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Title:

A recombinant human ADAMTS-13: first-in-human study evaluating pharmacokinetics, safety and tolerability in cTTP patients

Short title: Recombinant human ADAMTS-13 in Congenital TTP

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KEY POINTS

- In this first-in-human, phase 1 study, recombinant ADAMTS-13 was safe, non-immunogenic and well tolerated in patients with congenital TTP.

- Recombinant ADAMTS-13 demonstrated a PK profile comparable to plasma infusion studies, and showed evidence of pharmacodynamic activity.

ABSTRACT

Safety, tolerability and pharmacokinetics of recombinant ADAMTS-13 (rADAMTS-13; BAX 930; SHP655) were investigated in 15 patients diagnosed with severe congenital ADAMTS-13 deficiency (plasma ADAMTS-13 activity < 6%) in a prospective phase 1, first-in-human, multicenter dose escalation study. BAX 930 was well tolerated, no serious adverse events occurred, and no anti-ADAMTS-13 antibodies were observed. Following single dose administration of BAX 930 at 5, 20, or 40 U/kg body weight to adolescents and adults, there was approximate dose proportionality with respect to C_{max} and AUC. Dose related increases of individual ADAMTS-13:Ag and activity were observed and reached a maximum within 1 hour. With escalating BAX 930 doses administered, a dose-dependent persistence of ADAMTS-13-mediated VWF cleavage products and reduced VWF multimeric size were observed. This study demonstrated that pharmacokinetic parameters of BAX 930 were comparable to those estimated in previous plasma infusion studies and provided evidence of pharmacodynamic activity. The study was registered on www.clinicaltrials.gov under the number NCT02216084.

INTRODUCTION

The plasma metalloprotease, ADAMTS-13 (*a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13*), is a constitutively active enzyme that cleaves von Willebrand factor (VWF) at the Tyr1605-Met1606 bond in the A2 domain, an otherwise cryptic site rendered susceptible, by the application of shear stress, to regulate the size of VWF multimers.[1] VWF is a multimeric glycoprotein synthesized principally by vascular endothelial cells.[2] The inability to cleave ultra-large (UL) VWF multimers into smaller forms due to congenital or acquired ADAMTS-13 deficiency results in thrombotic thrombocytopenic purpura (TTP), a rare potentially fatal disorder of the microcirculation caused by increased binding of platelets to UL VWF.[3] The congenital form of TTP (cTTP, previously termed hereditary TTP or Upshaw-Schulman syndrome) is an ultra rare, though likely underestimated condition with prevalence of approximately 1 case per million.[4;5] It exhibits an autosomal recessive mode of inheritance caused by homozygous or compound heterozygous mutations in both ADAMTS-13 alleles on chromosome 9.[6] The nature of the mutations is diverse and includes single amino acid missense substitution (approximately 60%) as well as nonsense, frame-shift, splice site mutations, and deletions and insertions (collectively approximately 40%).[1,7,8,9]

The principal pathophysiology arises from platelet aggregates in the microcirculation affecting critical organs including the brain, heart and kidneys. TTP crises are associated with cerebral vascular incidents in at least 30% of patients, with a risk of neurologic sequelae in approximately 20% of patients.[10] Acute renal failure has been reported in 11% of patients with severe cTTP,[11] and chronic, possibly progressive renal involvement is often seen. Sudden cardiac death due to myocardial infarction, heart failure and arrhythmia has also been reported.[12]

Although considered a monogenetic disorder, the clinical presentation of cTTP is variable. Symptoms develop soon after birth in some patients, whereas others remain asymptomatic until the second or third decade of life. This phenotypic variability is thought to be related to the causative mutations and the level of plasma ADAMTS-13 activity.[13;14] In the newborn, cTTP typically presents as neonatal jaundice and thrombocytopenia,[3] while in early childhood, symptomatic episodes are often associated with intercurrent infections or vaccinations. Among cTTP patients presenting with a first TTP episode later in life, pregnancy is often the inciting event.[15] Intrauterine fetal death is common in cTTP patients who do not receive regular plasma therapy throughout pregnancy.[16;17] Other precipitants associated with increased VWF levels, such as infection, surgery and alcohol binge drinking provide additional triggers for acute TTP events.[18-22] Despite the wide range of ages of the first TTP event, most cTTP patients

subsequently demonstrate a chronic, relapsing course and require prophylactic treatment to prevent long-term neurological, renal and other sequelae.

There are no drugs currently approved for the specific treatment of cTTP. Acute TTP episodes are generally treated with infusions of fresh frozen plasma (FFP) or solvent/detergent (S/D) treated plasma, typically 10-20 mL/kg body weight (BW). Some intermediate purity FVIII:VWF concentrates have been shown to contain low levels of ADAMTS-13 and have been used as an alternative treatment in select patient populations.[23] Although the half-life of infused plasma ADAMTS-13 was found to be 2-4 days,[24] prophylaxis with 10-15ml plasma /kg body weight every 2-3 weeks has been shown to be effective in preventing acute episodes in the majority of TTP patients.[6,25,26]

While the treatment of TTP via plasma infusions is generally effective, the therapy is frequently complicated by allergic and anaphylactic reactions or volume overload.[27] Plasma infusions also carry risks of infection due to blood-borne pathogens. In addition, plasma infusions carried out in the hospital or outpatient settings are burdensome, time consuming, and can be stressful for younger patients. As such, the development of a recombinant ADAMTS-13 (BAX 930; SHP 655; rADAMTS-13) represents a potential new therapeutic option to improve the current standard of care.

In this Phase 1, first-in-human study, we investigated the safety, including immunogenicity, tolerability and pharmacokinetics of rADAMTS-13 in patients diagnosed with severe congenital ADAMTS-13 deficiency, to establish dosing for future studies.

METHODS

Design

This was a prospective, open-label, multicenter, first-in-human dose escalation study on safety, immunogenicity, tolerability and pharmacokinetics (PK) of BAX 930 in patients diagnosed with cTTP assigned to one of three dose cohorts, receiving a single dose of BAX 930 at 5, 20 or 40 U/kg body weight (BW), where one unit is approximately equivalent to the ADAMTS-13 activity in 1 mL of plasma. The study comprised two dose escalation steps. Fifteen patients were enrolled (out of 16 screened: one was unable to participate due to a scheduling conflict) and dosed sequentially. Subjects were recruited to the next higher dose level only after short-term safety had been demonstrated and reviewed by an independent Data Monitoring Committee (DMC) at the preceding dose level. The study was approved by the responsible Ethics Committees or institutional

review boards and regulatory authorities. The study was registered on www.clinicaltrials.gov under the number NCT02216084. All participants gave written informed consent. Data were analyzed by biostatisticians at Shire and Quintiles; all authors had access to primary clinical trial data.

