Clinical Study Protocol

EU PAS Number: EUPAS1000000870

Title: A Post-Authorization Safety Study (PASS) to Further Evaluate Real-World Safety in Patients with Congenital Thrombotic Thrombocytopenic Purpura (cTTP) Treated with Adzynma

Study Number: TAK-755-4007

Document Version and Date: Amendment 1, 28 May 2025

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

NON-INTERVENTIONAL SAFETY STUDY PROTOCOL

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Study number: TAK-755-4007

Version number: Amendment 1, 28 May 2025

Original, 15 January 2025

Ethics statement: This study will be conducted in compliance with the protocol, the Declaration of Helsinki, International Society for Pharmacoepidemiology Guidelines for Good Epidemiology Practices, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Guidelines for Methodological Standards in Pharmacoepidemiology, Good Pharmacovigilance Practices, and all applicable regulatory requirements.

Signature Page

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MAH (Marketing Authorization Holder):

Role	EU Regulatory [redacted]	**Printed Name**	[redacted]
Signature	Signed by: [redacted]	**Date (DD-MMM-YYYY)**	03-Jun-2025 | 14:19:03 JST

EU QPPV (European [redacted] Pharmacovigilance):

Role	EU QPPV	**Printed Name**	[redacted] MD [redacted] EU QPPV Office, Patient Safety and Pharmacovigilance Takeda Belgium NV Leonardo Da Vincilaan 7 1930 Zaventem Belgium
Signature	Signed by: [redacted]	**Date (DD-MMM-YYYY)**	03-Jun-2025 | 00:58:40 CEST

Investigator:

By signing below, the investigator acknowledges that he/she has read and understands this protocol, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, Clinical Trial Agreement, good pharmacovigilance practices, and all applicable regulatory requirements. If applicable, he/she will comply with the requirements for obtaining informed consent from all study patients prior to initiating any protocol-specific procedures and for obtaining written initial and ongoing ethics committee(s) protocol review and approval.

Role		**Printed Name**	
Signature		**Date (DD-MMM-YYYY)**	

Study Information

Title	A Post-Authorization Safety Study (PASS) to Further Evaluate Real-World Safety in Patients with Congenital Thrombotic Thrombocytopenic Purpura (cTTP) Treated with Adzynma
Protocol number	TAK-755-4007
Protocol version identifier	Amendment 1
Date of last version of protocol	15 January 2025
Catalogue of RWD studies number	N/A
Active substance	Recombinant ADAMTS13 (rADAMTS13) (apadamtase alfa [native] and cinaxadamtase alfa [variant])
Medicinal product	Adzynma
Product reference	EU/1/24/1837/001-002
Procedure number	EMEA/H/C/006198
Joint PASS	No
Research question and objectives	Research question: What are the estimated risks of developing neutralizing antibodies to ADAMTS13 and hypersensitivity reactions, the risks associated with treatment during pregnancy including pregnancy outcomes, and characteristics of long-term safety in patients with congenital thrombotic thrombocytopenic purpura (cTTP) treated with Adzynma? Primary objectives: 1. To estimate the real-world risk of developing neutralizing antibodies to ADAMTS13 during the 6 months following the index Adzynma infusion in paediatric and adult patients with cTTP. 2. To estimate the real-world risk of hypersensitivity reactions during the 7 days following the index Adzynma infusion in paediatric and adult patients with cTTP. Secondary objectives: 3. To estimate the long-term safety of Adzynma administration by assessing the real-world risk of developing neutralizing antibodies to ADAMTS13 following Adzynma infusion(s) in paediatric and adult patients with cTTP who have at least 6 months of follow-up time from their index infusion. 4. To estimate the long-term safety of Adzynma administration by assessing the real-world risk of hypersensitivity reactions following Adzynma infusion(s) in paediatric and adult patients with cTTP who have at least 6 months of follow-up time from their index infusion. 5. To estimate the real-world risk of hypersensitivity reactions following each administration of Adzynma following the index infusion, in paediatric and adult patients with cTTP. 6. To summarize the treatment-emergent adverse events in patients exposed to Adzynma. 7. To describe the pregnancy and infant outcomes for patients

	exposed to Adzynma during pregnancy. *Note: Index infusion is defined as the first Adzynma infusion date recorded in the medical record using commercially available Adzynma (excluding doses received in clinical studies or early access program).*
Countries of study	This study is planned to be conducted across several countries, including but not limited to, Austria, France, Germany, Italy, Poland, Spain, Switzerland, and the United Kingdom (UK).
Author	[redacted] Safety Pharmacoepidemiology Global Evidence & Outcomes Takeda Pharmaceutical Company Limited [redacted]
Marketing authorization holder (MAH)	Takeda Manufacturing Austria AG Industriestrasse 67 1221 Vienna Austria
MAH contact person	[redacted] EUCAN Regulatory [redacted] Takeda Pharmaceuticals International AG [redacted]

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2.0 LIST OF ABBREVIATIONS

Abbreviations	Definition
ADR	adverse drug reaction
AE	adverse event
CHMP	Committee for Medicinal Products for Human Use
CRO	contract research organization
cTTP	congenital thrombotic thrombocytopenic purpura
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
GVP	Good Pharmacovigilance Practices
HCP	healthcare provider
HMA	Heads of Medicines Agencies
ICF	informed consent form
ID	identification
IEC	independent ethics committee
IRB	institutional review board
IV	intravenous
MHRA	Medicines and Healthcare products Regulatory Agency
PASS	post-authorization safety study
PBRER	periodic benefit-risk evaluation report
PQC	product quality complaint
rADAMTS13	recombinant ADAMTS13
RMP	risk management plan
RWD	real-world data
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
SSR	special situation report
TEAE	treatment-emergent adverse event
TTP	thrombotic thrombocytopenic purpura
UL vWF	ultra-large von Willebrand factor
UK	United Kingdom
US	United States
vWF	von Willebrand factor

3.0 RESPONSIBLE PARTIES

Principal investigator: N/A

Co-investigator: N/A

Other responsible parties: N/A

The final list of investigators will be provided in the final study report and can be supplied as an appendix to this protocol.

4.0 ABSTRACT

Title	A Post-Authorization Safety Study (PASS) to Further Evaluate Real-World Safety in Patients with Congenital Thrombotic Thrombocytopenic Purpura (cTTP) Treated with Adzynma
Rationale and background	Congenital thrombotic thrombocytopenic purpura (cTTP) is an ultra-rare, chronic, blood-clotting disorder resulting from a deficiency in the ADAMTS13 enzyme—leading to acute events and debilitating chronic symptoms, such as thrombocytopenia, microangiopathic hemolytic anemia, and widespread microvascular thrombosis. Adzynma, a human recombinant ADAMTS13 (rADAMTS13), is indicated for the treatment of ADAMTS13 deficiency in children and adult patients with cTTP. In November 2023, Adzynma was granted an Orphan Drug Designation by the United States (US) Food and Drug Administration (FDA) for the treatment and prevention of acute thrombotic thrombocytopenic purpura (TTP) events. In March 2024, it was approved by Japan's Ministry of Health, Labour and Welfare for the treatment of TTP. On 30 May 2024, the Committee for Medicinal Products for Human Use (CHMP) recommended granting marketing authorization under exceptional circumstances in the European Union (EU) for treating ADAMTS13 deficiency in patients with cTTP. A Commission Decision granting marketing authorization in exceptional circumstances under Regulation (EC) No. 726/2004 was issued on 01 August 2024. Additionally, on 20 June 2024, the European Medicines Agency (EMA) Committee for Orphan Medicinal Products (COMP) recommended Adzynma as an orphan medicinal product for treating TTP. During the licensing procedure for Adzynma in the EU, the CHMP deemed a post-authorization safety study (PASS) necessary to collect additional safety data. The present study is proposed to provide further information about the safety of Adzynma used in real-world clinical practice. This includes monitoring important potential risks, such as neutralizing (inhibitory) antibodies to ADAMTS13 and hypersensitivity reactions. The study will also address long-term safety following Adzynma administration and missing information on pregnancy risks following Adzynma administration during pregnancy. Patients of all ages, including those who became pregnant during Adzynma treatment, will be enrolled in this PASS. The PASS is an EU risk management plan (RMP) category 2 commitment and a Specific Obligation of the Marketing Authorization.

