ORIGINAL ARTICLE

A Randomized, Controlled Trial of Oral Propranolol in Infantile Hemangioma

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ABSTRACT

BACKGROUND

Oral propranolol has been used to treat complicated infantile hemangiomas, although data from randomized, controlled trials to inform its use are limited.

METHODS

We performed a multicenter, randomized, double-blind, adaptive, phase 2–3 trial assessing the efficacy and safety of a pediatric-specific oral propranolol solution in infants 1 to 5 months of age with proliferating infantile hemangioma requiring systemic therapy. Infants were randomly assigned to receive placebo or one of four propranolol regimens (1 or 3 mg of propranolol base per kilogram of body weight per day for 3 or 6 months). A preplanned interim analysis was conducted to identify the regimen to study for the final efficacy analysis. The primary end point was success (complete or nearly complete resolution of the target hemangioma) or failure of trial treatment at week 24, as assessed by independent, centralized, blinded evaluations of standardized photographs.

RESULTS

Of 460 infants who underwent randomization, 456 received treatment. On the basis of an interim analysis of the first 188 patients who completed 24 weeks of trial treatment, the regimen of 3 mg of propranolol per kilogram per day for 6 months was selected for the final efficacy analysis. The frequency of successful treatment was higher with this regimen than with placebo (60% vs. 4%, P<0.001). A total of 88% of patients who received the selected propranolol regimen showed improvement by week 5, versus 5% of patients who received placebo. A total of 10% of patients in whom treatment with propranolol was successful required systemic retreatment during follow-up. Known adverse events associated with propranolol (hypoglycemia, hypotension, bradycardia, and bronchospasm) occurred infrequently, with no significant difference in frequency between the placebo group and the groups receiving propranolol.

CONCLUSIONS

This trial showed that propranolol was effective at a dose of 3 mg per kilogram per day for 6 months in the treatment of infantile hemangioma. (Funded by Pierre Fabre Dermatologie; ClinicalTrials.gov number, NCT01056341.)

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A complete list of the investigators who recruited patients for the trial is provided in the Supplementary Appendix, available at NEJM.org.

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Infantile hemangiomas are the most common soft-tissue tumors of childhood, occurring in 3 to 10% of infants.[1-4] Lesions are usually not developed at birth and are generally diagnosed during the first 4 to 6 weeks of life, with most growth during the first 5 months.[5] The characteristic evolution of nearly all infantile hemangiomas is proliferation, stabilization, and slow, spontaneous involution. Although most lesions follow an uncomplicated clinical course, approximately 12% result in complications requiring referral to a specialist.[6,7] Many infantile hemangiomas leave permanent sequelae, with potential psychological effects in the children and their parents.[8,9]

Historically, systemic glucocorticoids were the mainstay of treatment for complicated infantile hemangiomas,[10] with interferon alfa and vincristine used for lesions refractory to glucocorticoid therapy. The efficacy of these treatments is variable, and all have associated safety concerns.[9,11-14]

In 2008, several of the current authors reported cases of hemangioma regression in infants treated with oral propranolol, a nonselective β-adrenergic receptor–blocking agent.[15] Numerous retrospective studies and case reports[16-19] and two small, placebo-controlled trials[20,21] have subsequently supported the efficacy of this treatment (generally at a dose of 2 mg per kilogram of body weight per day). Propranolol is now widely considered to be first-line therapy for infantile hemangiomas, despite the paucity of randomized, controlled clinical trials and the previous lack of a pediatric formulation.[22] Here we report on a large, randomized, placebo-controlled trial involving patients treated for up to 24 weeks with a pediatric oral propranolol solution.

Methods

Participants

Eligible patients were 35 to 150 days of age, with a proliferating infantile hemangioma requiring systemic therapy (i.e., an evaluated lesion with a minimal diameter of 1.5 cm). Patients with life-threatening, function-threatening, or severely ulcerated hemangiomas were excluded for ethical reasons owing to the inclusion in the trial of a placebo control. Detailed eligibility criteria are presented in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Trial Oversight

The trial was performed in accordance with Good Clinical Practice guidelines. The study protocol was approved by the local ethics committee at each participating center and is available with the statistical analysis plan at NEJM.org. Parents or guardians gave written informed consent according to national regulations.

The sponsor (Pierre Fabre Dermatologie) was involved in the study design in collaboration with three of the academic authors and was responsible for trial management, analysis and interpretation of data, and the decision to submit the manuscript for publication. A data confidentiality agreement existed between the sponsor and the investigators during the trial. The first, penultimate, and last authors vouch for the integrity and completeness of the data and analyses and for the fidelity of this report to the protocol.