Patients

The principal inclusion criteria consisted of a documented diagnosis of severe congenital ADAMTS-13 deficiency (baseline plasma ADAMTS-13 activity <6%) confirmed by genetic testing, ages 12-65 years, and the absence of severe TTP symptoms at the time of screening. This included stable laboratory parameters (platelet count >100 x 10^9/L, LDH <3 times ULN [upper limit of normal]). Evidence of end organ damage such as stroke, heart, renal disease or abnormal liver function tests were further exclusions to study enrollment. Patients with a medical history or presence of functional neutralizing ADAMTS-13 inhibitor at screening, or a medical history of immunological or autoimmune disorders, or significant neurological events were excluded. A sample size of 14 was selected on the basis of feasibility.

Study drug and treatments

BAX 930 is a fully glycosylated recombinant human ADAMTS-13 protein produced in a Chinese hamster ovary (CHO) mammalian expression system in a plasma protein-free milieu. The cell culture and purification processes used in the manufacture of BAX 930 do not employ additives of human or animal origin. The purification process of BAX 930 is based on chromatography using conventionally available resins including anion exchange, hydroxyapatite, mixed mode (hydrophobic interaction) and cation exchange. In addition, BAX 930 undergoes two dedicated virus reduction steps: solvent/detergent (S/D) treatment and nanofiltration. The final product is lyophilized for intravenous (IV) injection. The sterile, lyophilized BAX 930 was stored in 10 mL vials, which were reconstituted with 5 mL of sterile water, giving the solution a nominal strength of 300 U/mL that is stable for 3 hours at room temperature after reconstitution. BAX 930 was infused at a rate of 2-4 mL/minute. In patients receiving regular prophylaxis, there was at least a 10-day window between their last prophylactic treatment and their BAX 930 dose.

Safety assessments

Patients were hospitalized for at least 96 hours following investigational product (IP) infusion for safety observation and PK assessments. Follow-up visits were scheduled 12

days and 30 days (or 6, 9 and 12 days for the two participating adolescents) post-infusion. Safety was evaluated through clinical assessment, hematology, serum chemistry, urinalysis, coagulation tests, antibodies against ADAMTS-13 or CHO cell protein, viral serology, cardiac troponin, D-dimers and seromarkers for brain or renal impairment. Adverse events (AEs) were recorded throughout the study, but specifically by the patient in a diary, beginning 96 hours post-infusion until the study completion visit.

ADAMTS-13 and VWF assays

ADAMTS-13 activity was calculated by analysis of fluorescence over time using the synthetic fluorogenic VWF73 peptide substrate (FRETS-VWF73) and a commercially available, chromogenic GST-VWF73 based ADAMTS-13-activity ELISA (Technozym® ADAMTS-13 Activity ELISA).[28;29] ADAMTS-13 antigen was measured using a validated sandwich ELISA employing anti-human-ADAMTS-13 antibodies.[30,31,32] VWF:RCo and VWF:Ag were determined as previously described.[33,34]

Analysis of VWF multimers was performed using SDS-agarose gel electrophoresis followed by Western blotting and sensitive luminescence detection.[4,35] VWF degradation products generated by ADAMTS-13-mediated cleavage were assessed by SDS-PAGE under reducing conditions followed by Western blotting and immunostaining with a horseradish peroxidase (HRP)-labeled polyclonal rabbit antihuman VWF antibody with enhanced chemiluminescence detection.[4,35,36]

Immunogenicity Assessments

Total binding antibodies to ADAMTS-13 were measured by ELISA-based assays, detecting total Ig (IgG, IgA, IgM). Neutralizing antibodies to ADAMTS-13 were measured using a Bethesda-like approach with the ADAMTS-13 activity assay.[37]

Pharmacokinetic assessments

PK parameters, including area under the concentration-time curve (AUC [h·U/mL]), plasma half-life ($t_{1/2}$ [hours]), clearance (Cl [mL/kg/hours]), mean residence time (MRT [hours]), volume of distribution at steady state (Vss [mL/kg]), maximum plasma concentration (C_{max} [U/mL]) and incremental recovery (IR [U/mL]) were assessed for ADAMTS-13 activity and ADAMTS-13 antigen (ADAMTS-13:Ag). Concentrations were measured at standardized time points: within 60 minutes pre-infusion; 15, 30, 60 minutes and 3, 6, 9, 12, 24, 48, 96, 144, 168, 192, 216, 240, 264 and 288 hours post-infusion in adults. The two adolescent subjects (16 and 17 years of age) had sparse sampling pre-infusion and at 6, 48, 144, 216 and 288 hours post-infusion. The

hematology and clinical chemistry assessments, conducted as part of the safety assessments (see above), were performed on EDTA anticoagulated whole blood and serum, respectively, at the screening visit, just prior to IP infusion, and at regular increments up to 288 hours post-infusion. The hematology panel included platelet counts and the clinical chemistry panel included serum LDH, both of which were used for assessing the pharmacodynamic effects of BAX 930.

Statistical analysis

ADAMTS-13 concentration data were analyzed using a non-compartmental approach and individual PK parameter estimates were derived. Total $AUC_{0-\infty}$ was calculated by the linear trapezoidal rule up to the last quantifiable concentration with a tail area correction. Terminal plasma half-life was determined from the terminal rate constant obtained by log-linear fitting of a regression line by the least squares deviation method to the last five quantifiable concentrations that were above pre-infusion levels. MRT was calculated as total area under the moment curve divided by the total area under the curve corrected for the duration of the infusion. Systemic clearance (Cl) was calculated as dose per body mass (kg) divided by $AUC_{0-\infty}$. IR was calculated as C_{max} divided by dose per body mass.