Research question and objectives	Research question: What are the estimated risks of developing neutralizing antibodies to ADAMTS13 and hypersensitivity reactions, the risks associated with treatment during pregnancy including pregnancy outcomes, and characteristics of long-term safety in patients with cTTP treated with Adzynma? Primary objectives: 1. To estimate the real-world risk of developing neutralizing antibodies to ADAMTS13 during the 6 months following the index Adzynma infusion in paediatric and adult patients with cTTP. 2. To estimate the real-world risk of hypersensitivity reactions during the 7 days following the index Adzynma infusion in paediatric and adult patients with cTTP. Secondary objectives: 3. To estimate the long-term safety of Adzynma administration by assessing the real-world risk of developing neutralizing antibodies to ADAMTS13 following Adzynma infusion(s) in paediatric and adult patients with cTTP who have at least 6 months of follow-up time from their index infusion. 4. To estimate the long-term safety of Adzynma administration by assessing the real-world risk of hypersensitivity reactions following Adzynma infusion(s) in paediatric and adult patients with cTTP who have at least 6 months of follow-up time from their index infusion. 5. To estimate the real-world risk of hypersensitivity reactions following each administration of Adzynma following the index infusion, in paediatric and adult patients with cTTP. 6. To summarize the treatment-emergent adverse events (TEAEs) in patients exposed to Adzynma. 7. To describe the pregnancy and infant outcomes for patients exposed to Adzynma during pregnancy. *Note: Index infusion is defined as the first Adzynma infusion date recorded in the medical record using commercially available Adzynma (excluding doses received in clinical studies or early access program).*
Study design	This non-interventional, retrospective, post-authorization safety, cohort study utilizes secondary data from medical records to evaluate the safety of Adzynma in real-world clinical practice. The data collection period is expected to last approximately 4.5 years, with the total study duration anticipated to be approximately 5.5 years.
Population	This study aims to enroll both paediatric and adult patients who have received Adzynma for the treatment of cTTP, either prophylactically or as on-demand therapy for acute episodes, including those who became pregnant during Adzynma treatment.
Inclusion/ Exclusion criteria	Inclusion criteria: 1. Is diagnosed with cTTP. 2. Had received commercially available Adzynma treatment for cTTP within the eligibility period, of which there must be a recorded date and dose of at least one Adzynma administration in their medical chart. 3. Provides a signed informed consent form (ICF; or assent and consent forms, if applicable), in accordance with local ethical and institutional requirements.

	Exclusion criteria: 1. Has a history or presence of a functional ADAMTS13 inhibitor (that is, neutralizing antibodies to ADAMTS13/rADAMTS13). 2. Has concurrent use of an investigational drug or is enrolled in another clinical trial at the time of index Adzynma infusion.
Variables	Key baseline variables to be collected include: • Date of informed consent (if applicable) • Demographic data • Clinical data • cTTP treatment history • Disease characteristics (for example, cTTP diagnosis details) • Medical history and comorbidities • Pregnancy status Adzynma treatment details will be collected, and will include the following: • Prophylactic or on-demand treatment • Infusion start and end date • Infusion dose and frequency • Treatment modifications • Type of treatment facility (for example, hospital, infusion center, home administration) • Adzynma naïve or experienced at baseline • Relevant concomitant medications Outcome variables associated with the primary and secondary objectives to be collected will include the following: • Hypersensitivity reactions that occur following Adzynma infusion(s) • Neutralizing antibodies to ADAMTS13 following Adzynma infusion(s) (including date and details of initial and confirmatory laboratory samples) • TEAEs, and additional variables including start/end date of the event, severity, causality, action taken with Adzynma, medication received, the outcome of the event, seriousness criteria Variables associated with pregnancy outcomes include the following: • Gestational age/trimester of Adzynma exposure • Pregnancy outcome (for example, spontaneous abortion, stillbirth, induced abortion, live birth) • Pregnancy complications • Gestational age at birth (for example, ≥37 gestational weeks, <37 gestational weeks) • Year of birth • Birth weight (for example, normal weight, small for gestational age) • Congenital anomaly detected (yes, no) and details, as available • Breastfeeding status while receiving Adzynma (categorized as yes, no, or

	unknown) • Infant growth and development outcomes (categorized as normal, abnormal [specify], or unknown)
Data sources	Medical records of enrolled patients from participating sites in countries where Adzynma is marketed.
Study size	The sample size for this study is approximately 50 patients, based on a feasibility survey involving investigators in 7 EU countries and the UK, a recent Periodic Safety Update Report, and a recently published multinational chart review study (Coppo et al. 2023). This sample size and an event rate of 4% would achieve an approximate precision of ±6.61% at a 95% CI.
Data analyses	Baseline demographic and disease characteristics and treatment details will be summarized descriptively. For the primary and secondary analyses, risks will be estimated using time at-risk, exposure-adjusted incidence rates, and 95% CIs. Other safety outcomes (for example, TEAEs) and pregnancy and infant outcomes will be summarized descriptively. A subset analysis of paediatric patients will be conducted to address Article 46 of the Paediatric Regulation EC 1901/2006 and of Regulation 78A (13) and (14) of the Human Medicines Regulations 2012.
Milestones	• Start of data collection: Q1 2026 • End of data collection: Q2 2030 • Interim study report or study progress report: Not applicable • Final study report: Q4 2030

5.0 AMENDMENTS AND UPDATES

None. Data collection has not started.

6.0 MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	Q1 2026	<date>	<text>
End of data collection (last patient data extraction; study completion)	Q2 2030*	<date>	<text>
Interim study report or study progress report	N/A	<date>	<text>
Final study report	Q4 2030*	<date>	<text>

* If data collection for 50 enrolled patients is completed ahead of schedule, enrollment will close early, and the Final Study Report will be submitted to EMA/UK MHRA within six months of the end of data collection (last patient data extraction) to fulfill the requirements of Article 46 of the Paediatric Regulation EC 1901/2006 and of Regulation 78A (13) and (14) of the Human Medicines Regulations 2012.

7.0 RATIONALE AND BACKGROUND

TTP is a rare and life-threatening microvascular disorder resulting from a deficiency in the ADAMTS13 enzyme. It is characterized by single or recurrent episodes of thrombocytopenia, microangiopathic hemolytic anemia, and widespread microvascular thrombosis. This condition

results in ischemic damage to multiple organs, and primarily affects the kidneys, heart, and brain (Alwan et al. 2019; George 2006). Without treatment, acute TTP events have a mortality rate exceeding 90% (van Dorland et al. 2019).

cTTP comprises no more than 5% of all TTP cases and is an ultra-rare, chronic condition that has an estimated prevalence of <1 in 1,000,000 people (Assiri et al. 2023; Jain et al. 2021). cTTP follows an autosomal recessive inheritance pattern and is caused by homozygous or double heterozygous mutations in the *ADAMTS13* gene. These mutations lead to a severe deficiency in the ADAMTS13 enzyme, which is responsible for cleaving vWF—a large plasma glycoprotein integral to both primary and secondary hemostasis. The resulting deficiency causes the accumulation of UL vWF multimers—a hallmark feature of TTP—that leads to the characteristic microvascular thrombosis observed in this disorder (Moake and McPherson 1989).

The clinical presentation of cTTP is quite variable. While some patients present with relatively asymptomatic anemia and thrombocytopenia, progressive organ dysfunction is frequently encountered, and rapidly progressive life-threatening organ failure may also be encountered (Furlan and Lammle 2001; Schneppenheim et al. 2003; Schneppenheim et al. 2006). Early diagnosis and management, including plasma exchange or rADAMTS13 enzyme replacement, are essential to prevent life-threatening complications and manage chronic symptoms.

