

ORIGINAL ARTICLE

Eltrombopag for the Treatment of Chronic Idiopathic Thrombocytopenic Purpura

James B. Bussel, M.D., Gregory Cheng, M.D., Mansoor N. Saleh, M.D.,
Bethan Psaila, M.D., Lidia Kovaleva, M.D., Balkis Meddeb, M.D.,
Janusz Kloczko, M.D., Habib Hassani, Ph.D., Bhabita Mayer, M.Sc.,
Nicole L. Stone, Ph.D., Michael Arning, M.D., Drew Provan, M.D.,
and Julian M. Jenkins, M.Sc.*

ABSTRACT

BACKGROUND

The pathogenesis of chronic idiopathic thrombocytopenic purpura (ITP) involves antibody-mediated platelet destruction and reduced platelet production. Stimulation of platelet production may be an effective treatment for this disorder.

METHODS

We conducted a trial in which 118 adults with chronic ITP and platelet counts of less than 30,000 per cubic millimeter who had had relapses or whose platelet count was refractory to at least one standard treatment for ITP were randomly assigned to receive the oral thrombopoietin-receptor agonist eltrombopag (30, 50, or 75 mg daily) or placebo. The primary end point was a platelet count of 50,000 or more per cubic millimeter on day 43.

RESULTS

In the eltrombopag groups receiving 30, 50, and 75 mg per day, the primary end point was achieved in 28%, 70%, and 81% of patients, respectively. In the placebo group, the end point was achieved in 11% of patients. The median platelet counts on day 43 for the groups receiving 30, 50, and 75 mg of eltrombopag were 26,000, 128,000, and 183,000 per cubic millimeter, respectively; for the placebo group the count was 16,000 per cubic millimeter. By day 15, more than 80% of patients receiving 50 or 75 mg of eltrombopag daily had an increased platelet count. Bleeding also decreased during treatment in these two groups. The incidence and severity of adverse events were similar in the placebo and eltrombopag groups.

CONCLUSIONS

Eltrombopag increased platelet counts in a dose-dependent manner in patients with relapsed or refractory ITP. (ClinicalTrials.gov number, NCT00102739.)

From Weill Cornell Medical College of Cornell University, New York (J.B.B., B.P.); Prince of Wales Hospital, Shatin, Hong Kong (G.C.); Georgia Cancer Specialists, Tucker, GA (M.N.S.); Hematology Research Center, Moscow (L.K.); Hôpital La Rabta, Tunis, Tunisia (B.M.); Akademia Medyczna, Białystok, Poland (J.K.); Glaxo-SmithKline, Greenford, United Kingdom (H.H., B.M.), and Collegeville, PA (N.L.S., M.A., J.M.J.); and Barts and the London School of Medicine, London (D.P.). Address reprint requests to Dr. Bussel at Weill Cornell Medical College of Cornell University, 525 E. 68th St., P695, New York, NY 10065, or at jbusssel@med.cornell.edu.

*Other study participants are listed in the Appendix.

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IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP) is an autoimmune disease in which antiplatelet antibodies accelerate the destruction of platelets. In addition, platelet production can be impaired¹ because the antiplatelet antibodies can also damage megakaryocytes.²⁻⁴ Although the thrombocytopenia of ITP can be severe, signs of bleeding are usually only minor. Persistently low platelet counts (<20,000 per cubic millimeter), however, are associated with an increased risk of serious bleeding, such as intracranial hemorrhage.^{5,6} The goal of managing chronic ITP is to maintain platelet counts, with the least possible intervention, at levels that prevent bleeding, thereby reducing treatment-related toxicity.⁷

Glucocorticoids and intravenous immunoglobulins increase platelet counts in ITP primarily by reducing the extent of platelet destruction. However, the recognition that platelet production in ITP is often suboptimal has led to the use of treatments that enhance thrombopoiesis. This approach has focused on thrombopoietin, the growth factor underlying megakaryocytopoiesis. Thrombopoietin is the ligand for the thrombopoietin receptor on megakaryocytes and platelets.⁸⁻¹¹ In many patients with ITP, however, serum levels of thrombopoietin are within the normal range despite the thrombocytopenia.^{12,13}

Two recent studies showed that AMG 531, a subcutaneously administered thrombopoiesis-stimulating protein, can increase platelet counts in patients with chronic ITP.^{14,15} In one study, single doses increased platelet counts substantially in 7 of 12 patients, and multiple doses increased platelet counts in 12 of 16 patients.¹⁴ Eltrombopag (SB-497115) is an oral, small-molecule, nonpeptide thrombopoietin-receptor agonist. The drug initiates thrombopoietin-receptor signaling by interacting with the transmembrane domain of the receptor, thereby inducing proliferation and differentiation of cells in the megakaryocytic lineage. Administration of eltrombopag increased platelet production in preclinical studies, in volunteers with normal platelet counts,¹⁶⁻²¹ and in patients with thrombocytopenia secondary to hepatitis C virus infection.²² This study was designed to assess whether eltrombopag could safely increase platelet counts in adults with relapsed or refractory chronic ITP.

METHODS

PATIENTS

Patients at 44 clinical sites were enrolled between February and November 2005. The protocol was approved by the human subjects committee at each institution, and all patients gave written informed consent before enrollment. Participants were at least 18 years of age, had at least a 6-month history of ITP, had received at least one previous treatment for ITP, and had a platelet count of less than 30,000 per cubic millimeter at enrollment. Patients receiving maintenance immunosuppressive regimens, primarily glucocorticoids, were eligible if the dose had been stable for at least 1 month. The dose had to remain unchanged throughout the study. Other treatments for ITP must have been completed at least 2 weeks before enrollment.

Patients with the following conditions were excluded: secondary immune thrombocytopenia (e.g., patients infected with human immunodeficiency virus or hepatitis C virus or patients with systemic lupus erythematosus), hemoglobin levels of less than 10 g per deciliter, congestive heart failure, arrhythmia, thrombosis within 1 year before enrollment, or myocardial infarction within 3 months before enrollment; women who were nursing or pregnant were also excluded. Women of childbearing age agreed to use contraception throughout the study. Values within the normal range were required for neutrophils, reticulocyte count, creatinine, and liver enzymes.

