

**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)
Division of Pharmacovigilance (DPV)**

PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM

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To: Nobuko Katagiri, PhD
Chair of the Review Committee
Office of Therapeutic Products

Through: Adamma Mba-Jonas, MD
Branch Chief, PB1

Meghna Alimchandani, MD
Deputy Director DPV
OBPV, CBER, FDA

Subject: Review of Pharmacovigilance Plan

Applicant: Takeda Pharmaceuticals

Product: ADZYNMA (ADAMTS13, recombinant-krhn)

Application Type / Number BLA / STN 125795/0

Proposed Indication Prophylactic or on-demand enzyme replacement
therapy for patients with congenital thrombotic
thrombocytopenic purpura (cTTP)

Submission Date: 17 March 2023

Action Due Date: 15 November 2023

1 OBJECTIVE

The purpose of this review is to assess the adequacy of the applicant's pharmacovigilance plan (PVP) submitted under the original BLA 125795/0 based on the safety profile of ADZYNMA (ADAMTS13, recombinant-krhn), also referred to as rADAMTS13 in this document. Our review will determine whether any safety-related studies such as Post-Marketing Requirements (PMRs) are warranted, whether there will be any agreed upon Post-Marketing Commitments (PMCs), or if Risk Evaluation and Mitigation Strategies (REMS) are required for ADZYNMA, should the indication for this product be approved. Please refer to Appendix A for the complete list of materials reviewed for this memorandum.

2 BACKGROUND

Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy (TMA) characterized by microvascular platelet-rich thrombi resulting in ischemic end organ damage, thrombocytopenia, and microangiopathic hemolytic anemia. Thrombotic thrombocytopenic purpura is caused by severely reduced activity of the von Willebrand factor-cleaving ADAMTS13 (A disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13) plasma protease, which is clinically defined as an activity level of <10% (George et al. 2022). ADAMTS13 cleaves ultralarge molecules of von Willebrand factor (vWF) that are secreted into plasma by endothelial cells but remain attached to the endothelial surface. Reduced ADAMTS13 activity results in accumulation of ultralarge vWF multimers on the endothelial surface and subsequent platelet attachment and accumulation, disseminated microthrombosis, and clinical sequelae.

The majority (>90%) of cases of TTP is immune-mediated and is caused by autoantibody-mediated inhibition of ADAMTS13 activity or clearance of the ADAMTS13 protein (George et al. 2023). Congenital TTP (also referred to as hereditary, inherited, or familial TTP; or Upshaw-Schulman syndrome) is a rare (one per one million population) autosomal recessive TMA caused by mutations in the ADAMTS13 gene. More than 200 pathogenic variants in the ADAMTS13 gene have been described. Congenital TTP (cTTP) is rare in adults (<5% of TTP cases) but is more common than immune TTP in infants and young children (George et al. 2023, Joly et al. 2019). The phenotype of cTTP is variable with severe cases requiring prophylactic plasma infusions and milder cases marked by long remission periods in the absence of prophylactic treatment. There are no therapies specifically approved for the treatment of cTTP. Current standard of care (SoC) treatment consists of ADAMTS13 replacement through plasma products administered on a symptomatic/on-demand or prophylactic basis. Plasma-based therapies are associated with long infusion times and risks including volume overload, transmissible infectious agents, and hypersensitivity reactions.

3 PRODUCT INFORMATION

3.1 Product Description

ADZYNMA is a purified rADAMTS13 protein expressed in Chinese Hamster Ovary (CHO) cells using recombinant DNA technology; trace quantities of CHO proteins may be present in the final product. ADZYNMA is a sterile, non-pyrogenic, preservative-free,

white powder supplied in single dose vials for intravenous (IV) use after reconstitution. Each single dose vial contains 500 IU or 1500 IU of rADAMTS13, sodium chloride (9.4 mg), calcium chloride dihydrate (1.6 mg), L-histidine (16.7 mg), mannitol (161.4 mg), sucrose (53.8 mg), and polysorbate 80 (2.7 mg). Upon reconstitution with 5 mL of sterile water for injection, the 500 IU and 1500 IU vials result in a potency of 100 IU/mL and 300 IU/mL, respectively, and appear as a clear and colorless solution that is free of particles.

Reviewer comment: ADZYNMA consists of a mixture of 2 versions of rADAMTS13: one protein is representative of the native ADAMTS13 sequence while the second protein is a variant sequence (rADAMTS13.R97) that differs from the native sequence by a single amino acid at position 97. Per the applicant, comparative characterization and analysis showed that the two ADAMTS13 versions have the same physiochemical, biochemical, and biological properties. Please refer to the CMC memo for details regarding the comparability between the two rADAMTS13 versions and any potential implications for the functionality or immunogenicity of the final drug product.

3.2 Proposed Indication

The applicant's proposed indication statement as submitted to the original BLA 125795/0 is prophylactic or on-demand enzyme replacement therapy (ERT) in patients with cTTP. There are two proposed intravenous dosing regimens, based on whether the product is administered on a prophylactic or on-demand basis:

- Prophylactic ERT
 - 40 IU/kg body weight once every other week
 - Dosing frequency may be adjusted to 40 IU/kg body weight once weekly based on prior prophylactic dosing regimen or clinical response
- On-demand ERT
 - Day 1: 40 IU/kg body weight
 - Day 2: 20 IU/kg body weight
 - Day 3 and thereafter: 15 IU/kg body weight until two days after the acute event is resolved

OBPV defers to product office on the final language for the indication statement. Please see the final version of the package insert submitted by the applicant for the final agreed-upon indication after FDA review.

4 PERTINENT REGULATORY HISTORY

Currently ADZYNMA is not marketed in any country. Pertinent U.S. regulatory history is summarized below:

- 29 July 2008: Orphan drug designation granted for treatment and prevention of TTP including its congenital, acquired idiopathic, and secondary forms
- 17 February 2017: Fast Track designation granted for treatment, prevention, and routine prophylaxis of acute episodes of TTP in patients with hereditary ADAMTS13 deficiency
- 06 March 2023: Rare pediatric disease designation granted for treatment of cTTP

5 DESCRIPTION OF ADZYNMA CLINICAL TRIAL SAFETY DATABASE

5.1 Clinical Studies

The clinical study safety data reviewed are from the Summary of Clinical Safety (SCS). OBPV defers to the product office on final review of the clinical database, including safety and efficacy outcomes, which will inform the final language in the USPI. Below is our focused review of the applicant data initially submitted to the BLA, to inform decisions pertaining to pharmacovigilance planning, should this BLA 125795/0 be approved. Please refer to the package insert for the final clinical safety data.

The applicant submitted data from three clinical studies: one completed Phase 1 study (Study 281101), an ongoing Phase 3 pivotal study (Study 281102), and an ongoing Phase 3b continuation study (Study 3002). Safety data were presented for each individual study and were also pooled for the two Phase 3 studies and presented as an integrated safety analysis. The applicant also provided safety data for 9 patients with cTTP who received ADZYNMA through compassionate use outside of clinical trials. Results of the Phase 1 uncontrolled, single-dose, dose-escalation study will not be reviewed in this memorandum since data from the study were not included in the label. Hence, this memorandum will focus primarily on the results of the integrated safety analysis. The applicant submitted a 120-day safety update, including an updated SCS, with a data cutoff date of 15 February 2023. During the safety update period, 7 subjects completed Study 281102 and were dosed in Study 3002, and an additional 13 new subjects received ADZYNMA in Study 3002. The review that follows includes data from the 120-day safety update (with exceptions noted). The two Phase 3 studies included in the integrated safety analysis are summarized in Table 1.

Table 1. Summary of Clinical Studies Supporting the Safety of ADZYNMA^a

Study	Number of Subjects Dosed	Description
Study 281102 Ongoing	Prophylactic cohort: 48 subjects ^b (47 unique subjects) On-demand cohort: 6 subjects ^c (5 unique subjects)	Phase 3, prospective, randomized, controlled, open-label, multicenter, 2 period crossover study with a single arm continuation evaluating the safety and efficacy of rADAMTS13 in the prophylactic and on-demand treatment of subjects with severe cTTP
Study 3002 Ongoing	57 subjects received prophylactic treatment with ADZYNMA ^d <ul style="list-style-type: none">• 36 roll-over subjects from Study 281102• 21 non-roll-over subjects^d On-demand cohort: 1 subject	Phase 3b, prospective, open-label, multicenter, single treatment arm, continuation study of the safety and efficacy of rADAMTS13 in the prophylactic and on-demand treatment of subjects with severe cTTP

^aAdapted from Table 4, Clinical Overview, STN 125795/0.24, Module 2.7.4, Day 120 Summary of Clinical Safety.