To better address the variability in baseline ADAMTS-13 levels, a population PK model was also developed. A two-compartment model with first order elimination and constant rate infusion was selected iteratively among different structural and stochastic candidates and provided population PK parameter estimates. Individual PK parameters from a non-compartmental approach and from the population PK model were similar.

Descriptive statistics were used to assess safety in terms of product-related AEs.

RESULTS

Fifteen patients received study drug: three each in the 5 U/kg and 20 U/kg dose cohorts, and 9 in the 40 U/kg dose cohort (Figure 1; Table 1); 2 patients in the 40 U/kg cohort were adolescents. All patients completed the study. Doses administered were within 0.3 U/kg of the planned doses, with the exception of one patient who received 47.5 U/kg instead of the planned 40 U/kg.

ADAMTS-13 Activity

Following the single infusion of BAX 930, dose-related increases in ADAMTS-13 FRETS-VWF73 concentrations were observed (data from the 40 U/kg cohort shown in Figure 2). ADAMTS-13 activity remained quantifiable for 24 hours in the 5 U/kg cohort,

for 240 hours in the 20 U/kg cohort, and for the full 288-hour study period in the 40 U/kg cohort. ADAMTS-13 activities measured by FRETS-VWF73 and chromogenic assay methods were highly comparable (Table 2).

In the 40 U/kg cohort, the geometric mean of IR was 0.0232 (U/mL·kg/U), mean terminal half-life was 59.2 hours and initial half-life was 17.0 hours for ADAMTS-13 activity (FRETS-VWF73). ADAMTS-13 activity, $C_{max,}$ and total exposures increased approximately in proportion to the dose escalations. The geometric mean C_{max} was 0.398 U/mL after 20 U/kg infusion and 0.948 U/mL after 40 U/kg infusion; the geometric mean $AUC_{(0\text{-}inf)}$ was 19.1 U·h/mL after 20 U/kg infusion and 53.1 U·h/mL after 40 U/kg infusion.

With the more sensitive chromogenic ELISA assay (LLOQ: 0.0073 U/mL compared with 0.05 U/mL for FRETS-VWF73), low levels of ADAMTS-13 activity were measurable at the pre-infusion time point in all patients except one adult and both adolescents.

Despite the differences in the LLOQ, activity measurements by FRETS-VWF73 and chromogenic assay methods were otherwise similar (Table 2).

ADAMTS-13 Antigen

ADAMTS-13 antigen (ADAMTS-13:Ag) concentrations at pre-dose (baseline) were low, ranging from 0.003 to 0.031 U/mL, but quantifiable in all but two patients (one patient each in the 5 U/kg and 40 U/kg dose cohorts). Individual post-dose ADAMTS-13:Ag levels remained quantifiable in all samples up to the last collection at 288 hours post-dose and were higher than baseline (pre-dose) values.

The geometric mean of ADAMTS-13:Ag Cl was 61.5 mL/h and of V_{ss} was 5300 mL (at 40 U/kg dose level), suggesting the protein distributed primarily within the intravascular compartment.[38] There was approximate dose proportionality with respect to C_{max} (geometric means of 0.323 µg/mL after 20 U/kg infusion and 0.672 µg/mL after 40 U/kg infusion) and $AUC_{(0\text{-}inf)}$ (geometric means of 18.3 µg·h/mL after 20 U/kg infusion and 36.0 µg·h/mL after 40 U/kg infusion).

The PK parameter estimates for ADAMTS-13:Ag were comparable to ADAMTS-13 activity. Over the 5 U/kg to 40 U/kg dose range, ADAMTS-13:Ag geometric mean C_{max} increased 5-fold between 5 U/kg and 20 U/kg, and approximately proportional to the dose between 20 U/kg and 40 U/kg (2.1-fold) (Table 2). The fold increases in geometric mean total exposures ($AUC_{(0\text{-}t)}$ and $AUC_{(0\text{-}inf)}$) were approximately proportional to the dose increase for both dose level comparisons.

ADAMTS-13 Activity and ADAMTS-13 Antigen in Adolescents

The available concentration data for both ADAMTS-13 activity and ADAMTS-13:Ag, did not suggest any major differences between adolescents and adults. Despite the low number of adolescents in the study (n=2) and reduced sampling per protocol, ADAMTS-13 activity, IR, $t_{1/2}$ and AUC were generally within the data ranges for adults treated at the same dose level (40 U/kg). The estimated clearances for the two adolescent subjects were 64.9 and 54.5 mL/h, respectively, which were within the range observed for adult subjects (n=7; range: 44.4 - 115 mL/h).

Pharmacodynamic Effects

In addition to the small, intermediate, and large multimeric sizes typically present in normal plasma, UL VWF multimers were observed in the samples collected prior to dosing, at screening or pre-dose, in all patients, and at most time points post-dose. The trend for decreasing large multimers, including UL multimers, and increasing levels of the intermediate fraction was observed over the first 12-24 hours post infusion in individual profiles at BAX 930 doses of 20 U/kg or 40 U/kg before slowly returning to pre-infusion levels over a 288-hour period (Figure 4B).

Likewise, an apparent dose-dependent effect was seen with the detection of ADAMTS-13-mediated VWF cleavage products. In the 5 U/kg dose cohort, ADAMTS-13-mediated VWF cleavage products were present up to 3 hours post-dose in all patients (100%), up to 6 hours post-dose in one patient (33.3%), and no longer detectable thereafter (Figure 4A). ADAMTS-13-mediated VWF cleavage products were observed over a longer period of time at higher dose levels: for 20 U/kg, up to 24 hours post-dose in all patients and up to 48 hours in two patients (66.7%); for 40 U/kg, up to 48 hours post-dose in all patients and as long as 264 hours in one patient (14.3%) (Figure 4C).

In addition, the function of VWF to bind platelet GPIb, as measured by the VWF:RCo assay, were lower than mean baseline levels at most timepoints across the 3 dose levels and decreased by approximately 30% within the first 9 hours. A modest decrease in LDH of 5%-10% relative to baseline was also observed in the first 48 hours post infusion. In addition, although subjects in this study were not experiencing acute manifestations of cTTP, there was an increasing trend in the platelet count up to six days after infusion in all dosing cohorts (Figure 5).