STUDY DESIGN

This multicenter, randomized, double-blind, placebo-controlled trial examined once-daily oral treatment with eltrombopag. Patients were randomly assigned (in a 1:1:1:1 ratio) to receive placebo or 30, 50, or 75 mg of eltrombopag per day for up to 6 weeks. Randomization was stratified according to concomitant ITP medication (yes or no), splenectomy (yes or no), and the baseline platelet count (>15,000 per cubic millimeter vs. ≤15,000 per cubic millimeter), with a block size of four within each stratum. To reduce the risk of thrombocytosis, treatment was discontinued when platelet counts exceeded 200,000 per cubic millimeter. Race was self-reported and recorded on the case report form by each participating center.

The primary end point was a platelet count of 50,000 or more per cubic millimeter on day 43 of the study. Secondary end points included safety and tolerability, signs of bleeding, serum thrombopoietin level (as measured by enzyme-linked immunosorbent assay, R&D Systems), and health-related quality of life (as measured by the Medical Outcomes Study 36-Item Short Form General Health Survey, version 2 [SF36v2]; Quality-Metric). The incidence and severity of bleeding were assessed at every visit according to the World Health Organization (WHO) bleeding scale (grade 0, no bleeding; grade 1, petechiae; grade 2, mild blood loss; grade 3, gross blood loss; grade 4, debilitating blood loss).

All patients were assessed weekly for safety, tolerability, and efficacy of the treatment during the 6-week treatment period and at 2-week intervals for 6 weeks after the study medication had been discontinued. In preclinical studies, cataract formation was found in rodents but not dogs, and patients therefore received ophthalmic evaluations before treatment, at the end of treatment, and 6 months after the last dose of the study medication. An independent safety committee reviewed the ocular findings. The study was conducted in accordance with the provisions of the Declaration of Helsinki, Good Clinical Practice guidelines, and local laws and regulations.

The protocol was developed by the academic principal investigators at the study sites and employees of the sponsor (GlaxoSmithKline). Data were collected and analyzed by the sponsor. Decisions related to the content and publication of the manuscript were made by the academic principal investigator of the study in consultation with the coauthors. All academic and nonacademic authors had access to the primary data and vouch for the completeness and accuracy of the data.

STATISTICAL ANALYSIS

An adaptive sequential design was applied.²³ Response to treatment was defined as achievement of the primary end point: a platelet count of 50,000 or more per cubic millimeter. All patients who were treated with at least one dose of study medication and who had a baseline platelet count of less than 30,000 per cubic millimeter were included in the analyses of the primary end point. Two interim analyses were planned when data

were available for one third and two thirds of the maximum intended sample size of 272 patients (68 per group). The trial had 90% statistical power at the 2.5% level of significance (one-sided) to detect a 30% difference in the proportion of patients with a response (platelet count $\geq 50,000$ per cubic millimeter) to patients without a response between the placebo group and each eltrombopag group, assuming that 30% of patients receiving placebo would have a response. A logistic-regression model with adjustment for the use or non-use of concomitant medication for ITP, splenectomy status, and baseline platelet count ($\leq 15,000$ per cubic millimeter vs. $>15,000$ per cubic millimeter) was used to test the global null hypothesis that the odds of a response were equal across all four study groups. If the null hypothesis was rejected, the odds of a response in each eltrombopag group were compared with the odds of a response in the placebo group by means of a closed testing procedure to maintain the overall type 1 error at 2.5% (one-sided). The interactions between treatment response and stratification variables were evaluated at the 10% level of significance.

The primary end point was analyzed by use of a prospectively defined last-observation-carried-forward imputation in which the last platelet count during treatment was carried forward to day 43 for patients who withdrew prematurely because of a platelet count of more than 200,000 per cubic millimeter. Patients who withdrew prematurely for any other reason were counted as not having had a response, irrespective of the platelet count (Fig. 1). Additional supportive analyses were performed with the use of only observed data at day 43, with no imputations.

For each planned interim analysis, critical boundaries for assessing efficacy and futility by means of step-down and step-up procedures, respectively, were derived with the use of EAST 3 software (Cytel Software). At the first interim analysis, performed by the study sponsor, a given dose of eltrombopag could be stopped for reasons of efficacy (one-sided $P \leq 0.0113$), futility (one-sided $P \geq 0.333$), or safety. In the first interim analysis, involving data from 104 patients, the groups receiving the two highest doses of eltrombopag met the predefined stopping criteria for efficacy under the closed testing procedure. The group receiving 30 mg of eltrombopag did not