^bOne participant was counted twice towards the total number of subjects in the prophylactic cohort, including once as discontinuing and once as completing Study 281102. The participant discontinued the study after experiencing an allergic reaction to SoC prophylaxis in Period 1 and was re-enrolled under a different subject number and received a different SoC prophylaxis and ADZYNMA.

^cOne participant was counted twice towards the total number of subjects in the on-demand (OD) cohort. The participant enrolled in the OD cohort twice, first receiving OD ADZYNMA and then OD SoC under a different subject number

^dOne subject (Subject 3002- (b) (6)), is included in the table as a non-rollover subject in Study 3002 but was excluded from the integrated safety analysis by the applicant. Per the applicant, the subject received ADZYNMA for >2 years through compassionate use prior to enrolling in Study 3002, making the subject exceptional.

Of note, during Study 281102, the bulk drug substance manufacturing site changed from (b) (4) to (b) (4) . Both product types were used in Study 281102, while the product containing bulk drug substance manufactured in (b) (4) was used exclusively in Study 3002. Per the applicant, the two product types demonstrated ADAMTS13 antigen and PK comparability during the PK-II period of Study 281102. Please refer to the CMC and clinical pharmacology review memos for details regarding product and PK comparability assessments.

5.2 Review of Clinical Safety Data

Study 281102

Study 281102 is a Phase 3, prospective, randomized, controlled, open-label, two-period crossover, multicenter study with a single arm continuation evaluating the safety and efficacy of ADZYNMA in the prophylactic and on-demand treatment of severe cTTP. The primary objective of the study is to determine the incidence of acute TTP events in subjects with severe cTTP receiving prophylactic ADZYNMA or SoC. Subjects in the prophylactic cohort were randomized to receive either 6 months of ADZYNMA (40 IU/kg weekly or every other week) followed by 6 months of a standard of care (SoC) treatment method, or the reverse sequence (referred to as treatment Periods 1 and 2). The majority of subjects receiving prophylactic SoC received fresh frozen plasma (FFP) or solvent/detergent-treated plasma. During Period 3, all prophylactic cohort subjects received ADZYNMA for an additional 6 months.

The dosing frequency used for ADZYNMA prophylaxis was determined by the subject's cTTP treatment frequency prior to enrollment. Subjects who received pre-study cTTP treatment at a weekly frequency were also to receive ADZYNMA weekly; all other subjects were to receive ADZYNMA every 2 weeks. Adjustments to the dosing frequency were permitted based on clinical events and/or laboratory results. The majority of subjects in the prophylactic cohort were on a 2 week dosing schedule; approximately 20% of subjects were on a weekly dosing regimen¹.

¹ Source: BLA 125795/0, Module 5.3.5.1, Clinical Study Report for Study 281102, page 161.

Subjects with acute TTP enrolling in the on-demand cohort were randomized to receive ADZYNMA (the same on-demand dosing regimen was used as that in the proposed USPI) or SoC. Upon completion of the on-demand treatment period, subjects could choose to join the prophylactic cohort or end their participation in the study.

For prophylactic cohort subjects, follow-up study visits were conducted every 2 weeks ± 2 days during Periods 1, 2, and 3, and a study completion visit was conducted at 28 days ± 3 days after the last dose of ADZYNMA. On-demand cohort subjects were followed daily until 2 days after resolution of the acute TTP event, and a study completion visit was conducted at 28 days ± 3 days after the last dose/termination of treatment. Safety outcome measurements included adverse events (AEs), vital signs, physical examinations, electrocardiograms (ECGs), labs (including viral serology, pregnancy testing, serum chemistry, hematology), and immunogenicity testing (binding and neutralizing antibodies against ADAMTS13). Descriptive statistics were used to summarize safety results and formal statistical comparisons were not performed for safety outcomes.

The study was ongoing at the time of the 120-day safety update; 10 subjects in the prophylactic cohort were still on study².

Study 3002

Study 3002 is a Phase 3b, prospective, open-label, single arm, multicenter, continuation study of the safety and efficacy of ADZYNMA in the prophylactic and on-demand treatment of subjects with severe cTTP. As a continuation study for Study 281102, Study 3002 enrolled subjects completing Study 281102 (also referred to as roll-over subjects) as well as individuals who did not participate in Study 281102. The primary objective of the study is to evaluate the long-term safety and tolerability of ADZYNMA in both the prophylactic and on-demand cohorts. The ADZYNMA dosing regimens were the same as those used in Study 281102. The majority (78.9%) of subjects receiving prophylactic ADZYNMA were on a 2 week dosing schedule³. The maximum duration of study participation for prophylactic cohort subjects was 3 years or until commercial availability of ADZYNMA or the decision not to launch in the country, whichever occurred first. The study duration for on-demand cohort subjects was approximately 1 month. Similar to Study 281102, on-demand cohort subjects could either join the prophylactic cohort or end their participation in the study upon completion of the on-demand cohort.

For prophylactic cohort subjects, follow-up study visits were conducted every 12 weeks ± 2 weeks and a study completion visit at 4 weeks ± 1 week after the last dose of ADZYNMA. On-demand cohort subjects were followed daily until resolution of the acute TTP event ± 2 days, and a study completion visit was conducted at 4 weeks ± 1 week

² Source: BLA 125795/0.24, Module 2.7.4, Day 120 Summary of Clinical Safety, Table 4, page 31.

³ Of the 57 subjects receiving prophylactic ADZYNMA in Study 3002, 45 subjects (78.9%) started the study on a 2 week dosing schedule. Three subjects receiving prophylactic ADZYNMA had at least one dose regimen modification during the study. Source: BLA 125795/0.24, Module 5.3.5.2, Study 3002 Day 120 Safety Update Tables, Tables 14.2.7.1 and 14.2.7.2.1, pages 147 and 189, respectively.

following the last dose of ADZYNMA. Safety outcome measurements were similar to that of Study 281102. The primary safety outcome was the incidence of related treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) in both the prophylactic and on-demand cohorts. Descriptive statistics were used to summarize safety results.

The study was ongoing at the time of the 120-day safety update: 55 subjects in the prophylactic cohort and 1 subject in the on-demand cohort were still on study².

5.2.1 Integrated (Pooled) Analysis

Across the two Phase 3 studies, 67 unique subjects received prophylactic ADZYNMA, including 47 subjects in Study 281102 (among whom were 36 subjects who also received ADZYNMA in Study 3002), and 20 non-rollover subjects in Study 3002. Three subjects received on-demand ADZYNMA (2 subjects in Study 281102 and 1 subject in Study 3002). A total of 48 subjects⁴ received prophylactic SoC, and 4 subjects received on-demand SoC⁵. For subjects who received prophylactic ADZYNMA, the total exposure to ADZYNMA was 100.6 subject-years, with a mean (SD) duration of exposure of 504.7 (341) days and mean number of infusions of 45.2 (36.6). Four subjects were exposed to ADZYNMA for ≥ 3 years, 22 subjects for ≥ 2 years, 36 subjects ≥ 1 year, and 55 subjects for ≥ 6 months⁶. The 3 subjects who received on-demand ADZYNMA had a total exposure of 0.05 subject-years, with the number of doses ranging from 4 to 7.

Reviewer comment: *The overall exposure to prophylactic ADZYNMA was more than twice the exposure to prophylactic SoC. For subjects receiving prophylactic SoC, the total duration of exposure was 28.8 subject-years, with a mean (SD) duration of exposure of 201.3 (99.6) days and mean number of infusions of 16.3 (7.1). The higher total exposure to ADZYNMA is due to all prophylactic cohort subjects receiving ADZYNMA for an additional 6 months during Period 3 after completion of the cross-over treatment sequence and the single treatment arm design of Study 3002. In order to facilitate a comparison of AE rates despite the differences in study drug exposure between the two treatment groups, the applicant calculated exposure-adjusted event rates (EAER) for select safety data in the integrated analysis of safety. The EAER represents the number of TEAEs divided by duration of subject exposure to study drug in years, which is then converted to units of 100 subject-years (SY).*

Demographic characteristics were comparable between the two prophylactic treatment groups with regards to age and sex. The mean age (SD) of subjects receiving prophylactic ADZYNMA was 29.9 (16.7) years, ranging from 2.0 to 68 years. There

⁴ One participant was counted twice, including once as discontinuing and once as completing Study 281102. The participant discontinued the study after experiencing an allergic reaction to SoC prophylaxis in Period 1 and was re-enrolled under a different subject number and received a different SoC prophylaxis.

