EUROPEAN UNION (EU) RISK MANAGEMENT PLAN (RMP)

For

ADZYNMA® (recombinant ADAMTS13 [rADAMTS13])

RMP Version number: 1.1

Date: 05-December-2024

[redacted]

[redacted]

EU Risk Management Plan (RMP) for ADZYNMA® (recombinant ADAMTS13 [rADAMTS13])

Administrative Information

RMP version to be assessed as part of this application:

RMP Version number: 1.1

Data lock point for this RMP: 29-September-2023

Date of final sign off: 05-December-2024

Rationale for submitting an updated RMP: The RMP is being updated to reflect the completion of study 281102.

Summary of significant changes in this RMP:

RMP Module:	Significant Changes:
Part I Product Overview	Not applicable
Part II Safety Specification	
• **Module SI Epidemiology of the indication(s) and target population(s)**	Not applicable
• **Module SII Non-clinical part of the safety specification**	Not applicable
• **Module SIII Clinical trial exposure**	Not applicable
• **Module SIV Populations not studied in clinical trials**	Not applicable
• **Module SV Post-authorisation experience**	Not applicable
• **Module SVI Additional EU requirements for the safety specification**	Not applicable
• **Module SVII Identified and potential risks**	Not applicable
• **Module SVIII Summary of the safety concerns**	Not applicable
Part III Pharmacovigilance plan	Not applicable.
Part IV Plans for post-authorisation efficacy studies	Study 281102 is completed and hence removed from the table Part VI.1.
Part V Risk minimisation measures	Not applicable
Part VI Summary of the risk management plan	Study 281102 is completed and hence removed from the II.C.1.
Part VII Annexes	Annex 5: Study 281102 is moved from ongoing to completed studies.

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP:

Version number: 1.0

Approved with procedure: EMEA/H/C/006198

Date of approval (opinion date): 01-August-2024

[redacted]

QPPV name: Jean-Marie Heim, MD

Please note that e-signature may also be performed by [redacted], Deputy European Union Qualified Person Responsible For Pharmacovigilance (EUQPPV), [redacted], Deputy EUQPPV or [redacted], Deputy EUQPPV, on behalf of the EU QPPV (i.e., 'per procurationem').

QPPV signature: [redacted] RMP signatures are kept on file.

[redacted]

Table of contents

PART I: PRODUCT(S) OVERVIEW 8

PART II: SAFETY SPECIFICATION 10

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S) 10

PART II: MODULE SII – NON-CLINICAL PART OF THE SAFETY SPECIFICATION 15

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE 19

PART II: MODULE SIV – POPULATIONS NOT STUDIED IN CLINICAL TRIALS 27

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme 27

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes 28

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes 29

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE 30

PART II: MODULE SVI – ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION 31

PART II: MODULE SVII – IDENTIFIED AND POTENTIAL RISKS 32

SVII.1. Identification of Safety Concerns in the Initial RMP Submission 32

SVII.2. New Safety Concerns and Reclassification With a Submission of an Updated RMP 32

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information 33

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS 37

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES) 38

III.1. Routine Pharmacovigilance Activities 38

III.2. Additional Pharmacovigilance Activities 38

III.3. Summary Table of Additional Pharmacovigilance Activities 39

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES 40

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES) 41

V.1. Routine Risk Minimisation Measures 41

V.2. Additional Risk Minimisation Measures 42

V.3. Summary of risk minimisation measures 43

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN 44

I. The Medicine and What It Is Used For 44

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks 44

II.A List of Important Risks and Missing Information 44

II.B Summary of Important Risks 45

II.C. Post-authorisation Development Plan 46

II.C.1. Studies Which Are Conditions of the Marketing Authorisation 46

II.C.2. Other Studies in Post-authorisation Development Plan 46

PART VII: ANNEXES 47

[redacted]

[redacted]

ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS 51

[redacted]

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE) 55

[redacted]

[redacted]

List of Abbreviations

Abbreviation	Definition/Description
ADA	Anti-drug Antibody
aRMM	Additional Risk Minimisation measure
ATC code	Anatomical Therapeutic Chemical classification system
BW	Body Weight
CHO	Chinese Hamster Ovary
CNS	Central Nervous System
cTTP	Congenital Thrombotic Thrombocytopenia Purpura
DLP	Data Lock Point
eCTD	electronic Common Technical Document
EEA	European Economic Area
ECG	Electrocardiogram
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EU QPPV	European Union Qualified Person Responsible For Pharmacovigilance
FVIII	Factor VIII
FFP	Fresh Frozen Plasma
hTTP	Hereditary Thrombotic Thrombocytopenic Purpura
HCP	Healthcare Professional
ICH	International Conference on Harmonisation
IP	Investigational Product
iTTP	Acquired Thrombotic Thrombocytopenia Purpura
IU	International Unit
IV	Intravenous
INN	International Non-proprietary Names
MAH	Marketing Authorisation Holder
NOAEL	No-Observed-Adverse-Effect Level
NZW	New Zealand White
PASS	Post-Authorisation Safety Study
PI	Product Information
PL	Package Leaflet
PT	Preferred Term
PV	Pharmacovigilance
QPPV	Qualified Person for Pharmacovigilance

[redacted]

Abbreviation	Definition/Description
RMP	Risk Management Plan
SAE	Serious Adverse Event
SCD	Sickle Cell Disease
SD	Sprague Dawley
SIRS	Systemic Inflammatory Response Syndrome
SmPC	Summary of Product Characteristics
TEAE	Treatment Emergent Adverse Event
TTP	Thrombotic Thrombocytopenic Purpura
ULN	Upper Limit of Normal
US	United States
VWF	Von Willebrand factor

[redacted]

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Recombinant ADAMTS13 (rADAMTS13) (apadamtase alfa/cinaxadamtase alfa)
Pharmacotherapeutic group(s) (ATC Code)	B01AD13
Marketing Authorisation Applicant	Takeda Manufacturing Austria AG, Industriestrasse 67 Donaustadt, 1221 Vienna, Austria
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	ADZYNMA
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: ADZYNMA is a human recombinant ADAMTS13 (A disintegrin and metalloproteinase with thrombospondin motifs 13).
	Summary of mode of action: rADAMTS13 is a recombinant form of the endogenous ADAMTS13. ADAMTS13 is a plasma zinc metalloprotease that regulates the activity of von Willebrand factor (VWF) by cleaving large and ultra-large VWF multimers to smaller units and thereby reducing the platelet binding properties of VWF and its propensity to form microthrombi. rADAMTS13 is expected to reduce or eliminate the spontaneous formation of VWF-platelet microthrombi that leads to platelet consumption and thrombocytopenia in patients with congenital thrombotic thrombocytopenic purpura (cTTP).
	Important information about its composition: Recombinant ADAMTS13 is a purified recombinant A disintegrin and metalloproteinase with thrombospondin motifs 13 (rADAMTS13). It is manufactured by recombinant deoxyribonucleic acid technology in the Chinese Hamster Ovary (CHO) cell line without the addition of any exogenous human- or animal-derived protein in the cell culture process, purification or final formulation. The rADAMTS13 consists of a heterogeneous mixture of 2 protein species: one protein species is representative of the native ADAMTS13 sequence (Apadamtase alfa), and the second protein species differs from the native sequence by a single amino acid exchange at position 23 with Glutamine (Q) in the native protein and Arginine (R) in the variant protein (Cinaxadamtase alfa). The common term rADAMTS13 is used throughout this document. rADAMTS13 is white lyophilized powder and solvent (clear, colourless) solution for injection. <u>Excipient with known effect</u> Each 500 International Units (IU) powder vial contains 3.7 mg

[redacted]

	sodium. Each 1,500 IU powder vial contains 3.7 mg sodium.
Hyperlink to the Product Information (PI)	Refer to eCTD Module 1.3.1 for proposed PI or latest approved PI.
Indication(s) in the EEA	Current: ADZYNMA is an enzyme replacement therapy (ERT) indicated for the treatment of ADAMTS13 deficiency in children and adult patients with cTTP. ADZYNMA can be used for all age groups.
	Proposed: Not applicable
Dosage in the EEA	Current: *Prophylactic enzyme replacement therapy* • 40 IU/kg of body weight once every other week. • The prophylaxis dosing frequency may be adjusted to 40 IU/kg once weekly based on clinical response. *On-demand enzyme replacement therapy for acute* thrombotic thrombocytopenic purpura (TTP) *episodes* In case of acute TTP episode, the recommended dose of ADZYNMA to treat acute TTP episodes is as follows: • 40 IU/kg of body weight on day 1. • 20 IU/kg of body weight on day 2. • 15 IU/kg of body weight starting day 3 once daily until two days after the acute event is resolved.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Powder and solvent for solution for injection. White lyophilised powder. The solvent is a clear and colourless solution. The reconstituted solution has a pH of 6.7-7.3 and an osmolality of no lower than 240 mOsmoL/kg. <u>ADZYNMA 500 IU powder and solvent for solution for injection</u> Each vial of powder contains nominally 500 IU rADAMTS13 activity as measured in terms of its potency. After reconstitution with the 5 mL solvent provided, the solution has a potency of approximately 100 IU/mL. <u>ADZYNMA 1,500 IU powder and solvent for solution for injection</u> Each vial of powder contains nominally 1,500 IU rADAMTS13 activity as measured in terms of its potency. After reconstitution with the 5 mL solvent provided, the solution has a potency of approximately 300 IU/mL.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

[redacted]

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

<table>
<tr><th colspan="2">Congenital Thrombotic Thrombocytopenia Purpura (cTTP)</th></tr>
<tr><td>Incidence:</td><td>Data on the incidence of cTTP was not found in an internal systematic literature review (Takeda, unpublished). Since incidence describes the number of new cases and cTTP is a genetic disorder with delays in diagnosis and no population screening data for the denominator, prevalence is a more appropriate measure of disease activity in this population. Incidence of cTTP-associated events are described below. Characteristics of newly diagnosed are described in sections addressing natural history and comorbidities.

Acute cTTP episodes occurred in 49% of 87 enrolled patients over a 4-year period in the international Hereditary TTP Registry (hTTP Registry). These 43 patients experienced 131 acute episodes with 69% of the episodes occurring in patients receiving regular prophylaxis [redacted] The annual incidence rate of acute cTTP episodes was 0.35 per person-year, higher in females (0.50) than males (0.22), and considerably higher in patients enrolled before the age of 10 years (1.18) compared to all other age groups (range: 0.14-0.35). More than one-third of acute episodes (n=51) were documented in children and were often triggered by infections. The most common acute episodes included petechiae or other bleeding (44%), GI symptoms (30%), fever (23%), neurologic symptoms (22%) (including seizure, transient ischemic attack, stroke), jaundice (14%), dark urine (12%), and acute renal failure (7%) [redacted].</td></tr>
<tr><td>Prevalence:</td><td>The prevalence of cTTP is frequently cited as 0.5 to 2 cases per 1 million population; estimates from recent studies are predominantly in this range. Differences in the prevalence estimates are due, in part, to differences in study design and case-finding approach and population characteristics.

The Genome Aggregation Database was used to estimate the genetic prevalence of cTTP using 2 case definitions: a) 239 known pathogenic variants and; b) 239 known pathogenic variants plus an additional 6 novel/likely pathogenic variants [redacted]. Globally, the genetic prevalence was 0.43 per million for the 239 known variants; and 1.1 per 1 million for the 245 known and novel variants. Subpopulation prevalence estimates are in the table below.