Safety

BAX 930 was well tolerated in all 15 patients and no patient exhibited anaphylaxis or other allergic manifestations. No serious adverse events, adverse events leading to discontinuation from the study, nor breakthrough TTP events were seen in the study after treatment. Overall, 12 of 15 patients (80.0%) reported at least one temporally emergent adverse event (TEAE; see Supplementary Table 1). Three subjects, all in the 40 U/kg BAX 930 cohort (40 U/kg: 3/9 subjects, 33.3%; overall: 3/15 subjects, 20.0%) reported a total of five TEAEs considered by the investigators to be temporally associated with BAX 930 infusion: decrease in VWF antigen and VWF activity at 30-minutes post-infusion, returning to normal activity levels at 1 hour post-infusion (n=1), flatulence (n=1), nausea on two separate days (n=1). No trends were observed over time or among the three dose cohorts in the laboratory parameters, vital sign assessments, ECG measurements, or physical examination.

Immunogenicity Evaluation

All anti-ADAMTS-13 neutralizing antibody results were <0.6 BU/mL across the three dose cohorts and at all three scheduled time points; i.e., screening, infusion pre-dose, and at study completion, day 28 ± 3 days. None of the 15 patients who received BAX 930 exhibited anti-ADAMTS-13 binding antibodies at any time in the study. Similarly, all patients tested negative for anti-CHO protein antibodies at all timepoints.

DISCUSSION

Recombinant ADAMTS-13 potentially offers a novel option for the treatment of cTTP, eliminating many of the risks associated with products derived from human plasma and facilitating the introduction of more precise and individualized dosing regimens.[24,39-43] In our prospective, dose escalating clinical trial we investigated the safety, tolerability and PK of BAX 930 infused for the first time in humans.

BAX 930 was expected to behave in the same way as endogenous ADAMTS-13, as demonstrated in several non-clinical *in vitro* and *in vivo* studies. In current clinical practice, infusions of 10-20 mL/kg FFP are recommended for treating acute episodes or prophylaxis of cTTP.[44-46] As such, a low dose of 5 U/kg, an intermediate dose of 20 U/kg, and a high dose of 40 U/kg BAX 930 were chosen for this study. The 40 U/kg dose has been calculated to correspond to doses of ADAMTS-13 typically administered during single volume plasma exchange sessions.[47]

As would be expected in this cTTP patient population, pre-dose baseline levels of ADAMTS-13:Ag and ADAMTS-13 activity (assessed by both FRETS-VWF73 and

chromogenic ELISA assays) were very low or below the lower limit of quantitation (LLOQ). Immediately following infusion of all doses of BAX 930 there was an increase in individual ADAMTS-13:Ag and activity observed, reaching a maximum within 1 hour post infusion. Similar ADAMTS-13:Ag, ADAMTS-13 FRETS-VWF73, and ADAMTS-13 activity ELISA profiles suggest good correlation between protein concentrations and activity. No apparent differences were observed for ADAMTS-13 activity and ADAMTS-13:Ag between adolescents (n=2) and adults (n=7), treated with the same BAX 930 doses.

Overall, there was evidence suggesting dose proportionality with respect to $AUC_{(0\text{-}inf)}$ and C_{max} (Table 2; Figure 3). The change in the geometric mean C_{max} for 5 U/kg to 20 U/kg was approximately 5-fold and approximately 2.4-fold for 20 U/kg to 40 U/kg. Greater increases were observed for geometric mean $AUC_{(0\text{-}inf)}$ (47-fold for 5 U/kg to 20 U/kg and 3.1-fold for 20 U/kg to 40 U/kg), which could be attributable to concentrations falling below the LLOQ at lower doses. Available data for $AUC_{(0\text{-}inf)}$ showed an approximately 2.8-fold increase in exposure for dose increases from 20 U/kg to 40 U/kg. Available data at the 20 U/kg and 40 U/kg dose levels show no major changes in Cl, V_{ss}, $t_{1/2}$, and $MRT_{(0\text{-}inf)}$ with increasing dose.

PK parameters derived from the non-compartmental and population PK approaches were consistent. In the population PK model, a shorter initial half-life was observed followed by a longer terminal half-life. Whether the initial phase is due to VWF binding, consumption of ADAMTS-13 activity or distribution to another physiologic compartment remains to be determined.

In addition to the PK results, evidence of pharmacodynamic activity was observed. With escalating BAX 930 doses, prolonged detectable ADAMTS-13-mediated VWF cleavage products were present, in line with dose-related increases of ADAMTS-13:Ag and activity. Specifically, detectable ADAMTS-13-mediated VWF cleavage products were present in all patients (100%) and up to 48 hours following the highest dose, 40 U/kg. Patients with cTTP typically exhibit UL molecular weight forms of VWF at baseline consistent with the severe reduction in ADAMTS-13 activity. A trend for decreasing large multimers, a fraction of which also included UL multimers, and increasing levels of the intermediate fraction was observed over the first 24 hours post infusion in individual profiles at BAX 930 doses of 20 U/kg or 40 U/kg. In addition, over the first 9 hours, the mean postdose VWF:RCo levels decreased by approximately 30%. There was also an increase in the platelet count in all dosing groups. Taken together, these findings provide evidence of *in vivo* ADAMTS-13 activity following BAX 930 administration.

This study demonstrated that the protein antigen and activity PK parameters of BAX 930 were comparable to those estimated from previous studies of ADAMTS-13 administered to cTTP patients as a constituent of FFP. Furlan et al[24] reported limited PK data in patients treated with FFP and demonstrated that the recovery was nearly 100% and the half-life was 2.1-3.3 days. Similar results were reported by Fujimura et al.[43] The comparability of plasma-derived and recombinant ADAMTS-13 pharmacokinetics suggests that dosing regimens in future studies of the long-term safety and efficacy of BAX930 can be modeled on the clinical experiences with plasma-based regimens. No patients developed an inhibitor to ADAMTS-13 during this single dose study. The lack of an apparent immune response will need to be confirmed in the upcoming pivotal study in which patients will be repeatedly exposed to BAX 930 for approximately one year.

In conclusion, BAX 930 appeared to be safe and well tolerated over a dose range of 5 to 40 U/kg in cTTP patients, and there was no evidence of an immune response to BAX 930 following a single infusion. The activity PK parameters were comparable to those estimated from FFP studies and demonstrated approximate dose proportionality with respect to C_{max} and AUC. Finally, there was evidence for BAX 930 activity *in vivo*, including effects on VWF multimers, platelet count, and serum LDH. These data provide the basis for proceeding to a phase 3 pivotal study in cTTP utilizing previously anticipated prophylactic and treatment dosing regimens.