⁵ A total of 48 unique subjects received SoC (either on a prophylactic or on-demand basis, or both): 44 subjects received prophylactic SoC, 3 subjects received both prophylactic and on-demand SoC, and 1 subject received on-demand SoC.

⁶ Source: BLA 125795/0.24, Module 2.7.4, Day 120 Summary of Clinical Safety, Table 8, pages 43-44.

were 18 pediatric subjects, with 5 subjects between 2 to <6 years, 7 subjects between 6 to <12 years, and 6 subjects between 12 to <18 years. The majority of subjects receiving prophylactic ADZYNMA were female (61.2%), white (53.7%), and enrolled in European study sites (58.2%; 17.9% subjects were enrolled in U.S. study sites). The numbers of Black or multiple race subjects were very small, and the proportion of subjects who did not report race were similar between the 2 arms (17.9% of subjects receiving prophylactic ADZYNMA and 18.8% of subjects receiving prophylactic SoC). The proportion of Asian subjects was higher in the prophylactic ADZYNMA group (23.9%) than the prophylactic SoC group (10.4%), and the proportion of White subjects was lower in the prophylactic ADZYNMA group (53.7%) than the prophylactic SoC group (66.7%). Among the 3 subjects receiving on-demand ADZYNMA, 2 were adult and 1 was pediatric.

The discussion of safety data primarily focuses on subjects receiving prophylactic treatment; safety data for subjects receiving on-demand treatment are noted where appropriate. The cTTP treatment history was comparable between the two prophylactic treatment groups. The majority (95.5%) of subjects receiving prophylactic ADZYNMA were on prophylactic cTTP treatment prior to the study, with FFP (71.6%) and solvent/detergent treated plasma (20.9%) being the predominant treatments. The most common (44.8%) treatment frequency prior to study start was every 2 weeks⁷.

Exclusion criteria for the Phase 3 studies included the following: any other TTP-like disorder (including acquired TTP), acute TTP episode <30 days prior to screening (for the prophylactic cohort only), history or presence of functional ADAMTS13 inhibitor, history of genetic or acquired immune deficiency, treatment with an immunomodulatory drug within 30 days prior to enrollment, hypersensitivity to hamster protein, known life-threatening hypersensitivity reaction to ADAMTS13 or other constituents of ADZYNMA (Study 3002), severe cardiovascular disease (NYHA class 3 or 4), end stage renal disease requiring dialysis, hepatic dysfunction, pregnancy or lactating at time of enrollment, and acute illness or another clinically significant concomitant disease which in the investigator's opinion posed additional risks to the subject.

Treatment-emergent Adverse Events

The percentage of subjects experiencing TEAEs were the same for both prophylactic groups (89.6%), although the EAER for TEAEs was lower during ADZYNMA prophylaxis (877.5 events/100 SY) than during SoC prophylaxis (1113.0 events/100 SY). Most TEAEs were mild to moderate in severity. The percentage of subjects experiencing severe TEAEs was 13.4% (9/67 subjects) for ADZYNMA and 14.6% (7/48 subjects) for SoC. The EAERs for severe TEAEs were 30.8 events/100 SY for ADZYNMA and 48.7 events/100 SY for SoC. The most common TEAEs (experienced by ≥10.0% of subjects) during ADZYNMA prophylaxis were COVID-19 (37.3%, 25 subjects); headache (31.3%, 21 subjects); cough (19.4%, 13 subjects); nasopharyngitis (17.9%, 12 subjects); dizziness (16.4%, 11 subjects); abdominal pain and diarrhoea (each 14.9%, 10 subjects); pyrexia and upper respiratory tract infection (URTI) (each

⁷ Source: BLA 125795/0.24, Module 5.3.5.3, ISS Day 120 Safety Update Tables, Table 14.1.4.1.1, page 43-47.

13.4%, 9 subjects); migraine, nausea, and viral infection (each 11.9%, 8 subjects); fatigue, oropharyngeal pain, and rhinitis (each 10.4%, 7 subjects). The most common TEAEs during SoC prophylaxis were headache (22.9%, 11 subjects); thrombocytopenia (16.7%, 8 subjects); fatigue and urticaria (each 14.6%, 7 subjects); abdominal pain (12.5%, 6 subjects); nasopharyngitis and vomiting (each 10.4%, 5 subjects)⁸.

There were 13 TEAEs with an EAER ≥ 10 events/100 SY in the prophylactic ADZYNMA group: headache (192.8 events/100 SY), migraine (33.8), abdominal pain (30.8), nasopharyngitis (29.8), COVID-19 (27.8), dizziness (19.9), cough (18.9), diarrhea (14.9), nausea (14.9), lethargy (14.9), cystitis (10.9), oropharyngeal pain (10.9), and URTI (10.9)⁹. In comparison, there were 28 TEAEs with an EAER ≥ 10 events/100 SY in the prophylactic SoC group: headache (264.3 events/100 SY), thrombocytopenia (52.2), nasopharyngitis (41.7), fatigue (34.8), urticaria (31.3), abdominal pain (24.3), vomiting (24.3), oropharyngeal pain (20.9), pyrexia (20.9), epistaxis (20.9), lethargy (20.9), rash (17.4), platelet count decreased (17.4), pruritis (17.4), drug hypersensitivity (13.9), arthralgia (13.9), migraine (13.9), nausea (13.9), paraesthesia (13.9), cystitis (13.9), allergic transfusion reaction (10.4), cough (10.4), COVID-19 (10.4), myalgia (10.4), tachycardia (10.4), URTI (10.4), diarrhea (10.4), and toothache (10.4)¹⁰.

A higher percentage of subjects experienced TEAEs occurring within 24 hours of infusion (i.e., temporally associated TEAEs) during SoC prophylaxis than ADZYNMA prophylaxis (60.4% (29/48 subjects) and 53.7% (36/67 subjects), respectively). The following temporally associated TEAEs were reported by ≥ 2 subjects during prophylactic treatment and had a higher frequency in the ADZYNMA group: abdominal pain (9.0%, 6 subjects for ADZYNMA; 2.1%, 1 subject for SoC), nausea (6.0%, 4 subjects; 2.1%, 1 subject), COVID-19 (4.5%, 3 subjects; 0%), feeling hot (4.5%, 3 subjects; 0%), nasopharyngitis (4.5%, 3 subjects; 2.1%, 1 subject), viral infection (4.5%, 3 subjects; 0%), decreased appetite (3.0%, 2 subjects; 0%), dizziness (3.0%, 2 subjects; 0%), SARS-CoV-2-test positive (3.0%, 2 subjects; 0%), and seasonal allergy (3.0%, 2 subjects; 0%). Temporally associated TEAEs that occurred at a higher frequency in the SoC group included headache (14.6%, 7 subjects for SoC; 13.4%, 9 subjects for ADZYNMA), urticaria (12.5%, 6 subjects; 1.5%, 1 subject), rash (8.3%, 4 subjects; 0%), allergic transfusion reaction (6.3%, 3 subjects; 0%), cough (4.2%, 2 subjects; 1.5%, 1 subject), thrombocytopenia (4.2%, 2 subjects; 1.5%, 1 subject), drug hypersensitivity (4.2%, 2 subjects; 0%), fatigue (4.2%, 2 subjects; 0%), infusion related hypersensitivity reaction (4.2%, 2 subjects; 0%), pruritis (4.2%, 2 subjects; 0%), tachycardia (4.2%, 2 subjects; 0%), oropharyngeal pain (2.1%, 1 subject; 1.5%, 1 subject), pyrexia (2.1%, 1 subject; 1.5%, 1 subject), toothache (2.1%, 1 subject; 1.5%, 1 subject), and vomiting (2.1%, 1 subject; 1.5%, 1 subject)¹¹.

⁸ Source: BLA 125795/0.24, Module 5.3.5.3, ISS Day 120 Safety Update Tables, Table 14.3.1.3, pages 235-254.