Trial Design

This randomized, placebo-controlled, double-blind, phase 2–3 trial had a two-stage adaptive design, with selection of the propranolol regimen (dose and duration) at the end of stage 1 (interim analysis) and further evaluation of the selected regimen in stage 2.[23,24] Prespecified possible adaptations to be made after the interim analysis, as outlined in the protocol and statistical analysis plan, were selection of one or two regimens, sample-size reassessment, and nonbinding stopping for futility. The aim was to show superiority of propranolol over placebo and to document long-term efficacy and safety; 56 centers in 16 countries worldwide participated (see the Supplementary Appendix).

In stage 1, patients received either placebo twice daily for 6 months or one of four propranolol regimens (1 or 3 mg of propranolol base per kilogram per day, divided into two daily doses, for 3 or 6 months). Patients were assigned to treatment through an interactive voice-response system, with the use of block randomization stratified according to age group (35 to 90 days vs. 91 to 150 days) and hemangioma location (facial vs. nonfacial) and applied in a 2:2:2:2:1 ratio (propranolol at 1 mg per kilogram per day for 3 months, propranolol at 1 mg per kilogram per day for 6 months, propranolol at 3 mg per kilogram per day for 3 months, propranolol at 3 mg per kilogram per day for 6 months, and placebo, respectively).

Different concentrations of propranolol were used (1.25, 2.50, or 3.75 mg per milliliter) in order to administer the same volume to each patient and thereby maintain blinding; patients assigned to 3-month propranolol regimens received placebo for the second 3 months. Propranolol was administered in the morning and late afternoon, immediately before, during, or immediately after feeding. For patients assigned to a regimen of 3 mg of propranolol per kilogram per day, the doses of propranolol were adjusted as follows: 1 mg per kilogram per day on day 0, 2 mg per kilogram per day on day 7, and 3 mg per kilogram per day on day 14. Propranolol doses (1 and 3 mg per kilogram per day, spanning the range used in off-label practice) and durations (3 and 6 months) were determined in discussions with the regulatory agencies.

In stage 2, patients were to receive either the propranolol regimen selected after the interim analysis or placebo (in a 2:1 ratio). After the 6-month treatment period (or the premature end of treatment), patients were followed for 72 weeks (to week 96) and could receive another treatment for infantile hemangioma, at the investigators' discretion.

EFFICACY AND SAFETY ASSESSMENTS

Participation involved the following 15 visits: at screening; baseline (day 0); days 7, 14, and 21; and weeks 5, 8, 12, 16, 20, 24, 36, 48, 72, and 96. Primary efficacy was assessed by centralized evaluation of standardized digital photographs (taken by investigators at each visit) by two independent, trained, validated readers who were unaware of the study-group assignments, with adjudication for discrepancies; interreader and intrareader reliability were assessed (see the Supplementary Appendix for details of assessment). Complete or nearly complete resolution of the target hemangioma (with nearly complete resolution defined as a minimal degree of telangiectasis, erythema, skin thickening, soft-tissue swelling, and distortion of anatomical landmarks), hemangioma evolution (improvement, stabilization, or worsening), and change in hemangioma size and color were assessed centrally. At each visit, investigators assessed hemangioma evolution since the previous visit, complete resolution and complete or nearly complete resolution versus baseline, presence and extent of sequelae (e.g., telangiectasis) if complete resolution occurred, complications, and hemangioma appearance. Parents or guardians also assessed hemangioma evolution since the previous visit. Use of any other treatment for hemangioma was recorded through week 96.

Safety was assessed by analysis of adverse events (i.e., any adverse change in condition between the time of informed consent and the end of the trial or 5 days after the last trial treatment); laboratory investigations, including measurement of glucose levels from finger-prick blood samples; physical examination, including pulmonary auscultation, liver palpation, assessment of vital signs, and assessment of neurodevelopment (normal or abnormal); and electrocardiography (with findings assessed independently). All assessors were unaware of the study-group assignments. Patients were closely monitored for known important risks associated with propranolol therapy (hypoglycemia, hypotension, bradycardia, and bronchospasm) during the 4 hours after dose administration at initiation and at visits involving dosage increases; parents or guardians were informed of precautionary measures and warning signs (see the Supplementary Appendix).

OUTCOME MEASURES

The primary outcome was success (complete or nearly complete resolution of the target hemangioma) or failure of trial treatment at week 24 versus baseline according to centralized evaluation. Patients who were withdrawn from trial treatment or who used other hemangioma treatment before week 24 were considered to have had a failure of treatment. The key secondary outcome was success or failure of trial treatment according to onsite assessments by the investigator at week 48 versus baseline. Other prespecified secondary outcomes that were based on centralized, investigator, and parent or guardian assessments are presented in the Supplementary Appendix.

