ORIGINAL ARTICLE

Recombinant ADAMTS13 in Congenital Thrombotic Thrombocytopenic Purpura

Marie Scully, M.D., Ana Antun, M.D., Spero R. Cataland, M.D., Paul Coppo, M.D., Ph.D., Claire Dossier, M.D., Nathalie Biebuyck, M.D., Wolf-Achim Hassenpflug, M.D., Karim Kentouche, M.D., Paul Knöbl, M.D., Johanna A. Kremer Hovinga, M.D., M. Fernanda López-Fernández, M.D., Ph.D., Masanori Matsumoto, M.D., Ph.D., Thomas L. Ortel, M.D., Ph.D., Jerzy Windyga, M.D., Ph.D., Indranil Bhattacharya, Ph.D., Michael Cronin, Pharm.D., Hong Li, Ph.D., Björn Mellgård, M.D., Ph.D., Munjal Patel, Ph.D., Parth Patwari, M.D., Sc.D., Shan Xiao, Ph.D., Pinghai Zhang, M.D., Ph.D., and Linda T. Wang, M.D., for the cTTP Phase 3 Study Investigators*

ABSTRACT

BACKGROUND

Congenital thrombotic thrombocytopenic purpura (TTP) results from severe hereditary deficiency of ADAMTS13. The efficacy and safety of recombinant ADAMTS13 and standard therapy (plasma-derived products) administered as routine prophylaxis or on-demand treatment in patients with congenital TTP is not known.

METHODS

In this phase 3, open-label, crossover trial, we randomly assigned patients in a 1:1 ratio to two 6-month periods of prophylaxis with recombinant ADAMTS13 (40 IU per kilogram of body weight, administered intravenously) or standard therapy, followed by the alternate treatment; thereafter, all the patients received recombinant ADAMTS13 for an additional 6 months. The trigger for this interim analysis was trial completion by at least 30 patients. The primary outcome was acute TTP events. Manifestations of TTP, safety, and pharmacokinetics were assessed. Patients who had an acute TTP event could receive on-demand treatment.

RESULTS

A total of 48 patients underwent randomization; 32 completed the trial. No acute TTP event occurred during prophylaxis with recombinant ADAMTS13, whereas 1 patient had an acute TTP event during prophylaxis with standard therapy (mean annualized event rate, 0.05). Thrombocytopenia was the most frequent TTP manifestation (annualized event rate, 0.74 with recombinant ADAMTS13 and 1.73 with standard therapy). Adverse events occurred in 71% of the patients with recombinant ADAMTS13 and in 84% with standard therapy. Adverse events that were considered by investigators to be related to the trial drug occurred in 9% of the patients with recombinant ADAMTS13 and in 48% with standard therapy. Trial-drug interruption or discontinuation due to adverse events occurred in no patients with recombinant ADAMTS13 and in 8 patients with standard therapy. No neutralizing antibodies developed during recombinant ADAMTS13 treatment. The mean maximum ADAMTS13 activity after recombinant ADAMTS13 treatment was 101%, as compared with 19% after standard therapy.

CONCLUSIONS

During prophylaxis with recombinant ADAMTS13 in patients with congenital TTP, ADAMTS13 activity reached approximately 100% of normal levels, adverse events were generally mild or moderate in severity, and TTP events and manifestations were rare. (Funded by Takeda Development Center Americas and Baxalta Innovations; ClinicalTrials.gov number, NCT03393975.)

The authors' affiliations are listed in the Appendix. Dr. Scully can be contacted at m.scully@ucl.ac.uk or at the Department of Haematology, University College London Hospitals, 250 Euston Rd., London NW1 2PG, United Kingdom.

*A complete list of investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Congenital thrombotic thrombocytopenic purpura (TTP) is an ultrarare thrombotic microangiopathy (prevalence, ≥0.5 cases per million population).[1-5] Congenital TTP results from severe hereditary deficiency (<10% of normal activity) of ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin motifs 13),[6-8] leading to accumulation of ultralarge von Willebrand factor multimers with high platelet-binding activity.[4,5] Spontaneous formation of platelet-rich microthrombi and organ ischemia lead to acute symptoms and long-term organ damage with associated illness and premature death[4,6-8]; platelet consumption manifests as thrombocytopenia, a hallmark of congenital TTP.[5,7]

The clinical presentation ranges from life-threatening, acute, overt TTP events to milder TTP manifestations, including thrombocytopenia, hemolytic anemia, abdominal pain, headache, and neurologic symptoms.[6,9,10] End-organ damage due to recurrent overt and nonovert TTP, such as stroke, chronic kidney disease, or cardiac involvement, can also develop.[9,10] Acute TTP events are triggered by infections, trauma, and pregnancy.[6,11,12]

Current standard therapy involves ADAMTS13 replacement through prophylactic or on-demand infusions of fresh-frozen plasma, plasma that had been treated with a solvent–detergent process, or ADAMTS13-containing plasma-derived factor VIII–von Willebrand factor concentrates.[13,14] These products are reliant on donor plasma and provide limited ADAMTS13 replacement.[13-18] Prophylaxis requires lengthy, burdensome infusions in the hospital[19]; allergic reactions to plasma, which can be severe and treatment-limiting, are prevalent.[20,21] Here, we present the results from a preplanned interim analysis of a phase 3, randomized, controlled, crossover trial in which adults and children with congenital TTP received recombinant ADAMTS13 (TAK-755; Takeda Pharmaceuticals U.S.A.) or standard therapy for prophylactic and on-demand treatment.