Patients can receive replacement therapy through infusions of fresh-frozen or solvent-/detergent-treated plasma. The achievable levels of ADAMTS13 enzyme are limited by the infusion volume, and patients may experience adverse reactions to these plasma infusions (Jain et al. 2021). Adzynma, a human rADAMTS13, has been developed for use as enzyme replacement therapy for children and adult patients with cTTP. In a Phase 3, open-label, crossover trial (Scully et al. 2024), 48 patients were randomly assigned in a 1:1 ratio to receive either rADAMTS13 prophylaxis or standard therapy for two 6-month periods, followed by the alternate treatment. Subsequently, all patients received an additional 6 months of rADAMTS13 treatment. The primary outcome was acute TTP events, with key secondary assessments including TTP manifestations, safety, and pharmacokinetics. No acute TTP events occurred during prophylaxis with rADAMTS13, whereas one event occurred with standard therapy. Thrombocytopenia was the most frequent TTP manifestation, with annualized event rates of 0.74 for rADAMTS13 and 1.73 for standard therapy. AEs were less frequent with rADAMTS13 (71%) compared to standard therapy (84%); AEs related to Adzynma occurred in only 9% of patients. No neutralizing antibodies developed during rADAMTS13 treatment. Additionally, the mean maximum ADAMTS13 enzyme activity levels were substantially higher with rADAMTS13 (101%) compared to standard therapy (19%). Based on these Phase 3 interim results, Takeda sought marketing authorization for Adzynma as the first rADAMTS13 replacement therapy for cTTP.

Adzynma received FDA approval in November 2023 for the prophylactic and on-demand treatment of adult and paediatric patients with cTTP (Takeda 2023). In March 2024, it was approved in Japan for individuals aged ≥12 years with cTTP (Takeda 2024). On 30 May 2024, the CHMP recommended granting marketing authorization under exceptional circumstances in the EU for treating ADAMTS13 deficiency in patients with cTTP (European Medicines Agency

2024). A Commission Decision granting a marketing authorization in exceptional circumstances under Regulation (EC) No. 726/2004 was issued on 01 August 2024. Additionally, on June 20, 2024, the EMA COMP recommended Adzynma as an orphan medicinal product for treating TTP. Adzynma has also been granted an Orphan Drug Designation by the US FDA for the treatment and prevention of acute TTP events and Japan's Ministry of Health, Labour and Welfare for the treatment of TTP.

During the licensing procedure for Adzynma in the EU, the CHMP deemed a PASS necessary to collect additional safety data. The present study is proposed to provide further information about the safety of Adzynma used in real-world clinical practice. This includes monitoring important potential risks, such as neutralizing (inhibitory) antibodies to ADAMTS13 and hypersensitivity reactions. The study will also address long-term safety following Adzynma administration and missing information on pregnancy risks following Adzynma administration during pregnancy. Patients of all ages, including those who became pregnant during Adzynma treatment, will be enrolled in this PASS.

The PASS is an EU RMP category 2 commitment and a Specific Obligation of the Marketing Authorization.

8.0 RESEARCH QUESTION AND OBJECTIVES

This PASS seeks to answer the following research question: 'What are the estimated risks of developing neutralizing antibodies to ADAMTS13 and hypersensitivity reactions, the risks associated with treatment during pregnancy including pregnancy outcomes, and characteristics of long-term safety in patients with cTTP treated with Adzynma?'

The objectives for this study are listed below.

Primary objectives:

1. To estimate the real-world risk of developing neutralizing antibodies to ADAMTS13 during the 6 months following the index Adzynma infusion in paediatric and adult patients with cTTP.
2. To estimate the real-world risk of hypersensitivity reactions during the 7 days following the index Adzynma infusion in paediatric and adult patients with cTTP.

Secondary objectives:

3. To estimate the long-term safety of Adzynma administration by assessing the real-world risk of developing neutralizing antibodies to ADAMTS13 following Adzynma infusion(s) in paediatric and adult patients with cTTP who have at least 6 months of follow-up time from their index infusion.
4. To estimate the long-term safety of Adzynma administration by assessing the real-world risk of hypersensitivity reactions following Adzynma infusion(s) in paediatric and adult patients with cTTP who have at least 6 months of follow-up time from their index infusion.

5. To estimate the real-world risk of hypersensitivity reactions following each administration of Adzynma following the index infusion, in paediatric and adult patients with cTTP.
6. To summarize the TEAEs in patients exposed to Adzynma.
7. To describe the pregnancy and infant outcomes for patients exposed to Adzynma during pregnancy.

Note: Index infusion is defined as the first Adzynma infusion date recorded in the medical record using commercially available Adzynma (excluding doses received in clinical studies or early access program).

9.0 RESEARCH METHODS

9.1 Study Design

This non-interventional, retrospective, post-authorization safety, cohort study utilizes secondary data from medical records to evaluate the safety of Adzynma in real-world clinical practice. Dedicated clinical research staff, in partnership with treating physicians (collectively referred to as 'site personnel'), will retrospectively extract all study data from medical records. The study aims to reflect routine clinical care in hematology specialist institutions across several countries, spanning from the time of Adzynma market availability in each country to the end of the study period. The data collection period is expected to last approximately 4.5 years, with the total study duration anticipated to be approximately 5.5 years.

Site personnel trained on data entry processes will enter anonymized data into a web-based eCRF, hosted on an EDC platform (see Section 9.6). Site personnel will conduct an initial screening of consecutive patients in their patient population, in accordance with the study eligibility criteria (see Sections 9.2.2 and 9.2.3) and eligibility period, which is defined as starting on the day of market authorization and going until 6 months prior to the end of data collection (last patient data extraction), to allow for a minimum follow-up time of at least 6 months.

Medical record data extraction will begin after EMA approval of the protocol, IRB/ethics approvals (as required), and site activations (anticipated to be at least 1 year after market availability in each country to allow time for the accumulation of medical record data). All study data will be extracted retrospectively, with no study data extracted after site activation (as this would constitute prospective data collection). This study aims to enroll approximately 50 patients across several countries, including but not limited to, Austria, France, Germany, Italy, Poland, Spain, Switzerland, and the UK. If the study encounters insufficient numbers of patients, country selection may be modified to meet sample size requirements.

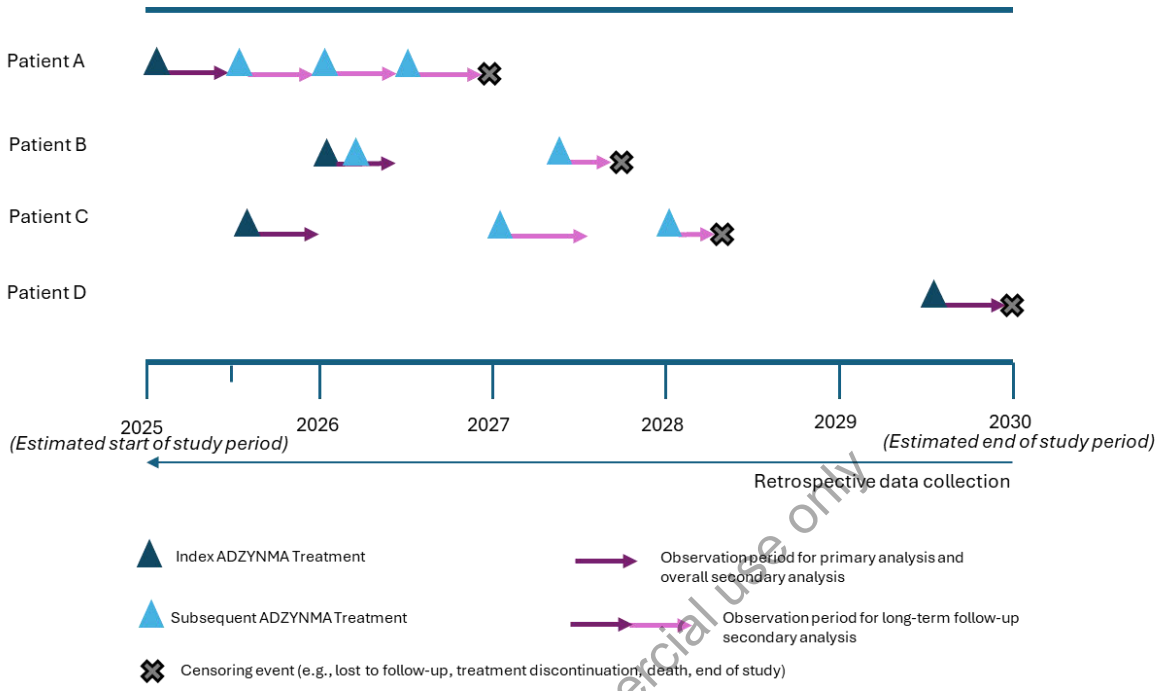
The study entry point for each patient is the index date, defined as the first commercially available Adzynma infusion date in the medical records, excluding doses received in clinical studies or early access program. Medical history related to cTTP, the primary and secondary outcomes, or exposure to Adzynma will be collected without specific time restrictions. Disease-specific history will be documented starting from diagnosis. A 90-day look-back period