STATISTICAL ANALYSIS

The sample size was calculated on the basis of conservative estimated success rates of 10% (placebo),[25,26] 20% (1 mg of propranolol per kilogram per day for 3 months), 30% (1 mg per kilogram per day for 6 months), 40% (3 mg per kilogram per day for 3 months), and 55% (3 mg per kilogram per day for 6 months) (see the Supplementary Appendix).[24] The planned sample size was 450 randomly assigned patients.

After the first 188 patients (stage 1) had completed 24 weeks of trial therapy (or had been withdrawn prematurely from trial therapy), an independent data and safety monitoring committee conducted the interim analysis. By this time, recruitment targets had been exceeded and the necessary sample size had been reached (460 patients). However, the sponsor decided, before unblinding, to maintain the interim analysis and the adaptive nature of the trial so that recruitment could continue if sample-size reassessment became necessary (this was important, since minimal data were available to estimate the success rates). Therefore, the prespecified week 24 analysis was maintained, and outcome data were collected for all regimens.

The superiority of the selected regimen versus placebo was tested with the use of the closed testing procedure and combination tests for all intersection hypotheses, with application of the Simes adjustment[24,27] (see the Supplementary Appendix). This testing method guaranteed that the familywise type I error rate was below the nominal and stringent one-sided significance level of 0.005. The week 24 analysis was performed, as planned, on the intention-to-treat population: all patients in stage 1 (regardless of regimen) plus patients in stage 2 who were randomly assigned to placebo or the selected propranolol regimen and who had received at least one dose of trial therapy. Sensitivity analyses with a broader definition of treatment failure were performed on the per-protocol population. Prespecified analyses of the primary end point with adjustment for stratification factors (age group and hemangioma location) and the randomization ratio (changed to aid recruitment) used an extension of the combination test for logistic regression.[24] Combination tests were used for an adaptive design in analyses of secondary end points. Unless otherwise specified, P values in the efficacy analyses are one-sided, as is common in adaptive-design methods.[23,24,28]

RESULTS

PATIENTS

Between February 2010 and November 2011, a total of 460 patients underwent randomization. Of those, 456 patients received treatment, 323 completed 24 weeks of trial treatment, 391 entered follow-up, and 343 completed follow-up to week 96 (last visit, November 2013) (Fig. 1). Demographic and baseline disease characteristics were similar across the study groups (Table 1).

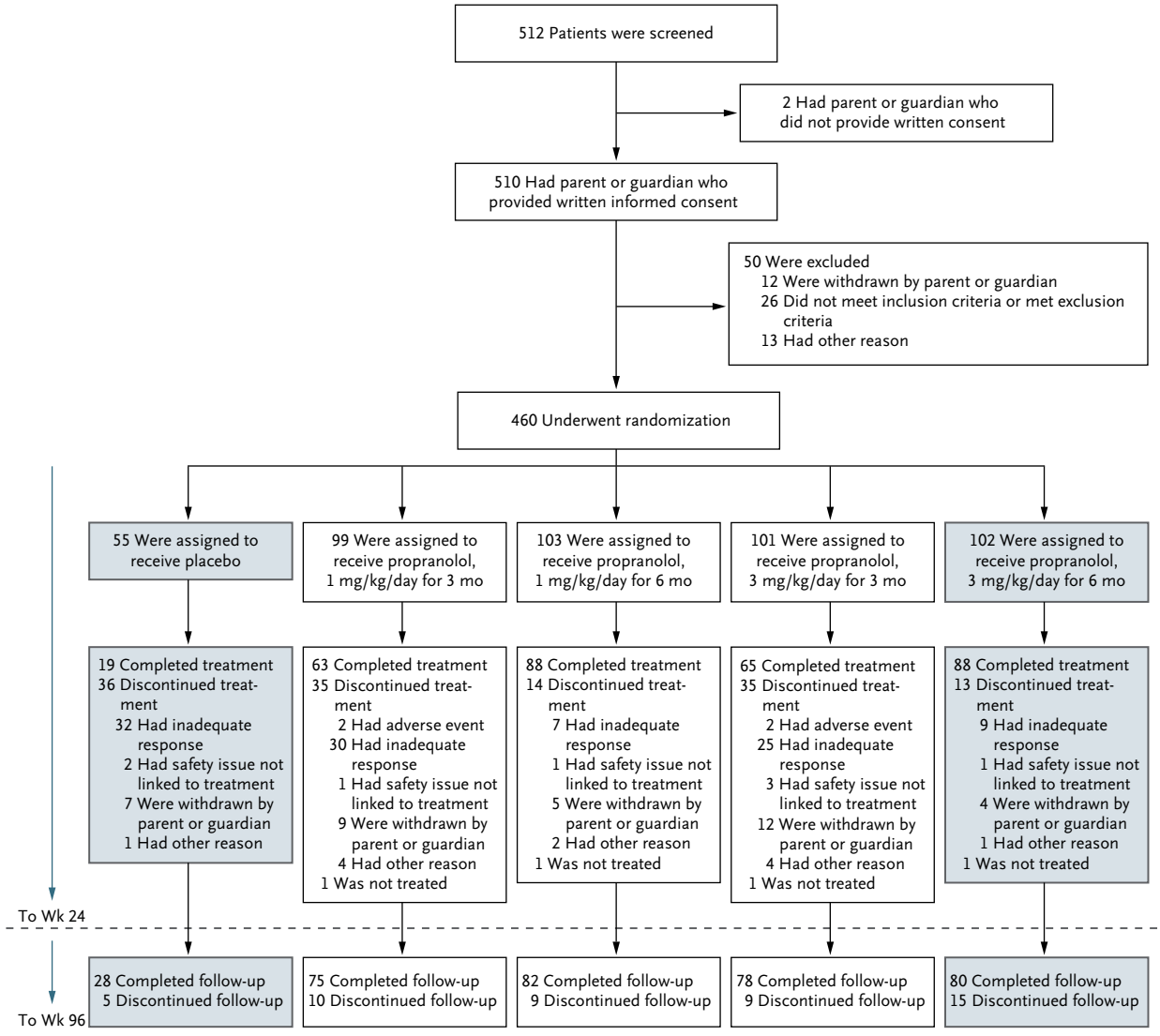
A total of 133 patients (29%) discontinued treatment prematurely, most frequently those receiving the 6-month placebo regimen (65%), with lower rates among those receiving the 3-month propranolol regimens (36% of patients receiving 1 mg per kilogram per day, and 35% of those receiving 3 mg per kilogram per day, mostly after the week-12 switch to placebo) and the lowest rates among those receiving the 6-month propranolol regimens (14% of patients receiving 1 mg per kilogram per day, and 13% of those receiving 3 mg per kilogram per day). Treatment inefficacy was the most frequent reason for discontinuation (Fig. S1 and Table S2 in the Supplementary Appendix).