METHODS

TRIAL SUMMARY

We are conducting a phase 3, multinational, prospective, open-label, randomized, controlled, two-period crossover trial to evaluate the efficacy and safety of recombinant ADAMTS13 and standard therapy administered as routine prophylaxis or on-demand treatment in patients with congenital TTP. In this interim analysis, data are reported for patients of all ages enrolled from October 13, 2017, to August 12, 2022 (data-cutoff date).

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The trial was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation at 34 sites in the European Union, the United States, the United Kingdom, and Japan. The institutional review board or ethics committee at each participating site approved the protocol (available with the full text of this article at NEJM.org), and all the patients or their legally authorized representatives provided written informed consent. An independent data monitoring committee periodically reviewed the safety data.

The trial was designed by the sponsors in conjunction with eight academic authors; the data were collected and analyzed by the sponsors. All the authors vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol. The first draft of the manuscript was prepared by the first author, with medical writing assistance (funded by the sponsors) provided for this and subsequent drafts under the direction of the authors. All the authors signed a confidentiality agreement with the sponsors preventing data disclosure without previous written consent.

TRIAL DESIGN AND TREATMENT

The trial included two cohorts: patients who received treatment to prevent TTP events (prophylactic cohort) and those who received treatment only if a TTP event occurred (on-demand cohort) (Fig. 1).[22] Eligible patients were 0 to 70 years of age at screening with congenital TTP (confirmed by means of molecular genetic testing and ADAMTS13 activity of <10%) who were able to receive standard therapy without unacceptable side effects (Table S1 in the Supplementary Appendix, available at NEJM.org). Patients without signs of an acute TTP event at screening were eligible for the prophylactic cohort. Patients could be enrolled in the on-demand cohort if they had an acute TTP event at screening as assessed by the investigator.