⁹ Source: BLA 125795/0.24, Module 2.7.4, Day 120 Summary of Clinical Safety, Table 21, page 72.

¹⁰ Source: BLA 125795/0.24, Module 2.7.4, Day 120 Summary of Clinical Safety, Table 22, page 73.

¹¹ Source: BLA 125795/0.24, Module 2.7.4, Day 120 Summary of Clinical Safety, Table 26, pages 82-83.

There were no TEAEs leading to interruption of study drug infusion, discontinuation of study drug, or study withdrawal during ADZYNMA prophylaxis. In Study 281102, one subject (Subject (b) (6)) receiving SoC prophylaxis experienced a hypersensitivity reaction (non-serious, moderate, widespread rash) leading to discontinuation of SoC and study withdrawal. The subject re-enrolled in the study and received a different SoC treatment (factor VIII-VWF concentrate). Additionally, 8 subjects receiving SoC prophylaxis in Study 281102 experienced 9 TEAEs leading to interruption of study drug infusion; 8 TEAEs were associated with hypersensitivity reactions (3 events of urticaria, 2 events of pruritis, 1 event of drug hypersensitivity, and 2 events of allergic transfusion reaction), and there was 1 TEAE of tachycardia.

There were no TEAEs reported during on-demand ADZYNMA treatment. Three of four subjects who received on-demand SoC experienced a total of 9 TEAEs; pruritis was experienced by 2 subjects while other TEAEs (headache, nausea, hypoaesthesia, blood LDH increased, thrombocytopenia, paresthesia, and tooth abscess) were experienced by 1 subject each. There were no TEAEs leading to study drug discontinuation or study withdrawal during on-demand treatment with ADZYNMA or SoC.

Reviewer comment: *Both the EAER and the proportion of subjects experiencing AEs should be considered when comparing AE profiles between treatment groups. As noted by the applicant, a limitation of using the EAER as a measure of AE frequency is that it only takes into account the number of events without taking into account the number of subjects experiencing that event. Hence, the EAER may become inflated by a few subjects experiencing a large number of events. For example, 1 subject experienced 11 events of cystitis during ADZYNMA prophylaxis, resulting in an EAER of 10.9 events/100 SY for cystitis.*

In the integrated analysis, infections and infestations were the most frequently reported TEAE SOC in prophylactic cohort subjects, occurring in 67.2% (45/67 subjects) of subjects during ADZYNMA prophylaxis and 39.6% (19/48 subjects) during SoC prophylaxis. As noted by the applicant, stochastically arising infections and infestations would be expected to occur in a higher percentage of subjects during ADZYNMA prophylaxis due to the greater total subject exposure to ADZYNMA (100.6 subject-years) compared to SoC (28.8 subject-years). However, both the percentage and EAER of subjects experiencing COVID-19 (37.3% (25/67 subjects) and 27.8 events/100 SY for ADZYNMA; 6.3% (3/48 subjects) and 10.4 events/100 SY for SoC) and URTI (13.4% (9 subjects) and 10.9 events/100 SY for ADZYNMA; 6.3% (3 subjects) and 10.4 events/100 SY for SoC) were higher during ADZYNMA prophylaxis than during SoC prophylaxis. Additionally, during the cross-over treatment periods in Study 281102, a greater proportion of subjects experienced COVID-19 (10.6%, 5 subjects for ADZYNMA; 6.3%, 3 subjects for SoC) and URTI (12.8%, 6 subjects for ADZYNMA; 6.3%, 3 subjects for SoC) during ADZYNMA prophylaxis. The underlying reason for the higher rates and percentages of subjects experiencing COVID-19 and URTI during ADZYNMA prophylaxis are unclear. The applicant hypothesized that the imbalances may be due to the SoC AE observation period having occurred earlier for most subjects than the longer ADZYNMA AE observation period, which may have coincided with later

waves of COVID-19 infection. The applicant noted that only 2 subjects reported COVID-19 AEs during 2020, with increasing numbers of COVID-19 AEs in 2021 and 2022. This reviewer finds the applicant's explanation for the imbalances in COVID-19 and URTI AEs to be plausible, especially since the imbalance in COVID-19 infections is of smaller magnitude during the Study 281102 cross-over periods.

Serious Adverse Events

During the cross-over treatment periods in Study 281102, 1 subject (2.1%) experienced an SAE (tachycardia, which was not reported as an SAE by any subject during SoC prophylaxis) during ADZYNMA prophylaxis. Seven subjects (14.6%) experienced SAEs during SoC prophylaxis. Across the two Phase 3 studies, both the percentage and the EAER of subjects experiencing SAEs were lower during ADZYNMA prophylaxis (14.9% (10/67 subjects) and 11.9 events/100 SY, respectively) than during SoC prophylaxis (16.7% (8/48 subjects) and 31.3 events/100 SY, respectively). Additionally, no SAE was reported in more than 1 subject during ADZYNMA prophylaxis. There were no SAEs that were considered related to ADZYNMA by the investigator. There was one SAE of pyrexia that was considered possibly related to SoC by the investigator.

There were no SAEs during on-demand treatment with ADZYNMA or SoC.

Deaths and Discontinuations from the Study

There were no deaths reported in Studies 281102 or 3002.

Three subjects discontinued from Study 281102:

- Subject 281102-(b) (6) was discontinued from the study for not meeting eligibility criteria; the subject was initially thought to have cTTP but was later determined to have iTTP.
- Subject (b) (6) (previously discussed in the section on TEAEs) was discontinued from the study after experiencing widespread rash during SoC prophylaxis (FFP) and was discontinued from the study. The subject was later re-enrolled in the study with a different SoC treatment (factor VIII-VWF concentrate).
- Subject 281102-(b) (6) discontinued from the study after receiving SoC in the on-demand cohort due to the subject's decision (and not as a result of a TEAE, per the applicant). The subject had a post-study follow-up visit 1 month after the last dose of study drug, and no AEs were reported.

In Study 3002, 2 rollover subjects were withdrawn from the study per protocol when it was discovered that they were pregnant; these 2 subjects are discussed in the pregnancy section later in this memo.

Adverse Events of Special Interest

The applicant did not identify any adverse events of special interest (AESIs) for Studies 281102 and 3002.

Antibody development: An AESI of concern to this reviewer included the development of antibodies. Immunogenicity is a concern with protein-based therapeutics, and antibodies can decrease product efficacy by increasing clearance of the product or by neutralizing product activity. Antibodies may also bind to and/or neutralize endogenous circulating protein. The applicant used a tiered approach for immunogenicity testing in Studies 281102 and 3002. Samples initially underwent a screening assay for binding antibodies to ADAMTS13; samples that screened positive were subjected to confirmatory testing for binding antibody and additional assays for neutralizing antibodies to ADAMTS13. This approach was used for all time points indicated in the schedule of assessments for both studies except during the screening period in Study 3002; non-rollover subjects in Study 3002 were tested for neutralizing antibodies during the screening period to confirm eligibility¹². Any positive results for neutralizing antibodies at any time were to be confirmed by repeat testing 2-4 weeks after the initial positive test; samples with positive confirmatory results were considered by the applicant to be truly indicative of the presence of neutralizing antibodies¹³. Participants in the two Phase 3 studies underwent immunogenicity testing at regular intervals; prophylactic cohort subjects were tested during screening, follow-up visits (every 4 weeks for Study 281102 and every 12 weeks for Study 3002), and study completion. On-demand cohort subjects were tested during dosing visits and at study completion.

Across the two studies, a total of 14 subjects (20.9% of 67 subjects) tested positive for ADAMTS13 binding antibodies during ADZYNMA treatment and 1 subject (2.1% of 48 subjects) tested positive for ADAMTS13 binding antibodies during SoC treatment. One subject (Subject (b) (6)) tested positive for both binding and neutralizing antibodies on Day 309; the subject was initially enrolled as a cTTP patient but was later confirmed by the investigator to have iTTP and was withdrawn from the study for not meeting eligibility criteria. No other subjects tested positive for neutralizing antibodies against plasma-derived or recombinant ADAMTS13. Subjects with positive immunogenicity testing are summarized below by study:

- Two subjects (both in the prophylactic cohort) were positive for ADAMTS13 binding antibodies in Study 281102. One subject (Subject (b) (6)) had low-titer binding antibodies at baseline (on Day -197, before exposure to ADZYNMA), and then intermittently during the study (on Days 1, 15, 41, 209, and 420) without increasing in titer. The other subject (Subject (b) (6)) was positive for binding and neutralizing antibodies against ADAMTS13 on Day 309. As previously discussed, the subject was initially thought to have cTTP but was later confirmed by the investigator to have iTTP and was subsequently withdrawn from the study for not meeting eligibility criteria. Two other subjects (Subjects (b) (6) [redacted], both in the prophylactic cohort) were positive for low-titer anti-Chinese hamster ovary (CHO) protein antibodies at a single time point; per the applicant, the positive tests were not temporally associated with any TEAEs and subsequent tests were negative.