EFFICACY

At the time of the interim analysis (January 2012), 2 of 25 patients (8%) receiving placebo had successful treatment at week 24, as compared with 4 of 41 patients (10%) receiving 1 mg of propranolol per kilogram per day for 3 months, 3 of 39 patients (8%) receiving 3 mg per kilogram per day for 3 months, 15 of 40 patients (38%) receiving 1 mg per kilogram per day for 6 months ($P=0.004$ for the comparison with placebo), and 27 of 43 patients (63%) receiving 3 mg per kilogram per day for 6 months ($P<0.001$ for the comparison with placebo) (Fig. 2A). The independent data and safety monitoring committee determined that the propranolol regimen with the highest benefit-to-risk ratio was 3 mg per kilogram per day for 6 months; the committee did not recommend adjusting the planned sample size. According to the prespecified plan, the week 24 efficacy analysis was conducted to test the superiority of the selected propranolol regimen over placebo.

Overall, 61 of 101 patients (60%) assigned to the selected propranolol regimen and 2 of 55 patients (4%) assigned to placebo had successful treatment at week 24 ($P<0.001$) (Fig. 2B). Results were consistent between trial stages, similar in the per-protocol population, and supported by sensitivity analysis (Tables S4 and S5 in the Supplementary Appendix).

The selected propranolol regimen remained



	Placebo	1 mg/kg/day for 3 Mo	1 mg/kg/day for 6 Mo	3 mg/kg/day for 3 Mo	3 mg/kg/day for 6 Mo	Total
			no. of patients			
Safety	55	98	102	100	101	456
Efficacy Stage 1 + Stage 2 — without Overrun (wk 24 analysis)						
Intention-to-Treat Population	55	41	40	39	101	276
Per-Protocol Population	53	38	38	37	93	259

Figure 1. Screening, Randomization, Treatment, and Follow-up of the Patients.

The safety population included all randomly assigned patients who received at least one dose of trial treatment. The intention-to-treat population included all randomly assigned patients in stage 1 (the phase 2 part of the trial, comparing each of the four propranolol regimens with placebo) plus all patients in stage 2 (the phase 3 part of the trial, comparing the selected regimen of propranolol [3 mg per kilogram per day for 6 months] with placebo) who received at least one dose of trial treatment. The per-protocol population included all patients in the intention-to-treat population with no major protocol deviation, except for prohibited treatments to treat infantile hemangiomas. "Overrun" indicates the subgroup of patients in stage 2 who were assigned to a regimen other than the selected regimen of propranolol or placebo. Patients could have more than one reason for study exclusion and for discontinuation of trial treatment. Shaded boxes indicate the week 24 efficacy analysis that was conducted to test the superiority of the selected propranolol regimen over placebo.