Allele frequency database prevalence calculations [redacted]
<table>
<tr><th></th><th>239 known and 6 novel variants</th><th>239 known variants</th></tr>
<tr><td>Total</td><td>1.1</td><td>0.43</td></tr>
<tr><td>African</td><td>5.64</td><td>0.94</td></tr>
<tr><td>Latino/Mixed American</td><td>1.48</td><td>0.56</td></tr>
<tr><td>Ashkenazi Jewish</td><td>0.05</td><td>0</td></tr>
<tr><td>East Asian</td><td>1.68</td><td>0.78</td></tr>
<tr><td>Finnish</td><td>0.008</td><td>0</td></tr>
<tr><td>Non-Finnish European</td><td>1.14</td><td>0.59</td></tr>
<tr><td>South Asian</td><td>1.12</td><td>0.44</td></tr>
</table></td></tr>
</table>

[redacted]

Congenital Thrombotic Thrombocytopenia Purpura (cTTP)	
	<table><tr><td>Other</td><td>0.73</td><td>0.11</td></tr></table> Using a structured case-finding approach in central Norway resulted in an unusually high prevalence estimate of 16.7 per million[redacted]. When cases were added from all of Norway, the overall prevalence in Norway decreased to 3.1 per 1 million; however less rigorous case-finding techniques were employed. This high prevalence in central Norway suggests that a structured case-finding approach may be more effective than other approaches for identifying cTTP patients. The results also suggest that prevalence of cTTP will vary depending on the isolation of a population.
Demographics of the target population in the indication:	The female: male ratio is often cited as 1:1, and this agrees with data from the international hTTP Registry (n=123 cases)[redacted] and the Norwegian cohort (n=18) [redacted]. The UK TTP Registry reported 70% of enrolled patients were female overall (n=73), but this varied by period of presentation [redacted]. The higher percentage of females is influenced by the 31 (42%) women with disease onset during pregnancy, and the 12 (17%) adult-onset patients, who were 75% female. Among patients with onset in the neonatal or childhood period, only 32% were female. Self-reported ethnicity in the international hTTP Registry was 53% Caucasian, 2.4% Hispanic, 42% Asian, and 2.4% other [redacted]. In the UK TTP Registry, patients with early onset (neonatal/childhood) were the most diverse: 39% white; 36% South Asian; 14% Arab; and 11% African compared to patients with later onset, who were predominantly white (e.g., pregnancy onset, 87% white; adult onset, 92% white) [redacted]. Age at disease presentation and diagnosis ranges from immediately after birth to late adulthood. In the UK TTP Registry, symptom onset was most frequent in the neonatal/childhood period (38%) and during pregnancy (42%). Additional details about age at disease onset and diagnosis are included in the Natural History section below.
Risk factors for the disease:	cTTP is an autosomal-recessive disorders; therefore, risk factors are inherent. More than 200 cTTP-related ADAMTS13 mutations have been identified, and most are confined to single families [redacted]. To calculate genetic prevalence, Zhao[redacted] conducted a systematic review and identified 245 pathogenic variants for cTTP: 239 known pathogenic and 6 novel/likely pathogenic variants. Two mutations are prominent in populations of European ancestry: p.R1060W, is broadly distributed in Europe; and the insertion c.4143_4144dupA, which clusters around the Baltic Sea, in central Europe, and in Scandinavia [redacted]. Mutations are more commonly found in families with documented parental consanguinity. The international hTTP Registry has enrolled 123 cTTP patients (from 117 families)[redacted]. The UK TTP Registry has enrolled 73 cTTP patients (from 66 families)[redacted]. Among patients with neonatal/childhood onset, the parents of 43% were consanguineous compared with 6.7% of patients with onset in adulthood. Clinical phenotypes vary widely, including the age of disease presentation (ranging from birth to late adulthood); disease symptoms and severity; triggers of acute episodes (e.g., pregnancy); and long-term outcomes.
The main existing treatment options:	Treatments goals are focused on replenishing ADAMTS13, maintaining a normal platelet count, and managing symptoms. This is accomplished through periodic on-demand or prophylactic plasma-based therapies (i.e., fresh frozen plasma [FFP], solvent/detergent-treated plasma, factor VIII [FVIII]). Plasma exchange may be required for serious manifestations. Prophylactic plasma infusions are administered approximately every 1 to

[redacted]

Congenital Thrombotic Thrombocytopenia Purpura (cTTP)

3 weeks, dosed as 10-20 mL/kg body weight (BW); however, the optimum ADAMTS13 level to prevent long-term end-organ damage is unknown [redacted]. Plasma infusion therapy is effective but has disadvantages, such as large infusion volume, repeated vascular access, potential risk of pathogen transmission and transfusion reactions, and patient burden.

Plasma-derived concentrates containing factor VIII have also been used in cTTP: antihemophilic factor (Koate-DVI) and intermediate purity factor VIII (BPL 8Y) [redacted]. These products offset some of the risks, but may require more frequent infusions [redacted]. Treatment guidelines from the International Society on Thrombosis and Haemostasis recommend against using FVIII concentrate products in cTTP patients who are in remission or pregnant, based on concerns about the variability of ADAMTS13 concentrations across products creating the potential for insufficient dosing; absence of reliable data; and lack of understanding of the mechanism of action [redacted]. For patients in remission, the panel recommends plasma infusion or a watch and wait strategy, and during pregnancy, prophylactic treatment instead of no prophylactic treatment or FVIII products.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

cTTP is a serious disorder characterized by episodic microangiopathic haemolytic anaemia, thrombocytopenia that can result in organ damage and premature death. Untreated cTTP can be immediately or progressively fatal. Improved disease recognition and prompt treatment with plasma infusion and/or exchange therapy has reduced the mortality rate of TTP from 85–95% to 10–20% over the past 4 decades [redacted]. Initial symptoms of cTTP may present immediately at birth, or later in life. Some patients remain asymptomatic for decades. Major morbidities and death at a young age are common.

Age at presentation and diagnosis from 3 sources are provided in the table below. Data from the UK TTP Registry demonstrate 2 peaks in age at presentation: neonatal/childhood (38%) and during pregnancy (42%).

	n	Median age (range)*	
		Disease onset	Diagnosis
hTTP Registry [redacted]	123	4.5 (0-69.8)	16.7 (0-69.8)
UK TTP Registry [redacted]	73		
Children	28	10m (<1m-12y)	3.5 (<1-12)
Pregnancy	31	26.5 (16-42)	29 (16-43)
Late onset	12	36 (16-67)	56 (27-71)
Family history	2	3.5 (0m-7y)	26.5 (1-50)
Norwegian cohort [redacted]	18		
Adults	15	--	34 (18-70)
Children	3	--	2 (1-4)

*Expressed in years unless otherwise noted; y=year, m=month
Compiled from van Dorland [redacted]; Alwin [redacted], and von Krogh [redacted].

Delays in diagnosis are most pronounced in late onset cTTP. The international hTTP Registry reported a median of 13.4 years (range: 0-70) between disease onset and diagnosis [redacted]. In the UK TTP Registry, 49% were not diagnosed initially, and the median period between first symptoms and correct diagnosis was 47 months (range: 2-516) [redacted]. Prior to the diagnosis of cTTP, these patients were incorrectly diagnosed with chronic immune thrombocytopenic purpura, immune-mediated TTP, and Evans syndrome and

[redacted]

<table>
<tr><th colspan="2">Congenital Thrombotic Thrombocytopenia Purpura (cTTP)</th></tr>
<tr><td></td><td>experienced the following medically significant complications:
Stroke/TIA (n=18, 25%)
Miscarriage/stillbirth (n=8, 11%)
3rd trimester pregnancy complications (n=4, 5.6%) (i.e., antepartum haemorrhage, foetal distress, placental abruption, and preeclampsia)
Visual defects (n=3, 4.2%)
Facial palsy (n=2, 2.8%)
Other n=1, 1.4%: pulmonary haemorrhage, retinal vein thrombosis, seizures
Acute episodes (as described in the incidence section above) may occur spontaneously or after a triggering event. The hTTP Registry reported the following triggers: infection (76%); alcohol consumption (5.8%); and pregnancy (6.9%) [redacted].

Sub-acute symptoms of cTTP include headaches, irritation, difficulties with concentration, abdominal discomfort, and subfebrile temperatures, and these symptoms typically resolve after plasma infusion. The degree to which this type of smoldering disease impacts long term outcomes, such as organ damage, is unclear.

Management of cTTP is accomplished through on-demand or prophylactic plasma infusions. In the UK TPP registry, prophylactic treatment was initiated in 23% due to thrombocytopenia; 66% due to symptoms such as lethargy, headaches, and abdominal pain, despite a normal platelet count; and 11% as primary prophylaxis, predominately siblings of patients with cTTP [redacted]. Following therapy, symptoms resolved for 80-100% of these patients.

Borogovac [redacted] examined published reports of mortality and survival in 226 patients with cTTP from 26 countries from 2001 through 2020. Severe jaundice was present at birth in 83 patients. However, only 3 infants were effectively treated. Nine patients died during infancy. Of the 217 patients who survived infancy, 73 (34%) had major morbidities including stroke, kidney injury, or cardiac injury that occurred at a median age of 21 years. Stroke occurred in 62 (29%) patients, 13 of which were children aged 10 years or younger. Of the 54 patients who survived their initial major cTTP-related event, 37 (69%) had sustained or subsequent major morbidities.

Thirty-nine patients were observed after 40 years of age, and 20 (51%) had experienced a major morbidity. Prophylaxis was initiated in 45 patients with a major morbidity, and of these, 11 had a recurrence after beginning prophylaxis. Compared with an age- and sex-matched United States (US) population, probability of survival was lower at all ages beginning at birth. Thirty-two (14%) of the 226 patients died. Over half (n=18, 56%) of the 32 deaths occurred before the age of 20 years. Death occurred in 4 distinct periods: neonatal, childhood, during pregnancy, and adulthood. Four women died during pregnancy (age 20-26 years) [redacted].</td></tr>
<tr><td>Important co-morbidities:</td><td>The conditions in the table below were reported as comorbidities present at the time of enrolment in the international hTTP Registry. However, delays between disease onset and diagnosis of cTTP may suggest that the some of these comorbidities are manifestations of cTTP.

Conditions reported at enrolment in the hTTP Registry, n=83*
<table>
<tr><th></th><th>n (%)</th></tr>
<tr><td>Arterial thromboembolic diseases</td><td>33 (28%)</td></tr>
<tr><td>Myocardial infarction</td><td>5 (4.2%)</td></tr>
</table></td></tr>
</table>

[redacted]

Congenital Thrombotic Thrombocytopenia Purpura (cTTP)

Transient ischemic attack	12 (10%)
Stroke	25 (21%)
Other	6 (5.0%)
Other neurological disorders	27 (22%)
Epileptic seizure	6 (5.0%)
Headache	5 (4.2%)
Various other	20 (17%)
Renal insufficiency	30 (25%)
Haemodialysis	12 (10%)
Kidney transplant	3 (2.5%)
Jaundice (haemolysis or liver disease)	59 (49%)
Hyperbilirubinemia in neonatal period	30 (25%)
Transfusion-transmitted viral infection	13 (11%)
HBV	3 (2.5%)
HCV	10 (8.3%)
HIV	1 (0.8%)

*Adapted from van Dorland[redacted]

In the absence of cTTP, limited evidence suggests that decreased ADAMTS13 activity is associated with comorbidities seen in cTTP patients. In the Rotterdam Study, a large population-based cohort study involving nearly 6000 individuals aged ≥ 55 years, low ADAMTS-13 activity was associated with an increased risk of coronary heart disease and ischemic stroke [redacted]. High VWF levels and low ADAMTS13 activity were associated with an increased risk of all-cause or cardiovascular mortality. This risk increased when both high VWF and low ADAMTS13 levels.

ADAMTS13 activity was evaluated in 178 critically ill patients, who did not have cTTP, presenting with either septic syndromes or non-infectious systemic inflammatory response syndrome (SIRS) [redacted]. Lower levels of ADAMTS13 were seen in patients with septic syndromes compared with those with non-infectious SIRS. ADAMTS13 levels were lower in patients with severe sepsis/septic shock compared to less severe sepsis. Decreased ADAMTS13 levels were associated with an increased risk of death in the intensive care unit in the study population overall, and in patients with septic syndromes.