is set for other recent medical history to decrease site burden and focus on clinically relevant medical history.

Disease characteristics will be extracted from the time of diagnosis or closest assessment to diagnosis as available in the medical records. Baseline data will be extracted from the nearest available point in the medical records before the index date. Follow-up data will be extracted from after the time of the index dose until 10 days after treatment discontinuation (that is, five half-lives), death, lost to follow-up, withdrawal of consent (as applicable), or until the last observation available in the medical record at the time of extraction, whichever occurs earlier. For women with exposures during pregnancy, follow-up data will be extracted from after the time of the index dose until 1 year after the last menstrual period, death, lost to follow-up, withdrawal of consent (as applicable), or until the last observation available in the medical record at the time of extraction, whichever occurs earlier. The observation period for the primary outcome analysis will start with the index dose date and extend up to 6 months after the index dose date. For the secondary outcome analyses, the observation period will start with the index dose date and extend up to the end of the data extraction for each patient (as defined in the previous paragraph). For long-term safety analyses on the development of neutralizing antibodies to ADAMTS13 and hypersensitivity reactions (secondary objectives numbers 3 and 4), only patients with at least 6 months of follow-up data after the index dose date will be included. For the other secondary outcomes (that is, overall safety of Adzynma by assessing risk of hypersensitivity reactions, TEAEs in patients exposed to Adzynma, and pregnancy and infant outcomes for patients exposed to Adzynma during pregnancy), all patients will be included regardless of the minimum observation period.

Patients with multiple Adzynma treatments will have multiple observation periods, and these will be summed to obtain the total person-time at risk for the development of neutralizing antibodies to ADAMTS13 and hypersensitivity reactions. Figure 9.a is a schematic of 4 hypothetical patients. The darker teal triangle represents the index treatment of Adzynma, and the darker purple arrow represents up to 6 months of post-treatment observation period relevant to the primary outcome analysis and the overall secondary outcome analysis. The lighter teal triangle represents the subsequent treatment of Adzynma, and the lighter purple arrow represents the available post-treatment observation period greater than 6 months (that is, long-term safety follow-up). For the secondary analyses, the observation period will begin with the index date and continue until censoring.

Figure 9.a Follow-Up Time After Each Adzynma Treatment



Specific at-risk windows for the development of neutralizing antibodies to ADAMTS13 and hypersensitivity reactions are pre-defined (Table 9.a). Events occurring beyond these at-risk windows will not be included in the exposure-adjusted incidence rates for the primary or secondary analyses. However, all events, regardless of their timing, will be summarized and reported (see Section 9.7.1). For example, if a hypersensitivity event were to occur outside the 7-day at-risk window, the event would not be included in the primary or secondary analysis; it would, however, still be summarized and reported. Further details will be provided in the SAP.

Table 9.a At-Risk Windows

Event	At-risk window (Days after an infusion)
Hypersensitivity reactions	7
ADAMTS13 inhibitor formation	180

9.2 Setting

9.2.1 Study Population

This study aims to enroll both paediatric and adult patients who have received commercially available Adzynma for the treatment of cTTP, either prophylactically or as on-demand therapy for acute episodes—including those who became pregnant during Adzynma treatment.

The site investigators will be instructed to select consecutive patients in chronological order to avoid selection bias and optimize retrospective data collection. The target population includes

patients treated with commercially available Adzynma in Europe. The source population is comprised of patients prescribed Adzynma, primarily from hematology specialist institutions and treatment centers, in a subset of countries in which Adzynma is commercially available.

Both experienced patients (that is, initial exposure during trials or expanded access programs prior to commercial availability of Adzynma) and Adzynma-naïve patients (that is, initial exposure was to commercially available product) are eligible to participate. However, their qualifying exposure (that is, index infusion), as specified in the inclusion and exclusion criteria, must be commercially available Adzynma. The date of index infusion is the beginning of the observation period for adverse events collected in this study. Adverse events will not be collected for prior exposures in clinical trials or expanded access programs, instead the event prior to commercial availability of Adzynma dose is collected as relevant medical history. Prior TAK-755 trial or expanded access program participation will be collected as part of their medical history, as available, including relevant dates and selected details. The study team will monitor the proportions of Adzynma-naïve patients enrolled through period review of selected variables in the EDC platform.

Based on the availability of the study population, sites will be selected from several countries, including but not limited to, Austria, France, Germany, Italy, Poland, Spain, Switzerland, and the UK. The list of study countries may be revised according to market uptake to achieve the target sample size. Conducting this study across several countries will enhance the representativeness of the study results.

Site recruitment will focus on healthcare providers (HCPs) who have experience with Adzynma. The MAH will explore the possibility to collaborate with the International Hereditary TTP Registry's (ttpregistry.net, Hereditary TTP Registry, Accessed 06 May 2025) principal investigator.

9.2.2 Inclusion Criteria

Eligible patients must have the following attributes documented in their medical records at the time of enrollment:

1. Is diagnosed with cTTP.
2. Had received commercially available Adzynma treatment for cTTP within the eligibility period, of which there must be a recorded date and dose of at least one Adzynma administration in their medical chart.
3. Provides a signed ICF (or assent and consent forms, if applicable), in accordance with local ethical and institutional requirements.

Note: All medical record data will be extracted retrospectively. Therefore, an exemption or waiver of informed consent will be sought from all associated IECs and IRBs. The eligibility period is defined as starting on the day of market authorization and going until 6 months prior to the end of data collection (last patient data extraction), to allow for a minimum follow-up of at least 6 months.

9.2.3 Exclusion Criteria

Patients will be ineligible to participate in the study if they have any of the following attributes:

1. Has a history or presence of a functional ADAMTS13 inhibitor (that is, neutralizing antibodies to ADAMTS13/rADAMTS13).
2. Has concurrent use of an investigational drug or is enrolled in another clinical trial at the time of index Adzynma infusion.

Note: The study will enroll deceased patients if they meet the eligibility criteria at the time of enrollment.

9.3 Variables

9.3.1 Exposure Variables

Commercially available Adzynma is the exposure of interest for all study objectives. Treatment details will be captured following index infusion (that is, the first Adzynma infusion date recorded in the medical record using commercially available Adzynma) and during the post-index follow-up.