Table 1. Baseline Characteristics of Study Patients and Hemangiomas.*

Characteristic	Placebo (N=55)	Propranolol (N=401)				Total (N=456)
		1 mg/kg/day for 3 mo (N=98)	1 mg/kg/day for 6 mo (N=102)	3 mg/kg/day for 3 mo (N=100)	3 mg/kg/day for 6 mo (N=101)	
Patients						
Sex — no. (%)						
Male	17 (31)	30 (31)	32 (31)	21 (21)	31 (31)	131 (29)
Female	38 (69)	68 (69)	70 (69)	79 (79)	70 (69)	325 (71)
Age at inclusion						
Days	103.9±31.1	103.6±33.1	102.6±30.1	107.5±30.1	101.6±31.0	103.8±31.0
35–90 days — no. (%)	20 (36)	36 (37)	38 (37)	36 (36)	37 (37)	167 (37)
>90 days — no. (%)	35 (64)	62 (63)	64 (63)	64 (64)	64 (63)	289 (63)
Hemangiomas						
Location — no. of patients (%)						
Facial	40 (73)	71 (72)	72 (71)	64 (64)	71 (70)	318 (70)
Nonfacial	15 (27)	27 (28)	30 (29)	36 (36)	30 (30)	138 (30)
Morphologic classification — no. of patients (%)						
Segmental	2 (4)	4 (4)	7 (7)	7 (7)	5 (5)	25 (5)
Localized	48 (87)	89 (91)	90 (88)	88 (88)	91 (90)	406 (89)
Indeterminate	5 (9)	5 (5)	5 (5)	5 (5)	5 (5)	25 (5)
Superficial component — no. of patients (%)						
Flat	4 (7)	9 (9)	6 (6)	9 (9)	9 (9)	37 (8)
Elevated						
Slightly	19 (35)	22 (22)	22 (22)	29 (29)	22 (22)	114 (25)
Moderately	15 (27)	35 (36)	43 (42)	24 (24)	31 (31)	148 (32)
Markedly	17 (31)	32 (33)	31 (30)	38 (38)	39 (39)	157 (34)
Deep component — no. of patients (%)†	35 (64)	74 (76)	66 (65)	79 (79)‡	72 (71)	326 (71)

* Plus–minus values are means ±SD. There were no significant differences among the study groups unless otherwise indicated.
† Values are for a possible or a definite deep component.
‡ P=0.04 for the comparison with placebo.

superior to placebo in analyses adjusting for age group, hemangioma location, and randomization ratio (Table S6 in the Supplementary Appendix). Improvement between baseline and week 5 (according to centralized assessment) occurred in 88% of patients assigned to the selected regimen and 5% of patients assigned to placebo (P<0.001); sustained improvement (maintained at each subsequent visit until week 24) occurred from week 5 in 73% and 5% of patients, respectively. A significantly greater mean reduction in hemangioma surface area and color intensity was achieved with the selected propranolol regimen than with placebo (Table S8 in the Supplementary Appendix). Results of an exploratory analysis of the primary end point for all regimens are shown in Table 2 (and Table S7 in the Supplementary Appendix).

On-site investigators' assessments of complete resolution (Table S9 in the Supplementary Appendix) and complete or nearly complete resolution (Table S8 in the Supplementary Appendix) of the target hemangioma differed from centralized assessments; 40% of the cases