[redacted]

Part II: Module SII – Non-clinical Part of the Safety Specification

Key safety findings from non-clinical studies and relevance to human usage:

Key Safety Findings	Relevance to human usage
Toxicity: **Single-dose toxicity** No separate single dose (acute) toxicity study was conducted with rADAMTS13 per ICH guideline M3(R2). No apparent test article-related changes were observed throughout the escalating-dose phase following administration of rADAMTS13 at 200 U/kg BW on Day 1 or 1,790 U/kg BW on Day 15 in cynomolgus monkeys. **Repeat-dose toxicity** In a 5-day repeat-dose toxicity study with a 2-week recovery in Sprague Dawley (SD) rats following once daily intravenous (IV) administration at 80, 200, or 400 U/kg BW, the no-observed-adverse-effect level (NOAEL) was 400 U/kg BW, and on Day 5 corresponded to a C_{max} of 6.04 U/mL for males and 4.30 U/mL for females and an AUC_{24} of 83.1 h*U/mL for males and 63.4 h*U/mL for females for ADAMTS13 activity. There were no test article-related adverse effects. In a 4-week repeat-dose toxicity study with a 2-week recovery in SD rats following IV administration every third day of 80, 400, or 800 U/kg BW rADAMTS13, the NOAEL was 800 U/kg BW, and on Day 28, corresponded to a C_{max} of 15.6 U/mL for males and 13.1 U/mL for females and an AUC_{72} of 313 h*U/mL for males and 176 h*U/mL for females for ADAMTS13 activity. Administration of rADAMTS13 was well tolerated. In a 30-day repeat-dose toxicity study with a 2-week recovery in SD rats following once daily IV administration at 800 or 1,820 IU/kg BW, rADAMTS13 was well tolerated with a NOAEL of 1,820 IU/kg BW/day, with Day 30 sex-combined C_{max} of 109 IU/mL and AUC_{24} of 1,150 h*IU/mL for ADAMTS13 activity. In a 26-week repeat-dose toxicity study with a 4-week recovery in SD rats following IV administration every third day of 80, 200, or 400 U/kg BW, recombinant ADAMTS13 (rADAMTS13) had no evidence of toxicity. The NOAEL was 400 U/kg BW, and on Day 181, corresponded to a C_{max} of 10.0 U/mL for males and 9.12 U/mL for females and an AUC_{72} of 268 h*U/mL for males and 177 h*U/mL for females for rADAMTS13 activity. In a 2-week repeat-dose toxicity study in New Zealand White (NZW) rabbits following IV administration every third day of rADAMTS13 at 80,	IV administration of rADAMTS13 in SD rats and cynomolgus monkeys was well tolerated up to 26-weeks in rats and 1-month in monkeys. The NOAEL was the highest dose tested in all pivotal studies. Assessment of repeat-dose toxicity in animal models supports the conclusion that rADAMTS13 is safe for human use.

Key Safety Findings	Relevance to human usage
400, or 800 U/kg BW, rabbits were determined to be an unsuitable species for further nonclinical evaluation (no evidence of VWF cleavage was observed, high incidence of neutralizing antibodies, and increased susceptibility to TTP). In a 4-week repeat-dose toxicity study in cynomolgus monkeys following once weekly IV administration of 800 U/kg BW, rADAMTS13 was well tolerated. In a pivotal 4-week repeat-dose toxicity study with 2-week recovery in cynomolgus monkeys following once weekly IV administration of 80, 200, or 400 U/kg BW rADAMTS13, the NOAEL was 400 U/kg BW, and on Day 29, corresponded to a sex-combined C_{max} of 5.35 U/mL and AUC_{72} of 19.6 h*U/mL for ADAMTS13 activity. Apadamtase alfa/cinaxadamtase alfa was well tolerated and did not cause any adverse clinical symptoms or findings that could be directly attributed to the test article.	
Reproductive and developmental toxicity In a placental transfer feasibility study in SD rats, single IV administration of rADAMTS13 at 3,200 U/kg BW on Gestation Day (GD) 21 exposure to foetus was minimal and not biologically relevant. There were no test-article related clinical observations or necropsy findings. In a fertility and early embryo-foetal development study in SD rats, IV administration every third day from 2 weeks before mating to GD 16 of rADAMTS13 at 80, 200, or 400 U/kg BW, the maternal and foetal NOAEL was 400 U/kg BW and on Day 31/34, corresponded to a C_{max} of 4.41 U/mL and an AUC_{54} of 97.6 h*U/mL for rADAMTS13 activity. rADAMTS13 was not associated with any adverse maternal findings or treatment-related effects on fertility, pregnancy performance, or foetal development. In a pre- and post-natal development study in SD rats, IV administration every third day from GD 6 to weaning (~Day 21) of 80, 200, or 400 U/kg BW, the maternal NOAEL was 400 U/kg BW. F0 animals had ADAMTS13 activities in plasma samples demonstrating exposure to rADAMTS13 at all dose levels and no anti-drug antibodies (ADAs) were detected. In the F1 generation, there was no effect on the physical or functional development or reproductive function. In F2 pups, there were no effects related to treatment with rADAMTS13 in F0 dams (i.e., no effects on survival BW, or external development) and no necropsy findings.	In reproductive and developmental toxicity studies in rats, there were no test-article related effects on maternal or foetal safety, no effect on fertility, and no effect on maternal performance or reproductive function. It is unknown whether rADAMTS13 will be excreted in human milk.
Genotoxicity Studies on the genotoxic potential of rADAMTS13 have not been performed.	Genotoxicity studies are not applicable to the assessment of safety of biotechnology-derived pharmaceuticals such as rADAMTS13 per ICH S6 (R1), "Preclinical

[redacted]

Key Safety Findings	Relevance to human usage
	Safety Evaluation of Biotechnology-Derived Pharmaceuticals," and therefore were not conducted.
Carcinogenicity Studies on carcinogenic potential of rADAMTS13 have not been performed. A 26-week repeat-dose toxicity study conducted in rats did not result in observations indicative of an increased carcinogenic potential for rADAMTS13 as no preneoplastic or neoplastic findings were observed.	Carcinogenicity studies are not applicable to the assessment of safety of biotechnology-derived pharmaceuticals such as rADAMTS13 per ICH S6 (R1) and therefore were not conducted. Replacement therapy with rADAMTS13 uses a protein comparable to the endogenous protein and is therefore of reduced concern regarding carcinogenicity.
Safety pharmacology In a 4-week repeat-dose toxicity study in cynomolgus monkeys, rADAMTS13 was well tolerated and did not result in any adverse effect on the cardiovascular system (telemetric electrocardiogram [ECG] measurements) or respiratory system (respiratory rate and blood pressure) at doses up to 400 U/kg BW, which was the highest dose tested. In repeat-dose toxicity studies in SD rats and cynomolgus monkeys, administration of rADAMTS13 up to 800 U/kg BW or 400 U/kg BW, respectively, observation of general conditions (including behaviour, appearance, BW, evidence of ill-health, or clinical signs indicative of central nervous system [CNS] toxicity) and histopathology did not identify any CNS-related clinical signs or symptoms.	There were no findings to indicate a risk to the CNS, respiratory, or cardiovascular systems.
Local tolerance In local tolerance study in NZW rabbits, IV, intraarterial (5 mL within 2 min), or paravenous (0.5 mL, bolus) administration of rADAMTS13 at 311 U/mL rADAMTS13, no changes in behaviour and no macroscopic changes at the injection sites or treatment-related adverse effects on the local tissue (histopathological analysis) were observed. In a local tolerance study in NZW rabbits, SC administration of rADAMTS13 at 300 U/mL (1 mL), no test article-related findings (clinical signs, dermal observations, BWs, body weight gains, food consumption, macroscopic necropsy findings, and histopathologic examinations) were observed.	Apadamtase alfa/cinaxadamtase alfa was well tolerated locally when administered IV, intra-arterially, paravenously, or subcutaneously.
Immunogenicity Antidrug antibodies (ADAs) were analysed during repeat-dose toxicity studies in SD rats, NZW rabbits, and cynomolgus monkeys to assist in the interpretation of nonclinical findings. The incidence of ADA (binding and neutralizing) formation in the rat was low and did not affect exposure. In the monkey, a high incidence of ADA (binding and neutralizing) was observed in repeat-dose studies	It is widely recognized that immune responses against therapeutic proteins may pose problems for both patient safety and product efficacy. As such, the sponsor has monitored clinical immunogenicity risk as it relates to the potential to provoke an antibody response. There are no animal models available to predict the immunogenicity of rADAMTS13 in patients. Therefore, specific studies on immunogenicity

[redacted]

Key Safety Findings	Relevance to human usage
and was associated with thrombopenia along with increased bilirubin and lactate dehydrogenase and histopathological findings of haematopoiesis in liver, extramedullary haematopoiesis and hypertrophy of the media of small vessels in the myocardium, proteinaceous casts in the kidneys) in some animals. These findings resembled known clinical findings indicative of an ADAMTS13 deficiency. While these effects were not observed in rats, repeated administration of rADAMTS13 did result in TTP-like effects in a preliminary rabbit study. In the monkey and rabbit, effects were associated with a high frequency/titre of ADA (binding and neutralizing) and considered related to the development of cross-reactive neutralizing ADA against endogenous monkey ADAMTS13.These findings were considered secondary to neutralizing ADA formation in monkeys and rabbits to a human protein, and not predictive of humans.	were not conducted for rADAMTS13 in the nonclinical setting, however, ADA was analysed during nonclinical repeat-dose toxicity studies to support the interpretation of potential pharmacological and toxicological findings. Formation of ADA, binding and neutralizing, occurred in the toxicity studies. These findings were expected given the repeat-administration of a heterologous protein. These findings were considered secondary to neutralizing ADA formation and not predictive of ADA formation in humans.

[redacted]

Part II: Module SIII - Clinical trial exposure

Table SIII.1: Duration of exposure

Cumulative for all indications (person time):		
Duration of exposure	**Patients**	**Person time***
1 day	23	0.07
>1 to 7 days	18	0.25
>7 days to <6 months	81	11.78
6 to <12 months	1	0.51
12 to <24 months	0	0
24 to <36 months	0	0
36 to <48 months	0	0
>=48 months	0	0
Total person time	**123**	**12.60**

Studies include: 281101, 281102, TAK-755-3002, SHP655-201, SHP655-101 and SHP655-2001.
Duration of exposure is the number of days the subject received infusion(s).
*Person time in years is calculated as the number of exposure days divided by 336 (12 x 28 days, where 28 days = 1 month).
Indications: cTTP, iTTP, and SCD

Person time per indication:		
Congenital thrombotic thrombocytopenic purpura (cTTP)		
Duration of exposure	**Patients**	**Person time***
1 day	9	0.03
>1 to 7 days	6	0.08
>7 days to <6 months	69	11.40
6 to <12 months	1	0.51
12 to <24 months	0	0
24 to <36 months	0	0
36 to <48 months	0	0
>=48 months	0	0
Total person time for indication	**85**	**12.01**

Studies include: 281101, 281102 and TAK-755-3002
Duration of exposure is the number of days the subject received infusion(s).
*Person time in years is calculated as the number of exposure days divided by 336 (12 x 28 days, where 28 days = 1 month).

Person time per indication:		
Acquired thrombotic thrombocytopenic purpura (iTTP)		
Duration of exposure	**Patients**	**Person time***
1 day	0	0
>1 to 7 days	12	0.16

[redacted]

Person time per indication:		
Acquired thrombotic thrombocytopenic purpura (iTTP)		
Duration of exposure	**Patients**	**Person time***
>7 days to <6 months	12	0.38
6 to <12 months	0	0
12 to <24 months	0	0
24 to <36 months	0	0
36 to <48 months	0	0
>=48 months	0	0
Total person time for indication	**24**	**0.54**

Studies include: SHP655-201 and SHP655-2001.
Duration of exposure is the number of days the subject received infusion(s).
*Person time in years is calculated as the number of exposure days divided by 336 (12 x 28 days, where 28 days = 1 month).