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AUTHORSHIP CONTRIBUTIONS:

B.E. designed the study; C.H., B.E., C.M., L.M. and J.D. interpreted data; M.S., P.K., K.K., L.R., J.W., Y.F., R.S., J.A.K.H, M.K and B.E. performed research; L.M. performed statistical analysis; B.E., C.H. and J.D. wrote the manuscript; B.E. supervised the research.

DISCLOSURE OF CONFLICTS OF INTEREST:

C.H., J.D, L.M. and B.E. are employees of Shire. C.M. is an employee of Quintiles, which assisted with the conduct of this study. P.K., K.K., L.R., J.W., R.S., Y.F., J.A.K.H, and M.K. received consultancy fees for conducting the research. MS received honoraria for speakers' fees for Baxalta/Shire and advisory boards.

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Table 1. Subject Demographic Data

Subject ID	Age (years)	Sex	Race	Age at diagnosis	Previous treatment type	Dosing Cohort	Platelet levels at screening (10^9/L)	LDH levels at screening (U/L)
1	22	F	White	15	Prophylaxis	5 U/kg	106*	294*
2	28	M	White	24	On Demand	5 U/kg	166	136
3	35	M	White	29	Prophylaxis	20 U/kg	154	170
4	21	F	Asian	<1	Prophylaxis	40 U/kg	167	151
5	24	F	Asian	17	Prophylaxis	20 U/kg	220	142
6	25	M	White	2	Prophylaxis	40 U/kg	190+	159
7	33	F	White	20	Prophylaxis	40 U/kg	223	165
8	32	F	White	10	On Demand	40 U/kg	221	146
9	40	M	White	16	Prophylaxis	40 U/kg	216	125
10	41	F	White	19	On Demand	5 U/kg	348	130
11	39	F	White	36	Prophylaxis	20 U/kg	252	259*
12	16	M	White	14	Prophylaxis	40 U/kg	214	153
13	17	F	White	<1	Prophylaxis	40 U/kg	353	140
14	33	M	White	26	Prophylaxis	40 U/kg	273	122+
15	30	M	Black	14	Prophylaxis	40 U/kg	297	185

Note: Table has been anonymized by permutation of the following columns: age and age at diagnosis.

* Abnormal

+ Baseline values provided; screening values not available

Table 2. Summary of key plasma ADAMTS-13 FRETS-VWF73 pharmacokinetic parameters in adults

Pharmacokinetic Parameters	Median (range)		
	5 U/kg (n = 3)	**20 U/kg (n = 3)**	**40 U/kg (n = 7)**
FRETS-VWF73			
IR, U/mL*kg/U	0.0154 (0.0125-0.0187)	0.0181 (0.0153-0.0290)	0.0228 (0.0185-0.0290)
$C_{max,}$ U/mL	0.075 (0.065-0.100)	0.361 (0.300-0.583)	0.941 (0.737-1.158)
$t_{max,}$ h [a]	1.00 (0.52-1.00)	0.33 (0.25-0.53)	0.37 (0.22-0.58)
$AUC_{(0\text{-}inf),}$ U*h/mL	ND[b]	18.1 (15.4-24.9)	52.3 (41.3-85.4)
$AUC_{(0\text{-}t),}$ U*h/mL	0.388 (0.0528-1.68)	14.9 (11.5-21.1)	46.5 (37.2-78.8)
$t_{1/2,}$ h	ND[b]	36.5 (29.5-69.2)	66.9 (44.1-77.8)
$MRT_{(0\text{-}inf),}$ h	ND[b]	48.876 (43.55-93.87)	92.468 (55.71-124.01)
Cl, mL/h	ND[b]	64.8 (53.3-100)	59.3 (44.4-115)
$V_{ss,}$ mL	ND[b]	4900 (2820-5000)	5250 (4100-6830)
Technozym			
IR, U/mL*kg/U	0.0170 (0.0160-0.0179)	0.0157 (0.0136-0.0254)	0.0212 (0.0144-0.0261)
$C_{max,}$ U/mL	0.087 (0.083-0.091)	0.308 (0.272-0.512)	0.844 (0.574-1.039)
$t_{max,}$ h [a]	0.25 (0.25-0.52)	0.55 (0.28-0.97)	0.30 (0.25-0.58)
$AUC_{(0\text{-}inf),}$ U*h/mL	6.68 (4.32-17.4)	21.8 (18.3-25.8)	45.6 (40.6-89.1)
$AUC_{(0\text{-}t),}$ U*h/mL	6.39 (4.26-8.43)	20.6 (15.9-25.4)	43.8 (37.3-80.4)
$t_{1/2,}$ h	66.2 (44.2-238)	64.4 (46.9-69.8)	62.6 (46.5-77.0)
$MRT_{(0\text{-}inf),}$ h	90.401 (69.41-383.36)	90.663 (65.38-114.38)	78.382 (63.54-124.58)
Cl, mL/h	51.8 (13.3-88.9)	54.7 (44.1-96.8)	68.4 (45.7-111)
$V_{ss,}$ mL	5090 (4680-6170)	6260 (4000-6330)	6010 (3130-8700)
ADAMTS13 Antigen			
IR, µg/mL*kg/µg	0.0176 (0.0171-0.0194)	0.0220 (0.0180-0.0354)	0.0247 (0.0205-0.0328)
$C_{max,}$ µg/mL	0.066 (0.062-0.066)	0.296 (0.238-0.480)	0.655 (0.549-0.879)
$t_{max,}$ h [a]	0.25 (0.25-0.52)	0.55 (0.53-0.97)	0.30 (0.22-1.12)
$AUC_{(0\text{-}inf),}$ µg*h/mL	4.14 (4.14-5.90)	18.1 (16.8-20.2)	33.4 (29.4-67.8)
$AUC_{(0\text{-}t),}$ µg*h/mL	4.05 (3.59-4.49)	16.4 (15.6-19.9)	30.4 (28.3-61.0)
$t_{1/2,}$ h	93.9 (56.2-122)	48.0 (47.0-82.3)	70.4 (50.9-86.3)
$MRT_{(0\text{-}inf),}$ h	131.365 (75.45-192.16)	67.210 (62.37-128.74)	87.134 (68.83-125.51)
Cl, mL/h	58.3 (27.3-64.8)	40.1 (35.8-83.1)	61.8 (41.9-116)
$V_{ss,}$ mL	5240 (4400-8510)	4610 (2690-5180)	4760 (3650-8150)

