Pharmacokinetics of plasma infusion in congenital thrombotic thrombocytopenic purpura

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Essentials

- Congenital thrombotic thrombocytopenic purpura (TTP) is primarily treated with plasma infusion.
- We present a pharmacokinetic analysis of ADAMTS-13 in 6 patients following plasma infusion.
- A median half-life of 130 hours was demonstrated, ranging between 82.6 and 189.5 hours.
- Investigation of interindividual clearance of ADAMTS-13 is necessary to optimize treatment.
Abstract
Background: Congenital thrombotic thrombocytopenic purpura (TTP) is defined by persistent severe deficiency of ADAMTS-13 in the absence of anti-ADAMTS-13 inhibitory antibodies, confirmed by mutational analysis. Replacement of the missing protease prevents disease relapse, primarily using plasma infusion (PI).

Objectives, Patients and Methods: There is scant evidence regarding optimal dose and frequency of treatment, tending to be empirically guided. We present a pharmacokinetic analysis of ADAMTS-13 in 6 patients with congenital TTP on established regimes following PI.

Results: We found a median clearance of 25.41 ml/h and half-life of 130 hours, ranging between 82.6 and 189.5 hours (3.4 to 7.9 days respectively). All patients reached baseline ADAMTS-13 level within 7-10 days post plasma. Median ADAMTS-13 activity peak post PI was 24.05 IU/dL. Variation was related to elimination rate, in turn affected by weight and metabolism, but not to von Willebrand factor antigen or activity levels.

Using the pharmacokinetic parameters, we simulated individualised protocols based on PI dose or frequency to target hypothetical optimal plasma levels of ADAMTS-13 of 10 and 50 IU/dL respectively. Results suggest a target trough ADAMTS-13 of 10 IU/dL is feasible but 50 IU/dL would not be achievable taking into account volume required.

Conclusions: Further work is needed to compare treatment of congenital TTP with PI versus recombinant ADAMTS-13. PI may provide longer duration of ADAMTS-13 effect, but is limited by plasma volume required, whereas recombinant therapy can provide a higher ADAMTS-13 peak. We propose that investigation of interindividual clearance of ADAMTS-13 is necessary to optimise treatment, to enable rationale for dose and frequency of prophylaxis.

Background
Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy, constituting a haematological emergency in the acute setting. Disseminated microvascular ischaemia quickly culminates in multiorgan dysfunction and a high mortality rate without prompt management. The vast majority of TTP is caused by autoantibodies which bind to ADAMTS-13 and impair function[1]. Congenital TTP is caused by biallelic mutations present in the ADAMTS-13 gene, with two loss-of-function mutations required to fully inactivate the ADAMTS-13 gene product. Compound heterozygous mutations are most common at 65%, inherited from asymptomatic parents who each carry a different mutation. Individual with homozygous mutations are more likely to have closely related parents [2]. Originally thought to be a disease of childhood, the
diagnosis of congenital TTP is increasingly made in adulthood, especially described in pregnancy[3,4]. There is considerable variation in the age of onset, severity and frequency of acute episodes, reflecting genetic heterogeneity and susceptibility to precipitants such as surgery, pregnancy, infections, ageing, hormonal changes and comorbidities.

Congenital TTP has been increasingly recognised over the last decade with improved diagnostic techniques. Treatment of congenital TTP is based on the use of plasma infusion (PI) or intermediate purity factor VIII concentrates, which contain ADAMTS-13. Both treatment modalities provide functional ADAMTS-13 levels, which promote the irreversible cleavage of the high molecular weight von Willebrand factor multimers (HMW VWF)[5–7]. In addition, both therapies have demonstrated efficacy in incrementing platelets acutely[7,8] and as prophylactic treatment[9,10]. However, there is little available evidence regarding the appropriate dosing requirements and interval between plasma infusions, with dose and dosing interval being selected empirically for each patient. Consequently, some patients are treated on demand due to circumstances such as pregnancy and infection, whereas others need regular infusions to prevent TTP[11].

Studies of clearance mechanisms of VWF have demonstrated a half-life of 8-15 hours, but with interindividual variation according to blood group, glycosylation and genetic mutations[12]. The behaviour of ADAMTS-13 has been less explored. An early study demonstrated half-life activity of von Willebrand factor (VWF)-cleaving protease in 2 brothers with congenital TTP suggesting a plasma half-life of 2-3 days[13]. A typical dosing interval of every 3 weeks would therefore appear too long, given such a half-life of ADAMTS-13, with a direct link between its levels and pharmacological activity.