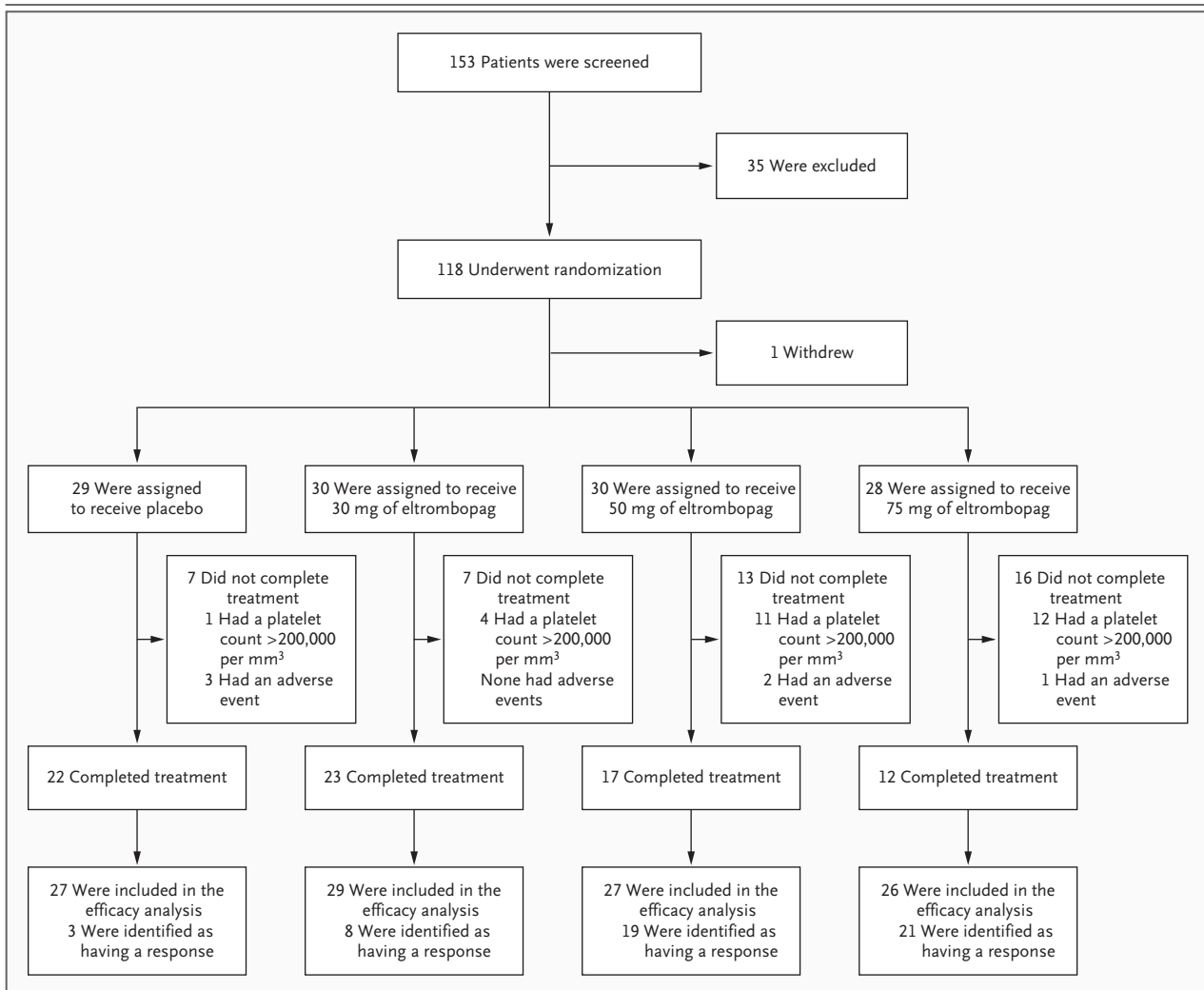


Figure 1. Enrollment, Group Assignments, and Outcome.

Patients eligible for screening had received previous treatment for chronic idiopathic thrombocytopenic purpura and had platelet counts of less than 30,000 per cubic millimeter. The efficacy population was defined as all patients who had undergone randomization and had been treated with at least one dose of eltrombopag or placebo. Eight patients were excluded from the efficacy analysis for these reasons: a platelet count greater than or equal to 30,000 per cubic millimeter (four patients), a missing baseline platelet count (one patient), and audit findings at one site (three patients). Four patients attained a platelet count of 200,000 or more per cubic millimeter but were not withdrawn from the study: one in the group receiving 30 mg of eltrombopag, one in the group receiving 50 mg, and two in the group receiving 75 mg. These four patients were therefore counted in the number completing the study. Adverse events leading to withdrawal from the study were as follows: placebo group — toxic hepatitis (in one patient), elevated bilirubin level (one), and convulsion (one); group receiving 50 mg of eltrombopag — menorrhagia (one) and hepatitis, embolism, and pulmonary embolism (one); group receiving 75 mg of eltrombopag — tonsillitis and urticaria (one). Other events leading to withdrawal from the study: placebo group — treatment with intravenous immunoglobulins before surgery for glaucoma (one) and patient's decision (two); group receiving 30 mg of eltrombopag — lack of efficacy (two) and treatment with rescue medication (one); group receiving 75 mg of eltrombopag — lack of efficacy (one), a baseline platelet count of greater than 30,000 per cubic millimeter (one), and use of prohibited medication (one).

meet the stopping criterion for either efficacy or futility (two-sided $P=0.340$); however, this dose was not continued because of high response rates for doses of 50 mg and 75 mg and a similar incidence of adverse events among patients in all four

study groups. After the decision was made to stop the study, the final analysis involving data from 118 patients, including 14 patients who enrolled after the interim cutoff date (September 2005), was performed and is presented here.

Descriptive statistics were used to summarize demographic and baseline clinical characteristics and safety data. All P values for these data were two-sided and were not adjusted for multiple testing.

RESULTS

STUDY POPULATION

Of 153 patients screened, 118 underwent randomization, and 117 were treated (Fig. 1). The most common reasons for ineligibility were a platelet count of 30,000 or more per cubic millimeter (18 patients) and withdrawal of consent before randomization (7 patients). The median age of enrolled patients was 50 years; 62% were women, and 79% were white (Table 1). Forty-seven percent of the patients had undergone splenectomy, 32% were re-

ceiving concomitant medication for ITP, and 48% had a platelet count of 15,000 or less per cubic millimeter. Seventy-four percent of the patients had previously received two or more treatments for ITP. Only 20 of the 117 patients had received therapy for ITP other than glucocorticoids or intravenous immune globulins within the 3 months preceding the start of the protocol treatment, and these 20 patients were equally distributed among the four treatment groups. Significant differences in median age and race (white vs. nonwhite) were observed between treatment groups at baseline (Table 1).

Of the 117 patients who began the trial, 7 in the placebo group and 36 in the eltrombopag groups did not complete 6 weeks of the study treatment (Fig. 1). Of these 43 patients, 28 withdrew early because they had a platelet count of

Table 1. Demographic and Clinical Characteristics at Baseline.