The EMA has authorized Adzynma for IV administration for patients of all ages as follows:

- *Prophylactic therapy:* 40 IU/kg body weight IV once every other week. The dose may be adjusted to once weekly, based on prior prophylactic dosing regimen or clinical response
- *On-demand therapy:* 40 IU/kg body weight on Day 1; 20 IU/kg body weight on Day 2; 15 IU/kg body weight on Day 3 and beyond, until 2 days after the acute event is resolved

Adzynma treatment details will be collected, and will include the following:

- Infusion start and end date
- Infusion dose and frequency
- Treatment modifications (for example, dose change, frequency change, date of treatment modification)
- Type of treatment facility (for example, hospital, infusion center, home administration)
- Prophylactic or on-demand treatment
- Adzynma-naïve or experienced at baseline (for example, previous exposure to treatment via clinical trial, early access program, or at another site)
- Relevant concomitant medications (that is, related to the exposure and disease of interest)

Note: The index date will be the first Adzynma infusion date recorded in the medical record using commercially available Adzynma (excluding doses received in clinical studies or early access program).

9.3.2 Outcome Variables

Outcome variables associated with the primary and secondary objectives will be collected, and will include the following:

- Hypersensitivity reactions that occur following Adzynma infusion(s)
- Neutralizing antibodies to ADAMTS13 following Adzynma infusion(s) (including date and details of initial and confirmatory laboratory samples)
- TEAEs, and additional variables, including start/end date of the event, severity, causality, action taken with Adzynma, medication received, the outcome of the event, seriousness criteria

Variables associated with pregnancy outcomes include the following:

- Gestational age/trimester of Adzynma exposure
- Pregnancy outcome (for example, spontaneous abortion, stillbirth, induced abortion, live birth)
- Pregnancy complications
- Gestational age at birth (for example, ≥37 gestational weeks, <37 gestational weeks)
- Year of birth
- Birth weight (for example, normal weight, small for gestational age)
- Congenital anomaly detected (yes, no) and details, as available
- Breastfeeding status while receiving Adzynma (categorized as yes, no, or unknown)
- Infant growth and development outcomes (categorized as normal, abnormal [specify], or unknown)

9.3.3 Demographic and Baseline Variables

Demographic and clinical data—including potential covariates and risk factors—will be collected, along with relevant study outcomes, to account for potential confounding variables during data analysis. Variables associated with demographic and clinical characteristics will be collected, and will include the following:

- Date of informed consent (if applicable)
- Demographic data (for example, age, sex)
- Clinical data (for example, body weight, height)
- Disease characteristics (for example, cTTP diagnosis details, confirmation by genetic testing, diagnosis date, disease type)
- cTTP treatment history (for example, prior on-demand or prophylaxis cTTP treatments)

- Medical history and comorbidities
- Pregnancy status

9.3.4 Schedule of Assessments

Table 9.b summarizes the schedule of assessments for the variables described in the preceding sections.

Table 9.b Schedule of Assessments

Variables [a]	Baseline [b]	Post-index follow-up [c]
Informed consent [d]	X	
Demographic and clinical data	X	
Disease characteristics and cTTP treatment history [e]	X	
Medical history and comorbidities [f]	X	
Pregnancy status	X	X
Adzynma treatment details		X
Relevant concomitant medications		X
TEAEs (including but not limited to hypersensitivity reactions, neutralizing antibodies to ADAMTS13)		X
Pregnancy outcomes [g]		X
Covariates and risk factors	X	X

[a] Variable details are specified in Section 9.3.

[b] Baseline is defined as the period closest to the index dose, as available in the medical records.

[c] Post-index follow-up period includes the index treatment course and additional treatment courses, up until the day before site activation. Follow-up data will be extracted from after the time of the index dose until 10 days after treatment discontinuation (that is, five half-lives), death, lost to follow-up, withdrawal of consent (as applicable), or until the last observation available in the medical record at the time of extraction, whichever occurs earlier.

[d] Informed consent will be collected as applicable when required by local regulations.

[e] Disease characteristics and cTTP treatment history will be extracted from the time of diagnosis or closest assessment to diagnosis as available in the medical records.

[f] Relevant medical history related to cTTP, primary and secondary outcomes, or exposure to Adzynma will be collected without specific time restrictions. Disease-specific history will be documented starting from diagnosis. A 90-day look-back period is set for other recent medical history.

[g] For women with exposures during pregnancy, follow-up data will be extracted from after the time of the index dose until 1 year after the last menstrual period, death, lost to follow-up, withdrawal of consent (as applicable), or until the last observation available in the medical record at the time of extraction, whichever occurs earlier.

9.4 Data Sources

The primary source for this retrospective study is the electronic/paper medical records of enrolled patients from participating sites in countries where Adzynma is marketed.
Site personnel will collect patient data from the medical records and enter these in a web-based

eCRF hosted on an EDC platform. The eCRF will be accessible via a standard web browser. The study variables to be collected are summarized in Section 9.3.

9.5 Study Size

Precision estimates were conducted to inform the appropriate sample size. Table 9.c illustrates the width of the 95% CIs and probability of at least one event for various sample size scenarios. Since the Phase 3 clinical trial of Adzynma did not have any events of hypersensitivity or neutralizing antibodies (n=21), we have assumed a few different low event rate scenarios (that is, 4%, 8%, and 12%) for these calculations.

The study aims to enroll approximately 50 patients, based on a feasibility survey involving investigators in 7 EU countries and the UK, a recent Periodic Benefit-Risk Evaluation Report (PBRER), and a recently published multinational chart review study (Coppo et al. 2023). The feasibility survey indicated that sites could enroll 2 patients on average, excluding outliers. However, the estimate has limitations: not all surveyed sites may qualify or remain interested, especially as commercial Adzynma becomes available in the upcoming years. Additionally, while the survey reflects anticipated enrollment over 5 years, the study's retrospective design limits enrollment to approximately 2 to 3 years per site, such that all enrollments occur before site activation. Enrollment will begin after at least 1 year following the commercial availability of Adzynma to the site, followed by retrospective data extraction.

A recent PBRER (data lock point 08 November 2024) identified 47 potentially eligible participants, including patients from the US and China, which are outside the study's target population in Europe. The multinational chart review study by Coppo et al. (2023) included a review of medical records from 9 sites in Europe and the US, enrolling 78 patients over an 8-year timeframe (2009–2017). Assuming that about half were from the US, this figure is reduced to approximately 39 patients from Europe and occurring over a longer enrollment period compared to this study. Collectively, these findings support the feasibility of the protocol's target sample size of 50.

The MAH will explore the possibility of collaborating with the principal investigator of the International Hereditary TTP Registry (ttpregistry.net, Hereditary TTP Registry, Accessed 06 May 2025). However, some potential challenges in leveraging this registry for data or identifying patients include its passive recruitment approach, which does not specifically target patients prescribed Adzynma. Additionally, the registry was not designed to capture specific adverse events like neutralizing antibodies and hypersensitivity reactions. Furthermore, increasing the reporting requirements to match Adzynma treatment frequencies could lead to poor compliance and incomplete data collection by physicians completing the registry follow-up forms.

Feasibility assessments will be updated sequentially as individual countries receive market authorisation. This sample size and an event rate of 4% would achieve an approximate precision of ±6.61% at a 95% CI.

Table 9.c Precision Estimates

N	Event rate	Lower limit of 95% CI [a]	Upper limit of 95% CI [a]	Precision (Half CI width)	Probability of ≥1 events
30	4.0%	0.17%	18.23%	9.03%	0.706
30	8.0%	1.28%	23.89%	11.31%	0.918
30	12.0%	3.06%	29.07%	13.00%	0.978
40	4.0%	0.33%	15.46%	7.57%	0.805
40	8.0%	1.80%	21.06%	9.63%	0.964
40	12.0%	3.90%	26.19%	11.14%	0.994
50	4.0%	0.49%	13.71%	6.61%	0.870
50	8.0%	2.22%	19.23%	8.51%	0.985
50	12.0%	4.53%	24.31%	9.89%	0.998

[a] 95% CIs and precision are calculated using exact methods.