In current practice, dosing and dose interval of plasma therapy is guided by clinical symptoms, platelet count and lactate dehydrogenase levels. It is widely known that the systemic clearance of a drug determines its exposure at steady-state. It also determines the elimination half-life in plasma and consequently informs the dosing rationale for therapies which show immediate pharmacodynamic effects [14].

**Objectives**

We hypothesise that the individualisation of treatment, both dose and dosing interval, can be guided by further evaluation of interindividual differences in the clearance of ADAMTS-13. Such an approach will allow for a more effective clinical management of the individual patient, which may not be predicted by empirically monitoring ADAMTS-13 levels. We therefore investigated the pharmacokinetics and interindividual variability in the elimination of ADAMTS-13 replacement using PI in six patients with confirmed congenital TTP.
Methods:

Patients
Six congenital TTP cases on a regular PI regime were selected from a single institution. Congenital TTP was confirmed by the presence of microangiopathic haemolytic anaemia and thrombocytopenia at presentation, ADAMTS-13 activity of less than 10%, no detectable anti-ADAMTS-13 IgG antibodies performed in both the acute phase and in remission after treatment and confirmation by mutational analysis of the ADAMTS-13 gene [15]. Patients with previous history of end organ damage, such as stroke, or those who had a normal platelet count, but experiencing severe headaches; were treated with PI to improve their symptomatology. All patients were clinically well at the time of PK measurement, with no suggestion of active thrombotic microangiopathy as reflected by their full blood counts and LDH. All consented to the study.

All patients received Octaplas LG which contains mean levels of ADAMTS-13 of 104% and mean VWF:RCo to VWF:Ag ratio of 0.55, which was consistent with a reduction in the number of HMW bands seen in the VWF multimer gels, typical of this product [16]. Each patient was on an established regime of dose and frequency of treatment was dictated by normalised platelet counts and LDH, ranging from 15.3ml/kg weekly to 7.2ml/kg every 3 weeks. Pharmacokinetic analysis was performed after a typical treatment dose and regimen for each patient.

Plasma samples
Citrated plasma samples were taken at baseline, pre-infusion of plasma, 1 hour and between 2-3 hours post infusion. Subsequent samples were taken daily for 7 days, with additional samples at day 10, 14 and 21 according to frequency of infusion.

VWF antigen/activity and Factor VIII: VWF antigen/ activity and Factor VIII were performed via Sysmex analysis, using Siemens kit (INNOVANCE®, VWF Ac. Siemens Healthcare Diagnostics, Marburg, Germany)[17].

ADAMTS-13 activity: ADAMTS-13 activity was performed using an in house FRETS- ADAMTS-13 activity assay (Fluorescence Resonance Energy Transfer) [18,19], with normal range being 64-132IU/dl.

ADAMTS-13 antigen: A novel ELISA was developed to determine the concentration of ADAMTS-13 antigen[20]. A monoclonal antibody directed against the metalloprotease domain (3H9, kindly provided by K Vanhoorelbeke) was used to capture the antigen, and two
biotinylated monoclonal antibodies directed against the 17G2 and the 19H4 domains used for detection. Dilutions of pooled normal plasma were used as the standard[20].

**Pharmacokinetic data analysis**

A population pharmacokinetic model was used to characterize the pharmacokinetics of ADAMTS-13 following intravenous infusions. Model building criteria included: (i) successful minimisation, (ii) standard error of estimates, (ii) termination of the covariance step, (iv) correlation between model parameters and (v) acceptable gradients at the last iteration. Fixed and random effects were introduced into the model in a stepwise manner. Inter-individual variability in pharmacokinetic parameters was assumed to be log-normally distributed. Goodness of fit was assessed by graphical methods, including population and individual predicted vs. observed concentrations, conditional weighted residual vs. observed concentrations and time. Comparison of hierarchical models was based on the likelihood ratio test[21]. Secondary pharmacokinetic parameters (AUC, Cmax and half-life) were then derived using non-compartmental principles. Modelling was performed using NONMEM version 7.3 and PsN 4.6.0. Statistical and graphical summaries were implemented in R version 3.3.2.