Characteristic	Placebo (N=29)	Eltrombopag			Total (N=117)	P Value
		30 mg (N=30)	50 mg (N=30)	75 mg (N=28)		
Age — yr						0.04*†
Median	42	51	45	55	50	
Range	18–85	23–79	23–81	18–85	18–85	
Sex — no. (%)						0.33‡
Female	16 (55)	16 (53)	21 (70)	20 (71)	73 (62)	
Male	13 (45)	14 (47)	9 (30)	8 (29)	44 (38)	
Race — no. (%)§						0.02†‡¶
Black	1 (3)	1 (3)	—	—	2 (2)	
Asian	2 (7)	4 (13)	12 (40)	3 (11)	21 (18)	
White	25 (86)	25 (83)	18 (60)	25 (89)	93 (79)	
Mixed	1 (3)	—	—	—	1 (<1)	
Stratification variables — no. (%)						
Splenectomy	14 (48)	15 (50)	15 (50)	11 (39)	55 (47)	0.82‡
Concomitant ITP medication	6 (21)	10 (33)	12 (40)	10 (36)	38 (32)	0.43‡
Platelets ≤15,000/mm ³	14 (48)	15 (50)	12 (40)	15 (54)	56 (48)	0.82‡
Prior therapies — no. (%)						0.52‡
≥1	28 (97)	29 (97)	30 (100)	26 (93)	113 (97)	
≥2	21 (72)	26 (87)	24 (80)	16 (57)	87 (74)	
≥3	14 (48)	17 (57)	18 (60)	11 (39)	60 (51)	
≥4	12 (41)	12 (40)	12 (40)	6 (21)	42 (36)	

* This value was based on a Kruskal–Wallis test across all treatment groups.

† This value is significant at the 5% level (two-sided).

‡ This value was based on the chi-square test across all treatment groups.

§ Race was self-reported.

¶ The P value was based on a comparison of whites and nonwhites.

|| The P value was based on the proportion of patients with at least one prior therapy across all study groups.

more than 200,000 per cubic millimeter. Four additional patients had a platelet count of more than 200,000 per cubic millimeter but did not withdraw from the trial. Efficacy was evaluated in 109 patients (Fig. 1); all 117 patients were evaluated for safety.

PLATELET COUNTS

The primary end point, a platelet count of 50,000 or more per cubic millimeter on day 43, was achieved in 81% of patients (21 of 26) given 75 mg of eltrombopag, 70% of patients (19 of 27) given 50 mg, and 28% of patients (8 of 29) given 30 mg; 11% of patients (3 of 27) in the placebo group reached the end point ($P<0.001$ for the groups taking 50 mg and 75 mg of eltrombopag) (Fig. 1). Results were similar in an analysis of data at day 43 with no last-observation-carried-forward imputation: 73% (8 of 11), 56% (9 of 16), and 22% (5 of 23) of patients given 75 mg, 50 mg, or 30 mg of eltrombopag, respectively, and 10% (2 of 21) of patients given placebo reached the primary end point (two-sided $P=0.002$ for the comparison of 50 mg with placebo and $P=0.001$ for the comparison of 75 mg with placebo). At the first visit (day 8), 44% of patients receiving 50 mg of eltrombopag and 62% of those receiving 75 mg had a platelet count of 50,000 or more per cubic millimeter. By day 15, 88% of patients receiving 50 mg and 81% of those receiving 75 mg had a response (Fig. 2A), with the median platelet count (last-observation-carried-forward data) approaching the normal range (i.e., 150,000 to 400,000 per cubic millimeter); at these two doses, the 25th percentile of the platelet counts was approximately 50,000 per cubic millimeter (Fig. 2B). After the first interim analysis showed that the two highest eltrombopag doses met predefined stopping criteria for efficacy, the trial was stopped by the sponsor. The median platelet count for patients who continued treatment (Fig. 1) was maintained at 50,000 or more per cubic millimeter at each subsequent visit during treatment in the groups receiving 50 mg or 75 mg of eltrombopag (observed data, Fig. 2C).

During the study, platelet counts rose to more than 200,000 per cubic millimeter in 4% of patients (1 of 27) in the placebo group and in 14% (4 of 29), 37% (10 of 27), and 50% (13 of 26) in the groups receiving 30, 50, and 75 mg of eltrombopag, respectively. The increase in the platelet

count to more than 200,000 per cubic millimeter occurred earlier in the group receiving 75 mg of eltrombopag than in the other eltrombopag groups. After 1 week of treatment (day 8), more than 10% of patients in the groups receiving 50 mg or 75 mg of eltrombopag had platelet counts of more than 200,000 per cubic millimeter, and by day 15, more than 25% of patients in these two groups had a platelet count of more than 200,000 per cubic millimeter. Median platelet counts in these two groups returned to levels near baseline within 2 weeks after discontinuation of therapy (Fig. 2C).

Further analyses showed no significant interaction between a response and prior splenectomy, age, or race (white vs. nonwhite). In all groups except those receiving 75 mg of eltrombopag, there was a higher percentage of responders among patients using concomitant ITP medication. Among patients who had a baseline platelet count of more than 15,000 per cubic millimeter, there was a substantially higher percentage of responders in all groups except for the group receiving 30 mg of eltrombopag (in which the overall percentage of responders was lowest) (two-sided $P=0.093$ for patients taking concomitant ITP medications and $P=0.042$ for patients with a baseline platelet count $>15,000$ per cubic millimeter) (Fig. 2D).

BLEEDING

During treatment with eltrombopag (50 mg or 75 mg), the incidence of bleeding (assessed according to the WHO bleeding scale) decreased (Fig. 3) as the platelet count increased and gradually returned to baseline levels during the 6 weeks of follow-up, as the platelet count returned to near-baseline levels. The incidence of bleeding events during treatment, regardless of grade and cause, was 14% in the placebo group and 17%, 7%, and 4% in the groups receiving 30, 50, and 75 mg of eltrombopag, respectively.