¹² Source: BLA 125795/0.24, Module 5.3.5.2, Clinical Study Report for Study 3002, page 59.

¹³ Source: BLA 125795/0.24, Module 2.7.4, Day 120 Summary of Clinical Safety, page 99.

- In Study 3002, 12 subjects (8 rollover subjects and 4 non-rollover subjects) were positive for low-titer (1:20 or 1:40) ADAMTS13 binding antibodies that did not increase in titer over time. The 8 rollover subjects who tested positive for binding antibodies in Study 3002 had all tested negative for binding antibodies in Study 281102 .

Reviewer comment: *The applicant stated that the detection of ADAMTS13 binding antibodies in Study 3002 is due to the lower assay threshold used in Study 3002. Different laboratories performed the ADAMTS13 binding assays for Studies 281102 and 3002, and the binding assay used in Study 281102 had a higher reporting threshold (minimum reportable titer of 1:80) compared to the binding assay used in Study 3002 (minimum reportable titer 1:20). Hence, the 12 subjects who tested positive for binding antibodies in Study 3002 would have been below the minimum reportable titer in Study 281102.*

The clinical relevance of the ADAMTS13 binding antibodies are unclear. The SCS, including the 120-day safety update, did not mention whether the ADAMTS13 binding antibodies had any impact on the pharmacokinetics (PK) of ADZYNMA. Per the applicant, the impact of immunogenicity on the PK of ADAMTS13 was not assessed in Study 281102 since no subjects developed neutralizing antibodies¹⁴. Additionally, in Study 3002, PK samples were not collected from subjects with positive ADAMTS13 binding antibodies¹⁵. In the initial BLA submission, the applicant stated that the binding antibodies were not temporally associated with any TTP events or any AEs¹⁶. Please refer to the clinical and the clinical pharmacology review memos for additional details regarding the potential impact of the binding antibodies on efficacy, safety, and pharmacokinetics of ADZYNMA.

Hypersensitivity: An additional AESI of concern to this reviewer is hypersensitivity, which can occur with any drug or biologic but especially with protein therapeutics. Hypersensitivity can also be a sequelae of immunogenicity/antibody development. Across both studies, the percentages and rates of subjects experiencing hypersensitivity AEs were greater during SoC prophylaxis compared to ADZYNMA prophylaxis: urticaria (14.6% and 31.3 events/100 SY for SoC; 3.0% and 2.0 events/100 SY for ADZYNMA), pruritis (6.3% and 17.4; 3.0% and 3.0), rash (8.3% and 17.4; 3.0% and 2.0), drug hypersensitivity (8.3% and 13.9; 0%), allergic transfusion reaction (6.3% and 10.4; 0%), infusion related hypersensitivity reaction (4.2% and 7.0; 0%), and infusion related reaction (2.1% and 3.5; 0%). With respect to temporally-associated hypersensitivity TEAEs (those that occurred on the same day as study drug infusion and were treated with an anti-allergy or anti-pyretic medication), 19 subjects experienced 29 TEAEs during SoC treatment, compared to zero subjects during ADZYNMA treatment. The only hypersensitivity AE reported by the on-demand cohort was pruritis, which was reported by 2 subjects receiving on-demand SoC¹⁷.

¹⁴ Source: BLA 125795/0, Module 5.3.5.1, Clinical Study Report for Study 281102, page 213.

¹⁵ Source: BLA 125795/0, Module 2.7.2, Summary of Clinical Pharmacology Studies, page 94.

¹⁶ Source: BLA 125795/0, Module 2.7.4, Summary of Clinical Safety, page 12.

¹⁷ Source: BLA 125795/0.24, Module 2.7.4, Day 120 Summary of Clinical Safety, page 82.

Reviewer comment: Hypersensitivity events occurred at a higher frequency and rate during SoC prophylaxis than ADZYNMA prophylaxis. Additionally, temporally associated hypersensitivity AEs occurred almost exclusively during SoC prophylaxis. The higher occurrence of hypersensitivity events in the SoC group is not unexpected. The majority of subjects receiving SoC prophylaxis received multiple infusions of plasma products, which are known to cause allergic reactions. Hypersensitivity/allergic reactions are one of the most common transfusion reactions and are seen in 1-3% of recipients of platelet or plasma components (Tobian 2022). Additionally, large volumes of plasma (typically 10 mL/kg) are required for ADAMTS13 replacement, resulting in patient exposure to a greater number of potential hypersensitivity-inducing plasma proteins and soluble substances compared to targeted ERT.

Clinical Laboratory Evaluations, Vital Signs, Physical Findings, and Electrocardiograms

Per the applicant, there were no clinically meaningful trends in laboratory parameters other than cTTP-relevant parameters (e.g., platelet count, LDH, and creatinine). Additionally, there were no clinically meaningful results or trends in vital signs, physical examinations, or electrocardiograms.

Pregnancies

Pregnant or lactating individuals were excluded from both studies, and female participants of childbearing potential and sexually active male participants were required to use birth control measures/contraception for the duration of the study. Two subjects in Study 3002 were exposed to ADZYNMA during pregnancy:

- Subject 281102-(b) (6) was a 23-year-old rollover subject who had a positive urine hCG test approximately 5 weeks after her last menstrual period (LMP) and 6 days after her most recent dose of ADZYNMA. She was discontinued from the study per protocol. Seven weeks after study discontinuation and more than 2 months after her last dose of ADZYNMA, the subject had a first-trimester spontaneous abortion. The investigator assessed the event as unrelated to ADZYNMA.
- Subject 281102-(b) (6) was a 35-year-old rollover subject who was found to be pregnant on an unknown date. The subject's LMP was approximately 1 month prior to her last dose of ADZYNMA and her estimated date of delivery being about 8 months after her last dose. The subject was discontinued from the study and pregnancy outcome was unknown at the time of the 120-day safety update.

Reviewer comment: The cause of the spontaneous abortion is unknown. It is estimated that spontaneous abortions occur in 15-20% of clinically recognized pregnancies (FDA 2020). Additionally, initial cTTP presentation or exacerbations are common during pregnancy, and complications of cTTP during pregnancy include intrauterine fetal death (George et al. 2023). The narrative did not state whether the participant received SoC treatment after study withdrawal and whether she experienced any acute TTP episodes during the time between study withdrawal and her miscarriage. For the reasons outlined above, it is possible that the spontaneous abortion had a

cause other than ADZYNMA. The limited information precludes a robust causality assessment.

Clinical Data from ADZYNMA Use Outside of Clinical Trials

The applicant summarized available safety and efficacy data for 9 patients with cTTP who received ADZYNMA through compassionate use outside of clinical trials¹⁸. Patients with life-threatening cTTP who could not be adequately treated with current SoC and were unable to enter a clinical trial were eligible for compassionate use. The dosing regimens for both prophylactic and on-demand treatment were the same as those used in Studies 381102 and 3002.

Nine female patients aged between 1.5 days to 72 years received ADZYNMA through the compassionate use program. There were 4 pediatric patients (a neonate, two 10-year-olds, and one 13-year-old) and 2 patients who received ADZYNMA during pregnancy. Three patients were located in the U.S. Treatment duration ranged from 12 weeks to ≥ 2 years. There was one AE reported in the compassionate use program: an event of flatulence, which was moderate in severity and considered by the investigator to be related to ADZYNMA. There were no reports of ADAMTS13 antibodies associated with the program.

Of the 2 pregnant patients, one patient was recently diagnosed with cTTP during the third trimester of her current pregnancy, which was complicated by ischemic stroke and thrombocytopenia. Since plasmapheresis did not adequately improve platelet counts, the patient was started on weekly ADZYNMA infusions at 33 weeks gestation, which resulted in normalization of ADAMTS13 activity levels and resolution of thrombocytopenia. The patient delivered an infant by caesarian section at 37 weeks gestation; the infant had normal Apgar scores and had a birthweight <1st percentile for gestational age. The second pregnant patient had 2 acute TTP events during her second trimester of pregnancy, including a stroke, and could not be adequately managed by SoC. Weekly infusions of ADZYNMA were initiated with subsequent resolution of the acute TTP event. The applicant reported in the 120-day safety update that the patient has delivered a healthy infant.