**Dose individualisation:** Using the individual pharmacokinetic parameters obtained for each patient, simulations were performed to explore the feasibility of optimising dose and dosing regimens. A hypothetical target ADAMTS-13 activity of 10IU/dl and 50IU/dl respectively were set as references for the purpose of this analysis. Total plasma volume and dosing intervals were then estimated from the simulated scenarios.

**Results**

Six cases of congenital TTP were studied, 5 of which presented de novo in pregnancy and one in childhood. The indications for regular plasma therapy were previous strokes (4 cases) and severe persistent headaches/migraine and lethargy (2 cases), which were significantly improved following initiation of PI. Each of these 6 patients had ADAMTS-13 activity of less than 5 IU/dL at diagnosis and mutational analysis of ADAMTS-13 gene to confirm the diagnosis of congenital TTP.

The clinical details, baseline ADAMTS-13 results, genetic mutations, indication for PI and individual regimens are shown in Table 1. The median plasma infused was 10mls/kg, whereas plasma infusion intervals range from 1-3 weeks. ADAMTS-13 activity was measured for each individual over time to allow pharmacokinetic modelling (Figure 1). The median IR was 0.023
IU/ml/IU/Kg. To exclude the impact of VWF contained in PI on ADAMTS-13 levels and clearance, there was no significant increase in VWF activity from baseline, measured throughout the timepoints (Figure 2).

**Pharmacokinetics of ADAMTS-13**

ADAMTS-13 activity was best described by a two-compartment pharmacokinetic model with linear elimination. Inter-individual variability was identified on clearance, central volume of distribution, intercompartmental clearance and the peripheral volume of distribution. The population clearance was found to be 25.41 ml/h (Table 2). All patients reached baseline ADAMTS-13 activity levels within 7-10 days of PI. ADAMTS-13 antigen showed a similar increase and subsequent decrease over the same period as ADAMTS-13 activity (supplementary data). The median Cmax and AUC were 24.05 IU/dl and 31.5IU*h/ml respectively (Table 3a).

Given the interindividual differences in clearance, the half-life of ADAMTS-13 in these patients ranged from 82.6 to 189.5 hours (3.4 – 7.9 days), with a median value of 130.3 hours (Table 3b).

**Dose individualisation**

The attained levels of ADAMTS-13 in these patients were below circulating levels seen in non-TTP patients in the general population (Figure 1). The optimal target ADAMTS-13 activity level is not known. We simulated an individualised dose appropriate for each patient based on a hypothetical target trough ADAMTS-13 activity of i) 10IU/dl (Figure 3) and ii) 50IU/dL (Figure 4). Simulations were performed for each patient to compare dose necessary to maintain this target trough given their current dosing interval, or optimal dosing interval for each patient based on their current dose.

For dose amount, or plasma volume, our simulations show that ADAMTS-13 amount of 59.2-502IU (mean 241.3) would be required to achieve a target ADAMTS-13 activity of 50IU/dL, considerably reduced at 11.8-100.4IU (mean 48.3) to target a trough ADAMTS-13 of 10IU/dL using plasma.

Similarly, our simulations show that plasma treatment every 1.5-3 days (mean 2.3) would be required to achieve target ADAMTS-13 activity of 50IU/dL but only every 4-10 days (mean 7.3) to target a trough ADAMTS-13 of 10IU/dL using plasma.
Conclusions
This is the largest formal study investigating the pharmacokinetics of ADAMTS-13 in patients receiving PI for congenital TTP. The structural and functional relationship of ADAMTS-13 with ultra-large von Willebrand factor (VWF) has been well described, with consequent cleavage of VWF[22]. However, there is a paucity of data regarding the proteolysis, degradation and/or clearance of ADAMTS-13.

We have investigated the impact of PI on ADAMTS-13 activity, VWF and Factor VIII in 6 females with congenital TTP. All but one was diagnosed after de novo episodes in pregnancy. Patients had a heterogeneous clinical picture; with therapy initiated for end organ damage, primarily stroke; or to prevent symptomatology, such as headaches/migraines, despite normal platelet and LDH levels.

Our data demonstrates an ADAMTS-13 elimination half-life of 82.6 to 189.5 hours (3.4 to 7.9 days) following plasma therapy for congenital TTP. In addition, our data shows that ADAMTS-13 clearance is not linked to higher VWF activity or antigen levels, as two patients with the highest VWF activity and antigen had low clearance and consequently long half-lives for ADAMTS-13 activity (144.6 and 149.4 hours). Ultimately, it is the individual clearance of ADAMTS-13 that should guide dose and dosing interval. Such half-life and clearance data should clarify individual treatment rationale.