THROMBOPOIETIN LEVELS

Median baseline serum thrombopoietin levels were 54 ng per liter in the placebo group and 56, 57, and 54 ng per liter in the eltrombopag groups receiving 30, 50, and 75 mg, respectively — all within the range in healthy volunteers (26 to 209 ng per liter).¹¹ Similar median serum thrombopoietin levels were observed at day 43 (59 ng per liter in the placebo group and 49, 52, and 45 ng

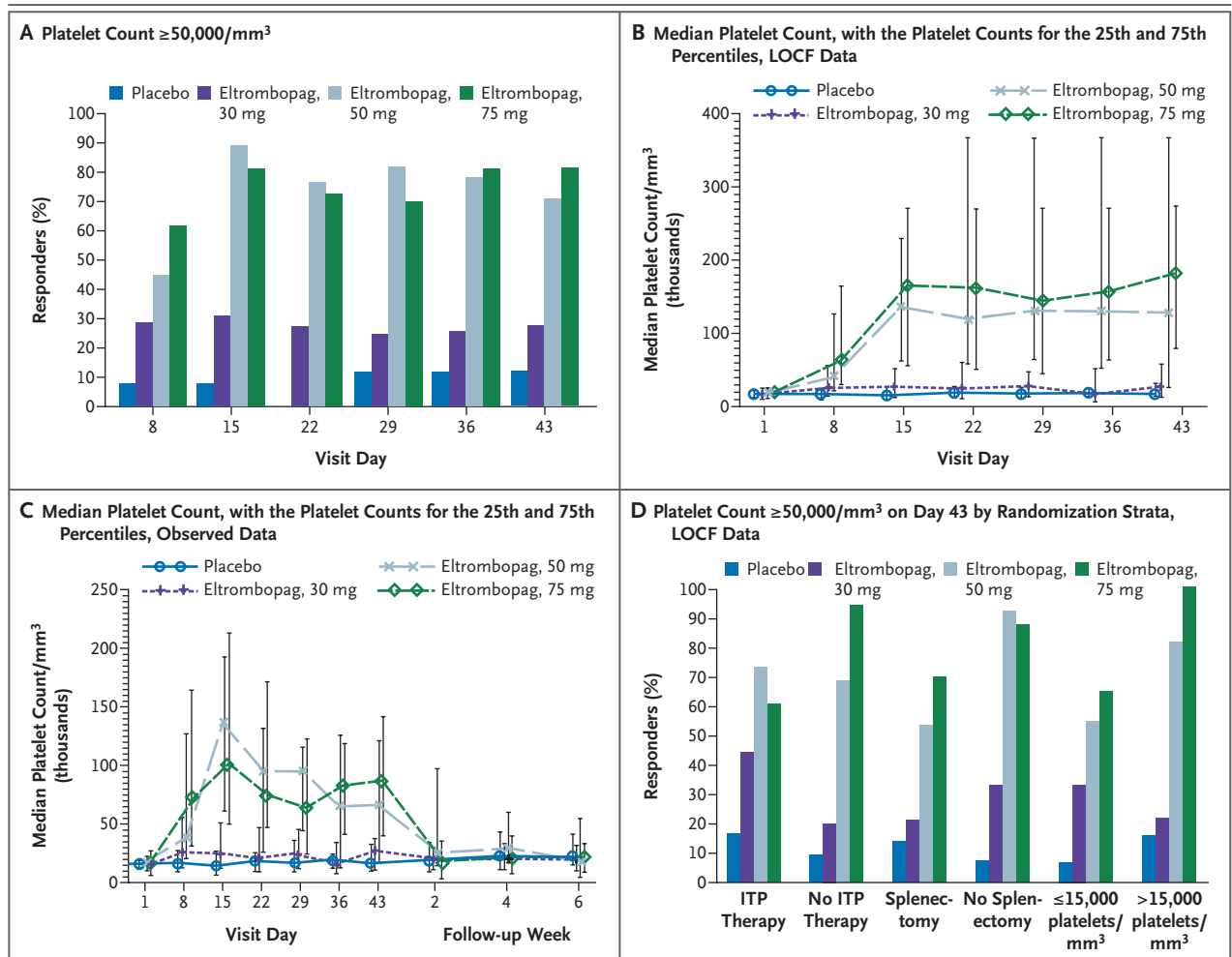


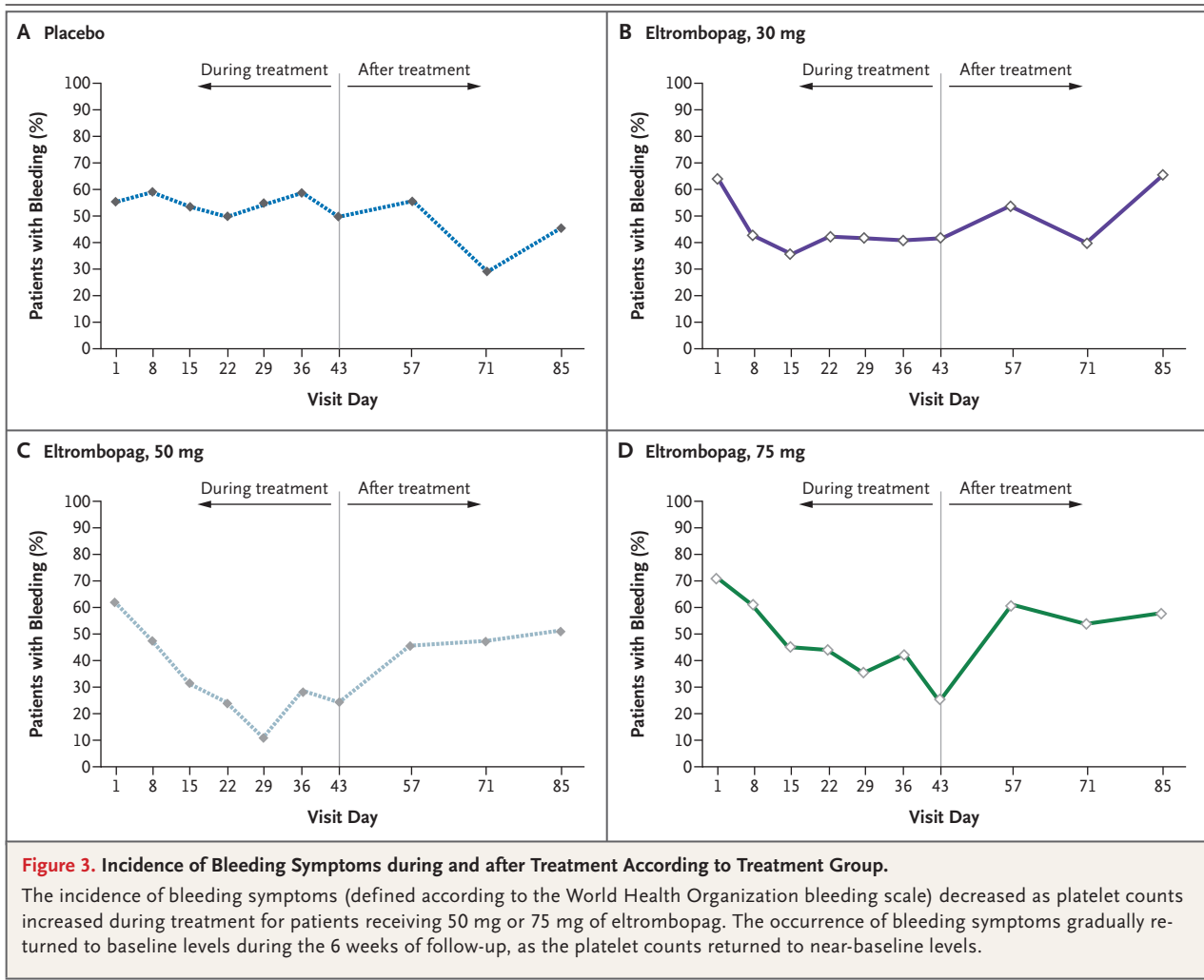
Figure 2. Analyses of Platelet Counts and Responses.