In addition to compassionate use, eligible cTTP patients are able to receive ADZYNMA as part of the Named Patient Program (NPP). The purpose of the NPP is to bridge treatment gaps between the end of a clinical trial and the availability of marketed product. Up through the 120-day safety period, there was 1 subject who reported 2 serious TEAEs in a patient from the NPP. A 32-year-old female with cTTP experienced hypotension and tachycardia during her third infusion of ADZYNMA. She received epinephrine and dexamethasone, and the hypotension and tachycardia resolved without sequelae. The investigator initially assessed the events as related to ADZYNMA but changed the causality assessment to not related.

¹⁸ The Compassionate Use Report included in the initial BLA submission had a data cutoff date of 01 December 2022. The 120-day safety update used a data cutoff date of 15 February 2023 for compassionate use data.

Reviewer comment: *The events of hypotension and tachycardia experienced by the patient participating in the Named Patient Program appear to be consistent with a severe systemic hypersensitivity reaction (such as anaphylaxis) and in this reviewer’s opinion, is most likely related to ADZYNMA due to the strong temporal relationship (i.e., event onset during a subsequent ADZYNMA infusion).*

6 SUMMARY OF POSTMARKETING EXPERIENCE

ADZYNMA is currently not marketed in any country and is a first-in-class product.

7 APPLICANT’S PHARMACOVIGILANCE PLAN

The applicant submitted an initial pharmacovigilance plan (PVP) (Core Risk Management Plan, version 2.0, dated 24 February 2023) proposing routine pharmacovigilance (PV) activities, which includes the review and reporting of adverse reactions from the postmarketing setting, periodic signal detection, aggregate safety reports, and literature review. Following Information Requests from OBPV/DPV to add “use in treatment-naïve patients” as missing information and to conduct enhanced pharmacovigilance activities for all AEs involving development of antibodies for 3 years following licensure, the applicant submitted a revised PVP, version 2.3. The revised PVP, version 2.3, will be the focus of this review. The applicant’s summary of important identified risks, important potential risks, and missing information is outlined in Table 2.

Table 2. Applicant’s Pharmacovigilance Plan

Type of Concern	Safety Concern	Proposed Action
Important Identified Risk	None	N/A
Important Potential Risk	Neutralizing (inhibitory) antibodies to rADAMTS13	Routine risk minimization measures: Labeling (USPI Sections 5.2 and 12.6) Routine PV activities Additional PV activities: Enhanced pharmacovigilance (please see details under <i>Missing Information – Use in treatment-naïve patients</i>) and ongoing Phase 3 studies, including completion of Study 3002
Important Potential Risk	Hypersensitivity reactions	Routine risk minimization measures: Labeling (USPI Sections 4 and 5.1) Routine PV activities Additional PV activities: Ongoing Phase 3 studies (Studies 281102 and 3002)

Missing Information	Use in pregnancy and lactation	<p>Routine risk minimization measures: Labeling (USPI Sections 8.1 and 8.2)</p> <p>Routine PV activities</p> <p>Additional PV activities: none</p>
Missing Information	Use in treatment-naïve patients	<p>Routine risk minimization measures: none</p> <p>Routine PV activities</p> <p>Additional PV activities: FDA-required enhanced PV activities for 3 years following licensure, which consists of the following activities below.</p> <ul style="list-style-type: none"> • Submission of expedited reports (i.e., 15-day reports) for all AEs involving development of neutralizing antibodies, regardless of label status or seriousness • Submission of license holder’s assessment (based on interval and cumulative data) of the risk of development of neutralizing antibodies to rADAMTS13, with specific analysis of this risk among treatment-naïve patients, in periodic safety reports • Targeted questionnaire for AEs involving the development of antibodies to rADAMTS13 (i.e., the ADZYNMA inhibitor questionnaire) <p>Ongoing Phase 3 studies, including completion of Study 3002*</p> <p><i>*Applicant plans to evaluate immunogenicity in treatment-naïve or minimally treated patients if feasible</i></p>

*Adapted from Appendix 4 (Tables 6 and 7), Core Risk Management Plan (RMP) for Recombinant ADAMTS13 (rADAMTS13), STN 125795/0.60, Module 1.16.1, Risk Management Plan v2.3.

8 ANALYSIS OF APPLICANT'S PHARMACOVIGILANCE PLAN

8.1 Important Identified Risks

There are no important identified risks in the submitted PVP.

8.2 Important Potential Risks

8.2.1 Neutralizing (inhibitory) antibodies to rADAMTS13

Immunogenicity is a concern with protein-based therapeutics and particularly in the setting of protein/enzyme replacement. Antibodies can decrease product efficacy by increasing product clearance or by neutralizing product activity. Antibodies may also pose safety issues through formation of immune complexes or inhibition of endogenous cross-reactive proteins. Across the two Phase 3 studies, no subjects with confirmed cTTP tested positive for neutralizing antibodies against plasma-derived or recombinant ADAMTS13. One subject who tested positive for neutralizing antibodies was later confirmed to have iTTP and was withdrawn from the study. Excluding the subject with iTTP, a total of 13 subjects were positive for low-titer ADAMTS13 binding antibodies during ADZYNMA treatment, and 1 subject was positive for binding antibodies during SoC treatment. The applicant stated that the binding antibodies were not temporally associated with any TTP events or any AEs¹⁸. The clinical relevance of the non-neutralizing ADAMTS13 antibodies are unclear. Non-neutralizing antibodies in the setting of iTTP are thought to increase the clearance of ADAMTS13 from the circulation or interfere with ADAMTS13 interaction with cells or other plasma proteins (Furlan et al. 1998, Tsai et al. 1998, Scheiflinger et al 2003). However, non-neutralizing ADAMTS13 antibodies have also been detected in healthy individuals; one study showed that 4% of healthy individuals have low-affinity and non-neutralizing anti-ADAMTS13 antibodies (Rieger et al. 2005). The applicant did not assess the potential impact of the non-neutralizing ADAMTS13 antibodies on the PK of ADZYNMA.

It is noted that all subjects across the two Phase 3 studies had a history of cTTP treatment (i.e., ADAMTS13 exposure through plasma products) prior to study start. Of the 67 subjects receiving prophylactic ADZYNMA, 64 subjects (95.5%) were on prophylactic cTTP treatment while 3 subjects (4.5%) had received on-demand treatment prior to the study. Of the 3 subjects receiving on-demand ADZYNMA, 2 subjects (66.7%) were on prophylactic treatment while 1 subject (33.3%) had received on-demand treatment prior to the study. Hence, the immunogenicity data may not be representative of the risk in cTTP treatment-naïve patients, who may be at increased risk for developing ADAMTS13 antibodies. Please refer to the Important Missing Information section of this memo for further discussion.

Routine risk minimization measures proposed by the applicant includes risk communication in the USPI. Section 5.2 Immunogenicity (under Section 5, Warnings and Precautions) states that there is a potential for immunogenicity and that antibodies to rADAMTS13 could potentially result in a decreased or lack of response to

rADAMTS13. Section 12.6 Immunogenicity (Under Section 12, Clinical Pharmacology), states that 13 subjects in the clinical trials tested positive for low-titer binding antibodies against ADAMTS13; although clinical impact of the binding antibodies was not observed, the effect of the binding antibodies on the PK, PD, safety, and/or efficacy on ADZYNMA is unknown. In their response to OBPV/DPV's Information Requests dated 30 August 2023 and 07 September 2023, the applicant acknowledged that if ADZYNMA is approved, they will be required by FDA to conduct enhanced pharmacovigilance activities for all AEs involving development of antibodies for a period of 3 years following licensure.

Additional data regarding immunogenicity will be acquired through the ongoing Phase 3 studies, including completion of Study 3002, and postmarketing use. OBPV/DPV may recommend additional risk minimization measures in the future as needed.