9.6 Data Management

Data management will be conducted in accordance with the data management plan and relevant SOPs. The data management plan will outline the study's data management strategies, including but not limited to, data cleaning/validation, and data handling processes and responsibilities.

After all study data are extracted in accordance with the case report form completion guidelines and reviewed according to the data review plan, the database will be locked for analysis.

Should informed consent be required as per local regulations, and the written informed consent of a patient is known not to be available, data for this patient will not be entered into the database or deleted if already entered.

Patient confidentiality will be strictly maintained. Access to the EDC system will be regulated through a hierarchical username and password control system. Patient data will be de-identified by designing data entry fields to minimize the risk of entering identifying information, such as initials, date of birth, or site-assigned patient identifiers. Only trained site personnel will enter data into the eCRFs. Patients' ages in whole years—but not their dates of birth—will be recorded. Race and ethnicity data will not be collected. No patient identifiers used by sites will be entered; instead, the EDC program will automatically assign a study ID number to each patient. The de-identified data within the EDC system will be visible to the CRO and the sponsor. However, only site personnel will be able to trace a study ID number back to a patient's identity, which is necessary for site personnel to respond to data queries.

The completed original eCRFs are the sole property of the sponsor and will not be made available in any form to third parties without written permission from the sponsor—except for authorized representatives or appropriate regulatory authorities.

To enable evaluations and/or audits from regulatory authorities or the sponsor, the investigator agrees to keep records—including the identities of all patients (sufficient information to link records [for example, eCRFs and medical records]), source documents, detailed records of patient disposition, and adequate documentation of relevant correspondence (for example, letters,

meeting minutes, and telephone calls/reports). The investigator should retain the records for the length of time specified in local regulations or in the site contract agreement (whichever period is longer).

If the investigator becomes unable, for any reason (for example, retirement or relocation), to continue to retain study records for the required period, the sponsor should be notified. The study records must be transferred to a designee approved by the sponsor, such as another investigator, another institution, or to an independent third party arranged by the sponsor. The investigator must obtain the sponsor's written permission before disposing of any records, even if retention requirements have been met.

9.6.1 Data Collection Tool

The study site will receive data collection tools (eCRFs, access to EDC, and so on). Whenever possible, complete datasets should be entered. Data entry should follow the eCRF completion guidelines.

This study will host a web-based EDC system to serve as an integrated, transparent tool to collect and manage data, and track study progress at the site and patient levels. Data in the EDC system will be kept in a central database.

The EDC system will meet approved, established standards for the security of health information, will be validated, and will be 21 Code of Federal Regulations Part 11 compliant. To ensure that patient data (and other confidential data) remain secure and intact, SOPs and quality control processes that address patient data security will be followed. The EDC system will have built-in edit checks and validations and will support electronically generated and manual queries.

The study site's responsible investigator must provide signatures to confirm the collected data is accurate and complete.

9.6.2 Data Flow

The data flow for this chart review study is summarized below:

- Patients' medical records (for example, electronic and/or paper charts) stored at the site will serve as the source for the collected data.
- Site personnel will be trained by the CRO to perform chart extraction (including data entry) and how to retrieve and respond to data queries in the EDC system. It is assumed that all sites will be able to complete data entry into the eCRFs via the EDC system.
- The EDC system includes logic checks to minimize data entry errors. Data inconsistencies outside the logic checks will be managed by manual queries issued by data management within the EDC system for site completion. All queries will be monitored until resolution within the EDC through the electronic query report.
- Each study investigator has ultimate responsibility for the collection and reporting of all data entered into the eCRFs and any other data collection forms (source documents); and

ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The eCRFs must be electronically signed prior to database lock by the study investigator, attesting that the data contained are correctly recorded.

- The data entered into the EDC system will be used to create a custom study database for analysis in this study.

9.7 Data Analysis

The SAP will provide detailed descriptions of all planned analyses, which will be performed on the full analysis set (unless otherwise specified). All computations and generation of tables, listings, and figures will be performed using SAS version 9.4 or higher (SAS Institute, Cary, NC, US), or a comparable statistical software.

9.7.1 Statistical Methods

Characteristics of the study population will be reported using descriptive summary statistics. Categorical variables will be presented as frequencies and percentages. Continuous variables will be presented as mean with SD or SE and range for normally-distributed variables; and as mean and SD, median, IQR, and range for non-normally-distributed variables.

A subset analysis of paediatric patients will be conducted, which will be detailed in the SAP, to address Article 46 of the Paediatric Regulation EC 1901/2006 and Regulation 78A (13) and (14) of the Human Medicines Regulations 2012.

9.7.1.1 Primary Analyses

For the primary analysis, the risk of hypersensitivity reactions and inhibitor formation events during the 6 months following the index Adzynma infusion will be estimated separately, using time at-risk, exposure-adjusted incidence rates, and 95% CIs (Liu et al. 2006; Qiuhong et al. 2020). This approach includes only the time at-risk for each patient in the denominator, and thereby, more accurately summarizes the safety profile (Liu et al. 2006).

Exposure-adjusted incidence rates will be calculated as the number of patients experiencing each event (that is, hypersensitivity reactions or inhibitor formation) during the at-risk period, divided by the sum of at-risk person-time for all patients, specific to each event. For the primary analysis, person-time at-risk will be calculated for the first occurrence of each event, and truncated after the patient experiences that event; although the patient may continue to contribute person-time for the other event, as available in the database.

For each treatment course, a patient's person-time is counted from the first Adzynma dose until the earliest of the following:

1. Patient completes the at-risk window.
2. Patient experiences the event.

3. Patient becomes lost to follow-up (that is, the patient's data are no longer available in the medical record).
4. Patient withdraws consent (at sites where informed consent is required by the IEC/IRB).

For a patient with multiple treatment courses during the data window, all increments of at-risk person-time will be summed for the patient's total at-risk person-time. Total at-risk person-time for all patients will be summed for the overall person-time in the denominator. Detailed definitions for treatment courses will be provided in the SAP.

9.7.1.2 Secondary Analyses

For the secondary analysis, the long-term safety risk of hypersensitivity reactions and inhibitor formation events among patients who have at least 6 months of follow-up time from their index infusion will be estimated separately, using time at-risk, exposure-adjusted incidence rates, and 95% CIs. The analytic approach will be the same as that followed for the primary analysis (Section 9.7.1.1).

The risk of hypersensitivity reactions will also be evaluated during the 7 days after each administration of Adzynma following the index infusion.

All TEAEs in patients exposed to Adzynma occurring during the study period will be summarized using descriptive summary statistics, presented by MedDRA Preferred and System Organ Class terms.

Patients with pregnancy exposures are expected to be rare; therefore, these data will be summarized and reported using descriptive summary statistics.

Further details of these analyses will be outlined in the SAP.

9.7.2 Bias and Confounding

To evaluate potential confounders, hypersensitivity reaction events and inhibitor formation events may be stratified by demographic and baseline characteristics, risk factors, and treatment details (for example, prophylactic and on-demand use), as sample size allows. Detailed information on the stratification of these characteristics will be outlined in the SAP.

9.7.3 Missing Data

Analyses will be conducted using available data, and missing values will not be imputed (unless specified in the SAP). Given the observational nature of the study, some missing values are expected. However, sites should make all reasonable efforts to minimize missing data. Exposure-adjusted incidence rates will exclude hypersensitivity reaction events and inhibitor formation events with missing or partial dates for the event and/or Adzynma treatment. These events will be summarized and reported using descriptive summary statistics.

9.7.4 Interim Analyses

Interim analyses are not planned for this study.

9.7.5 Changes from Planned Analyses

Any known deviations from the planned analyses, the reason for such deviations, and all alternative or additional statistical analyses that may be performed—and the final statistical analysis—will be described in a revised SAP before completion of data collection.
All later deviations or alterations will be summarized in the final study report.