A crossover design was used for the prophy-

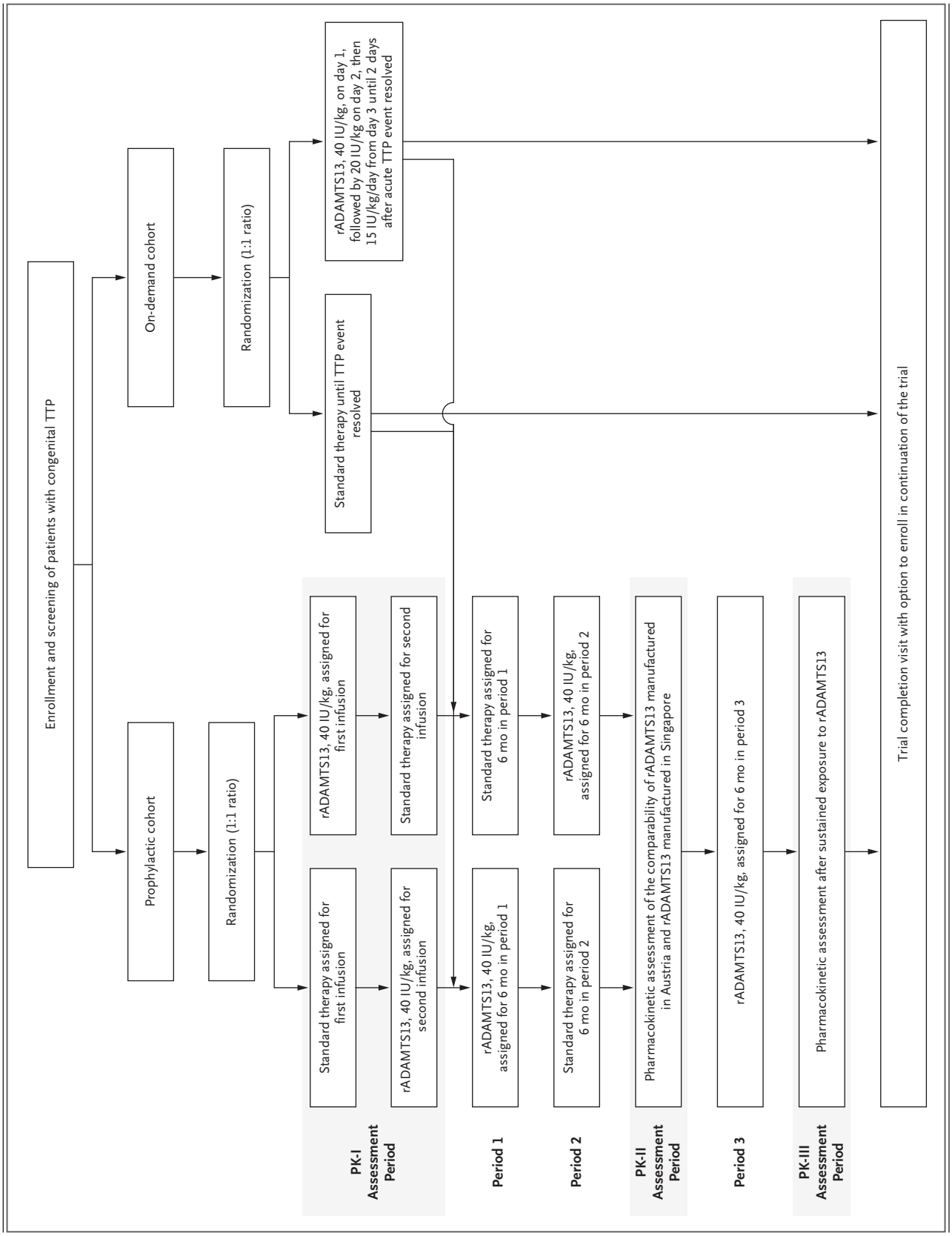


Figure 1 (facing page). Trial Design.

Shown is the design of this phase 3, multicenter, prospective, open-label, randomized, controlled, two-period crossover trial with a single-group continuation to assess the safety and efficacy of recombinant ADAMTS13 (rADAMTS13) in patients with congenital thrombotic thrombocytopenic purpura (TTP) either for regular preventive treatment (prophylactic cohort) or for urgent treatment of acute TTP events (on-demand cohort). Patients who were enrolled in the prophylactic cohort generally received treatment every week or every other week, depending on their pretrial frequency of dose administration while receiving standard therapy. During the first pharmacokinetic (PK-I) assessment period, each patient received a single infusion of standard therapy or rADAMTS13, followed by the alternate infusion. Periods 1 and 2 were the controlled 6-month crossover periods of the trial and were followed by a single-group continuation of the trial in period 3, in which all the patients received rADAMTS13 (40 IU per kilogram of body weight). Acute TTP events in the prophylactic cohort were treated with the agent that the patient was receiving in the current period. The initial prophylactic dose frequency of rADAMTS13 could be increased from every other week to every week on the basis of the response to treatment. A second pharmacokinetic (PK-II) assessment examined the comparability of rADAMTS13 manufactured at two different sites (Austria and Singapore). A third pharmacokinetic (PK-III) assessment was conducted in certain patients to examine pharmacokinetics after sustained exposure to rADAMTS13. Adapted from Jain et al.[22]

lactic cohort owing to disease rarity, which allowed a within-patient controlled comparison between recombinant ADAMTS13 and standard therapy to minimize the effects of any imbalances between randomized groups. Patients were randomly assigned in a 1:1 ratio to start with recombinant ADAMTS13 (40 IU per kilogram of body weight) or standard therapy in the crossover pharmacokinetic assessment period, and then the patients moved into period 1 (6 months) with the same treatment assignment (Fig. 1). In period 2 (6 months), patients received the alternate treatment. All patients subsequently received recombinant ADAMTS13 for period 3 (6 months) for a longer-term evaluation of the efficacy and safety of recombinant ADAMTS13 treatment.

For standard therapy, the investigator chose from among three types of pooled plasma products: fresh-frozen plasma, plasma treated with a solvent–detergent process, or plasma-derived factor VIII–von Willebrand factor concentrates. All treatments in the prophylactic cohort were given either weekly or every 2 weeks, on the basis of previous treatment and investigators' assessment (see the Supplementary Methods in the Supplementary Appendix).

In the on-demand cohort, patients were randomly assigned in a 1:1 ratio to receive recombinant ADAMTS13 or standard therapy. Recombinant ADAMTS13 was administered at a dose of 40 IU per kilogram on day 1, 20 IU per kilogram on day 2, and 15 IU per kilogram daily from day 3 until 2 days after the acute TTP event had resolved. After resolution of the acute TTP events in the on-demand cohort, patients could opt to join the prophylactic cohort.

OUTCOME MEASURES

The primary outcome was acute TTP events among patients receiving prophylaxis with recombinant ADAMTS13 or standard therapy (periods 1, 2, and 3) in the modified full analysis population, as defined in Figure S1. An acute TTP event was defined as a decrease in the platelet count by at least 50% from baseline or to less than 100,000 per microliter and an elevation of the lactate dehydrogenase (LDH) level to more than 2 times the baseline value or more than 2 times the upper limit of the normal range (ULN) (Table S2). Only new acute TTP events occurring during prophylactic treatment contributed to this outcome.

Secondary efficacy outcomes included TTP manifestations (e.g., thrombocytopenia [a decrease in the platelet count by ≥25% from baseline or to <150,000 per microliter], an elevated LDH level [to >1.5 times the baseline value or >1.5 times the ULN], an increased creatinine level [to >1.5 times the baseline value], neurologic symptoms, and abdominal pain). Safety was assessed in terms of adverse events that started or worsened after the first dose of trial treatment, serious adverse events (including relatedness to treatment), and recombinant ADAMTS13 immunogenicity according to the presence of binding and inhibitory antibodies to ADAMTS13 (assessed every 4 weeks). Serious adverse events were defined as events that were fatal or life threatening, resulted in or prolonged hospitalization, resulted in a persistent or clinically significant disability or a congenital anomaly, or were otherwise medically important. No adverse events of special interest were defined in the protocol.