8.2.2 Hypersensitivity reactions

Hypersensitivity can occur with any drug or biologic and may also be a sequelae of immunogenicity/antibody development. In general, hypersensitivity events, including temporally associated hypersensitivity AEs, occurred at a higher frequency and rate during SoC prophylaxis than ADZYNMA prophylaxis. Hypersensitivity events reported during ADZYNMA prophylaxis included rash, urticaria, and pruritis; none were serious. Hypersensitivity AEs were not reported during on-demand ADZYNMA treatment. Anaphylactic/anaphylactoid reactions associated with ADZYNMA were not reported during the clinical trials. However, a cTTP patient who received ADZYNMA through the applicant's Named Patient Program experienced a reaction that is consistent with anaphylaxis and in this reviewer's opinion, is related to ADZYNMA.

Hypersensitivity reactions are included as an important potential risk. The applicant proposes routine pharmacovigilance for hypersensitivity, which includes risk communication through labeling. Section 4 Contraindications if the proposed USPI states that ADZYNMA is contraindicated in patients who have experienced life-threatening hypersensitivity reactions to ADZYNMA or its components. Section 5.1 Hypersensitivity (under Section 5, Warnings and Precautions) states that allergic-type hypersensitivity, including anaphylactic reactions, may occur, and that ADZYNMA administration should be immediately discontinued in the setting of severe allergic reactions. Given that hypersensitivity reactions have occurred less frequently than with SoC in the clinical trials and are adequately addressed in the proposed USPI, the applicant's proposal to conduct routine pharmacovigilance is acceptable.

8.3 Important Missing Information

8.3.1 Use in pregnancy or lactation

Although pregnant or lactating individuals were excluded from the clinical trials of ADZYNMA in cTTP, it is expected that these individuals will be treated with ADZYNMA if it is approved. Initial cTTP presentation or exacerbations are common during pregnancy, and complications of cTTP during pregnancy include intrauterine fetal death. In one registry, 5% of TTP episodes (including both congenital and immune forms) occurred in the setting of pregnancy (Scully et al. 2008, Scully et al 2014). Additionally,

delayed cTTP diagnosis and treatment is associated with negative pregnancy outcomes. In the United Kingdom Thrombotic Thrombocytopenic Purpura (UK TTP) Registry, fetal loss occurred in 16 of 38 (42%) pregnancies before cTTP was diagnosed but in none of the 15 subsequently managed pregnancies (Scully et al. 2014). In a Japanese cTTP registry, the percentage of pregnancies resulting in live births were higher in patients whose pregnancies were subsequent to their cTTP diagnosis (92%) compared to patients whose pregnancies preceded their cTTP diagnosis (50%) (Sakai et al. 2020).

Per the applicant, ADZYNMA, which has a molecular weight of 172 kDa, is not expected to cross the placenta in clinically relevant amounts since drugs with a molecular weight of >1,000 Da have limited ability to do so. The applicant conducted a placental transfer feasibility study in rats which did not show biologically relevant placental transfer. Additionally, per the applicant, reproductive and developmental toxicity studies in rats did not show any adverse effects on fertility, pregnancy performance, fetal development, and postnatal development and sexual maturity at doses up to 400 IU/kg, which was the highest dose tested¹⁹. Please refer to the pharmacology/toxicology review memo for the final interpretation of preclinical study data relevant to reproductive and developmental toxicity.

The applicant provided information on 4 individuals who were exposed to ADZYNMA during pregnancy: 2 clinical trial subjects and 2 cTTP patients participating in the compassionate use program. One clinical trial subject had a first-trimester spontaneous abortion more than 2 months after her last dose of ADZYNMA (please refer to Section 5.2.1 of this memo for details). The second clinical trial subject was exposed to ADZYNMA 1 month after her LMP (estimated date of delivery was 8 months after her last dose of ADZYNMA) and the pregnancy outcome was unknown. The 2 compassionate use patients received weekly ADZYNMA infusions during the later stages of their pregnancies without reported safety concerns.

The applicant proposes routine pharmacovigilance for the important missing information of use in pregnancy or lactation. Proposed risk minimization measures include risk communication in the USPI. Section 8.1 Pregnancy states that the safety of ADZYNMA for use during pregnancy has not been established in controlled clinical trials and summarizes the human data on the individuals who were exposed to ADZYNMA during pregnancy. Section 8.2 Lactation states that it is not known whether rADAMTS13 is present in human milk, affects milk production, or has effects on the breastfed infant, and that due to its high molecular weight, ADZYNMA is not likely to be excreted in human milk. The applicant's proposal to conduct routine pharmacovigilance is acceptable, considering that ADZYNMA is not anticipated to cross the placenta and be excreted in human milk in significant amounts, and the negative findings of the applicant's placental transfer and reproductive and developmental toxicity studies in rats. Additionally, due to the rarity of cTTP (estimated prevalence in U.S. is <1,000

¹⁹ Source: BLA 125795/0, Module 2.4, Nonclinical Overview, pages 15, 22-23.

individuals²⁰) a pregnancy registry is likely infeasible. Although in the setting of immunogenicity, placental transfer of maternal ADAMTS13 antibodies is possible (and hence, hypothetical fetal iTTP), the ADAMTS13 antibodies associated with ADZYNMA have been low titer and non-neutralizing to date.

8.3.2 Use in treatment-naïve cTTP patients

There were no subjects enrolled in the Phase 3 studies who were treatment-naïve prior to receiving ADZYNMA. There is a potential safety concern that cTTP patients who receive ADZYNMA without prior exposure to ADAMTS13 via plasma products will be at increased risk for developing neutralizing antibodies to ADAMTS13. Given that ADZYNMA, if approved, will be the first commercially available therapeutic for cTTP and the lack of data regarding immunogenicity in treatment-naïve subjects exposed to ADZYNMA, it will be important for the applicant to gather additional information post-approval to ensure that the benefit-risk profile of ADZYNMA is favorable in this population.

It will be challenging to obtain data on immunogenicity risk in treatment-naïve individuals, given the rarity of cTTP and the difficulty in finding treatment-naïve individuals, as symptomatic TTP/TTP-like episodes are often presumptively treated prior to diagnostic confirmation. In their response to OBPV/DPV's Information Request dated 30 August 2023, the applicant agreed to add "use in treatment-naïve patients" as missing information to the safety specifications of their PVP. Additionally, the applicant acknowledged that if ADZYNMA is approved, they will be required to conduct enhanced pharmacovigilance activities for all AEs involving the development of antibodies for a period of 3 years following licensure. Additionally, this reviewer agrees with the clinical reviewer's recommended revisions to Section 5.2 Immunogenicity of the proposed USPI to specify that there are no data on immunogenicity in treatment-naïve subjects exposed to ADZYNMA.

Additional data regarding ADZYNMA use in treatment-naïve individuals with cTTP will be acquired through postmarketing use and also potentially through the ongoing Phase 3 studies, including the completion of Study 3002. The applicant confirmed that minimally treated or treatment-naïve cTTP patients are able to enroll in Study 3002^{21,22}. OBPV/DPV may recommend additional risk minimization measures in the future as needed, based on available postmarketing safety data.

9 DPV ASSESSMENT

The submitted data show that overall, the safety profile of ADZYNMA is comparable to SoC and may be associated with less frequent hypersensitivity reactions. Neutralizing antibodies to ADAMTS13 were not reported in the clinical trials to date, although there

²⁰ Source: National Center for Advancing Translational Sciences, Genetic and Rare Diseases Information Center, Congenital thrombotic thrombocytopenic purpura, accessed on 03 August 2023 from <https://rarediseases.info.nih.gov/diseases/9430/congenital-thrombotic-thrombocytopenic-purpura>

²¹ Source: BLA 125795/0.51, Module 1.11.3, Response to FDA Request for Information (Clinical IR 7) Dated 10 Oct 2023.

²² Source: BLA 125795/0.54, Module 1.11.3, Response to FDA Request for Information (Clinical IR 8) Dated 11 Oct 2023.

were no treatment-naïve subjects enrolled in the Phase 3 studies who may be at increased risk for immunogenicity. Thirteen subjects tested positive for low-titer binding antibodies against ADAMTS13; the clinical significance of non-neutralizing ADAMTS13 antibodies is unknown at this time. Neutralizing antibodies are included as an important potential risk in the applicant's PVP, and in the event of approval, the applicant will be required to conduct enhanced pharmacovigilance activities for all AEs involving the development of neutralizing antibodies for a period of 3 years post-licensure. Use in treatment-naïve cTTP patients is included as missing information. OBPV/DPV agrees with the completion of Study 3002, which will yield additional efficacy and safety data for ADZYNMA. Use in pregnancy and lactation is included as important missing information in the applicant's PVP, for which OBPV/DPV agrees with the applicant's proposal for routine risk minimization, including labeling.