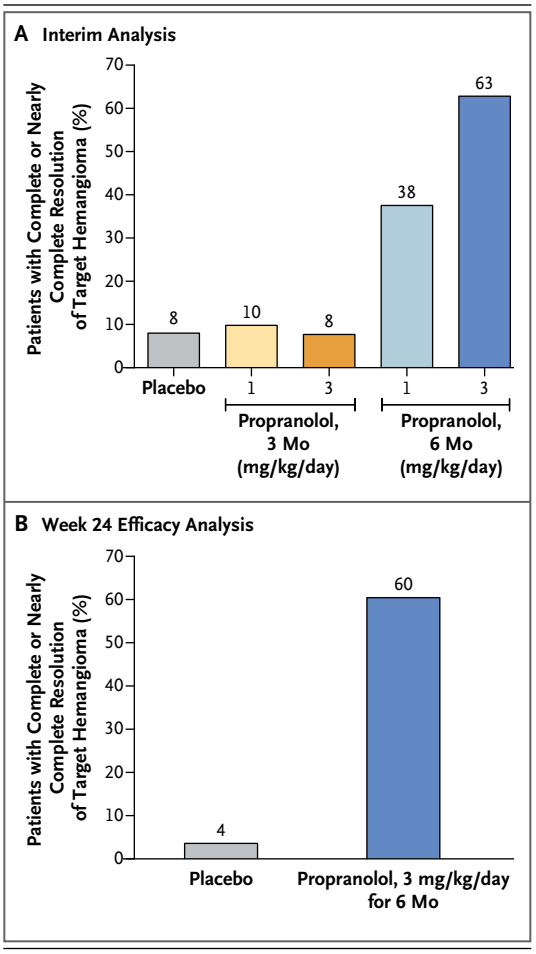


Figure 2. Interim Analysis and Week 24 Efficacy Analysis of Complete or Nearly Complete Resolution of the Target Hemangioma at Week 24 versus Baseline.

Nearly complete resolution was defined as a minimal degree of telangiectasis, erythema, skin thickening, soft-tissue swelling, and distortion of anatomical landmarks. In the interim analysis (Panel A), differences in complete or nearly complete resolution between patients receiving propranolol and those receiving placebo were significant only for the 6-month regimens (1 mg per kilogram per day for 3 months, P=0.40; 3 mg per kilogram per day for 3 months, P=0.52; 1 mg per kilogram per day for 6 months, P=0.004; and 3 mg per kilogram per day for 6 months, P<0.001). In accordance with the protocol and the statistical analysis plan, the interim analysis involved the first 188 patients assigned to any of the five treatment regimens (corresponding to the patients in stage 1) who received at least one dose of trial treatment and who either had completed the week 24 visit or had been withdrawn prematurely from the trial treatment (i.e., the intention-to-treat population in stage 1). For the primary efficacy end point of complete or nearly complete resolution of the target hemangioma at week 24 according to centralized assessment, the P values for the four propranolol regimens (vs. placebo) were calculated with the use of a one-sided z-test for proportions with pooled variance estimates. In the week 24 efficacy analysis (Panel B), the difference in complete or nearly complete resolution between patients receiving propranolol at a dose of 3 mg per kilogram per day for 6 months and those receiving placebo was significant (P<0.001). This analysis involved the intention-to-treat population for the selected regimens at an interim analysis (i.e., all patients in stage 1 [regardless of regimen] and patients in stage 2 who were assigned to either placebo or the selected regimen of propranolol and who received at least one dose of trial treatment). The objective was to test the superiority of the selected regimen ($H0,sel:\theta sel \leq 0$ against the alternative $H1,sel:\theta sel > 0$) with the use of the method described by Heritier et al.,[24] for an adaptive confirmatory design with a single selection at an interim analysis, guaranteeing that the familywise type I error rate was maintained at the nominal level of 0.005.

judged centrally as having been treated successfully were assessed by local investigators as showing complete or nearly complete resolution (Table S10 in the Supplementary Appendix; see also examples of discrepancies and discussion). However, the rate of investigator-assessed sustained improvement from week 5 to week 24 (71%) (Table S8 in the Supplementary Appendix) was similar to the rate determined by centralized assessments.

Successful treatment at week 24 was sustained to week 96 in 35 of 54 patients assigned to the selected propranolol regimen (65%) and in 2 of 2 patients assigned to placebo, without any additional hemangioma treatment. Only 6 patients assigned to the selected propranolol regimen (10%) required reintroduction of systemic hemangioma treatment from week 24 to week 96 (7 patients [11%] required any additional hemangioma treatment).

SAFETY

Corresponding to rates of premature discontinuation of trial treatment, mean exposure was lowest for placebo (83 days), higher for 3-month propranolol treatment (143 days for 1 mg per kilogram per day and 147 days for 3 mg per kilogram per day), and highest for 6-month propranolol treatment (157 days for 1 mg per kilogram per day and 161 days for 3 mg per kilogram per day). During treatment, 33 serious adverse events occurred in 26 patients, with no significant difference overall or according to individual events between the placebo group and the group receiv-

Table 2. Exploratory Analysis of the Primary Efficacy Outcome in the Intention-to-Treat Population with Overrun.*

Variable	Placebo (N=55)	Propranolol (N=401)			
		1 mg/kg/day for 3 mo (N=98)	1 mg/kg/day for 6 mo (N=102)	3 mg/kg/day for 3 mo (N=100)	3 mg/kg/day for 6 mo (N=101)
Complete or nearly complete resolution of target hemangioma at wk 24 — no. (%)†					
Yes	2 (4)	8 (8)	50 (49)	12 (12)	61 (60)
No	53 (96)	90 (92)	52 (51)	88 (88)	40 (40)
P value‡		0.14	<0.001	0.04	<0.001

* "Overrun" indicates patients in stage 2 of the trial who were assigned to a regimen other than the selected regimen of propranolol or placebo.
† Nearly complete resolution was defined as a minimal degree of telangiectasis, erythema, skin thickening, soft-tissue swelling, and distortion of anatomical landmarks.
‡ P values for the four propranolol regimens (vs. placebo) were calculated with the use of a one-sided z-test for proportions with pooled variance estimates.

ing the selected propranolol regimen (Table 3, and Tables S11 and S12 in the Supplementary Appendix).