Person time per indication:		
Sickle cell disease (SCD)		
Duration of exposure	**Patients**	**Person time***
1 day	14	0.04
>1 to 7 days	0	0
>7 days to <6 months	0	0
6 to <12 months	0	0
12 to <24 months	0	0
24 to <36 months	0	0
36 to <48 months	0	0
>=48 months	0	0
Total person time for indication	**14**	**0.04**

Studies include: SHP655-101.
Duration of exposure is the number of days the subject received infusion(s).
*Person time in years is calculated as the number of exposure days divided by 336 (12 x 28 days, where 28 days = 1 month).

Table SIII.2: Age group and gender

Cumulative for all age/gender groups (person time):				
Age group	**Patients**		**Person time**	
	Male	**Female**	**Male**	**Female**
<2 years	0	0	0	0
2 to <6 years	3	4	0.125	0.220
6 to <12 years	4	5	0.321	0.277
12 to <18 years	5	7	0.432	0.518
18 to <65 years	39	57	3.339	7.205

[redacted]

Cumulative for all age/gender groups (person time):				
Age group	**Patients**		**Person time**	
	Male	**Female**	**Male**	**Female**
>=65 years	3	1	0.092	0.012
Total	**51**	**72**	**4.369**	**8.232**

Studies include: 281101, 281102, TAK-755-3002, SHP655-201, SHP655-101 and SHP655-2001.
Duration of exposure is the number of days the subject received infusion(s).
*Person time in years is calculated as the number of exposure days divided by 336 (12 x 28 days, where 28 days = 1 month).
The total number of female/male subjects is different from the summation of the number of female/male subjects who belong to each age category. The [redacted] and [redacted] are included into two age categories, "12 to <18 years" and "18 to <65 years".
The [redacted] and [redacted] are included into two age categories, "12 to <18 years" and "6 to <12 years".
Indications: cTTP, iTTP, and SCD.

Person time per age/gender group:				
Congenital thrombotic thrombocytopenic purpura (cTTP)				
Age group	**Patients**		**Person time***	
	Male	**Female**	**Male**	**Female**
<2 years	0	0	0	0
2 to <6 years	3	4	0.125	0.220
6 to <12 years	4	5	0.321	0.277
12 to <18 years	5	7	0.432	0.518
18 to <65 years	23	38	3.185	6.911
>=65 years	1	0	0.027	0
Total	**33**	**52**	**4.089**	**7.926**

Studies include: 281101, 281102 and TAK-755-3002.
Duration of exposure is the number of days the subject received infusion(s).
*Person time in years is calculated as the number of exposure days divided by 336 (12 x 28 days, where 28 days = 1 month).
The total number of female/male subjects is different from the summation of the number of female/male subjects who belong to each age category. The [redacted] and [redacted] are included into two age categories, "12 to <18 years" and "18 to <65 years".
The [redacted] and [redacted] are included into two age categories, "12 to <18 years" and "6 to <12 years".

Person time per age/gender group:				
Acquired thrombotic thrombocytopenic purpura (iTTP)				
Age group	**Patients**		**Person time***	
	Male	**Female**	**Male**	**Female**
<2 years	0	0	0	0
2 to <6 years	0	0	0	0
6 to <12 years	0	0	0	0
12 to <18 years	0	0	0	0
18 to <65 years	7	14	0.188	0.280

[redacted]

Person time per age/gender group:				
Acquired thrombotic thrombocytopenic purpura (iTTP)				
Age group	**Patients**		**Person time***	
	Male	**Female**	**Male**	**Female**
>=65 years	2	1	0.065	0.012
Total	**9**	**15**	**0.253**	**0.292**

Studies include: SHP655-201 and SHP655-2001.
Duration of exposure is the number of days the subject received infusion(s).
*Person time in years is calculated as the number of exposure days divided by 336 (12 x 28 days, where 28 days = 1 month).

Person time per age/gender group:				
Sickle cell disease (SCD)				
Age group	**Patients**		**Person time***	
	Male	**Female**	**Male**	**Female**
<2 years	0	0	0	0
2 to <6 years	0	0	0	0
6 to <12 years	0	0	0	0
12 to <18 years	0	0	0	0
18 to <65 years	9	5	0.027	0.015
>=65 years	0	0	0	0
Total	**9**	**5**	**0.027**	**0.015**

Studies include: SHP655-101.
Duration of exposure is the number of days the subject received infusion(s).
*Person time in years is calculated as the number of exposure days divided by 336 (12 x 28 days, where 28 days = 1 month).

Table SIII.3: Dose

Cumulative for all doses of exposure (person time):		
Dose of exposure	**Patients**	**Person time***
5 IU/kg	4	0.024
15 IU/kg	6	0.060
20 IU/kg	11	0.036
40 IU/kg	110	12.452
Missing	46	1.387
Single dose	14	0.042
Once a day	9	0.185
Twice a day	12	0.188
Three days a week	3	0.027
Twice a week	11	0.107
Once a week	23	3.387

[redacted]

Cumulative for all doses of exposure (person time):		
Dose of exposure	**Patients**	**Person time***
Once every other week	64	7.122
Once every 3 weeks**	2	0.009
80 IU/kg	6	0.021
Single dose	5	0.015
Twice a day	1	0.006
160 IU/kg	4	0.012
Single dose	4	0.012
Total	**123**	**12.604**

Studies include: 281101, 281102, TAK-755-3002, SHP655-201, SHP655-101 and SHP655-2001. SHP655-2001 is an ongoing blinded study.
Duration of exposure is the number of days the subject received infusion(s).
*Person time in years is calculated as the number of exposure days divided by 336 (12 x 28 days, where 28 days = 1 month).
The total number of subjects is different from the summation of the number of subjects who belong to each dose level as some subjects are included into multiple dose levels.
Indications: cTTP, iTTP, and SCD.
**The data was captured as of cutoff date for DLP 29-September-2023 during the ongoing study, which was confirmed afterwards that no patients had received Q3W TAK-755 dosing in this study.
The total number of subjects is different from the summation of the number of subjects who belong to each dose level as some subjects are included into multiple dose levels.

Person time per dose of exposure:		
Congenital thrombotic thrombocytopenic purpura (cTTP)		
Dose of exposure	**Patients**	**Person time***
5 IU/kg	4	0.024
15 IU/kg	6	0.060
20 IU/kg	11	0.036
40 IU/kg	82	11.899
Missing	46	1.387
Single dose	9	0.027
Once a week	17	3.354
Once every other week	64	7.122
Once every 3 weeks**	2	0.009
80 IU/kg	0	0
160 IU/kg	0	0
Total	**85**	**12.018**

Studies include: 281101, 281102, and TAK-755-3002.
Duration of exposure is the number of days the subject received infusion(s).
*Person time in years is calculated as the number of exposure days divided by 336 (12 x 28 days, where 28 days = 1 month).
**The data was captured as of cutoff date for DLP 29-September-2023 during the ongoing study, which was confirmed afterwards that no patients had received Q3W TAK-755 dosing in this study.

[redacted]

The total number of subjects is different from the summation of the number of subjects who belong to each dose level as some subjects are included into multiple dose levels.

Person time per dose of exposure:		
Acquired thrombotic thrombocytopenic purpura (iTTP)		
Dose of exposure	**Patients**	**Person time***
5 IU/kg	0	0
15 IU/kg	0	0
20 IU/kg	0	0
40 IU/kg	23	0.539
Once a day	9	0.185
Twice a day	12	0.188
Three days a week	3	0.027
Twice a week	11	0.107
Once a week	6	0.033
80 IU/kg	1	0.006
Twice a day	1	0.006
160 IU/kg	0	0
Total	**24**	**0.545**

Studies include: SHP655-201 and SHP655-2001. SHP655-2001 is an ongoing blinded study.
Duration of exposure is the number of days the subject received infusion(s).
*Person time in years is calculated as the number of exposure days divided by 336 (12 x 28 days, where 28 days = 1 month).

Person time per dose of exposure:		
Sickle cell disease (SCD)		
Dose of exposure	**Patients**	**Person time***
5 IU/kg	0	0
15 IU/kg	0	0
20 IU/kg	0	0
40 IU/kg	5	0.015
Single dose	5	0.015
80 IU/kg	5	0.015
Single dose	5	0.015
160 IU/kg	4	0.012
Single dose	4	0.012
Total	**14**	**0.042**

Studies include: SHP655-101.
Duration of exposure is the number of days the subject received infusion(s).
*Person time in years is calculated as the number of exposure days divided by 336 (12 x 28 days, where 28 days = 1 month).

[redacted]

Table SIII.4: Ethnic origin

Cumulative for all racial groups (person time):		
Ethnic origin	**Patients**	**Person time***
American Indian or Alaska Native	0	0
Asian	23	2.40
Black or African American	23	0.43
White	59	8.12
Native Hawaiian or Other Pacific Islander	0	0
Multi Racial or Other	3	0.16
Unknown/Not reported	12	1.43
Missing	3	0.05
Total	**123**	**12.60**

Studies include: 281101, 281102, TAK-755-3002, SHP655-201, SHP655-101 and SHP655-2001.
Duration of exposure is the number of days the subject received infusion(s).
*Person time in years is calculated as the number of exposure days divided by 336 (12 x 28 days, where 28 days = 1 month).
Indications: cTTP, iTTP, and SCD

Person time per racial groups:		
Congenital thrombotic thrombocytopenic purpura (cTTP)		
Ethnic origin	**Patients**	**Person time***
American Indian or Alaska Native	0	0
Asian	21	2.34
Black or African American	4	0.28
White	45	7.83
Native Hawaiian or Other Pacific Islander	0	0
Multi Racial or Other	1	0.10
Unknown/Not reported	12	1.43
Missing	2	0.02
Total	**85**	**12.01**

Studies include: 281101, 281102, and TAK-755-3002.
Duration of exposure is the number of days the subject received infusion(s).
*Person time in years is calculated as the number of exposure days divided by 336 (12 x 28 days, where 28 days = 1 month).

Person time per racial groups:		
Acquired thrombotic thrombocytopenic purpura (iTTP)		
Ethnic origin	**Patients**	**Person time***
American Indian or Alaska Native	0	0
Asian	2	0.07
Black or African American	5	0.10

[redacted]

Person time per racial groups:		
Acquired thrombotic thrombocytopenic purpura (iTTP)		
Ethnic origin	**Patients**	**Person time***
White	14	0.29
Native Hawaiian or Other Pacific Islander	0	0
Multi Racial or Other	2	0.06
Unknown/Not reported	0	0
Missing	1	0.03
Total	**24**	**0.54**

Studies include: SHP655-201 and SHP655-2001.
Duration of exposure is the number of days the subject received infusion(s).
*Person time in years is calculated as the number of exposure days divided by 336 (12 x 28 days, where 28 days = 1 month).

Person time per racial groups:		
Sickle cell disease (SCD)		
Ethnic origin	**Patients**	**Person time***
American Indian or Alaska Native	0	0
Asian	0	0
Black or African American	14	0.04
White	0	0
Native Hawaiian or Other Pacific Islander	0	0
Multi Racial or Other	0	0
Unknown/Not reported	0	0
Missing	0	0
Total	**14**	**0.04**

Studies include: SHP655-101.
Duration of exposure is the number of days the subject received infusion(s).
*Person time in years is calculated as the number of exposure days divided by 336 (12 x 28 days, where 28 days = 1 month).

[redacted]

Part II: Module SIV – Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Subject has been diagnosed with any other TTP-like disorder (microangiopathic haemolytic anaemia), including acquired TTP	
Reason for exclusion:	The specific population studied is with diagnosis of cTTP. Hence, subjects with any other TTP-like disorder are considered as an exclusion criterion.
Is it considered to be included as missing information?:	No
Rationale:	rADAMTS13 is indicated for treatment of cTTP. cTTP patients are unlikely to have other TTP-like disorders.