$AUC_{(0\text{-}inf)}$ = Area under the plasma-time concentration curve from zero to infinity;
$AUC_{(0\text{-}t)}$ = Area under the plasma-time concentration curve from zero to the last measured timepoint;
Cl = Systemic clearance; C_{max} = Maximum concentration following infusion;
IR = Incremental recovery; max = Maximum; min = Minimum; MRT = Mean residence time;
ND = not determined; $t_{1/2}$ = Half-life; t_{max}: Minimum time to reach C_{max};
V_{ss} = Volume of distribution at steady state
[a] Median (min - max)
[b] n = 1 for $AUC_{(0\text{-}inf)}$, $t_{1/2,}$ $MRT_{(0\text{-}inf),}$ Cl, and V_{ss}

Figure 1. Study population disposition.

Figure 2. Observed ADAMTS-13 activity over time.
ADAMTS-13 activity in plasma was measured at baseline and at time points up to 288 hours using the FRETS-VWF73 assay following a 40 U/kg administration of BAX 930.

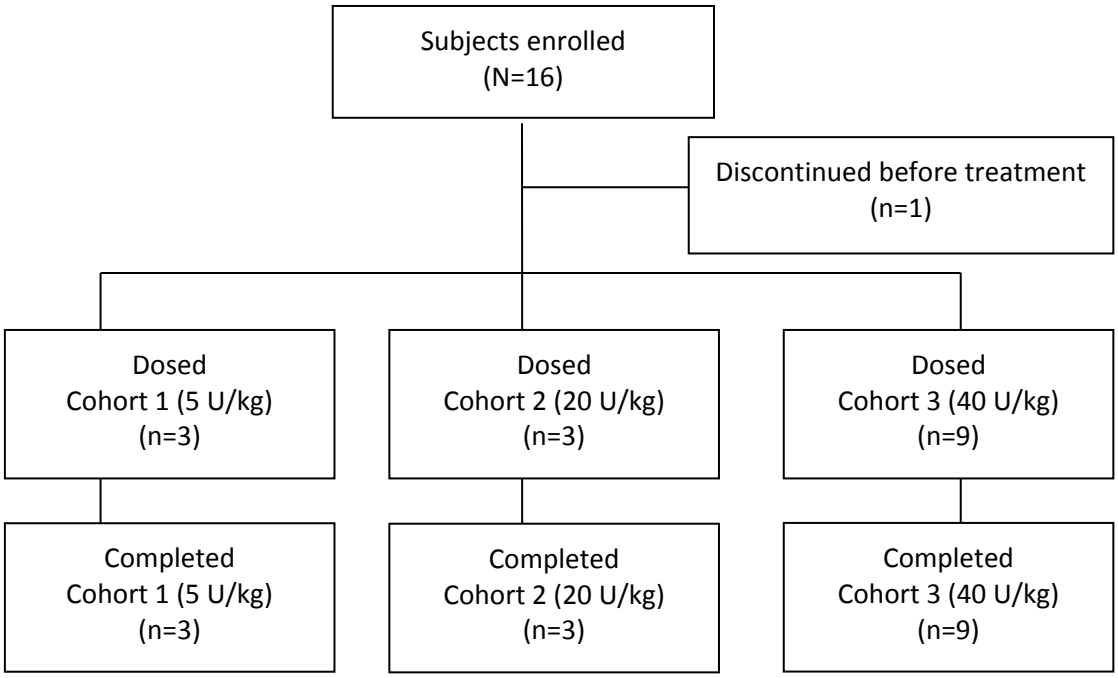
Figure 3. Predicted PK Estimates from Two-Compartment Model.
Predicted FRETS-VWF73 activity time profiles are depicted based on a two-compartmental model according to linear and log concentrations. Both display approximate dose proportionality. The use of the two compartment (n=9) and the non-compartmental (NCA; n=7) models yield comparable results.

Figure 4. VWF Structural Analyses pre- and post-infusion of BAX 930.
(A) Representative SDS-agarose gel pattern of pretreatment TTP plasma depicting ultralarge, large, intermediate, and small size VWF multimers.
(B) The proportions of intermediate and large/ultralarge multimers of plasma VWF were estimated from SDS-agarose gels at various times prior to and following infusion of 40 U/kg BAX 930. The observed concentration of large and ultralarge multimers tended to decrease in all treated patients in the first 12 hours, before gradually returning to pre-infusion levels.
(C) Time course of the 176 kDa ADAMTS-13 VWF cleavage product following administration of 5 U/kg, 20 U/kg, and 40 U/kg BAX 930. High levels of detectable VWF cleavage products are apparent just after dosing, which gradually return to pre-infusion levels in a dose-related manner.

Figure 5. Changes in platelet counts following BAX 930 administration.
Changes in mean platelet counts over time are depicted following administration of 5 U/kg, 20 U/kg, and 40 U/kg of BAX 930. An increasing trend in platelet levels was observed in all dosing cohorts.