The overall incidence of adverse events was higher among patients receiving the propranolol regimens (90% with 1 mg per kilogram per day for 6 months to 96% with 3 mg per kilogram per day for 6 months) than among patients receiving placebo (76%) (Table 3). The most common events were either expected in the infant population (e.g., nasopharyngitis, pyrexia, and teething) (Table S13 in the Supplementary Appendix) or known side effects of propranolol (e.g., diarrhea, sleep disorders, events potentially related to bronchial hyperreactivity, and cold hands and feet) (Table 3). Most events were classified as mild or moderate in severity, with onset within 3 months after treatment initiation. When events occurring only during propranolol treatment were considered (i.e., excluding events that occurred during the placebo phase of the 3-month propranolol regimens), infants receiving the 3-mg dose (vs. the 1-mg dose) appeared to have a higher incidence of diarrhea (22% vs. 14%) and of events potentially related to bronchial hyperreactivity (9% vs. 6%). Bronchospasm occurred in four patients (two receiving propranolol and two receiving placebo, including one who had previously received the regimen of 3 mg of propranolol per kilogram per day for 3 months), leading to temporary discontinuation of treatment in two patients (one receiving placebo).

In all propranolol groups during the 4 hours after the initial dose and after subsequent dose adjustments, the mean heart rate and mean systolic blood pressure decreased (by approximately 7 beats per minute and approximately 3 mm Hg across groups) and the PR interval increased, without appreciable differences between doses (Fig. S2, S4, and S5 in the Supplementary Appendix). Heart-rate decreases occurred within 1 hour after dose administration, with minimal changes thereafter. Overall differences observed in these variables as compared with placebo decreased between week 5 and week 8 and had disappeared by week 24. Bradycardia was reported in two patients assigned to propranolol during the dose-adjustment phase (one patient had a serious adverse event in the context of enterocolitis, and the other had no visible symptoms). One serious adverse event, second-degree atrioventricular block (with preexisting cardiac conditions later documented; see Tables S11 and S12 in the Supplementary Appendix), occurred after dose administration on day 0 (treatment was discontinued).

Hypotension (without apparent associated manifestations) occurred in seven patients (six of whom were receiving propranolol, four during the dose-adjustment phase). Mild hypoglycemia without visible manifestations occurred in two patients (both receiving propranolol during the dose-adjustment phase). No events of hypotension or hypoglycemia led to treatment discontinuation. During follow-up (Tables S14 and S15 in the Supplementary Appendix), no appreciable differences were noted between the propranolol groups and the placebo group in growth, neurodevelopment, or cardiovascular variables.

Table 3. Adverse and Serious Adverse Events with Propranolol or Placebo to Week 24 (Safety Population).*

Variable	Placebo (N=55)	Propranolol (N=401)			
		1 mg/kg/day for 3 mo (N=98)	1 mg/kg/day for 6 mo (N=102)	3 mg/kg/day for 3 mo (N=100)	3 mg/kg/day for 6 mo (N=101)
	number of patients (percent)				
Adverse-event summary†					
≥1 Serious adverse event	3 (5)	5 (5)	3 (3)	9 (9)	6 (6)
≥1 Adverse event that occurred during treatment	42 (76)	89 (91)	92 (90)	92 (92)	97 (96)
≥1 Adverse event that occurred during treatment, leading to definitive treatment discontinuation	6 (11)	4 (4)	2 (2)	6 (6)	3 (3)
Adverse events					
Known important risks associated with propranolol therapy					
Hypotension	1 (2)	2 (2)	1 (1)	3 (3)	0
Bronchospasm	1 (2)	0	0	2 (2)‡	1 (1)
Bradycardia	0	0	1 (1)	1 (1)	0
Hypoglycemia	0	0	1 (1)	0	1 (1)
Other risks associated with propranolol therapy§					
Diarrhea	4 (7)	16 (16)	14 (14)	17 (17)	28 (28)
Sleep disorder¶	7 (13)	28 (29)	14 (14)	19 (19)	22 (22)
Bronchitis	1 (2)	5 (5)	8 (8)	11 (11)	17 (17)
Vomiting	3 (5)	16 (16)	13 (13)	10 (10)	13 (13)
Bronchiolitis	3 (5)	6 (6)	7 (7)	6 (6)	10 (10)
Cold hands and feet	1 (2)	8 (8)	10 (10)	1 (1)	10 (10)
Agitation‖	6 (11)	12 (12)	18 (18)	8 (8)	7 (7)
Constipation	1 (2)	9 (9)	6 (6)	9 (9)	4 (4)
Decreased appetite	1 (2)	5 (5)	3 (3)	5 (5)	1 (1)
Somnolence	1 (2)	6 (6)	4 (4)	1 (1)	1 (1)