Panel A shows the percentage of patients with a response in the four study groups at each weekly treatment visit, on the basis of last-observation-carried-forward (LOCF) data. On day 8, among patients treated with eltrombopag, 44% and 62% of patients receiving 50 mg and 75 mg, respectively, had a platelet count of more than 50,000 per cubic millimeter, and 88% and 81% of patients in these groups had a response by day 15. Panel B shows the median platelet counts at each visit, with the 25th and 75th percentiles shown as I bars, on the basis of LOCF data. By day 15, the median platelet counts for the groups receiving 50 mg and 75 mg of eltrombopag approached the normal range and remained there for the duration of the 6-week treatment period. Panel C shows the median platelet count at each weekly visit during the treatment period and at each biweekly visit after the treatment period on the basis of observed data. Patients who withdrew before day 43 were included in the follow-up. Discontinuation of treatment with 50 or 75 mg of eltrombopag before completion of the 6-week treatment period was primarily due to achievement of a platelet count of more than 200,000 per cubic millimeter. The median observed platelet counts remained elevated at 50,000 or more per cubic millimeter for the duration of the treatment in the groups receiving 50 mg and 75 mg of eltrombopag and returned to or were close to baseline levels within 2 weeks after the cessation of treatment. Panel D shows response rates according to the three stratification variables — use or nonuse of concomitant ITP therapy (primarily prednisone or prednisolone), splenectomy status, and baseline platelet count ($>15,000$ per cubic millimeter or $\leq 15,000$ per cubic millimeter). A dose–response relationship was observed for each stratification variable.

per liter in the groups receiving 30, 50, and 75 mg of eltrombopag, respectively). Patients with a response generally had platelet counts within the normal range as well as normal thrombopoietin levels.

QUALITY OF LIFE

Health-related quality of life, based on the physical and mental component scores of the SF36v2 survey, was similar at baseline and at the end of the study. Individual dimension scores, such as



those for physical health and vitality, remained similar. The single exception was a significant decrease from baseline in the mean emotional-role score for the group receiving 75 mg of eltrombopag ($P=0.02$).

SAFETY AND ADVERSE EVENTS

The incidence and severity of adverse events were similar for all four study groups (Table 2). The most common adverse event in each group, including the placebo group, was mild to moderate headache. The number of patients experiencing grade 3 or 4 adverse events²⁴ during the study, or within 30 days after discontinuation of the study treatment, was similar among all four study groups. A single case of cataract progression was

reported 181 days after the last dose of study medication in a 60-year-old woman with a history of glucocorticoid use and cigarette smoking who received 75 mg of eltrombopag daily for 8 days. The event was assessed by the investigator as not related to the study drug.

The only death occurred in a 66-year-old man who had undergone a pneumonectomy for non-small-cell lung cancer and entered the study with chronic obstructive pulmonary disease, asthma, and peripheral edema. He received 50 mg of eltrombopag for 21 days and had grade 3 pneumonia, hepatitis, and renal insufficiency and grade 4 exacerbation of chronic obstructive pulmonary disease. Twenty-five days after entering the study, the patient died of cardiopulmonary failure, with

Table 2. Adverse Events in 5% or More of Patients in Any Study Group.

Event	Placebo (N=29)	Eltrombopag		
		30 mg (N=30)	50 mg (N=30)	75 mg (N=28)
Total*	17 (59)	14 (47)	14 (47)	17 (61)
Total grade 3 or 4 events†	4 (14)	2 (7)	4 (13)	3 (11)
Headache	6 (21)	4 (13)	3 (10)	6 (21)
Aspartate aminotransferase elevation	—	1 (3)	—	2 (7)
Constipation	2 (7)	1 (3)	—	2 (7)
Fatigue	5 (17)	—	1 (3)	2 (7)
Rash	1 (3)	1 (3)	—	2 (7)
Anemia	2 (7)	1 (3)	1 (3)	1 (4)
Diarrhea	2 (7)	—	—	1 (4)
Peripheral edema	2 (7)	—	1 (3)	1 (4)
Taste disturbance	2 (7)	—	—	1 (4)
Abdominal distention	2 (7)	1 (3)	—	—
Arthralgia	3 (10)	1 (3)	—	—
Epistaxis	—	4 (13)	—	—
Hemorrhoids	2 (7)	—	—	—
Pain in extremity	1 (3)	2 (7)	—	—

* The total represents the total number of patients with at least one adverse event during treatment.