Subject has known hypersensitivity to hamster proteins	
Reason for exclusion:	rADAMTS13 is synthesized by a genetically engineered CHO cell line. Hence, patients with known hypersensitivity to hamster proteins will place them at risk of potentially life-threatening reactions.
Is it considered to be included as missing information?:	No
Rationale:	Not applicable. Hypersensitivity is an important potential risk.

Subject has a medical history or presence of a functional ADAMTS13 inhibitor at screening	
Reason for exclusion:	Known functional inhibitors could affect the activity of rADAMTS13 and render it ineffective
Is it considered to be included as missing information?:	No
Rationale:	Functional inhibitors could indicate another underlying disease than cTTP and hence, not the population of interest for clinical trials for cTTP.

Subject with end stage renal disease requiring chronic dialysis	
Reason for exclusion:	Altered renal function may contribute to impaired coagulation or coagulation complications.
Is it considered to be included as missing information?	No
Rationale:	As per review performed by Borogovac et al [redacted], on comparison of age- and sex-matched US population, probability of survival was lower at all ages beginning at birth. No different safety profile anticipated in population with renal disease as it is unlikely to

[redacted]

Subject with end stage renal disease requiring chronic dialysis	
	precipitate in the renal tubules.

Subject has been diagnosed with hepatic dysfunction, as evidenced by, but not limited to, any of the following:- **a. Serum alanine aminotransferase (ALT) ≥2× upper limit of normal (ULN)** **b. Severe hypoalbuminemia <24 g/L** **c. Portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of oesophageal varices)**	
Reason for exclusion:	Altered liver function may contribute to impaired coagulation or coagulation complications.
Is it considered to be included as missing information?:	No
Rationale:	As per review performed by Borogovac et al [redacted], on comparison of age- and sex-matched US population, probability of survival was lower at all ages beginning at birth. No different safety profile is anticipated in population with liver disease.

The subject has a medical history of immunological disorders, excluding seasonal allergic rhinitis/conjunctivitis/mild asthma, food allergies or animal allergies.	
Reason for exclusion:	Underlying immune deficiency disease and concomitant administration of immunosuppressive medications may confound the assessment of immunogenicity from rADAMTS13 administration.
Is it considered to be included as missing information?:	No
Rationale:	No different safety profile anticipated in this population.

If female, subject is pregnant or lactating at the time of enrolment	
Reason for exclusion:	As TAK-755 is an investigational product (IP) under clinical development, pregnant women were excluded from the clinical trials.
Is it considered to be included as missing information?:	Yes
Rationale:	Pregnant patients are vulnerable population considering TAK-755 is an IP under clinical development.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions or adverse reactions with a long latency.

[redacted]

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: - Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
- Patients with hepatic impairment	Subjects diagnosed with hepatic dysfunction, as evidenced by, but not limited to, any of the following are excluded from clinical trials: a) Serum alanine aminotransferase (ALT) ≥2×ULN b) Severe hypoalbuminemia <24 g/L c) Portal vein hypertension (e.g., presence of otherwise unexplained splenomegaly, history of oesophageal varices)
- Patients with renal impairment	Subjects with end stage renal disease requiring chronic dialysis are excluded from clinical trials
- Patients with cardiovascular impairment	Subjects with severe cardiovascular disease (New York Heart Association classes 3 to 4) are excluded from clinical trials
- Immunocompromised patients	Subjects with medical history of genetic or acquired immune deficiency that would interfere with the assessment of product immunogenicity, including subjects who are HIV-positive with an absolute cluster of differentiation 4 (CD4) count <200/mm^3 or who are receiving chronic immunosuppressive drugs are excluded from clinical trials.
- Patients with a disease severity different from inclusion criteria in clinical trials	Subjects diagnosed with any other TTP-like disorder (microangiopathic haemolytic anaemia), including acquired TTP are excluded from clinical trials.
Population with relevant different ethnic origin	Not applicable
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Other	Not applicable

[redacted]

Part II: Module SV - Post-authorisation experience

Not applicable

[redacted]

Part II: Module SVI – Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

Not applicable

[redacted]

Part II: Module SVII – Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP:

None

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Not applicable

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP:

Important Identified Risks	Risk-benefit impact
None	

Important Potential Risks	Risk-benefit impact
Neutralizing (inhibitory) antibodies to rADAMTS13	As with all therapeutic proteins, there is a potential for immunogenicity. Neutralizing antibodies were not reported in patients treated with rADAMTS13 in the cTTP clinical trials. Patients may develop antibodies to rADAMTS13 following treatment with rADAMTS13 which could potentially result in a decreased response to rADAMTS13.
Hypersensitivity reactions	Hypersensitivity reactions including anaphylaxis is an anticipated risk due to the nature of the product. Subjects must be closely monitored for any symptoms throughout the infusion period. Subjects should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If these symptoms occur, the administration should be discontinued immediately. In case of shock, standard medical treatment for shock should be implemented. However, as per the current knowledge, there is no experience of hypersensitivity in any clinical trial patients.

Missing Information	Risk-benefit impact
Risks in case of pregnancy and lactation	No studies on the effect of rADAMTS13 on pregnant and lactating women have been conducted to date.
Long-term Safety	The long- term safety has not been established for the rADAMTS13 via controlled clinical studies. It is not anticipated to have a different safety profile after long term administration. To further characterize the safety concerns of rADAMTS13.

SVII.2. New Safety Concerns and Reclassification With a Submission of an Updated RMP

Not applicable

[redacted]

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of important identified risks and important potential risks

Important potential risk: Neutralising (inhibitory) antibodies to rADAMTS13	
Potential mechanisms:	This was a known class effect to differentiate or identify increased risk related to immunogenicity with the Q97R variant versus wild-type protein of rADAMTS13 and is supported by completed and ongoing clinical studies.
Evidence source(s) and strength of evidence:	Clinical trials and literature
Characterisation of the risk:	Fifteen unique subjects in the 281101 study and 55 unique subjects in the 281102 and TAK-755-3002 studies combined received the IP (32 subjects in study TAK-755-3002 are rollover subjects from study 281102 and therefore were not counted twice). Neutralizing (inhibitory) anti-rADAMTS13 antibodies were detected in 1 subject in study 281102 who was later confirmed by updated medical history and genetic analysis to have iTTP and as a result, discontinued from the study as not meeting enrolment criteria. Neutralising (inhibitory) anti-rADAMTS13 antibodies were not detected in any subjects with cTTP. In Study 281101, the presence of neutralising antibodies against rADAMTS13 was assessed for up to 28 ± 3 days. No neutralising antibodies against ADAMTS13 were detected after administration of a single dose of rADAMTS13 in this study. In studies 281102 and TAK-755-3002 in cTTP subjects overall, the risk of formation of inhibitory antibodies to rADAMTS13 in patients with cTTP remains low. There are no other safety concerns as of the cut-off date. In Study SHP655-201 in iTTP subjects, 28 subjects were enrolled, and 20 subjects received rADAMTS13. Overall, a similar proportion of subjects tested positive for anti-ADMATS13 binding antibodies at baseline (82.1% subjects) and post treatment (85.7% subjects), and a similar proportion of subjects tested positive for anti-ADAMTS13 inhibitory antibody at baseline (60.7% subjects) and post treatment (67.9% subjects). There are no reports of safety concerns. In Study SHP655-101 in SCD subjects, 14 subjects were administered single doses of ADAMTS13 at 40 IU/kg, 80 IU/kg, and 160 IU/kg. No neutralizing antibodies were detected during the study (with 28 days of follow-up after dosing).
Risk factors and risk groups:	In iTTP patients with existing anti-ADAMTS13 antibodies, administration of rADAMTS13 may induce an anamnestic response while in cTTP patients there could be lack of efficacy.
Preventability:	So far, no neutralising antibodies to rADAMTS13 were detected. The mitigation of the risk is managed by routine risk minimisation measures.
Impact on the risk-benefit balance of the product:	The development of neutralising (inhibitory) antibodies may lead to lack of efficacy. No additional risk minimization measures are required, routine risk minimization will be done through product labelling.
Public health impact:	No events have been reported during clinical trials for neutralising

[redacted]

Important potential risk: Neutralising (inhibitory) antibodies to rADAMTS13	
	(inhibitory) antibodies. Hence, public health impact is considered low.

Important potential risk: Hypersensitivity reactions	
Potential mechanisms:	This was a known class effect and supported by bibliographic data.
Evidence source(s) and strength of evidence:	Clinical trials and literature
Characterisation of the risk:	Anaphylaxis is a dramatic expression of systemic allergy. The lifetime prevalence of anaphylaxis is currently estimated at 0.05-2% in the USA and ~3% in Europe. Several population-specific studies have noted a rise in the incidence, particularly in the hospitalizations and emergency room visits due to anaphylaxis[redacted]. The incidence of anaphylaxis does not appear to vary significantly between countries. Rates globally range from 1-3 cases per 10,000 in the general population [redacted]. However, hypersensitivity drug reactions represent approximately one third of adverse drug reactions, which can affect 7% of the general population and up to 20% of hospitalized patients [redacted]. As of data lock point (DLP), no safety findings related to the risk were observed/identified from the non-clinical studies conducted. In study 281102, 1 serious adverse event (SAE) of hypersensitivity was reported in a subject receiving the standard of care treatment who experienced an allergic reaction to FFP. In study SHP655-201, 1 SAE of drug hypersensitivity was reported with rituximab.
Risk factors and risk groups:	Patients with known hypersensitivity to the parent molecule, any component of rADAMTS13 or hamster proteins are at increased risk of developing potentially life-threatening reactions.
Preventability:	Apadamtase alfa/cinaxadamtase alfa should be administered with caution in patients with known hypersensitivity to any of the components of rADAMTS13. As with any intravenous (IV) protein product, allergic-type hypersensitivity reactions are possible. Subjects must be closely monitored for any symptoms throughout the infusion period. Subjects should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If these symptoms occur, the administration should be discontinued immediately. In case of shock, standard medical treatment for shock should be implemented.
Impact on the risk-benefit balance of the product:	Hypersensitivity to the drug or its ingredients is a concern of any medicinal product and may result in a serious medical condition or potentially lead to fatal outcome. No additional risk minimization activities are required, routine risk minimization will be done through product labelling.
Public health impact:	No events have been reported during clinical trials for hypersensitivity. Hence, public health impact is considered low.

[redacted]

SVII.3.2. Presentation of the missing information

Missing information: Risks in case of pregnancy and lactation	
Evidence source:	Pregnancy: Due to its high molecular weight, rADAMTS13 is expected to have limited, if any, placenta transfer. In rat studies, there was no biologically relevant placental transfer, no reproductive or developmental toxicity at doses up to 400 U/kg, and no effects on fertility at up to 400 U/kg. In human studies, there have been four cTTP patients (2 roll-over subjects in Study 3002 and 2 patients who received TAK-755 through compassionate use program), who have been exposed to TAK-755 during pregnancy. Of these roll-over patients, 1 patient was found to be pregnant approximately one week following her last dose of TAK-755 and was discontinued from the study to comply with protocol requirements. Two months later, the patient had first trimester miscarriage which was assessed as unrelated to TAK-755. The other patient was found to be pregnant during the 3002 study, after which her last dose was withheld, and she was discontinued from the study. Following a short period of SoC treatment, the patient received TAK-755 in a compassionate use program and delivered a full-term healthy baby. No adverse events related to TAK-755 were reported. The remaining two cTTP patients were treated with TAK-755 in a compassionate use program during pregnancy. In both these cases, live babies, one premature and one at term, were delivered with no safety concerns reported due to TAK-755. Whether TAK-755 should be used in pregnancy is solely up to the medical judgment of the healthcare providers/ physicians. Lactation: There is insufficient information on whether rADAMTS13 is present in human milk, affects milk production, or has effects on the breastfed infant. Due to its high molecular weight, rADAMTS13 is not likely to be excreted in human milk and the gastrointestinal absorption of the intact protein in infants is unlikely. The decision either to discontinue nursing or discontinue ADZYNMA should take into account the importance of the drug to the mother. **Population in need of further characterisation:** Since there is limited reproductive and developmental toxicity data for TAK-755, use during pregnancy are insufficient to inform a drug associated risk of adverse developmental outcomes. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Based on the rare occurrence of congenital thrombotic thrombocytopenic purpura, experience regarding the use of ADZYNMA in pregnancy is limited. In determining whether ADZYNMA should be used in pregnancy, healthcare providers should balance the potential benefits with the potential risks. Whether ADZYNMA should be used in pregnancy is solely up to the medical judgment of the healthcare provider.