9.8 Quality Control

The CRO will perform remote site monitoring for data quality, compliance, and timely data collection, in accordance with the monitoring plan. During the study, the site investigator is required to maintain a study site file that will include the following essential documents and other documents as specified in the monitoring plan:

- Written agreement between the sponsor and the study site.
- Study protocol and any amendments.
- Signed and dated protocol agreement and amendment agreements.
- List of participating patients.
- Written IEC/IRB approval and vote, according to local regulations.
- Authority approval, according to local regulations.
- Patient information sheet and/or ICF in local language, approved by IECs/IRBs, and including the original signed forms, as required. *(Note: An exemption or waiver of informed consent will be sought from all relevant IECs/IRBs. This item applies to sites that do not receive approval of the waiver.)*

9.8.1 Data Validation

Data entered by sites into the EDC system will be validated according to relevant SOPs.

Edit checks will be programmed and might include data type (integer, decimal, text), range, length (maximum characters or number length), precision (decimal places), date ranges, missing data in required fields, and overlapping data. In addition, data can be compared against absolute values (for example, study start), values on the same screen, values in other data entry sessions, calculated (dynamic) values, and multiple values. Any corrections made after the original data are saved will be documented in an audit trail.

The clinical data manager will review data issues raised by online and post-entry checks, using validation programs and data listings.

If clarifications are needed, data queries will be created through the web-based application. Site personnel are required to respond to the queries and correct the study database if needed. The site investigator will retain full responsibility for the accuracy and authenticity of all eCRF data. Additional details will be provided in the data management plan.

9.8.2 Archiving of Study Documentation

The site investigator must maintain adequate and accurate records to enable verification of the study conduct and the study data. After the final database lock, the site investigator is required to store the list of participating patients, signed ICFs (as applicable), and other documents outlined during site initiation on site for 5 years. After that period, the documents may be destroyed or retained, as required by local regulations and site requirements. The sponsor must be notified in advance if the site investigator plans to assign the study records to another party or move them to another location. Following study completion, a complete copy of the study data will be provided to the sponsor for archival purposes.

9.8.3 Audits and Inspections

The sponsor's quality assurance unit may audit the study to ensure that study procedures comply with the protocol and SOPs, and that the study data are correct and complete. Representatives from IECs/IRBs or competent authorities may, in rare cases, wish to inspect the study on site. Upon receiving notification of such inspection, the site investigator must immediately contact the sponsor and make the records available, as requested.

9.9 Limitations of the Research Methods

Due to the rare nature of the disease, a small sample size is projected—which limits the precision of risk estimates. To maximize the sample size, the study will aim to enroll all available patients at the site, rather than limiting enrollment by site or country. Patients will be enrolled consecutively by index date to minimize selection bias at the patient level and maximize post-index follow-up time. In addition, eligibility criteria are streamlined to avoid excluding patients unless the criteria directly impact the primary objectives. The representativeness of the study population might be impacted by selection bias. The study sites are hematology specialist institutions and treatment centers, whose patient populations may have disproportionately higher numbers of severe cases than the overall target population.

Given the retrospective nature of this study, data quality and completeness will depend on the quality of information in the medical records, and the accuracy and consistency of data entry. Site personnel will be trained for data entry and will be given detailed guidance for accurate eCRF completion. Remote central monitoring will be conducted promptly after data entry so that queries can be raised promptly. In addition, the EDC system includes edit checks designed to deliver data that is predominantly clean upon data entry. A risk-based monitoring approach will be used to review the accuracy of critical variables. Missing exposure and outcome dates in medical records will not be imputed, thus avoiding information bias.

Considering the retrospective nature of this non-interventional post authorization safety study, which relies on existing medical records of patients treated with commercially available Adzynma and mirrors routine clinical practice, there may be challenges in obtaining information related to the outcome of pregnancy during exposure with commercially available Adzynma. Some variables, such as breastfeeding status, pregnancy outcomes, infant growth and development, would likely necessitate access to infant medical records and collaboration with

paediatricians, which exceeds the scope of the planned study design. However, select variables, outlined in Section 9.3.2, will be extracted in this study, if available in the medical records of the patient.

10.0 PROTECTION OF PARTICIPATING PATIENTS

The study will be considered a PASS and will comply with the definition of the non-interventional (observational) study provided in the Guideline on Good Pharmacovigilance Practices (GVP): Module VIII – Post-Authorisation Safety Studies (European Medicines Agency 2017).

This study will be conducted in accordance with the current version of the Declaration of Helsinki (World Medical Association 2013), the International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices (pharmacoepi.org/resources/policies/guidelines-08027/, Accessed 06 May 2025), and the ENCePP Guide on Methodological Standards in Pharmacoepidemiology (encepp.eu/standards_and_guidances/methodologicalGuide.shtml, Accessed 06 May 2025). The ENCePP Checklist for Study Protocols (https://encepp.europa.eu/encepp-toolkit/encepp-checklist-study-protocols_en, Accessed 06 May 2025) will be completed (Annex 2), and the study will be registered in the HMA-EMA Catalogue of RWD studies (https://catalogues.ema.europa.eu/catalogue-rwd-studies). Additionally, the study will adhere to local regulations and the General Data Protection Regulation (2016/679) (European Parliament and The Council of European Union 2016).

The study does not impact the day-to-day lives of the patients. This retrospective, observational, non-interventional study is based on the collection of existing data from patients' medical records previously collected for routine clinical care, and not for research purposes. There are no study visits, procedures, interventions, or prospective data collection. Therefore, it is unlikely that this study would adversely affect the rights and welfare of the patients, increase their risk for harm, or impact their medical care.

In a retrospective medical record review study with reasonable and appropriate data protections, risks related to a breach of confidentiality are minimal. In this study, the risk will be minimized in the following ways:

- The patient's identity will only be known to the participating sites and site investigators.
- All medical record data will be processed in a fully confidential manner.
- No identifiable/contact information will be collected from patients' records for the study.
- All patient-level data will be pseudonymized and assigned a unique study ID number, which will be generated by the EDC system.
- The eCRF will not collect any personal or identifiable information.

10.1 Informed Consent

All medical record data will be extracted retrospectively; therefore, an exemption or waiver of informed consent will be sought from all associated IECs/IRBs. If informed consent is required, it will be collected from patients by the site investigators, in accordance with local ethical and institutional requirements. If required, as part of the informed consent process, the patient must agree that sponsor personnel, their representatives, or IEC/IRB/competent authority personnel (national or other) may require direct access to their medical records, which were collected, processed, and stored in an anonymous form for evaluation of this study and any later overviews. The patient must also agree that their data may be transferred in anonymous form to third parties (for example, to other companies or authorities) that may be located in other countries.

10.2 Ethical Review

Full ethical approval will be sought with relevant IECs/IRBs (as applicable). Other required reviews of the study protocol by specific committees will be obtained in accordance with applicable national and local regulations. The study will adhere to the local regulations and decisions of the IECs/IRBs from the participating sites and countries. According to applicable regulations, the sponsor, appointed CRO, or site investigator will obtain approval of the protocol and associated documents from the relevant IECs/IRBs (as applicable). Other required documentation (such as periodic updates on the study progress, notification of the end of the study, and a summary of the study results) will be submitted to the IEC/IRB. The sponsor or the appointed CRO will send the required documents to the competent authority and/or other national/regional authorities. The sponsor or the appointed CRO will keep an updated list of submission and approval dates and a copy of all documents submitted.

11.0 MANAGEMENT AND REPORTING OF AEs/ADVERSE REACTIONS

11.1 Definitions

11.1.1 Adverse Events

An AE is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, a disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

11.1.2 Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death. Note that death is an outcome of an event. The event[s] causing death should be recorded.

- In the view of the HCP, places the patient at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- An SAE may also be any other medically important event that, in the opinion of the HCP, may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

11.1.3 Adverse Drug Reactions

An ADR is an AE for which there is at least a reasonable suspicion of a causal relationship between an AE and a suspected medicinal product.