† Grade 3 and grade 4 adverse events²⁴ were reported as follows. In the placebo group, one patient had nausea, vomiting, and salmonella gastroenteritis and one patient each had toxic hepatitis, varicose-vein rupture, and convulsion. In the group receiving 30 mg of eltrombopag, one patient each had pain in both legs and pneumonitis. In the group receiving 50 mg of eltrombopag, one patient each had a rectal hemorrhage, herpes zoster, and thrombocytopenia, and one patient had pneumonia, hepatitis, renal failure, and chronic obstructive pulmonary disease. In the group receiving 75 mg of eltrombopag, one patient each had trigger finger, menorrhagia, and rash.

clinical signs of sepsis. Thromboemboli were noted in the small vessels of the liver and kidneys on autopsy.

DISCUSSION

This dose-ranging study of eltrombopag, an oral small-molecule nonpeptide platelet growth factor, showed that a daily dose of 50 or 75 mg of the drug is an effective short-term treatment for chronic ITP. At these doses, eltrombopag elevated platelet counts to 50,000 or more per cubic millimeter in more than 80% of patients within 2 weeks. Platelet counts rose above 200,000 per cubic millimeter in 37% of patients receiving 50 mg of eltrombopag and in 50% of patients receiving 75 mg — and this level was reached sooner in patients receiving the 75-mg dose. Patients with refractory disease after splenectomy responded in

the same way as patients who had not undergone splenectomy. There was no significant difference between the placebo and eltrombopag groups in the incidence and severity of adverse events. The trial was stopped by the sponsor after the first interim analysis showed that the two highest doses (50 and 75 mg per day) met the predefined stopping criteria for efficacy. **These data confirm that a treatment designed to increase platelet production in ITP can be effective,** as was demonstrated with the thrombopoiesis-stimulating protein AMG 531.^{14,15}

Our patients had normal thrombopoietin levels, a finding that has been reported in other patients with ITP.^{5,25,26} In this study, thrombopoietin levels were unaffected by treatment with eltrombopag.

At the two highest doses of eltrombopag, bleeding decreased as the platelet count increased,

indicating the hemostatic efficacy of the newly produced platelets. Rates of adverse events were similar in the placebo group and the three groups receiving eltrombopag, with no evidence of dose-limiting toxicity. Cataracts had been observed in studies of eltrombopag in rodents, but no treatment-related cataracts were observed in this study. We are continuing to evaluate the risk of cataracts in our patients, who have multiple risk factors for cataracts (e.g., advanced age and long-term use of glucocorticoids).

Unanswered questions about the use of eltrombopag and other thrombopoietic growth factors concern their role and safety in long-term treatment and whether such agents are effective in patients receiving myelosuppressive chemotherapy. It is also not known whether patients whose platelet counts do not respond to 75 mg of eltrombopag would have a response to higher doses.

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APPENDIX

In addition to the authors, the following investigators participated in the TRA100773 Eltrombopag Study: *QEII Health Sciences Centre, Halifax, NS, Canada* — D. Anderson; *Comprehensive Cancer Care Specialists, Boca Raton, FL* — A. Berliner; *Sunnybrook Regional Cancer Centre, Toronto* — J. Callum; *Ocala Oncology Center, Ocala, FL* — T. Cartwright; *Tri-Service General Hospital, Taipei, Taiwan* — Y.C. Chen; *Hematology and Oncology Specialists, New Orleans* — T. Cosgriff; *SPSK-1, Lublin, Poland* — A. Dmoszynska; *Hôpital Habib Bourguiba, Sfax, Tunisia* — M. Elloumi; *Hospital Gregorio Marañón, Madrid* — A. Escudero Soto; *Jeroen Bosch Ziekenhuis, Den Bosch, the Netherlands* — R. Fijnheer; *Minnesota Oncology Hematology, Minneapolis* — P. Flynn; *New Mexico Oncology-Hematology Consultants, Albuquerque, NM* — R. Giudice; *Utah Cancer Specialists, Salt Lake City* — W. Harker; *Cancer Center of Colorado Springs, Colorado Springs, CO* — D. Headley; *Hospital la Paz, Madrid* — V. Jimenez Yuste; *Hôpital Maisonneuve Rosemont, Montreal* — J. Kassis; *University of Minnesota, Minneapolis* — R. Kasthuri; *Hôpital Farhat Hached, Sousse, Tunisia* — A. Khelif; *Jefferson City Medical Group, Jefferson City, MO* — A. Khojasteh; *Hematology Research Center, Moscow* — N. Khoroshko, E. Pustovaya, and T. Safonova; *Korea University Hospital, Seoul* — S. Kim; *Academisch Medisch Centrum, Amsterdam* — H. Koene; *University of Pennsylvania Medical Center—Presbyterian Hospital, Philadelphia* — B. Konkle; *Queen Mary Hospital, Pokfulam, Hong Kong* — R. Liang; *Kerckhoff-Klinik, Bad Nauheim, Germany* — K. Madlener; *Caritasklinik St. Theresia, Saarbrücken, Germany* — A. Matzdorff; *Arizona Clinical Research Center, Tucson* — M. Modiano; *Hôpital Militaire, Montfleury, Tunisia* — F. M'Sadek; *Royal London Hospital, London* — A. Newland; *General Hospital of Athens "Evangelismos," Athens* — E. Nikiforakis; *UMC St. Radboud, Nijmegen, the Netherlands* — V. Novotny; *Centre Hospitalier de l'Université de Montreal, Hôpital Notre-Dame, Montreal* — H. Olney; *Uniwersytet Medyczny w Łodzi, Łódź, Poland* — T. Robak; *Justus-Liebig-Universität Gießen, Frankfurt, Germany* — M. Rummel; *Charité Universitätsmedizin Berlin, Berlin* — A. Salama; *Ziekenhuis Leyenburg, The Hague, the Netherlands* — M. Schipperus; *Johns Hopkins University School of Medicine Clinical Trials Unit, Baltimore* — J. Segal; *Spitalul Clinic Fundeni, Bucharest, Romania* — R.A. Stoia, A.M. Vladareanu; *Carolina Physicians Research, Raleigh, NC* — S. Tremont; *Virginia Cancer Institute, Richmond* — D. Trent; *Civic Parkdale Clinic, Ottawa* — P. Wells; *SoonChun-Hyang University Hospital, Seoul* — J. Won; and *Pomorska Akademia Medyczna, Szczecin, Poland* — B. Zdzarska.