Missing information: Long-term Safety	
Evidence source:	Given that cTTP is rare [redacted], knowledge of the long-term safety effects of prolonged exposure to ADZYNMA use is currently limited in clinical trials.
Anticipated risk/consequence	Long-term safety data is limited. Existing non-clinical and clinical

[redacted]

Missing information: Long-term Safety	
of the missing information	data does not suggest a specific safety concern with long-term use of ADZYNMA at this time. Study TAK-755-3002 provides additional safety information on the long-term use of ADZYNMA.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	• Neutralizing (inhibitory) antibodies to rADAMTS13 • Hypersensitivity reactions
Missing information	• Risks in case of pregnancy and lactation • Long-term safety

[redacted]

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

None

Specific adverse reaction follow-up questionnaires for important potential risk "Neutralizing (inhibitory) antibodies to rADAMTS13"

Standardized collection of information via ADZYNMA inhibitor questionnaire to facilitate better characterisation of the risk.

Specific adverse reaction follow-up questionnaires for missing information "Risks in case of pregnancy and lactation"

Standardized collection of information via "TAK-755 and Pregnancy Questionnaire" for better characterisation of the missing information.

Other forms of routine pharmacovigilance activities:

None

III.2. Additional Pharmacovigilance Activities

TAK-755 PASS study
Study short name and title: TAK-755 PASS: Retrospective cohort study evaluating the safety of TAK-755 in patients with cTTP
Rationale and study objectives: To evaluate specific safety concerns potentially related to TAK-755 in patients with cTTP, including the important potential risks and missing information delineated in the EU RMP, including neutralizing (inhibitory) antibodies to rADAMTS13, hypersensitivity reactions, risks in case of pregnancy, and long-term safety following TAK-755 administration. This is designed to meet an EMA specific obligation. Objectives: 1. Estimate risk of neutralizing antibodies to rADAMTS13 and hypersensitivity reactions 2. Characterize long-term safety 3. Describe pregnancy exposures and outcomes, as available
Study design: Non-Interventional Post-Authorisation Safety Study, global chart review study. No comparator group is planned.
Study population: Infant, children and adults who received TAK-755 for the treatment of cTTP, including patients who have been during treatment.
Milestones: Final Report: December-2030

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit risk)				
TAK-755 PASS study Planned	In order to further evaluate the safety concerns of rADAMTS13 in patients with cTTP, the marketing authorization holder (MAH) shall conduct and submit the results of a post-authorisation safety study (PASS) in patients receiving rADAMTS13 according to an agreed protocol.	• Neutralizing (inhibitory) antibodies to rADAMTS13 • Hypersensitivity reactions • Risks in case of pregnancy and lactation • Long-term safety	Final Report	Estimated: December-2030
Category 3 - Required additional pharmacovigilance activities				
None				

Part IV: Plans for Post-authorisation Efficacy Studies

Table Part IV.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Study TAK-755-3002 Ongoing	In order to further evaluate the long-term efficacy and safety of rADAMTS13 in patients with cTTP, the MAH shall submit the final results of study TAK-755-3002, a phase 3b, prospective, open-label, multicentre, single treatment arm.	Long-term safety and efficacy	Clinical Study Report	September -2027

[redacted]

Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Neutralizing (inhibitory) antibodies to rADAMTS13	**Routine risk communication:** Sections 4.4 in the summary of product characteristics (SmPC) Sections 2 of the Package Leaflet (PL) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC section 4.4 recommends that as with all therapeutic proteins, there is a potential for immunogenicity. Patients may develop antibodies to rADAMTS13 following treatment with ADZYNMA which could potentially result in a decreased response to rADAMTS13. **Other routine risk minimisation measures beyond the Product Information:** None proposed.
Hypersensitivity reactions	**Routine risk communication:** Sections 4.4 in the SmPC Sections 2 of the PL **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC section 4.4 recommends that allergic-type hypersensitivity including anaphylactic reactions may occur. Patients should be informed of the early signs of hypersensitivity reactions including but not limited to tachycardia, tightness of the chest, wheezing and/or acute respiratory distress, hypotension, generalised urticaria, pruritus, rhinoconjunctivitis, angioedema, lethargy, nausea, vomiting, paresthesia, restlessness, and may progress to anaphylactic shock. If signs and symptoms of severe allergic reactions occur, immediately discontinue administration of ADZYNMA and provide appropriate supportive care. **Other routine risk minimisation measures beyond the Product Information:** None proposed.
Risks in case of pregnancy and lactation	**Routine risk communication:** Sections 4.6 in the SmPC Sections 2 of the PL **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC section 4.6 recommends that the use of ADZYNMA if necessary, may only be considered after a thorough individual risk benefit analysis by the treating physician before and during treatment. **Other routine risk minimisation measures beyond the Product Information:** None proposed.

[redacted]

Safety concern	Routine risk minimisation activities
Long-term safety	**Routine risk communication:** Sections 4.4 and 4.6 in the SmPC Sections 2 of the Package Leaflet (PL) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None proposed.

V.2. Additional Risk Minimisation Measures

Educational materials for Healthcare Professionals (HCP):

Objective- Inform healthcare providers and patients/caregivers of the risk of hypersensitivity with home/self-administration with ADZYNMA.

Rationale for the additional risk minimisation activity- The HCP Guide will provide information on the nature of hypersensitivity in the context of ADZYNMA, provide important factors for determining eligibility on important factors for determining eligibility for home/self-administration. The HCP guide will also ensure that the HCPs provide consultation to the patient on signs and symptoms and actions to be taken by the patient and provide the patient with the patient alert card.

Target audience and planned distribution path- Target audience are healthcare professionals. Distributed to eligible prescribers, via acceptable pathways in each country e.g., sales and/or medical field personnel, professional societies, etc. Where applicable, the information will also be distributed electronically.

Plans to evaluate the effectiveness of the interventions and criteria for success- Given the ultra-low prevalence of the disease and concomitant difficulty in recruiting a sufficient sample size, the MAH proposes no effectiveness evaluation for this additional risk minimisation measure (aRMM).

Educational materials for patients and caregivers:

Patient Alert Card

Objective- To inform patients/caregivers of the risk of hypersensitivity with home/self-administration with ADZYNMA. Help them recognize signs and symptoms of serious adverse reactions due to hypersensitivity with home infusion/ self-administration with ADZYNMA and instruct them on actions to be taken.

Rationale for the additional risk minimisation activity- The Patient Alert Card will inform the patient/caregivers about the signs and symptoms of Hypersensitivity. The Patient Alert card is suggested for the ease of use (i.e., access and carry [either as a wallet card or digitized to phone]).

Target audience and planned distribution path- Distributed to patients/caregivers by the prescriber.

Plans to evaluate the effectiveness of the interventions and criteria for success- Given the ultra-low prevalence of the disease and concomitant difficulty in recruiting a sufficient sample size, the MAH proposes no effectiveness evaluation for this aRMM.

[redacted]

V.3. Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Neutralizing (inhibitory) antibodies to rADAMTS13	**Routine risk communication:** Sections 4.4 in the SmPC Section 2 of the PL **Additional risk minimisation measures** None proposed	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** ADZYNMA inhibitor questionnaire. **Additional pharmacovigilance activities** TAK-755 PASS study
Hypersensitivity reactions	**Routine risk communication:** Sections 4.4 in the SmPC Section 2 of the PL **Additional risk minimisation measures** Educational Tools for HCP Educational tools for patients and caregivers (for home and self-administration)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities** TAK-755 PASS study
Risks in case of pregnancy and lactation	**Routine risk communication:** Sections 4.6 in the SmPC Section 2 of the PL **Additional risk minimisation measures** None proposed	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TAK-755 & Pregnancy Questionnaire **Additional pharmacovigilance activities** TAK-755 PASS study
Long-term safety	**Routine risk communication:** Sections 4.4 and 4.6 in the SmPC Section 2 of the PL **Additional risk minimisation measures** None proposed	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities** TAK-755 PASS study

[redacted]

Part VI: Summary of the Risk Management Plan

Summary of risk management plan for ADZYNMA (recombinant ADAMTS13 [rADAMTS13])

This is a summary of the risk management plan (RMP) for ADZYNMA. The RMP details important risks of ADZYNMA, how these risks can be minimised (through routine pharmacovigilance [PV], clinical studies and signal detection), and how more information will be obtained about ADZYNMA's risks and uncertainties (missing information).

ADZYNMA's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how ADZYNMA should be used.

This summary of the RMP for ADZYNMA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of ADZYNMA's RMP.

I. The Medicine and What It Is Used For

ADZYNMA is authorised for Congenital TTP (see SmPC for the full indication). It contains ADZYNMA as the active substance and it is given by intravenous route.

Further information about the evaluation of ADZYNMA's benefits can be found in ADZYNMA EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/adzynma.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of ADZYNMA, together with measures to minimise such risks and the proposed studies for learning more about ADZYNMA's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of Important Risks and Missing Information

Important risks of ADZYNMA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of ADZYNMA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine);

[redacted]

List of important risks and missing information	
Important identified risks	None
Important potential risks	• Neutralizing (inhibitory) antibodies to rADAMTS13 • Hypersensitivity reactions
Missing information	• Risks in case of pregnancy and lactation • Long-term safety

II.B Summary of Important Risks

The safety information in the proposed product information is aligned to the reference medicinal product.

Important potential risk: Neutralizing (inhibitory) antibodies to rADAMTS13	
Evidence for linking the risk to the medicine	Clinical trials and literature
Risk factors and risk groups	In iTTP patients with existing anti-ADAMTS13 antibodies, administration of rADAMTS13 may induce an anamnestic response while in cTTP patients there could be lack of efficacy.
Risk minimisation measures	**Routine risk minimisation measures:** Sections 4.4 in the SmPC Section 2 of the PL **Additional risk minimisation measures:** No additional risk minimisation measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** TAK-755 PASS study See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Hypersensitivity reactions	
Evidence for linking the risk to the medicine	Clinical trials and literature
Risk factors and risk groups	Patients with known hypersensitivity to the parent molecule, any component of rADAMTS13 or hamster proteins are at increased risk of developing potentially life-threatening reactions.
Risk minimisation measures	**Routine risk minimisation measures:** Sections 4.4 in the SmPC Section 2 of the PL **Additional risk minimisation measures:** Educational Tools for HCP Educational tools for patients and caregivers (for home and self-administration)
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** TAK-755 PASS study See section II.C of this summary for an overview of the post-authorisation development plan.

[redacted]

Missing information: Risks in case of pregnancy and lactation	
Risk minimisation measures	**Routine risk minimisation measures:** Sections 4.6 in the SmPC Section 2 of the PL **Additional risk minimisation measures:** No additional risk minimisation measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** TAK-755 PASS study See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Long-term safety	
Risk minimisation measures	**Routine risk minimisation measures:** Sections 4.4 and 4.6 in the SmPC Section 2 of the PL **Additional risk minimisation measures:** No additional risk minimisation measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** TAK-755 PASS study See section II.C of this summary for an overview of the post-authorisation development plan.