ADAMTS13 activity was analyzed before treatment and at defined intervals after treatment with the use of the FRETS-VWF73 assay (see the Supplementary Methods).[23] Key pharmacokinetic variables included maximum ADAMTS13 activity after infusion (C_{max}), average ADAMTS13 activity for a 0-to-168-hour administration interval ($C_{ave[0–168h]}$), area under the curve of ADAMTS13 activity over time, and time with ADAMTS13 activity of 10% or higher. Anti-ADAMTS13 binding antibodies were assessed by means of an enzyme-linked immunosorbent assay, and anti-ADAMTS13 neutralizing antibodies were assessed by means of a modified Bethesda assay according to FRETS-VWF73 activity. Serial samples for von Willebrand factor multimer analysis were obtained during the crossover pharmacokinetic assessment period (see the Supplementary Methods).

Other exploratory efficacy outcomes included composite TTP manifestations (i.e., the occurrence of ≥1 of the aforementioned TTP manifestations) and subacute TTP events. Subacute events were two or more of the following (including ≥1 laboratory measurement): a decrease in the platelet count by at least 25% from baseline or to less than 150,000 per microliter, an increase in the LDH level to more than 1.5 times the baseline value or more than 1.5 times the ULN, or organ-specific signs or symptoms of TTP.

STATISTICAL ANALYSIS

Because congenital TTP is ultrarare, the phase 3 trial was planned to evaluate the benefit–risk profile of recombinant ADAMTS13 on the basis of clinical efficacy, safety, pharmacokinetics, and pharmacodynamic data (see the Supplementary Methods). A preplanned interim analysis was to be performed after 30 adults or adolescents in the prophylactic cohort had completed period 3.

Owing to the rarity of congenital TTP, the trial did not have sufficient power to enable statistical hypothesis testing. All results (i.e., efficacy and pharmacokinetics in adults or adolescents and safety in patients of all ages) are reported as point estimates with 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects. Annualized mean rates of acute TTP events were estimated for periods 1 and 2 with the use of a generalized linear mixed-effects model with a negative binominal distribution, logarithmic link function, treatment as a fixed effect, patient as a random effect, and the logarithm of follow-up time as an offset; categorical variables included period and treatment sequence. If the full model failed to converge, a reduced model that excluded the treatment sequence effect was fit. If the reduced model still did not converge, raw event rates for individual patients were calculated and summarized. Similar analyses were performed for TTP manifestations and subacute TTP events.

RESULTS

TRIAL POPULATION

Of 51 patients screened, 48 underwent randomization and received prophylaxis with recombinant ADAMTS13 or standard therapy (Fig. S1). At the interim analysis, 32 patients (all adolescents or adults) had completed the trial in the prophylactic cohort; 14 patients (8 who were <12 years of age, 1 adolescent, and 5 adults) were continuing in the trial. Two adults discontinued the trial — 1 owing to a severe allergic reaction to prophylaxis with standard therapy and 1 after a diagnosis of immune-mediated TTP was confirmed. Safety data were included for all 48 patients. The prophylactic cohort included 46 patients in the modified full analysis population, after exclusion of the patient with immune TTP and an adult patient who could not receive the trial treatment as randomly assigned.

For on-demand treatment of acute TTP events, 5 patients were randomly assigned to receive recombinant ADAMTS13 or standard therapy. All the patients completed the on-demand treatment; 3 moved to the prophylactic cohort and 2 ended their participation in the trial.

Prophylactic treatments that were administered before the trial are shown in Table 1. Eight patients (17%) had a history of acute TTP events in the previous 12 months, and 10 patients had a history of stroke or transient ischemic attack.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Safety Analysis Population).*

Characteristic	Recombinant ADAMTS13→ Standard Therapy (N=21)	Standard Therapy→ Recombinant ADAMTS13 (N=27)	Total (N=48)
Age			
Median (range) — yr	42 (3–54)	27 (5–68)	33 (3–68)
Distribution — no. (%)			
≥18 yr	16 (76)	20 (74)	36 (75)
12 to <18 yr	1 (5)	3 (11)	4 (8)
6 to <12 yr	1 (5)	3 (11)	4 (8)
<6 yr	3 (14)	1 (4)	4 (8)
Sex — no. (%)			
Male	9 (43)	11 (41)	20 (42)
Female	12 (57)	16 (59)	28 (58)
Median BMI (range)†	27.3 (15.3–37.7)	22.7 (15.1–33.3)	24.1 (15.1–37.7)
Race — no. (%)‡			
Asian	2 (10)	3 (11)	5 (10)
Black or African American	0	1 (4)	1 (2)
White	15 (71)	17 (63)	32 (67)
Multiple	0	1 (4)	1 (2)
Not reported	4 (19)	5 (19)	9 (19)
Median age at diagnosis (range) — yr	20 (0–50)	4 (0–58)	10 (0–58)
Blood group — no. (%)			
A	9 (43)	5 (19)	14 (29)
B	4 (19)	3 (11)	7 (15)
AB	2 (10)	5 (19)	7 (15)
O	6 (29)	14 (52)	20 (42)
Acute TTP event in the 12 mo before enrollment — no. (%)	5 (24)	3 (11)	8 (17)
Subacute TTP event in the 12 mo before enrollment — no. (%)	2 (10)	3 (11)	5 (10)
Pretrial treatments for congenital TTP — no. (%)§	21 (100)	26 (96)	47 (98)
Fresh-frozen plasma	16 (76)	17 (63)	33 (69)
Plasma treated with solvent–detergent process	5 (24)	6 (22)	11 (23)
Plasma-derived factor VIII–von Willebrand factor concentrates	0	3 (11)	3 (6)

* The safety analysis population included all the patients who received at least one dose of recombinant ADAMTS13 or standard therapy after randomization. Percentages may not total 100 because of rounding. TTP denotes thrombotic thrombocytopenic purpura.
† The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
‡ Race was reported by the patient as allowed by local regulations.
§ Pretrial treatment for congenital TTP was not reported for one patient in the standard-therapy group.

