	16	25	10
Western Europe	N=35	N=51	N=41	N=56	N=52
Responder	1 (3%)	5 (10%)	19 (46%)	8 (14%)	27 (52%)
Non-Responder	34	46	22	48	25
Other Europe and Oceania	N=11	N=22	N=23	N=19	N=25
Responder	0 (0%)	1 (4.5%)	19 (58%)	4 (21%)	20 (80%)
Non-Responder	11	21	14	15	5

Source: Sponsor's Table 4 of efficacy-informatin-amendment.pdf in 0007 Submission

Reference ID: 3433600

Table 26 Sponsor's Subgroup Analysis Results by Region for PP Data Set

Primary Endpoint	Placebo	V0400SB 1 mg/kg/day 3 months	V0400SB 1 mg/kg/day 6 months	V0400SB 3 mg/kg/day 3 months	V0400SB 3 mg/kg/day 6 months
USA-Canada & Other America	N=9	N=23	N=28	N=25	N=23
Responder	1 (11.%)	2 (8%)	12 (43%)	0 (0%)	13 (57%)
Non-Responder	8	21	16	25	10
Western Europe	N=33	N=48	N=38	N=52	N=46
Responder	0 (0%)	5 (10%)	18 (47%)	8 (15%)	24 (52%)
Non-Responder	33	43	20	44	22
Other Europe and Oceania	N=11	N=21	N=32	N=19	N=24
Responder	0 (0%)	1 (4.8%)	19 (59%)	4 (21%)	19 (79%)
Non-Responder	11	21	13	15	5

Source: Sponsor's Table 4 of efficacy-informatin-amendment.pdf in 0007 Submission

5. SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

Although Study 201 was originally planned by an adaptive design, before the interim analysis (IA) was performed at the end of Stage 1 and the IDMC meeting took place on January 06, 2012 for the IA results, the sponsor had already recruited all of the needed patients in a conventional trial setting and randomized those patients to all five treatment groups.

According to the efficacy results shown from the trial, the 3mg/kg/day of propranolol in 6 months is the single dose demonstrated efficacy. Nevertheless, when we consider Study 201 as a traditional five fixed armed parallel trial with one IA, the 1 mg/kg/day & 6 months of propranolol seems to also be significantly superior to placebo.

As articulated above, Study 201 appears to be a positive study that supports the efficacy of both 6 months regimens of propranolol. However, since the primary efficacy analysis counted the patients who did not discontinue the study early as responders, the analysis results might yield a bias in favor of propranolol in that much more placebo patients dropped out the study (66% dropout rate in the placebo group versus 13.7% in the 3 mg/kg/day of propranolol 6 months group). It is strange that a much higher rate of placebo patients was from the Western Europe and the majority was from France. In addition, the dropouts in the placebo group dropped out very early, took prohibited IH medications after dropping out and most the prohibited medication was propranolol. All these make the statistical reviewer concern that the blind might not have been maintained.

As explained above, based on this reviewer's sensitivity analyses, the p-values for the comparison between the propranolol 3 mg x 6 month regimen and placebo are not close to 0.001 level, though they are mostly < 0.05.

Reference ID: 3433600

5.2 CONCLUSIONS AND RECOMMENDATIONS

Study V00400 SB 201 appeared to support the propranolol's efficacy for both 3 mg and 1 mg 6 months regimens. However, there were differential dropout rates between the placebo and the study doses and between different regions/countries (most placebo dropouts were from Western Europe and France). While it can be argued that a much higher dropout rate in the placebo group might lend an additional assurance for propranolol's efficacy, that the placebo group had a much higher dropout rate and dropped out early and most placebo dropouts took propranolol as the prohibited medications after dropping out might have yielded a bias in favor of propranolol. Hence the strength of evidence for the propranolol efficacy is probably overstated by the nominal p-value based on a number of the reviewer's sensitivity analyses.

_____
Yeh-Fong Chen, Ph.D.
Mathematical Statistician

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HFD-710/Dr. Hung

Reference ID: 3433600

6. Appendix: Sponsor's Sensitivity Analyses Per FDA's Request
(Mostly Directly Extracted from 0007 Submission)

(1) Exploratory analyses (to understand the impact of these "failures" on the primary efficacy endpoint) using 168-day (24 W) as the cutoff for any patient who took concomitant medications (which could include some patients on placebo who had been discontinued before W24) – i.e., completers

The photo at W24 was not read to evaluate the complete/nearly complete resolution at W24 for patients who had been discontinued before W24 and for patients who had continued the follow-up period.

Among the patients in the placebo group who discontinued treatment prematurely, follow-up was initiated for 14/36 patients and photo at W24 was performed for 10/14 patients. In the propranolol 3 mg/kg/day group 6 months, follow-up was initiated for 8/14 patients and photo at W24 was performed for 7/8 patients (Table 16).

In the placebo group, all patients (14/14) with early discontinuations and follow-up received at least one IH treatment between early discontinuation and W24. In the propranolol group, 8/8 patients with early discontinuations and follow-up received at least one treatment between early discontinuation and W24 and 5/8 of these treatments were for IH.