11.1.4 Product Quality Complaints

A PQC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, strength, purity, effectiveness, or performance of a product or device and combination product after it is released for distribution.

11.1.5 Special Situation Reports

An SSR includes any of the following events:

- Pregnancy: Any case in which a pregnant patient is exposed to a Takeda Product or in which a female patient or female partner of a male patient becomes pregnant following treatment with Takeda Product. Exposure is considered either through maternal exposure or via semen following paternal exposure.
- Breastfeeding: Infant exposure from breast milk.
- Overdose: All information of any accidental or intentional overdose.
- Drug abuse, misuse, or medication error: All information on medicinal product abuse, misuse, or medication error (potential or actual).
- Suspected transmission of an infectious agent: Suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product.
- Lack of efficacy of Takeda Product.
- Accidental/Occupational exposure.

- Use outside the terms of the marketing authorization, also known as "off-label" and "off-label use" for unintended benefit.
- Use of a falsified medicinal product.
- Use of a counterfeit medicinal product.
- Drug-drug interactions and drug-food interactions.
- Inadvertent or accidental exposure with or without an AE.
- AEs occurring in the paediatric or elderly population, as described in GVP Module VI.

An SSR should be reported even if there is no associated AE.

11.2 Collection and notification of Adverse Events, Special Situation Reports and Product Quality Complains to Takeda Pharmacovigilance or Takeda Quality

- SAEs, AEs, ADRs, SSRs, and PQCs in the healthcare records or other applicable source data that are part of the study objectives or endpoints

  Events/complaints that are part of the study objectives or endpoints will be systematically identified and collected from healthcare records or other applicable source records and summarized in aggregate as part of any interim analysis and in the final study report. Such events do not need to be notified as individual reports to Takeda Pharmacovigilance and/or Takeda Quality.

- SAEs, AEs, SSRs, and PQCs in the healthcare records or other applicable source data that are not part of the study objectives and endpoints

  Events/complaints which are not part of the study objectives and endpoints will not be extracted or collected from healthcare records or other applicable source records.

- SAEs, AEs, ADRs, SSRs, and PQCs spontaneously reported to the investigator(s) or research team

  If during the conduct of the study the investigator(s) or a member of the research team is spontaneously informed by an HCP or patient of an SAE, AE, ADR, SSR, or PQC where the event/complaints pertains to a Takeda Product (or unbranded generic), such information should be forwarded to the relevant Takeda Pharmacovigilance and/or Takeda Quality department **within 1 business day for fatal or life-threatening SAEs and PQCs, within 4 calendar days for other SAEs, and within 7 calendar days for all other events**. This includes events spontaneously notified to the investigator(s) or research team which are study endpoints and also events spontaneously notified which are not study endpoints. As such reports are spontaneously notified, causality of any AEs should be assumed unless there is evidence to the contrary.

  The investigator may be contacted by Takeda to obtain additional information on the event or for data clarification.

AE reports and SSRs shall be reported centrally to: PVSafetyAmericas@takeda.com.

PQCs shall be sent to the following contact: PQC@takeda.com.

12.0 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The sponsor will ensure that study results are made publicly available, as required by local authorities. The sponsor will publish the protocol and results in the HMA-EMA Catalogue of RWD studies. The sponsor may post the results of the study on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws, and regulations. The final study report will be available to regulatory authorities, as described in Section 6.0. Site investigators will be informed about the results when the report is finalized. The sponsor will adhere to regulatory reporting requirements, as specified in official communications.

The sponsor has the right to use the data and results for regulatory purposes, and for internal presentation within the company and to partners. Published study results will follow the recommendations of the International Committee of Medical Journal Editors (icmje.org/recommendations/, Accessed 06 May 2025). Communication in appropriate scientific venues will be considered. When reporting the study results, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology checklist will be followed (von Elm et al. 2014).

12.1 Non-Interventional Studies with Paediatric Patients

If a Takeda-sponsored, non-interventional study includes paediatric patients, and Takeda is the marketing authorization holder of the medicinal product in the EU/European Economic Area and/or the UK, the final study report will be submitted to the EU/UK within 6 months of study completion (as described in Section 6.0) to fulfil the requirements of Article 46 of the Paediatric Regulation EC 1901/2006 and of Regulation 78A (13) and (14) of the Human Medicines Regulations 2012.

13.0 REFERENCES

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APPENDICES

Annex 1 List of Stand-Alone Documents

None

Annex 2 ENCePP Checklist for Study Protocols

Doc. Ref. EMA/540136/2009

Adopted by the ENCePP Steering Group on 15/10/2018

ENCePP Checklist for Study Protocols (Revision 4)

Study Title: A Post-Authorization Safety study (PASS) to Further Evaluate Real-World Safety in Patients with Congenital Thrombotic Thrombocytopenic Purpura (cTTP) Treated with Adzynma

HMA-EMA Catalogue of real-world studies: N/A (will be updated upon completion of final protocol)
Study reference number (if applicable): TAK-755-4007

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section number**
1.1 Does the protocol specify timelines for:				
1.1.1 Start of data collection [a]	☒	☐	☐	6.0
1.1.2 End of data collection [b]	☒	☐	☐	
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the HMA-EMA Catalogue of real-world studies	☐	☐	☒	
1.1.6 Final report of study results	☒	☐	☐	

N/A=not applicable.

[a] Date from which information on the first study is first recorded in the study database, or in case of secondary use of data, the date from which data extraction starts.

[b] Date from which the analytical dataset is completely available.

Comments:

Section 2: Research question		**Yes**	**No**	**N/A**	**Section number**
2.1	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7.0, 8.0
	2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	
	2.1.2 The objective(s) of the study?	☒	☐	☐	
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

N/A=not applicable.

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary, or combined data collection?	☒	☐	☐	9.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	N/A
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11.0

N/A=not applicable.

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section number**
4.1	Is the source population described?	☒	☐	☐	9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2
	4.2.2 Age and sex	☒	☐	☐	
	4.2.3 Country of origin	☐	☒	☐	
	4.2.4 Disease/indication	☒	☐	☐	
	4.2.5 Duration of follow-up	☒	☐	☐	
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

N/A=not applicable.

Comments:

The study population is defined in terms of age but not sex (See Section 9.2.1).

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	N/A
5.3	Is exposure categorized according to time windows?	☒	☐	☐	9.3
5.4	Is the intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3
5.5	Is exposure categorized based on the biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	N/A
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	N/A

N/A=not applicable.

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2, 9.7
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.7
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	N/A
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilization, burden of disease or treatment, compliance, disease management)	☐	☐	☒	N/A

N/A=not applicable.

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section number**
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.3, 9.7
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.2, 9.9
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

N/A=not applicable.

Comments:

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section number**
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☒	☐	☐	9.3

N/A=not applicable.

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	N/A
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	N/A
	9.3.3 Covariates and other characteristics?	☐	☒	☐	N/A
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	N/A

N/A=not applicable.

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3	Are descriptive analyses included?	☒	☐	☐	9.7
10.4	Are stratified analyses included?	☒	☐	☐	9.7
10.5	Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	N/A

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section number**
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	N/A

N/A=not applicable.

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	N/A

N/A=not applicable.

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	N/A
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

N/A=not applicable.

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section number**
13.1 Have the requirements of the Ethics Committee/Institutional Review Board been described?	☒	☐	☐	10.0
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	N/A
13.3 Have data protection requirements been described?	☒	☐	☐	10.0

N/A=not applicable.

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5.0, 9.7.5

N/A=not applicable.

Comments:

Protocol amendments will be documented in section 5.0 of the protocol. Protocol deviations will be summarized in the final study report. Deviations from the planned analysis will be summarized in the SAP.

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12.0
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12.0

N/A=not applicable.

Comments:

Name of the main author of the protocol: [redacted]

Date:

03-Jun-2025 | 21:15:41 JST

Signature:

Signed by:

[redacted]