EFFICACY

Incidence of Acute and Subacute TTP Events

No patient had an acute TTP event while receiving prophylaxis with recombinant ADAMTS13 during period 1, 2, or 3. One patient had an acute TTP event (due to a viral infection not related to severe acute respiratory syndrome coronavirus 2) while receiving prophylaxis with standard therapy. Owing to the low event rate, the mixed-effects models did not converge, and a summary of the raw rates is reported. The mean annualized event rate with standard therapy was 0.05 (95% confidence interval [CI], 0.00 to 0.14).

No subacute TTP events occurred in patients receiving recombinant ADAMTS13 in periods 1 and 2. In comparison, five subacute events occurred in four patients receiving standard therapy in periods 1 and 2 (raw mean annualized event rate, 0.25; 95% CI, 0.05 to 0.53). In period 3, two events occurred in two patients receiving recombinant ADAMTS13 (raw mean annualized event rate, 0.07; 95% CI, 0.00 to 0.18). Details of subacute TTP events are provided in Table S3.

Incidence of TTP Manifestations

Thrombocytopenia was the most frequently observed TTP manifestation (Fig. 2). During periods 1 and 2, the fully adjusted model-based annualized event rate of thrombocytopenia was 0.74 (95% CI, 0.37 to 1.50) for recombinant ADAMTS13 and 1.73 (95% CI, 0.92 to 3.23) for standard therapy. For the prespecified TTP manifestations of elevated LDH level, neurologic symptoms, and abdominal pain, the descriptive mean model-based event rates suggested that the rates were lower during recombinant ADAMTS13 treatment than during standard therapy (Fig. 2). Few cases of increased creatinine levels were reported; most creatinine values were marginally above the protocol-defined threshold of 1.5 times the baseline value and were below the ULN. Results were similar in the unadjusted analyses based on raw event rates (Table S4).

In a post hoc analysis, the mean platelet count during periods 1 and 2 was 256×10^9 per liter (95% CI, 121 to 391) for recombinant ADAMTS13 and 239×10^9 per liter (95% CI, 113 to 364) for standard therapy. A total of 80% of the patients had a higher mean platelet count

Outcome	rADAMTS13	Standard Therapy	Estimated Ratio (95% CI)
	least-squares mean annualized incidence rate (95% CI)		
Prespecified TTP manifestations			
Thrombocytopenia	0.74 (0.37–1.50)	1.73 (0.92–3.23)	0.4 (0.3–0.7)
Elevated LDH level	0.26 (0.10–0.72)	0.74 (0.38–1.44)	0.4 (0.1–1.1)
Increased creatinine level	0.10 (0.02–0.47)	0.08 (0.02–0.36)	1.3 (0.2–7.8)
Neurologic symptoms	0.18 (0.06–0.51)	0.29 (0.11–0.78)	0.6 (0.3–1.2)
Abdominal pain	0.11 (0.03–0.39)	0.17 (0.06–0.52)	0.6 (0.2–2.3)
Exploratory outcomes			
Composite TTP manifestations	2.28 (1.35–3.88)	3.68 (2.23–6.08)	0.6 (0.5–0.9)
Other TTP manifestations	0.32 (0.14–0.72)	0.81 (0.44–1.49)	0.4 (0.2–0.9)

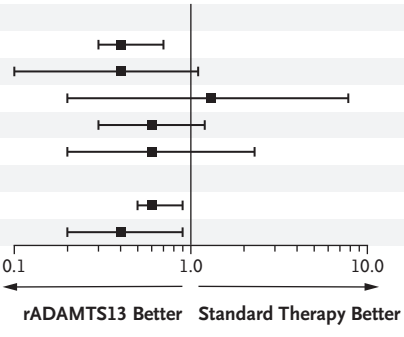


Figure 2. Incidence of TTP Manifestations.

Shown are estimates of annualized incidence rates among adult and adolescent patients in periods 1 and 2 (modified full analysis population), calculated with the use of a negative binomial generalized linear mixed-effects model. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects. Thrombocytopenia was defined as a decrease in the platelet count by at least 25% from baseline or to less than 150,000 per microliter. An elevated lactate dehydrogenase (LDH) level was defined as an increase to more than 1.5 times the baseline value or more than 1.5 times the upper limit of the normal range. An increased creatinine level was defined as an increase in the serum level to more than 1.5 times the baseline value. "Composite TTP manifestations" was defined as the occurrence of at least one of the prespecified manifestations. The ad hoc analysis of "other TTP manifestations" was intended to capture all TTP-related events reported by investigators that were not prespecified TTP manifestations (e.g., fatigue or nausea).

with recombinant ADAMTS13 than with standard therapy (Fig. S2).