* The safety population included all randomly assigned patients who received at least one dose of trial therapy during stage 1 or 2. Adverse events were any events that occurred or worsened during trial treatment or up to 5 days after the last day of trial treatment; they were tabulated for each study group according to the preferred terms from the *Medical Dictionary for Regulatory Activities* (MedDRA).

† With regard to the 3-month propranolol regimens, the week 24 analysis did not separate events observed during the first 3 months (active-treatment phase) from those observed during the second 3 months (placebo phase).

‡ One event of bronchospasm occurred during the placebo phase, after the active-treatment phase had ended.

§ Shown are events observed in at least 5% of patients in any propranolol group, listed by decreasing order of incidence among patients who received 3 mg of propranolol per kilogram per day for 6 months.

¶ The term "sleep disorder" includes the following MedDRA preferred terms: sleep disorder, middle insomnia, hypersomnia, insomnia, poor quality sleep, initial insomnia, terminal insomnia, and nightmare.

‖ The term "agitation" includes the following MedDRA preferred terms: restlessness, agitation, anxiety, psychomotor hyperactivity, nervousness, stress, and irritability.

DISCUSSION

This large-scale, randomized, placebo-controlled trial showed that propranolol is effective in treating infantile hemangioma, with a favorable risk–benefit profile. Our adaptive design, involving an initial comparison of four propranolol regimens with placebo, allowed selection of a more effective dose (3 mg rather than 1 mg per kilogram per day) and treatment duration (6 months rather

than 3 months). Treatment with propranolol at a dose of 3 mg per kilogram per day for 6 months resulted in a significantly higher success rate (primary outcome) as compared with placebo (60% vs. 4%). Results were supported by a per-protocol analysis and a sensitivity analysis involving a broader definition of treatment failure.

The observed divergence between centralized and investigator evaluations of complete or nearly complete resolution of the target hemangioma after treatment with propranolol may be explained by limited investigator training and the lack of validation or monitoring (for logistic reasons) as compared with the training and validation of central readers. A review of the discrepant cases (see examples in the Supplementary Appendix) suggests that investigators applied a more stringent threshold for nearly complete resolution, especially regarding the presence of residual telangiectasis. Investigators' assessments of sustained improvement from week 5 to week 24 were highly concordant with the centralized assessments (both >70%).

Adverse events were more frequent among the patients who received propranolol than among those who received placebo; for some events, the greater frequency may be partly explained by the longer duration of treatment with propranolol than with placebo, largely owing to more frequent discontinuations for lack of efficacy in the placebo group. Important risks anticipated with the use of propranolol,[6] including bronchospasm, bradycardia, hypotension, and hypoglycemia, were infrequent but occurred more often in the propranolol groups than in the placebo group. With regard to these four risks, only one patient who received propranolol had a serious adverse event (bradycardia in the context of enterocolitis). Heart-rate decreases typically occurred within 1 hour after dose administration. The risk of hypoglycemia may be minimized with proper education of parents or guardians about the importance of administering propranolol as prescribed (i.e., during or right after feeding).

The current trial confirms and builds on the results of previous case series[16,18,19] and smaller placebo-controlled trials.[20,21] For example, one placebo-controlled trial involving 39 patients showed that the administration of propranolol (2 mg per kilogram per day) was associated with a 60.0% decrease in hemangioma volume at week 24, as compared with a 14.1% decrease with placebo.[20] In our study, only 10% of successfully treated hemangiomas required systemic retreatment within 72 weeks after the end of trial treatment. This finding is consistent with that of a prior report, in which 12% of the patients who had a response had relapses requiring retreatment.[29]

Limitations of this trial include the lack of a validated assessment for the evolution of infantile hemangiomas. However, assessment of our outcome involved standardized photographic procedures and independent, centralized, blinded, and validated reading. We did not include a group treated with 2 mg of propranolol per kilogram per day, a dose frequently used in practice, but the doses we studied (1 mg and 3 mg per kilogram per day) span the range used empirically in practice. Although patients with high-risk hemangiomas were excluded owing to the placebo control, other case series support the efficacy of oral propranolol in high-risk cases.[30-37]

In conclusion, this trial shows that oral propranolol at a dose of 3 mg per kilogram per day for 6 months is effective in the treatment of infantile hemangioma.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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