REFERENCES

- Gernsheimer T, Stratton J, Ballem PJ, Slichter SJ. Mechanisms of response to treatment in autoimmune thrombocytopenic purpura. *N Engl J Med* 1989;320:974-80.
- Chang M, Nakagawa PA, Williams SA, et al. Immune thrombocytopenic purpura (ITP) plasma and purified ITP monoclonal autoantibodies inhibit megakaryocytopoiesis in vitro. *Blood* 2003;102:887-95.
- McMillan R, Nugent D. The effect of antiplatelet autoantibodies on megakaryocytopoiesis. *Int J Hematol* 2005;81:94-9.
- Ballem PJ, Segal GM, Stratton JR, Gernsheimer T, Adamson JW, Slichter SJ. Mechanisms of thrombocytopenia in chronic autoimmune thrombocytopenic purpura: evidence of both impaired platelet production and increased platelet clearance. *J Clin Invest* 1987;80:33-40.
- Cines DB, Blanchette VS. Immune thrombocytopenic purpura. *N Engl J Med* 2002;346:995-1008.
- Butros LJ, Bussel JB. Intracranial hemorrhage in immune thrombocytopenic purpura: a retrospective analysis. *J Pediatr Hematol Oncol* 2003;25:660-4.
- Cines DB, Bussel JB. How I treat idiopathic thrombocytopenic purpura (ITP). *Blood* 2005;106:2244-51.
- Vainchenker W, Debili N, Methia N, Mouthon MA, Wendling F. Hematopoiesis and its regulation: comparison between erythropoiesis and megakaryocytopoiesis. *Bull Acad Natl Med* 1994;178:753-78. (In French.)
- Kuter DJ, Begley CG. Recombinant human thrombopoietin: basic biology and evaluation of clinical studies. *Blood* 2002;100:3457-69.
- von dem Borne A, Folman C, van den Oudenrijn S, Linthorst G, de Jong S, de Haas M. The potential role of thrombopoietin in idiopathic thrombocytopenic purpura. *Blood Rev* 2002;16:57-9.
- Geddis AE, Linden HM, Kaushansky K. Thrombopoietin: a pan-hematopoietic cytokine. *Cytokine Growth Factor Rev* 2002;13:61-73.
- Chang M, Suen Y, Meng G, et al. Differential mechanisms in the regulation of endogenous levels of thrombopoietin and interleukin-11 during thrombocytopenia: insight into the regulation of platelet production. *Blood* 1996;88:3354-62.
- Aledort LM, Hayward CP, Chen MG,

- Nichol JL, Bussel J. Prospective screening of 205 patients with ITP, including diagnosis, serological markers, and the relationship between platelet counts, endogenous thrombopoietin, and circulating antithrombopoietin antibodies. *Am J Hematol* 2004;76:205-13.
14. Newland A, Caulier MT, Kappers-Klunne M, et al. An open-label, unit dose-finding study of AMG 531 a novel, thrombopoiesis stimulating peptibody, in patients with immune thrombocytopenic purpura. *Br J Haematol* 2006;135:547-53.
15. Bussel JB, Kuter DJ, George JN, et al. AMG 531, a thrombopoiesis-stimulating protein, for chronic ITP. *N Engl J Med* 2006;355:1672-81. [Erratum, *N Engl J Med* 2006;355:2054.]
16. Kalota A, Brennan K, Erickson-Miller CL, Danet G, Carroll M, Gewirtz A. Effects of SB559457, a novel small molecule thrombopoietin receptor (TpoR) agonist, on human hematopoietic cell growth and differentiation. *Blood* 2004;104:2913. abstract.
17. Jenkins J, Williams D, Deng Y, et al. Phase 1 clinical study of eltrombopag, an oral, nonpeptide thrombopoietin receptor agonist. *Blood* 2007;109:4739-41.
18. Sellers T, Hart T, Semanik M, Murthy K. Pharmacology and safety of SB-497115-GR, an orally active small molecular weight TPO receptor agonist, in chimpanzees, rats and dogs. *Blood* 2004;104:2063. abstract.
19. Erickson-Miller CL, Luengo JI, Nicholl R, et al. In vitro and in vivo biology of a small molecular weight TPO receptor agonist, SB-497115. Presented at the 96th Annual Meeting of the American Association for Cancer Research, Anaheim, CA, April 16–20, 2005. abstract.
20. Erhardt J, Erickson-Miller CL, Tapley P. SB 497115-GR, a low molecular weight TPOR agonist, does not induce platelet activation or enhance agonist-induced platelet aggregation in vitro. *Blood* 2004;104:3888. abstract.
21. Provan D, Saleh M, Goodison S, et al. The safety profile of eltrombopag, a novel, oral platelet growth factor, in thrombocytopenic patients and healthy subjects. *J Clin Oncol* 2006;24:18S:18596. abstract.
22. McHutchinson JG, Afdhal NH, Dushenko G, et al. Efficacy and safety of eltrombopag an oral platelet growth factor in subjects with HCV-associated thrombocytopenia: final results from a phase II multicenter, randomized, placebo-controlled, double-blind, dose-ranging study. Presented at the 57th Annual Meeting of the American Association for the Study of Liver Diseases, Boston, October 27–31, 2006. abstract.
23. Jennison C, Turnbull BW. Group sequential methods with applications to clinical trials. Boca Raton, FL: Chapman & Hall/CRC Press, 1999.
24. Cancer Therapy Evaluation Program. Common terminology criteria for adverse events, version 3.0. Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, August 9, 2006. (Accessed November 2, 2007, at <http://ctep.cancer.gov/forms/CTCAEv3.pdf>.)
25. Kosugi S, Kurata Y, Tomiyama Y, et al. Circulating thrombopoietin level in chronic immune thrombocytopenic purpura. *Br J Haematol* 1996;93:704-6.
26. Emmons RV, Reid DM, Cohen RL, et al. Human thrombopoietin levels are high when thrombocytopenia is due to megakaryocyte deficiency and low when due to increased platelet destruction. *Blood* 1996; 87:4068-71.

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