On-Demand Treatment

After on-demand treatment of acute TTP events (seven events in six patients, including one event during prophylaxis with standard therapy), improved platelet counts were accompanied by a mean ADAMTS13 activity, measured 1 hour after infusion, of 1.14 IU per milliliter (range, 0.87 to 1.41) with recombinant ADAMTS13 and 0.18 IU per milliliter (range, 0.08 to 0.24) with standard therapy. Details are provided in Figure S3.

SAFETY AND IMMUNOGENICITY

The percentage of patients who reported adverse events during the controlled comparison periods 1 and 2 was 71% (95% CI, 56 to 84) with recombinant ADAMTS13 and 84% (95% CI, 70 to 93) with standard therapy; during period 3, the percentage of patients who reported adverse events with recombinant ADAMTS13 was consistent with that during periods 1 and 2 (72%; 95% CI, 55 to 86). Most adverse events were mild to moderate in severity. Severe adverse events were observed in 7% of patients receiving recombinant ADAMTS13 and 14% of those receiving standard therapy in periods 1 and 2 (Table 2). Headache, migraine, nasopharyngitis, and diarrhea were the most frequently reported adverse events with recombinant ADAMTS13 in periods 1 and 2 (Table S5). Four patients (9%) had adverse events considered by investigators to be related to recombinant ADAMTS13, whereas 21 patients (48%) had adverse events considered to be related to standard therapy. No bleeding adverse events were considered to be related to trial treatment.

No patient receiving recombinant ADAMTS13 had adverse events that led to trial-drug interruption or discontinuation, whereas 7 patients receiving standard therapy had adverse events leading to trial-drug interruption and 1 patient had an adverse event leading to trial-drug discontinuation. None of the patients receiving prophylaxis with recombinant ADAMTS13 reported adverse events consistent with hypersensitivity reactions, whereas 16 patients receiving standard therapy had 24 such events.

In periods 1 and 2, one serious adverse event was observed with recombinant ADAMTS13, and seven serious adverse events were observed with standard therapy (Table S6). In period 3, five serious adverse events occurred during recombinant ADAMTS13 treatment. None of the serious adverse events in period 1, 2, or 3 were considered to be related to recombinant ADAMTS13, whereas one serious adverse event (pyrexia) in period 1 was considered to be related to standard therapy.

No neutralizing antibodies were detected in any patient with confirmed congenital TTP, and no instances of increased levels of binding antibodies were observed. One patient had low-titer anti–recombinant ADAMTS13 binding antibodies at baseline but no increase in the titer during the trial.

PHARMACOKINETICS

Among patients of all ages in the safety analysis population, the median weight-adjusted ADAMTS13 dose delivered by recombinant ADAMTS13 was 40.0 IU per kilogram (range, 38.6 to 41.0), and the median dose delivered by standard therapy (fresh-frozen plasma and plasma treated with a solvent–detergent process) was 8.9 IU per kilogram (range, 0.7 to 22.3) (Table S7). The median duration of infusion was 4.96 minutes (range, 1.8 to 19.2) for recombinant ADAMTS13 and 131.94 minutes (range, 0.7 to 851.1) for standard therapy.

The ADAMTS13 kinetics after recombinant ADAMTS13 and standard therapy followed biexponential pharmacokinetic profiles (Fig. 3). The mean C_{max} was 1.01 IU per milliliter (95% CI, 0.92 to 1.09) with recombinant ADAMTS13 and 0.19 IU per milliliter (95% CI, 0.15 to 0.22) with standard therapy (Table S8); in other words, on average the maximum ADAMTS13 activity was 101% of normal levels with recombinant ADAMTS13 and 19% with standard therapy. The mean time with ADAMTS13 activity of 10% or higher was 5.2 days (95% CI, 4.9 to 5.5) after recombinant ADAMTS13 administration and 1.7 days (95% CI, 1.2 to 2.2) after standard therapy. These findings are in alignment with the mean $C_{ave(0–168h)}$, which was 0.26 IU per milliliter (95% CI, 0.24 to 0.29) after recombinant ADAMTS13 administration and

Table 2. Summary of Adverse Events in Patients of All Ages in the Safety Analysis Population.*