All 6 patients demonstrate a remarkably similar trend of ADAMTS-13 antigen level in relation to ADAMTS-13 activity. This trend would be expected in congenital TTP, since there is no inhibitory activity interfering as there would be in acquired TTP, and provides a useful confirmation of ADAMTS-13 activity. Our data supports the close correlation of ADAMTS-13 activity and antigen as they peak post plasma infusion, and degrade at a relatively constant rate despite variations in the impact of mutations in congenital TTP.

Furlan et al published data regarding 2 brothers, both with a “constitutional deficiency of von Willebrand factor-cleaving protease and no inhibitor”[13]. Following daily plasma exchange for 4 and 3 days respectively, the protease, or ADAMTS-13, was analysed by VWF multimer assay, describing half-lives of 3.3 days and 2.1 days in each patient respectively. Four further patients had half-life estimation following 3-5 mls/kg of plasma, and similar results were identified, i.e. a mean half-life of 2.8 days[23]. Overall it was considered that such half-lives were uniquely long for a proteolytic enzyme, since these are usually rapidly inactivated. Subsequent work has suggested that duration of ADAMTS-13 effect is firstly due to resistance of its VWF substrate to cleavage due to circulation in a closed conformation[24,25] and secondly, the requirement for shear-induced unfolding of VWF for ADAMTS-13 to access the cleavage site [26]. It is also noted
that multimeric assays are sensitive to low ADAMTS-13 activity levels but will be less accurate in the mid-normal range with recognition of this being a cumbersome method requiring expertise[27].

ADAMTS-13 is recognised as a plasma reprolysin-like metalloproteinase, primarily synthesised by the liver[26,28]. Our estimated model parameters are in accordance with ADAMTS-13 as a plasma protein, i.e., its central volume of distribution at 3.6 L indicates that it is constrained to the plasma compartment. Clearance estimates (25.4 mL/h) seem to reflect the range of values observed for other plasma proteins, including coagulation factors and immunoglobulin[29–32].

We demonstrate a large interindividual variability in elimination half-life observed in the currently presented cohort (ranging between 82.6 and 189.5 hours, or 3.4 to 7.9 days). This is clearly higher than that observed by Furlan et al but difficult to extract meaning from direct comparison due to small patient numbers in both studies and different means of analysis.

Regulation of ADAMTS-13 in physiological conditions is poorly understood. Previous work has shown that VWF levels are not correlated to ADAMTS-13 activity in individuals with normal VWF levels and likely normal multimer distributions. In VWF deficiency however, such as type 3 von Willebrand disease, ADAMTS-13 levels may be up to 30% higher. In congenital TTP, it is more plausible that variability in ADAMTS-13 half-life is related to clearance mechanisms rather than plasma VWF concentrations. Clearance itself will reflect the ratio between elimination rate and ADAMTS-13 plasma concentration.

Our data shows that the population clearance of ADAMTS-13 is 25.4 mL/hour, resulting in a median half-life of 130 hours (or 5.4 days). Shorter half-lives are therefore a consequence of faster rate of elimination from plasma, which in turn may be caused by differences in body weight and basal metabolism.

Review of VWF levels in our cohort, whether activity or antigen, shows a less consistent pattern, matched by Factor VIII. The most direct effect of ADAMTS-13 is on proteolysis of high molecular weight VWF, which we did not directly measure. Furthermore, the plasma used in these cases does not have significant HMW VWF multimers. ADAMTS-13 should not unduly affect the measured antigen and activity, as reflected by our results.

There were minimal changes in von Willebrand factor activity, either absolute or relative to baseline (Figure 2), suggesting that it is HMW VWF turnover that may determine duration of ADAMTS-13 effect. This is consistent with Furlan's earlier data: both the purported half-life of ADAMTS-13 and enduring effect related to being a plasma-bound protein[13].