A planned sensitivity analysis of the primary endpoint has been conducted using the centralized Type 2 assessment and taking into account premature discontinuation as described hereafter:

For patients who prematurely discontinued the study drug:

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

This planned sensitivity analysis confirmed the results of the primary analysis (significant superiority of the active treatment regimen) despite the relaxation of the definition of failures resulting in a high increase of the success rate in the placebo regimen (from 2 to 15 patients: 3.6% to 27.3%) when only one additional patient in the active treatment regimen was considered a success. In this sensitivity analysis of the ITT population, 61.4% of patients had complete/near complete resolution for the propranolol 3 mg/kg/day 6 months.

Reference ID: 3433600

To further demonstrate the robustness of the primary analysis, an additional post-hoc analysis was performed. This analysis is quite similar to the planned sensitivity analysis in that:

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

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

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

In this sensitivity analysis (see Table 27 below), the success rate with placebo was increased to 30.9% and the success rate with propranolol 3 mg/kg/day 6 months (61.4%) was in line with other analyses of the primary criterion.

Table 27 Sponsor's Sensitivity Analyses for Study 201

Primary endpoint: Complete or nearly complete resolution of target IH at week 24				
		Placebo (N = 55)	V0400SB 3 mg/kg/day 6mths (N = 101)	P value
ITT population	Overall/combined			
	n/missing	55 / 0	101 / 0	<.0001
	Yes	2 (3.6%)	61 (60.4%)	
	No	53 (96.4%)	40 (39.6%)	
PP population	Overall/combined			
	n/missing	53 / 0	93 / 0	<.0001
	Yes	1 (1.9%)	56 (60.2%)	
	No	52 (98.1%)	37 (39.8%)	
Planned sensitivity analysis of ITT population	Overall/combined			
	n/missing	55 / 0	101 / 0	<.0001
	Yes	15 (27.3%)	62 (61.4%)	
	No	40 (72.7%)	39 (38.6%)	
Unplanned post-hoc sensitivity analysis of ITT population	Overall/combined			
	n/missing	55 / 0	101 / 0	<.001
	Yes	17 (30.9%)	62 (61.4%)	
	No	38 (69.1%)	39 (38.6%)	
Unplanned post-hoc analysis of completers in the ITT population	Overall/combined			
	n/missing	19 / 0	88 / 0	<.0001
	Yes	2 (10.5%)	61 (69.3%)	
	No	17 (89.5%)	27 (30.7%)	

Source: Table 17 of Efficacy-Information-Amendment.pdf from 0007 Submission

Reference ID: 3433600

Another post-hoc analysis was performed on patients having completed the D0-W24 period (see the above Table 27). This analysis, by not taking into account all premature discontinuations, carries the risk of overestimating the efficacy in the group with the highest discontinuation rate due to inefficacy and is therefore a very conservative analysis.

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

These results show a very significant difference in favor of propranolol 3 mg/kg/day 6 months in all analyses.

2. Exploratory analyses considering those who dropped out before W24, not as failures but using an imputation method (e.g., multiple imputation method) to understand the noise associated with early discontinuation/failures from various causes.

New post-hoc handling of early discontinuations was performed using multiple imputation method, which consists of replacing any missing value by multiple plausible values, instead of single imputation. This method was implemented using SAS proc MI and SAS proc MIANALYZE.

As an underlying condition, it was assumed that data were "missing at random" (MAR), i.e. the missingness depends on the observed outcome values, and is independent of the unobserved outcome values.

To perform the analysis, the following variables were chosen as dependent variables to predict missing values of the primary endpoint at W24:

- (b) (4)
-
-
-
-
-
-
-
-

Reference ID: 3433600

(b) (4)

Table 28 Sponsor's Sensitivity Analysis – Multiple Imputation

	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
Logistic regression after multiple imputation					
Estimation of percentage of Success	13.8%	15.4%	55.0%	19.0%	67.9%
Treatment effect vs Placebo (after Bonferroni Adjustment), p =		1.0000	0.0098	1.0000	0.0006

Source: Table 17 of Efficacy-Information-Amendment.pdf from 0007 Submission

The robustness of the primary endpoint was confirmed by this additional sensitivity analysis. In conclusion, all planned and post-hoc sensitivity analyses do confirm the results of the primary analysis and the absence of any bias generated by the definition of early withdrawals as failures.

Reference ID: 3433600

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/s/

YEH FONG CHEN
01/08/2014

HSIEN MING J HUNG
01/13/2014

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 205410 **Applicant:** Pierre Fabre Dermatologie **Stamp Date:** June 28, 2013

Drug Name: Propranolol **NDA/BLA Type:** standard

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	×			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	×			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	×			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	×			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ____ Yes**____**

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	×			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	×			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	×			
Appropriate references for novel statistical methodology (if present) are included.	×			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			×	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	×			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Reviewing Statistician Date

Supervisor/Team Leader Date

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/s/

YEH FONG CHEN
06/28/2013

HSIEN MING J HUNG
06/30/2013