Adverse Event	Periods 1 and 2: Recombinant ADAMTS13 (N=45)			Periods 1 and 2: Standard Therapy (N=44)			Period 3: Recombinant ADAMTS13 (N=36)		
	No. of Patients	Percentage of Patients (95% CI)	No. of Events	No. of Patients	Percentage of Patients (95% CI)	No. of Events	No. of Patients	Percentage of Patients (95% CI)	No. of Events
Any adverse event	32	71 (56–84)	229	37	84 (70–93)	278	26	72 (55–86)	176
Adverse event related to recombinant ADAMTS13 or standard therapy†	4	9 (3–21)	10	21	48 (33–63)	37	1	3 (0–15)	6
Adverse events by maximum severity									
Mild	17	38 (24–54)		14	32 (19–48)		13	36 (21–54)	
Moderate	12	27 (15–42)		17	39 (24–55)		8	22 (10–39)	
Severe	3	7 (1–18)		6	14 (5–27)		5	14 (5–30)	
Hypersensitivity adverse event‡	0	0 (0–8)	0	16	36 (22–52)	24§	0	0 (0–10)	0
Any serious adverse event	1	2 (0–12)	1	7	16 (7–30)	7	4	11 (3–26)	5
Serious adverse event related to recombinant ADAMTS13 or standard therapy†	0	0 (0–8)	0	1	2 (0–12)	1	0	0 (0–10)	0
Adverse event leading to trial discontinuation	0	0 (0–8)	0	0	0 (0–8)	0	0	0 (0–10)	0
Adverse event leading to trial-drug discontinuation	0	0 (0–8)	0	1	2 (0–12)	1	0	0 (0–10)	0
Adverse event leading to trial-drug interruption	0	0 (0–8)	0	7	16 (7–30)	8	0	0 (0–10)	0
Adverse event leading to death	0	0 (0–8)	0	0	0 (0–8)	0	0	0 (0–10)	0

* All data reported are for adverse events that started or worsened after the first dose of recombinant ADAMTS13 or standard therapy. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects.

† The relatedness of adverse events to recombinant ADAMTS13 or standard therapy was determined by the investigators.

‡ Results are for an ad hoc analysis of adverse events that were consistent with hypersensitivity reactions (standardized *Medical Dictionary for Regulatory Activities* query of hypersensitivity, events occurring on the same day as the trial-drug infusion, and events treated with an allergy medication or antipyretic medication).

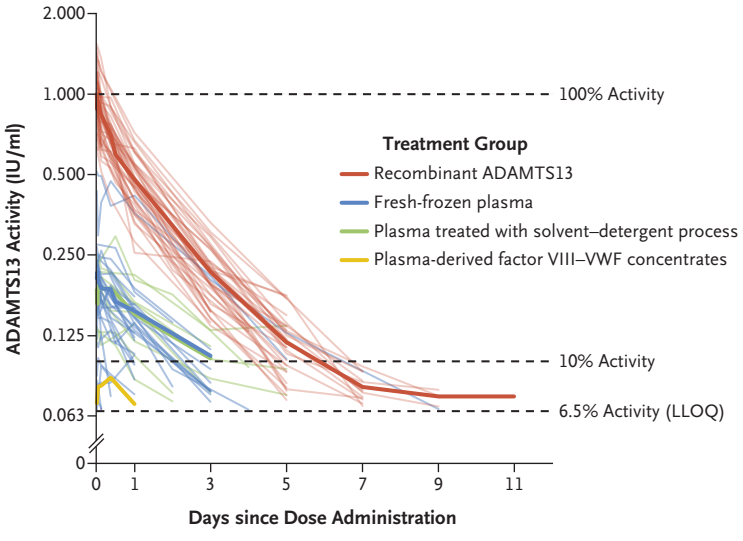
§ Results include adverse-event terms in more than two patients: urticaria (six events in four patients), rash (five events in four patients), drug hypersensitivity (four events in four patients), and pruritus (three events in three patients).

0.07 IU per milliliter (95% CI, 0.05 to 0.09) after standard therapy. The median half-life was 46.6 hours (range, 28.4 to 83.3) for recombinant ADAMTS13 and 55.1 hours (range, 26.1 to 144) for standard therapy. Results of the von Willebrand factor multimer analysis showed a decline related to recombinant ADAMTS13 administration that peaked 9 hours after administration (Table S9).

DISCUSSION

Until recently, no medications were specifically approved for routine prophylaxis in patients with congenital TTP. Recombinant ADAMTS13 was approved by the Food and Drug Administration in November 2023 for prophylactic or on-demand ADAMTS13 replacement therapy in adults and children with congenital TTP.[24] Here we describe results from an interim analysis of a phase 3, randomized, controlled trial evaluating the efficacy and safety of recombinant ADAMTS13 as compared with standard therapy. Patients who received prophylaxis with recombinant ADAMTS13 had no acute TTP events and a low number of TTP manifestations, and approximately 100% of normal ADAMTS13 activity levels were achieved.

Thrombocytopenia was the most frequently observed TTP manifestation, a finding consistent with the central role of platelet consumption and platelet-rich microthrombi in acute TTP pathology.[7] However, the higher mean platelet counts observed with recombinant ADAMTS13 than with standard therapy, even with platelet counts of more than 150,000 per microliter, suggest that subclinical disease activity is ongoing in patients with congenital TTP. Indeed, congenital TTP registry cohorts have shown a high prevalence of stroke by 40 to 50 years of age,[11]



No. of Patients						
Recombinant ADAMTS13	36	39	34	31	13	3
Fresh-frozen plasma	23	27	11	2		1
Plasma treated with solvent–detergent process	7	9	5	3		
Plasma-derived factor VIII–VWF concentrates	2	1				

Figure 3. Time Series of ADAMTS13 Activity after Intravenous Administration of Recombinant ADAMTS13 and Standard Therapy.