II.C. Post-authorisation Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorisation

TAK-755 PASS Study

To evaluate specific safety concerns potentially related to TAK-755 in patients with cTTP, including the important potential risks and missing information delineated in the EU RMP, including neutralizing (inhibitory) antibodies to rADAMTS13, hypersensitivity reactions, risks in case of pregnancy, and long-term safety following TAK-755 administration. This is designed to meet an EMA specific obligation.

Objectives:

- Estimate risk of neutralizing antibodies to rADAMTS13 and hypersensitivity reactions
- Characterise long-term safety
- Describe pregnancy exposures and outcomes, as available

Study TAK-755-3002

Purpose of the study: To evaluate the long-term safety and tolerability of TAK-755 (rADAMTS13) in terms of related treatment-emergent adverse events (TEAEs) and related serious adverse events (SAEs) in both the prophylactic and the on-demand cohorts.

II.C.2. Other Studies in Post-authorisation Development Plan

There are no studies required for ADZYNMA.

[redacted]

Part VII: Annexes

Table of contents

[redacted]

Annex 4: Specific adverse drug reaction follow-up forms

[redacted]

Annex 6: Details of proposed additional risk minimisation activities (if applicable)

[redacted]

[redacted]

[redacted]

[redacted]

Annex 4: Specific adverse drug reaction follow-up forms

Annex 4.1: ADZYNMA inhibitor questionnaire

Annex 4.2: TAK-755 and Pregnancy Questionnaire

[redacted]

Annex 4.1: ADZYNMA inhibitor questionnaire

[redacted]

FORM

Form Number:	FORM-xxxxxx	**Page:**	1 of 7
Version Number:	1.0		
This version replaces:			
Parent Document:	TOOL-0003834		
Title:	Adzynma Inhibitor Questionnaire		

Introduction:
Refer to *TOOL-0003834 Targeted Follow-up Job Aid* for guidance on use of this form.

Instructions for Sender (**Takeda representative**), prior to sending:

- Enter Case ID from Argus, on next page
- Enter email address to which the form should be returned to, on next page
- Delete this instructional page
- Send form

Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to Takeda at: _____**

I. REPORTER INFORMATION

Name/Title:	Email:	
Postal Address:	Phone:	Fax:

Reporter Type: ☐ Physician ☐ Pharmacist ☐ Nurse ☐ Other Health Care Professional ☐ Consumer / Other Non-Health Care Professional ☐ Unknown

2. PATIENT INFORMATION

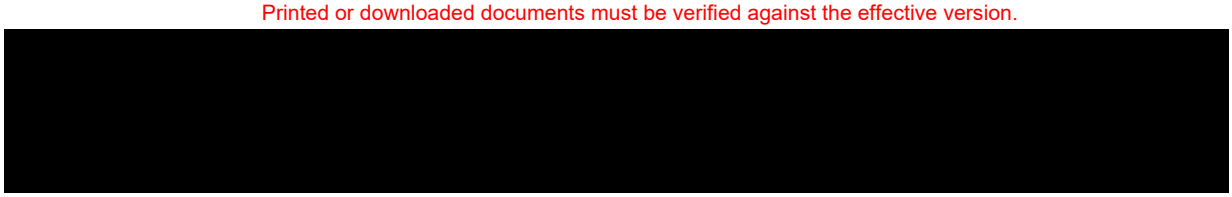
Patient initials	Gender	Date of Birth or Age	Height	Weight
	☐Male ☐Female ☐Not Reported	DOB (ddmmmyyyy) or Age	☐cm ☐in	☐kg ☐lb
			Waist circumference:	

Ethnicity:	**Race:**
☐ Hispanic or Latino ☐ Not Hispanic or Latino	☐ American Indian or Alaska Native ☐ Asian ☐ Black or African American ☐ Pacific Islander ☐ White If Other, please specify:

3. RELEVANT MEDICAL HISTORY / CONCURRENT ILLNESS ☐None ☐Unknown ☐Not reported

Diagnosis (including, but not limited to: Thrombocytopenia, stroke, microangiopathic hemolytic anemia, skin or mucosal hemorrhage, dyspnea, headaches, seizure, renal impairment, infection, surgery, trauma, pregnancy)	Onset Date (ddmmmyyyy)	End Date (ddmmmyyyy)	Check if ongoing
			☐
			☐
			☐
			☐
			☐
			☐

Smoker? ☐Yes ☐No ☐Unknown If Yes, state quantity and duration:



Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to Takeda at: _____**

Alcohol Use? ☐Yes ☐No ☐Unknown If Yes, state quantity and duration:

Drug abuse? ☐Yes ☐No ☐Unknown

Allergies? ☐Yes ☐No ☐Unknown If Yes, list allergies:

Is there a family history of cTTP? ☐ Yes ☐ No ☐ Unknown ☐ Not Reported

Is there a family history of ADAMTS13 inhibitor development? ☐ Yes ☐ No ☐ Unknown ☐ Not Reported

Provide ADAMTS13 genotype (if known): ☐ Unknown ☐ Not Reported

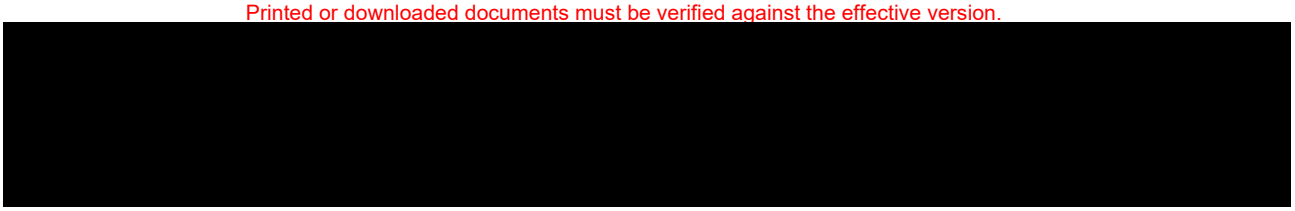
Additional relevant inhibitor medical history? (please list):

cTTP Treatment History

Date of cTTP diagnosis: _____

Current and previous cTTP Treatments

Name	Dose/Frequency/ Route of Administration	Start Date (ddmmmyyyy) Stop Date (ddmmmyyyy)	Check if Ongoing
	Dose : Route: Freq:	Start: Stop:	☐
	Dose : Route: Freq:	Start: Stop:	☐
	Dose : Route: Freq:	Start: Stop:	☐
	Dose : Route: Freq:	Start: Stop:	☐



Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to Takeda at: _____**

Please include additional medical information in section 3 comments below:

Section 3 Comments:

4. RELEVANT LAB DATA If not available, indicate ☐ Unknown

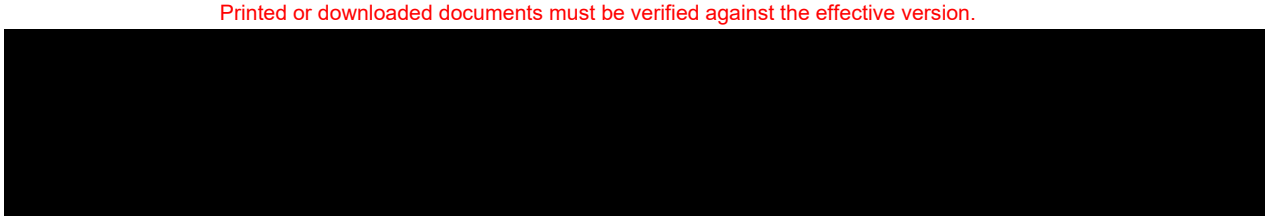
Test Name (including, but not limited to: ADAMTS13 activity, Lactate dehydrogenase, platelet count, Bilirubin, reticulocytes, ADAMTS13 antibody test, ADAMTS inhibitor, Creatinine, hemoglobin, schistocytes, HIV serology, HCV serology, HBV	Date (ddmmmyyyy)	Result	Normal Range

Please include additional relevant lab data:

Section 4 Comments:

5. SUSPECT PRODUCT INFORMATION ☐Unknown ☐Not Reported

*Suspect Product Name	Indication	**Dose/ Frequency / Route	***Vial Size / Lot number If lot# is unknown provide reason	Number of exposure days if known	Start and Stop Date (ddmmm yyyy)	Check if On-going	****Action taken with product
		Dose: Route:	Vial: Lot:		Start: Stop:	☐	



Case ID: **Patient/Study ID:**					**Send completed questionnaire by email to Takeda at: _____**		
		Freq:					
		Dose: Route: Freq:	Vial: Lot:		Start: Stop:	☐	
		Dose: Route: Freq:	Vial: Lot:		Start: Stop:	☐	

Please include additional suspect product Information in the section 5 comments below:

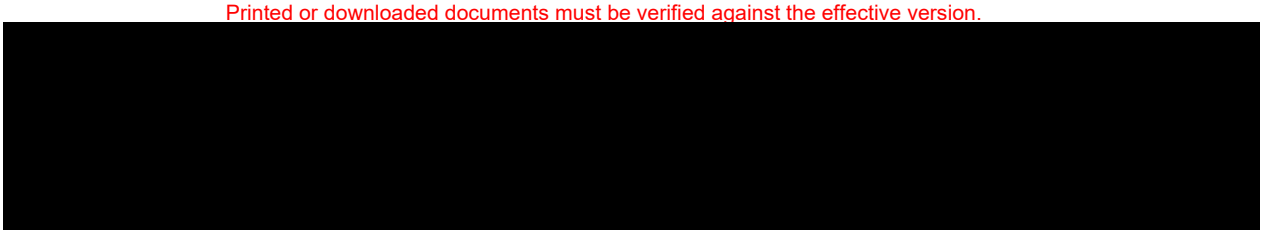
Section 5 Comments:

6. CONCOMITANT MEDICATION ☐**None** ☐**Unknown** ☐**Not reported**

Name	Dose/Frequency/ Route of Administration	Indication(s)	Start Date (ddmmmyyyy) Stop Date (ddmmmyyyy)	Check if Ongoing
	Dose : Route: Freq:		Start: Stop:	☐
	Dose : Route: Freq:		Start: Stop:	☐
	Dose : Route: Freq:		Start: Stop:	☐

Please include additional Concomitant medication in section 6 comments below:
Section 6 Comments:

7. INHIBITOR INFORMATION



Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to Takeda at: _____**

Date of inhibitor detection (ddmmmyyyy): ☐Unknown ☐Not reported
Inhibitor level: BU/mL
Inhibitor level at first laboratory detection: BU/mL Date (ddmmmyyyy):
Max inhibitor level: BU/mL Date (ddmmmyyyy):
Most recent inhibitor level: BU/mL Date (ddmmmyyyy):
Local lab cut-off for positive inhibitor result: BU/mL Date (ddmmmyyyy):
Assay Type?
Did the inhibitor result in any of the following? ☐No ☐Yes
If Yes, please specify:
☐Hospitalization from (ddmmmyyyy) to ddmmmyyyy)
☐Medically Significant ☐Life-Threatening ☐Disability ☐Death
Death of (ddmmmyyyy): Cause(s):

Is the inhibitor related to treatment with the Takeda product? ☐No ☐Yes ☐Unknown
Has the patient recovered? ☐Recovered on (ddmmmyyyy) ☐Recovered with Sequelae ☐
Recovering ☐Fatal ☐Not recovered ☐Unknown ☐Not reported

Symptoms associated with inhibitor occurrence

Symptoms (including, but not limited to: bleeding events, lack of response, hypersensitivity /anaphylactic reaction)	Onset Date (ddmmmyyyy)	End Date (ddmmmyyyy)	Check if ongoing
			☐
			☐
			☐

8. TREATMENT GIVEN for INHIBITOR?

☐ **Yes, complete below** ☐**None** ☐**Unknown** ☐**Not Reported**

Drug Name / Name of Non-	Dose / Frequency /	Start Date	Stop Date	Check

Case ID: **Patient/Study ID:**			**Send completed questionnaire by email to Takeda at: _____**	
Drug Name	Route of Administration	(ddmmmyyyy)	(ddmmmyyyy)	if On-going
	Dose : Route: Freq:			☐
	Dose : Route: Freq:			☐
	Dose : Route: Freq:			☐
Section 8 Comments:				
9. ADDITIONAL INFORMATION				

QUESTIONNAIRE COMPLETED BY	Printed Name:	Today's Date:
	Signature:	
	Address:	
	Contact Number:	Email:

[redacted]

Annex 4.2: TAK-755 and Pregnancy Questionnaire

[redacted]

GLOBAL FORM

Form Number:	**FORM-0009962**	**Page:**	1 of 6
Version Number:	**2.0**		
Parent Document:	**TOOL-0003834**		
Title:	**Global Form, TAK-755 & Pregnancy Questionnaire**		

Introduction:

Refer to TOOL-0003834 *Targeted Follow-up Job Aid* for guidelines on use of this Follow-up form.