Figures

Figure 1. Study population disposition



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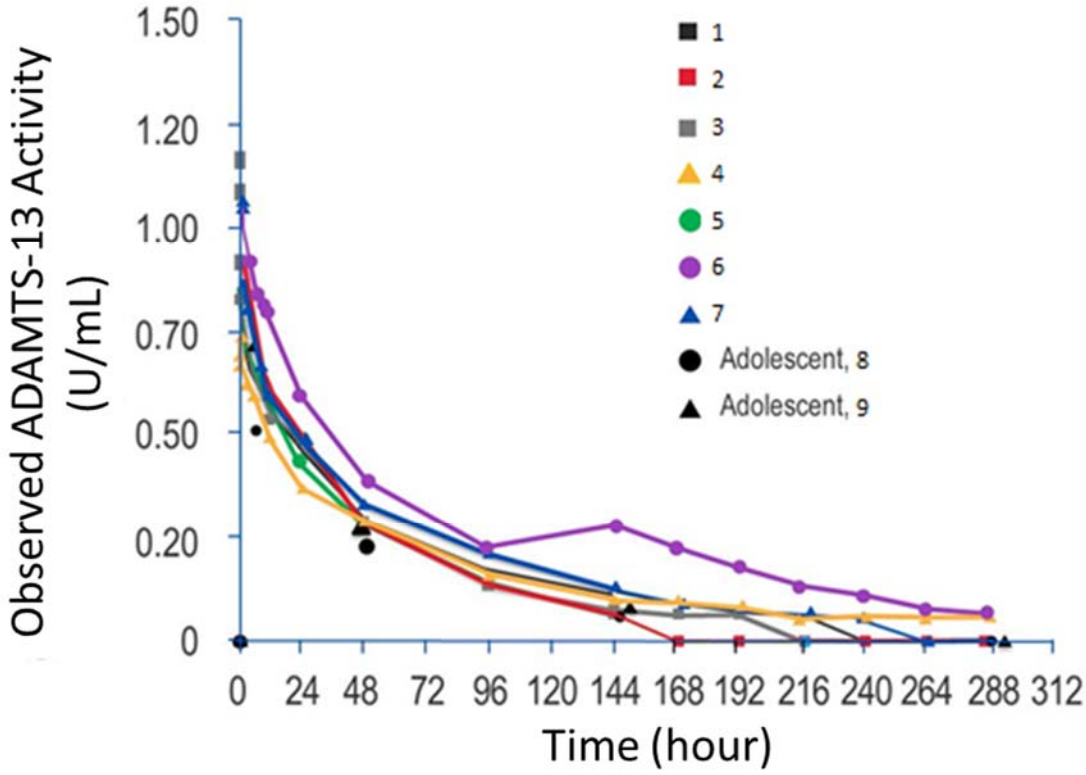

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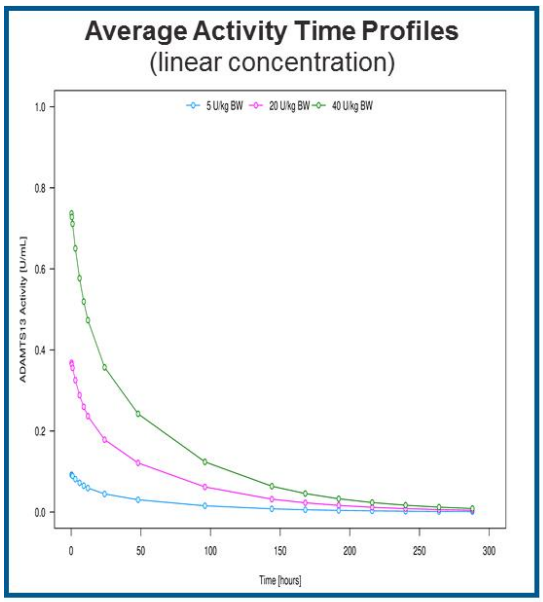
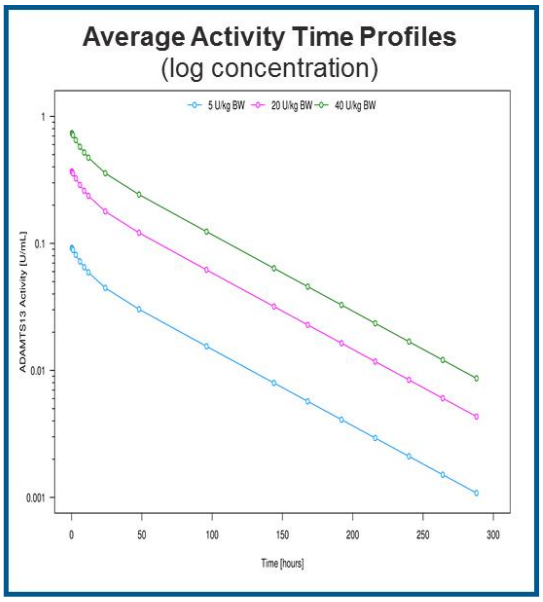
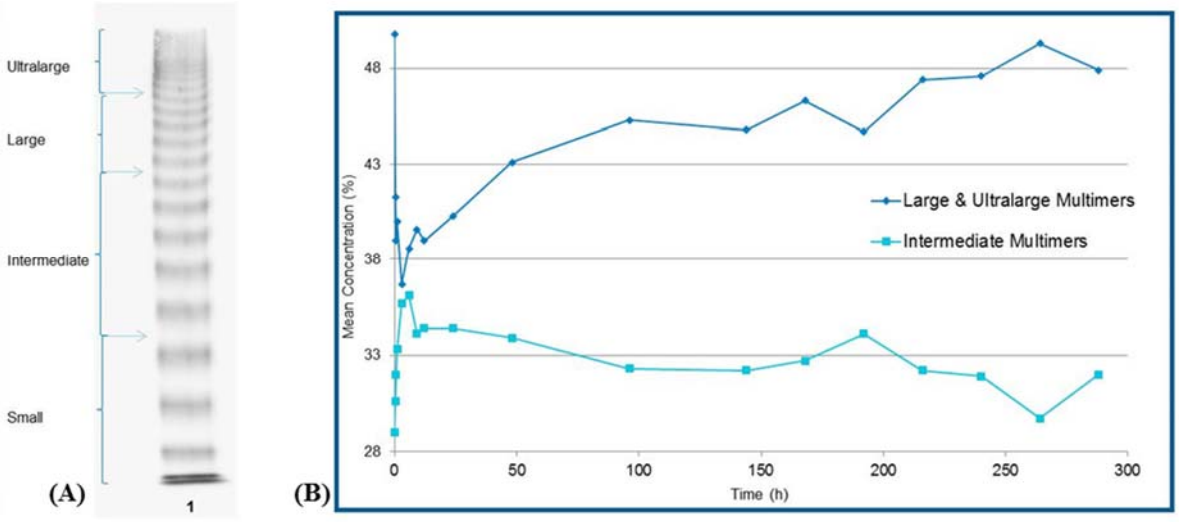




Parameter, unit	Two Compartment	NCA model
C_{max}, U/mL	0.867	0.957
IR, (U/mL)/(U/kg)	0.021	0.0234
Terminal half-life, h	57.087	60.5
MRT, h	77.593	87.656