Data are from adults and adolescents in the pharmacokinetic full analysis population. ADAMTS13 activity was measured after a single, 40-IU-per-kilogram dose of recombinant ADAMTS13 as part of the PK-I assessment. The individual ADAMTS13 activity (fine lines) and mean activity grouped according to treatment type (thick lines) are plotted on a logarithmic scale. An ADAMTS13 activity of 1 IU per milliliter represents 100% (top dashed horizontal line), and the lower limit of quantification (LLOQ) for the assay was 6.5% (bottom dashed horizontal line). VWF denotes von Willebrand factor.

as well as a reduction in nonovert signs and symptoms of congenital TTP, including thrombocytopenia, with regular prophylaxis.[6] Thus, prophylaxis with recombinant ADAMTS13 may allow the treatment landscape for congenital TTP to evolve toward preventing long-term organ damage by minimizing the formation of platelet-rich microthrombi.

Recombinant ADAMTS13 appeared to have a more acceptable side-effect profile than standard therapy. The better safety and higher average ADAMTS13 activity levels observed with recombinant ADAMTS13 than with standard therapy in this clinical trial may, in clinical practice, help expand patient access to long-term prophylaxis.

Although the risk of immunogenicity exists, neutralizing antibodies did not develop in any patient during 12 months of prophylaxis with recombinant ADAMTS13. Historically, an important consideration with recombinant hematologic products has been the development of inhibitors against the product, such as factor VIII.[25,26] By comparison, in the Hereditary TTP Registry,[11] no development of neutralizing antibodies was reported among 114 cases. Given these findings and the results reported here, the overall immunogenic potential for ADAMTS13 replacement in patients with congenital TTP appears to be low.

Comprehensive pharmacokinetic characterization showed that administration of all types of standard therapy resulted in high variability of ADAMTS13 activity and associated pharmacokinetic characteristics, findings consistent with those of previous reports.[13,15,16] In contrast, pharmacokinetic exposure variables from this trial suggest higher and more prolonged ADAMTS13 activity with lower variability after a recombinant ADAMTS13 dose of 40 IU per kilogram than with standard therapy.

It is difficult to compare rates of TTP events reported here with those in previous observational studies, because the event criteria varied.[6,11,27] In this trial, criteria were designed to be objective and laboratory-based but were probably conservative as compared with clinical practice and existing literature.[6,27] For example, the Hereditary TTP Registry reported a higher rate of acute TTP events among patients receiving regular prophylaxis.[27] The burden of plasma infusions has limited the real-world use of prophylaxis,[28] which — together with the differing definitions of TTP events — may explain the varying rates across different types of studies.

A limitation of the trial is the open-label design, which was necessary because the substantial differences in volume between recombinant ADAMTS13 and standard therapy could not be masked. Owing to the rarity of congenital TTP, limited available data on the natural history of the disorder, and lack of data from controlled clinical trials, our trial did not have sufficient power to detect differences between comparator groups. The trial is ongoing, with 14 patients continuing in the trial at the time of the preplanned interim analysis. The efficacy analyses presented here focus on adults and adolescents, because the available data from pediatric patients are limited by age-staggered enrollment.

This trial showed that recombinant ADAMTS13 was an effective prophylactic therapeutic approach for patients with congenital TTP. In this interim analysis of a randomized, controlled trial, recombinant ADAMTS13 treatment was associated with approximately normal maximum ADAMTS13 activity and low levels of disease-related events and manifestations. No safety concerns were noted with recombinant ADAMTS13, and no neutralizing antibodies to ADAMTS13 were detected.

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APPENDIX

The authors' affiliations are as follows: the Department of Haematology, University College London Hospitals, London (M.S.); the Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta (A.A.); the Department of Internal Medicine, Ohio State University, Columbus (S.R.C.); the Department of Hematology and National Reference Center for Thrombotic Microangiopathies, Hôpital Saint-Antoine, Assistance Publique–Hôpitaux de Paris (AP-HP) and Sorbonne Université (P.C.), the Department of Pediatric Nephrology, Robert Debré Hospital, AP-HP and University of Paris (C.D.), and the Department of Pediatric Nephrology, Hôpital Universitaire Necker–Enfants Malades, AP-HP (N.B.) — all in Paris; the Department of Pediatric Hematology and Oncology, University Medical Center Hamburg-Eppendorf, Hamburg (W.-A.H.), and the Section of Hematology and Oncology, Department of Pediatrics and Adolescent Medicine, Universitätsklinikum Jena, Jena (K.K.) — both in Germany; the Department of Medicine 1, Division of Hematology and Hemostasis, Medical University of Vienna, Vienna (P.K.); the Department of Hematology and Central Hematologic Laboratory, Bern University Hospital, University of Bern, Bern, Switzerland (J.A.K.H.); the Hematology and Hemotherapy Service, Mother and Child Hospital, Biomedical Research Institute of A Coruña, University Hospital Complex of A Coruña, A Coruña, Spain (M.F.L.-F.); the Department of Blood Transfusion Medicine, Nara Medical University, Kashihara, Japan (M.M.); the Division of Hematology, Department of Medicine, and Department of Pathology, Duke University, Durham, NC (T.L.O.); the Department of Hemostasis Disorders and Internal Medicine, Institute of Hematology and Transfusion Medicine, Warsaw, Poland (J.W.); and Takeda Development Center Americas, Cambridge, MA (I.B., M.C., H.L., B.M., M.P., P.P, S.X., P.Z., L.T.W.).

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