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A recent phase I study has examined the PK profile of BAX-930, a recombinant ADAMTS-13[33]. The study confirmed the safety and tolerability of the product during its first in-human use, with PK results suggesting comparable pharmacokinetic parameters to that seen following plasma infusions of the naturally occurring metalloprotein. Whilst a different method was used in the pharmacokinetic data analysis, our results are consistent with their findings for ADAMTS-13. By contrast, one should note that recombinant ADAMTS-13 has a clearance twice as high as that of naturally occurring ADAMTS-13. An immediate implication of such differences is that significantly higher doses of the recombinant ADAMTS-13 are required to attain the same levels observed at steady state with the natural moiety. Clearance values for the recombinant ADAMTS-13 ranged from 59.3ml/h (after 40U/kg dose) to 64.8ml/h (after 20U/kg dose) versus ADAMTS-13 systemic clearance of 16.5 to 37.7ml/hour observed in this study. Despite the requirement for higher doses, this may not represent a limitation, given that recombinant ADAMTS-13 can achieve higher ADAMTS-13 peak levels than PI, whose dose and dosing regimen is primarily restricted by the maximum allowable infusion volumes.

The observed ADAMTS-13 half-life in our patient group was higher than expected based on previous PI data, and higher than that determined with recombinant ADAMTS-13.

Further work is necessary to define the optimal target ADAMTS-13 during the clinical management of TTP patients. We have used simulations to explore the feasibility of individualised protocols for each patient based on either dose or frequency of PI to target a plasma level of ADAMTS-13 of 10IU/dL or 50 IU/dL respectively. Targeting a hypothetical optimal ADAMTS-13 of >10IU/dL with either dose or interval (Figure 3) to prevent symptoms potentially associated with TTP may be sufficient as well as clinically practical.

Achieving a level of >50 IU/dL represents a ‘normal’ level in the non-TTP population, but such a level was not witnessed in our cohort receiving PI, even at peak levels. The simulation models suggest that either scheme is not possible in clinical terms to achieve a level of 50IU/dL: either the plasma volume required is too high or the frequency of PI would be too difficult to safely achieve the dose needed (Figure 4).

Future attempts to individualise and optimise therapy with either naturally occurring ADAMTS-13 in allogeneic plasma and/or recombinant ADAMTS-13, will need to consider whether clearance is indeed the best surrogate for the duration of effect of ADAMTS-13. If our therapeutic aim is to ensure continued presence of ADAMTS-13, we firstly need to investigate whether we should treat more frequently than every 3-4 weeks, which has been derived from the historic estimate of half-life of ADAMTS-13 of 2-3 days. A dose interval of less than 5 half-lives of ADAMTS-13 may be more clinically appropriate. Secondly, given the varied values in
this current cohort of between 3.4 and 7.9 days, we should consider undertaking half-life analysis in patients, to maintain a higher ADAMTS-13 level in between infusions, which would require more frequent dosing, eg every 1-2 weeks as in some of these cases. Limitations of our study include the small number of patients studied, performing PK analysis after one PI per patient- albeit in steady state- and rarity of the disease. It should also be noted that PK results are heterogeneous, with clear individual variation. With a larger study number, future work could include multivariate analysis of the various factors affecting the individual PK such as age, weight, platelet count, VWF level, LDH and genetic mutations. The FRETS assay results are less sensitive at the lower end of range, which should be taken into account. There is also the possibility of ADAMTS-13-binding antibodies enhancing clearance, but not detected in the anti-ADAMTS-13 IgG ELISA.

In optimising the treatment of congenital TTP, further research is required to explore the individual determinants of catabolism and clearance. Moreover, one needs to identify metrics for the long-term protective effects of ADAMTS-13. Without allowing overt disease relapse, judging symptomatology of TTP can be subtle. Objective measures should indicate whether treatment is warranted and how we calculate rationale for dose and frequency of prophylaxis requires further investigation. This is particularly pertinent and achievable in the upcoming era of recombinant ADAMTS-13 as an alternative to plasma infusion.

Addendum
A. Taylor performed research, analysed data and wrote the paper.