Figure 4. VWF Structural Analyses pre- and post-infusion of BAX 930



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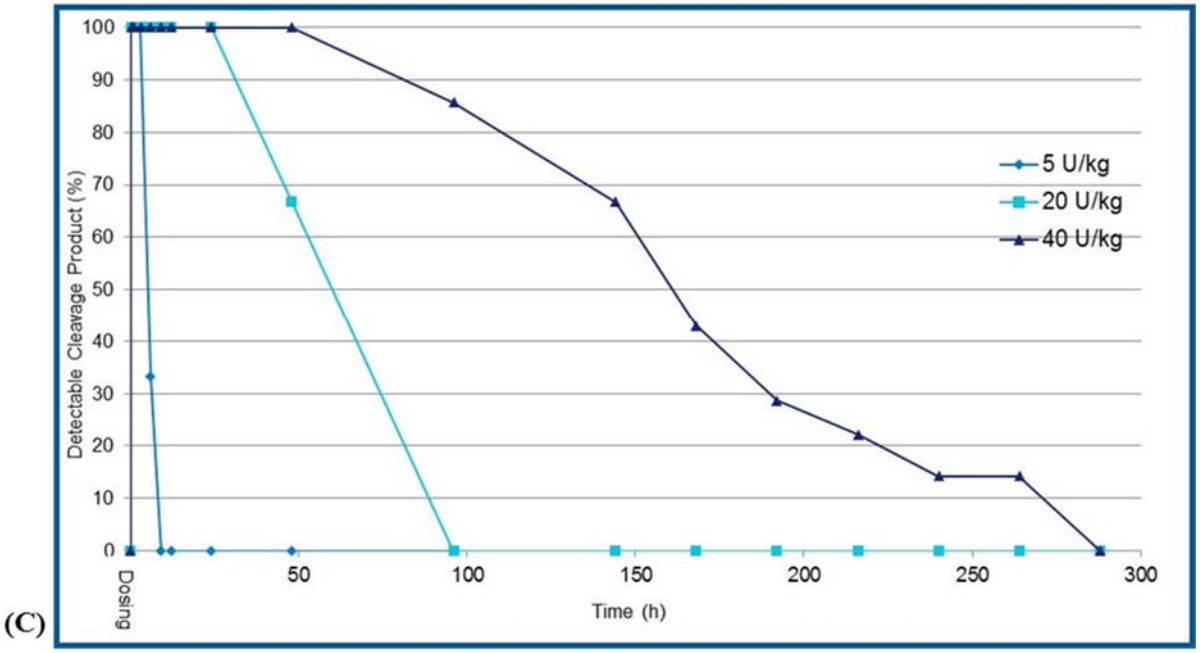

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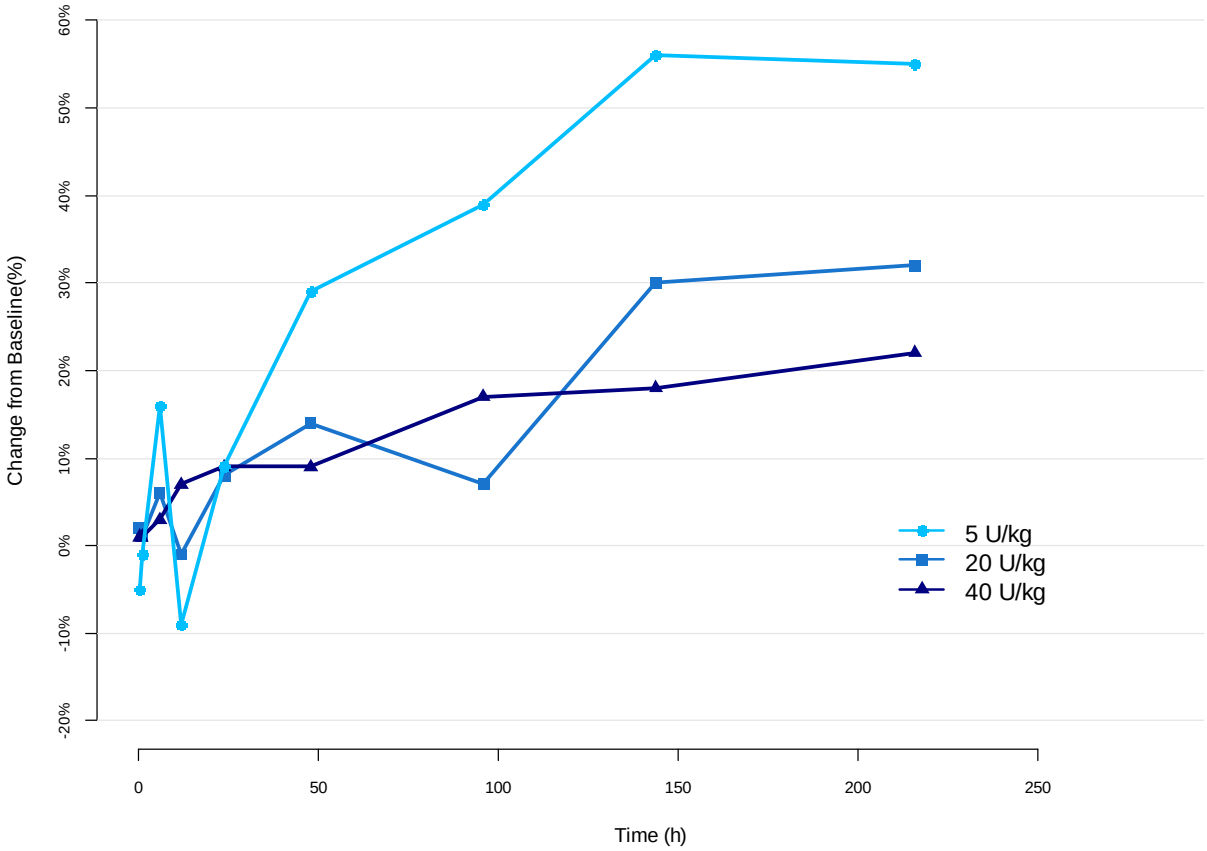

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A recombinant human ADAMTS-13: first-in-human study evaluating pharmacokinetics, safety and tolerability in cTTP patients

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