Instructions:

- Enter Case ID from Argus, on next page
- Enter email address to which the form should be returned to, on next page
- Enter drug name in section 4
- Delete this instructional page
- Send form

[redacted]

Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to Takeda at: _____**

1. Reporter

Completed By	Print Name:	Today's Date (dd/mmm/yyyy):
	Signature:	
	Address:	
	Contact Number:	Email

2. CASE TYPE (check all that apply)

☐ Spontaneous ☐ Pregnancy ☐ Lactation ☐ Regulatory Authority ☐ Observational Study
☐ Clinical Study, if checked: Protocol No.: EudraCT No.: Study Title:

3. PATIENT EXPOSURE INFORMATION

Exposure	Site No. (if study) Subject ID (if study)	Date of Birth (mmm/yyyy)	Age	Race	Weight	Height
☐ Maternal ☐ Paternal					☐kg ☐ lb	☐cm ☐in

4. TTP Treatment

Product Name	Unit Dose	Form	Route	Frequency	Drug Product Lot#/ Ser#	Dates (ddmmmyyyy)	Indication	Action Taken with Drug
						Start: Stop:		
						Start: Stop:		
						Start: Stop:		
						Start: Stop:		

5. ADVERSE EVENT INFORMATION – if any

Adverse Event(s) or Diagnosis or abuse, misuse, overdose, medication error	**Dates (dd/mmm/yyyy)**	**Stage1**	**De-challange2**	**Re-challenge3**	**Reporter Causality**	**Serious Criteria**	**Event Outcome**
	Start: **Stop:**						
	Start: **Stop:**						
	Start: **Stop:**						

[redacted]

Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to Takeda at: _____**

	Start: Stop:						
1 in what stage did adverse event occur? 2If suspected product was withdrawn, did even abate? 3 If suspect product was re-introduced, did event re-occur?							

6. IN-PATIENT HOSPITALIZATION / DEATH (complete only if patient was admitted to hospital, or died)

A. Patient was Hospitalized:
- ☐ Due to the Adverse Event
- ☐ Before the event, but Hospitalization was Prolonged due to the Event
- ☐ Before the event, but Hospitalization was not Prolonged Due to the Event
- ☐ Not Due to the Event

Reason not Due to the Event:

Admission Date (dd/mmm/yyyy): Discharge Date (dd/mmm/yyyy):
Duration of Hospitalization (days):

☐ Hospital Report is on local file and available upon request ☐ Unavailable

B. Complete this Section if Patient Died:

Date of Death (dd/mmm/yyyy): Cause(s) of Death:
Autopsy Performed?: Autopsy Date (dd/mmm/yyyy):
☐ Autopsy Report on local file and available upon request ☐Unavailable

7. CONCOMITANT AND TREATMENT MEDICATIONS (relevant to the AE) – Include treatment meds below

Did the mother receive any concomitant medications during the pregnancy, labor, delivery, or lactation

☐ None ☐Unknown ☐ Not Reported

Drug Name	Concomitant medication or Treatment	Dose	Form	Route	Frequency	Dates	Indication	Ongoing?
						Start: Stop:		☐ Yes ☐ No
						Start: Stop:		☐ Yes ☐ No
						Start: Stop:		☐ Yes ☐ No
						Start: Stop:		☐ Yes ☐ No

8. FAMILY HISTORY OF BIRTH DEFECTS, GENETIC DISORDERS, FETAL ABNORMALITIES OR PREGNANCY COMPLICATIONS

Total number of pregnancies and outcome of previous pregnancies	
Abortions (fetal death < 20 weeks):	
Fetal death (>20 weeks):	
Premature delivery (>20 weeks):	

[redacted]

Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to Takeda at: _____**
Living (>20 weeks)	
neonatal death (<28 days post delivery)	

9. RELEVANT PATERNAL HISTORY (include family history if applicable) ☐ Not applicable

☐ Yes ☐No ☐Unknown ☐ Not Reported

(if Yes, provide details below)

Details:

10. PREGNANCY INFORMATION ☐ Not applicable

Last Menstrual Period (LMP)	Date of Pregnancy was Confirmed (dd/mmm/yyyy)	Method of Confirmation

Estimated Delivery Date (dd/mmm/yyyy)	Estimated Gestational Age (EGA) at time of Primary Event (weeks):

Did the mother experience any adverse events noted during the pregnancy?
Did the fetus experience any adverse events during the pregnancy?
Were any congenital anomalies detected during the pregnancy?

Did Mother form ADAMTs13 inhibitory antibodies ☐ Yes ☐No ☐Unknown ☐ Not Reported

If yes: Date of inhibitor detection (ddmmmyyyy): ☐Unknown ☐Not reported

Local lab cut-off for positive inhibitor result: BU Date (ddmmmyyyy):

Max inhibitory level during last episode: BU Date (ddmmmyyyy):

Is the inhibitor related to treatment with the Takeda product? ☐No ☐Yes ☐Unknown

Did inhibitor resolve? ☐No ☐Yes

Did Mother form ADAMTs13 binding antibodies ☐ Yes ☐No ☐Unknown ☐ Not Reported

If yes: Date of binding antibody detection (ddmmmyyyy): ☐Unknown ☐Not reported

Local lab cut-off for positive binding result: BU Date (ddmmmyyyy):

Max binding level during last episode: BU Date (ddmmmyyyy):

Is the binding antibody related to treatment with the Takeda product? ☐No ☐Yes ☐Unknown

Did antibody level resolve? ☐No ☐Yes

11. PREGNANCY OUTCOME ☐ Not applicable

The mother delivered a healthy baby?	☐ Yes ☐ No
If no, How did the pregnancy end?	☐ Unknown ☐ Not Available
Any adverse events experienced by the mother during labor or deliver	☐ Yes ☐ No
Delivery	Date (dd/mmm/yyyy): Time:

[redacted]

Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to Takeda at: _____**
Maternal age at the time of delivery	Years: ☐ Unknown ☐ Not Reported ☐ Not Applicable
Estimated Gestational Age (AGE) at delivery	Weeks: ☐ Unknown ☐ Not Reported ☐ Not Applicable

Were there any relevant procedures / non-drug medication interventions / relevant test(s), laboratory data performed during labor and/or delivery?

☐ Yes ☐ No ☐ Unknown
If Yes, specify
☐Spontaneous Abortion Date (dd/mmm/yyyy) or Weeks:
☐Elective Abortion Date (dd/mmm/yyyy) or Weeks:
☐Still Birth
☐Perinatal Death (<29 weeks up to 7th day of life) Reason:

Did the Neonate experience any adverse events during labor, delivery, or post-natal?

☐Yes ☐No ☐Unknown
If Yes, specify
Did the neonate have any of the following TTP clinical manifestations? ☐Yes, please specify ☐No

Diagnosis (including, but not limited to: Thrombocytopenia, stroke, microangiopathic hemolytic anemia, skin or mucosal hemorrhage, dyspnea, seizure, renal impairment)	Onset Date (ddmmmyyyy)	End Date (ddmmmyyyy)	Check if ongoing
			☐
			☐
			☐
			☐
			☐

Did the neonate have ADAMTs13 inhibitory antibodies ☐ Yes ☐No ☐Unknown ☐ Not Reported
If yes: Max inhibitory level during last episode: BU Date (ddmmmyyyy):
Local lab cut-off for positive inhibitor result: BU Date (ddmmmyyyy):
Did inhibitor resolve? ☐No ☐Yes
Date of inhibitor detection (ddmmmyyyy): ☐Unknown ☐Not reported
Is the inhibitor related to treatment with the Takeda product? ☐No ☐Yes ☐Unknown

Did neonate have ADAMTs13 binding antibodies ☐ Yes ☐No ☐Unknown ☐ Not Reported
If yes: Date of binding antibody detection (ddmmmyyyy): ☐Unknown ☐Not reported
Local lab cut-off for positive binding result: BU Date (ddmmmyyyy):

[redacted]

Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to Takeda at: _____**

Max binding level during last episode: BU Date (ddmmmyyyy):
Is the binding antibody related to treatment with the Takeda product? ☐No ☐Yes ☐Unknown
Did antibody level resolve? ☐No ☐Yes
Were there abnormalities diagnosed? ☐Yes ☐No ☐Unknown
If yes, provide the data of diagnosis and pathology results
Date of Diagnosis (dd/mmm/yyyy):
Pathology results:

12. NEONATE OUTCOME (If mother has delivered) ☐ Not applicable

Live Birth APGAR Scores: 1 minute:	5 minutes:	10 minutes:
Gender	☐Male ☐Female ☐Unknown ☐Not reported	
Birth Weight	☐kg ☐lb ☐Unknown ☐Not Reported	
Birth Length	☐cm ☐in ☐Unknown ☐Not Reported	
Head Circumference	☐cm ☐in ☐Unknown ☐Not Reported	

☐Breast Fed ☐Bottle Fed ☐Unknown ☐Not Reported

13. CURRENT INFANT OUTCOME (at 30 days or 1 year post delivery) ☐ Not applicable

Weight Percentile	% or	kg / pounds
Height Percentile	% or	cm / inches

Were there abnormalities diagnosed? ☐Yes ☐No ☐Unknown
If yes, provide the data of diagnosis and pathology results
Date of Diagnosis (dd/mmm/yyyy):
Pathology results:

14. SUPPLEMENTAL PAGES

This section is optional – Use this page as need to record additional information
☐Yes If yes, number of supplemental pages:
☐No

15. ADDITIONAL INFORMATION

[redacted]

Annex 6: Details of proposed additional risk minimisation activities (if applicable)

Prior to the use of ADZYNMA in home/self-administration, the MAH must agree about the content and format of the educational materials for use of ADZYNMA in home administration/ self-administration, including communication media, distribution modalities and any other aspects of the programme, with the National Competent Authority.

The educational materials for the use are aimed at providing guidance on how to manage risks of hypersensitivity with home infusion/ self-administration.

The MAH shall ensure that in each Member State where ADZYNMA is marketed, all Healthcare Professionals who are expected to prescribe and patients/caregivers who are expected to use ADZYNMA have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

Physician educational material:

- The Summary of Product Characteristics
- HCP Guide for Hypersensitivity in home infusion/ self-administration for ADZYNMA
- Patient/Caregiver Alert Card for Hypersensitivity in home infusion/ self-administration for ADZYNMA
- **Guide for Healthcare professionals:**
    - The HCP will receive information on the risk of hypersensitivity associated with ADZYNMA
    - Likelihood of hypersensitivity should be factored into the eligibility assessment for home/self-administration
    - The HCP should communicate the signs and symptoms of hypersensitivity and action steps to advise the patient should take if hypersensitivity occurs
    - The HCP will be provided with the key points to counseling patients on the risk and the use of the Patient Alert Card
- **Patient/Caregiver Alert Card**
    - Hypersensitivity reactions may occur while on ADZYNMA
    - Information on signs and symptoms related to Hypersensitivity reactions and when to seek attention from healthcare professionals
    - Understand the action steps (i.e., seek immediate medical attention) should signs and symptoms occur
    - Contact details of ADZYNMA prescriber

Patient information pack:

- Patient information leaflet

[redacted]