C. Vendramin performed research, analysed data and reviewed the paper.

S. Oosterholt analysed data and reviewed the paper.

O. Della Pasqua analysed data and reviewed the paper.

M. Scully designed the research, wrote and reviewed the paper.

Disclosure of Conflict of Interest
The authors state that they have no conflict of interest.
References


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### Tables, figures and legends

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<thead>
<tr>
<th>Patient</th>
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<th>4</th>
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<td>41</td>
<td>31</td>
<td>35</td>
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<td>Age at diagnosis (years)</td>
<td>21</td>
<td>39</td>
<td>28</td>
<td>33</td>
<td>21</td>
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<td>Migraines, MAHA in pregnancy, intrauterine fetal death</td>
<td>Strokes, MAHA in pregnancy</td>
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<td>Pre-PI ADAMTS13 antigen (%)</td>
<td>2.9</td>
<td>4</td>
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**Table 1:** Summary of patient characteristics.
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<td>Current treatment</td>
<td>800ml plasma weekly (15.3ml/kg)</td>
<td>800ml plasma every 3 weeks (8.6 ml/kg)</td>
<td>800ml plasma weekly (10 ml/kg)</td>
<td>600ml plasma every 3 weeks (11.8ml/kg).</td>
<td>600ml plasma every 3 weeks (7.2ml/kg)</td>
<td>600ml plasma every 2 weeks (8.3ml/kg)</td>
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<td>Plasma sampling frequency (post PI)</td>
<td>Baseline. 1, 3, and 5 h post. Daily for next week.</td>
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<td>Baseline, 15 and 30 min post. Day 1, 2, 4, 7, 8, 9, 10, 11, 12, 14.</td>
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(key: 'Het' = heterozygous mutation; 'Hom' = homozygous mutation

MAHA- microangiopathic haemolytic anaemia

MCA- middle cerebral artery)
Table 2: Estimated model parameter values for a two-compartment model with linear elimination (ADAMTS13 activity)

<table>
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<tr>
<td>Clearance (L/h)</td>
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<td>IIV Central volume of distribution (CV%)</td>
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<td>IIV Intercompartmental clearance (CV%)</td>
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Table 3a: Median, 5th and 95th percentiles of secondary pharmacokinetic parameters (ADAMTS13 activity)

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<th>Dose (IU/kg)</th>
<th>AUC (IU*h/mL)</th>
<th>Cmax (IU/dL)</th>
<th>Half-life (h)</th>
<th>MRT (h)</th>
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<td>10.5</td>
<td>31.5</td>
<td>24.05</td>
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<td>(21.0-40.7)</td>
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Table 3b: Individual secondary pharmacokinetic parameters

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<td>20.3</td>
<td>82.6</td>
<td>118.6</td>
</tr>
</tbody>
</table>

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Figure 1: Visual predictive plot of ADAMTS13 activity over time.

Solid line represents the median predicted individual activity, the shaded area represents the 90% confidence interval. Observed values are shown as dots.
Figure 2: Change in von Willebrand factor activity over time.

Activity relative to the baseline values are represented in the left panel while the right panel shows the absolute change in activity from baseline.
Figures 3 and 4: Simulated dose and frequency requirements of plasma infusion individualised for each patient based on target ADAMTS13 trough of >10 IU/dL and >50 IU/dL respectively.

ADAMTS13 dosing is determined by Octaplas content, and therefore volume of plasma. Octaplas ADAMTS13 mean content is 1.13 IU/ml, +/-0.17. In practice, since ADAMTS13 dosing is limited by the volume of plasma necessary to deliver ADAMTS13, frequency of PI is adapted accordingly.

Figure 3 shows each patient's simulation based on a target trough ADAMTS13 level of >10 IU/dL. Simulations were firstly based on dose amount (at fixed frequency), to continue at current dose frequency of weekly up to 3-weekly. Dosing ranged from 11.8 IU/kg weekly to 100.4 IU/kg every 2 weeks accordingly. Simulations were secondly based on dose frequency (at fixed dose), to continue at current dose amount. Treatment would be required every 4 to 10 days for our cohort with dose amount kept same as current.

Figure 4 shows each patient's simulation based on a target trough ADAMTS13 level of >50 IU/dL. Simulations were firstly based on dose amount (at fixed frequency) to continue at current dose frequency of weekly up to 3-weekly. Dosing ranged from 59.2 IU/kg weekly to 502 IU/kg every 2 weeks accordingly. Simulations were secondly based on dosing frequency (at fixed dose). Treatment would be required every 1.5 to 3 days for our cohort with dose amount kept same as current.
Figure 3: Individualised simulations of maintaining target trough ADAMTS13 >10IU/dL with total dose amount (fixed frequency) or dosing interval (fixed dose amount)
Figure 4: Individualised simulations of maintaining target trough ADAMTS13 >50 IU/dL with total dose amount (fixed frequency) or dosing interval (fixed dose amount)