10 DPV RECOMMENDATIONS

The submitted pharmacovigilance plan for ADZYNMA (version 2.3, dated 20 October 2023) is adequate for the proposed indication of prophylactic or on-demand enzyme replacement therapy in patients with cTTP. The available data do not indicate a safety signal which would require a REMS or PMR study that is specifically designed to evaluate a particular safety issue as a primary endpoint, and there are no agreed upon PMCs for safety studies. Please see the final version of the package insert submitted by the applicant for the final agreed-upon language for the label. OBPV/DPV recommends the following for postmarketing safety monitoring of ADZYNMA:

- Routine pharmacovigilance activities proposed by the applicant in the Core Risk Management Plan, version 2.3, dated 20 October 2023, which includes adverse event reporting in accordance with 21 CFR 600.80.
- Enhanced pharmacovigilance activities for AEs involving the development of neutralizing antibodies for a period of 3 years post-licensure. Enhanced pharmacovigilance activities include:
 - Expedited reporting of all AEs involving development of antibodies, regardless of label status or seriousness
 - Submission of the applicant's assessment of the risk of development of antibodies to ADZYNMA (based on interval and cumulative data), with specific analyses of this risk among treatment-naïve patients, in periodic safety reports.
 - The use of a targeted data collection tool, such as an event-specific questionnaire, to gather detailed information for all adverse events involving the development of antibodies. Information that will be collected through the tool include cTTP treatment history prior to starting ADZYNMA, relevant laboratory results (e.g., ADAMTS13 evaluation, including ADAMTS13 activity, inhibitor, and/or antibody test results), and associated clinical symptoms.
- Completion of Study 3002, which will yield additional efficacy and safety data for ADZYNMA. The potential enrollment of minimally treated or treatment-naïve patients may result in additional safety and efficacy data in this population. OBPV defers to OTP for review of Study 3002 final study report when available.

REFERENCES

1. George JN and Cuker A. Pathophysiology of TTP and other primary thrombotic microangiopathies (TMAs). In *UpToDate*. Topic last updated 29 November 2022. Retrieved 21 March 2023 from https://www.uptodate.com/contents/pathophysiology-of-ttp-and-other-primary-thrombotic-microangiopathies-tmas?sectionName=Deficient%20ADAMTS13%20activity&search=congenital%20TTP&topicRef=101504&anchor=H199371&source=see_link#H199371.
2. George JN and Cuker A. Hereditary thrombotic thrombocytopenic purpura (hTTP). In *UpToDate*. Topic last updated 17 February 2022. Retrieved 21 March 2023 from https://www.uptodate.com/contents/hereditary-thrombotic-thrombocytopenic-purpura-http?search=congenital%20TTP&source=search_result&selectedTitle=1~34&usage_type=default&display_rank=1.
3. Berangere JS, Coppo P, Veyradier A. An update on pathogenesis and diagnosis of thrombotic thrombocytopenic purpura. *Expert Review of Hematology* 2019;12:383-395.
4. Tobian A. Immunologic transfusion reactions. In *UpToDate*. Topic last updated 06 September 2022. Retrieved 26 April 2023 from https://www.uptodate.com/contents/immunologic-transfusion-reactions?sectionName=FEBRILE%20NONHEMOLYTIC%20TRANSFUSION%20REACTIONS&search=ffp,%20hypersensitivity&topicRef=7920&anchor=H3&source=see_link#H1384219212
5. Furlan M, Robles R, Galbusera M et al. von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. *N Engl J Med* 1998;339:1578-1584.
6. Tsai HM, Lian EC. Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. *N Engl J Med* 1998;339:1585-1594.
7. Scheifflinger F, Knobl P, Trattner B, et al. Nonneutralizing IgM and IgG antibodies to von Willebrand factor-cleaving protease (ADAMTS-13) in a patient with thrombotic thrombocytopenic purpura. *Blood* 2003;102:3241-3243.
8. Rieger M, Mannucci PM, Hovinga JAK et al. ADAMTS13 autoantibodies in patients with thrombotic microangiopathies and other immunomediated diseases. *Blood* 2005;106:1262-1267.
9. Scully M, Yarranton H, Liesner R, et al. Regional UK TTP Registry: correlation with laboratory ADAMTS13 analysis and clinical features. *Br J Haematol* 2008;142: 819-826.

10. Scully M, Thomas M, Underwood M, et al. Thrombotic thrombocytopenic purpura and pregnancy: presentation, management, and subsequent pregnancy outcomes. *Blood* 2014;124:211-219.
11. Sakai K, Fujimura Y, Nagata Y, et al. Success and limitations of plasma treatment in pregnant women with congenital thrombotic thrombocytopenic purpura. *J Thromb Haemost* 2020;18:2929-2941.

**APPENDIX A
Materials Reviewed**

Table A1: Materials reviewed in support of this assessment

Date	Source	Document Type	Document(s) Reviewed
17 March 2023	Takeda Pharmaceuticals	STN 125795/0	Module 1.14.1.3 Draft Labeling Text
17 March 2023	Takeda Pharmaceuticals	STN 125795/0	Module 1.16.1, Risk Management Plan v2.0
17 March 2023	Takeda Pharmaceuticals	STN 125795/0	Module 2.5, Clinical Overview
17 March 2023	Takeda Pharmaceuticals	STN 125795/0	Module 2.7.2, Summary of Clinical Pharmacology Studies
17 March 2023	Takeda Pharmaceuticals	STN 125795/0	Module 2.7.4, Summary of Clinical Safety
17 March 2023	Takeda Pharmaceuticals	STN 125795/0	Module 2.7.6, Synopsis of Individual Studies
17 March 2023	Takeda Pharmaceuticals	STN 125795/0	Module 5.3.5.1, Clinical Study Report for Study 281102 including select individual narratives and safety data tables
17 March 2023	Takeda Pharmaceuticals	STN 125795/0	Module 5.3.5.2, Clinical Study Report for Study TAK-755-3002 including select individual narratives and safety data tables
17 March 2023	Takeda Pharmaceuticals	STN 125795/0	Module 5.3.5.3, Integrated Summary of Safety and Efficacy (ISS/ISE Table of Contents, Tables)
17 March 2023	Takeda Pharmaceuticals	STN 125795/0	Module 5.3.5.4, Compassionate Use Report
06 July 2023	Takeda Pharmaceuticals	STN 125795/0.24	Module 1.14,1.3 Draft Labeling Text, revised June 2023
06 July 2023	Takeda Pharmaceuticals	STN 125795/0.24	Module 2.7.4 Day 120 Summary of Clinical Safety
06 July 2023	Takeda Pharmaceuticals	STN 125795/0.24	Module 5.3.5.1, Study 281102 Day 120 Safety Update Tables
06 July 2023	Takeda Pharmaceuticals	STN 125795/0.24	Module 5.3.5.2, Study 3002 Day 120 Safety Update Tables
06 July 2023	Takeda Pharmaceuticals	STN 125795/0.24	Module 5.3.5.3, ISS Day 120 Safety Update SAE Narratives, Tables
26 July 2023	Takeda Pharmaceuticals	STN 125795/0.31	Module 1.11.3, Response to FDA Request for Information (Clinical IR 5) Dated 18 July 2023
06 Sept 2023	Takeda Pharmaceuticals	STN 125795/0.37	Module 1.11.3, Response to FDA Request for Information (Pharmacovigilance IR 1) Dated 28 August 2023
06 Sept 2023	Takeda Pharmaceuticals	STN 125795/0.37	Module 1.16.1, Risk Management Plan v2.1

Date	Source	Document Type	Document(s) Reviewed
14 Sept 2023	Takeda Pharmaceuticals	STN 125795/0.40	Module 1.11.3, Response to FDA Request for Information (Pharmacovigilance IR 2) Dated 07 September 2023
14 Sept 2023	Takeda Pharmaceuticals	STN 125795/0.40	Module 1.16.1, Risk Management Plan v2.2
11 Oct 2023	Takeda Pharmaceuticals	STN 125795/0.51	Module 1.11.3, Response to FDA Request for Information (Clinical IR 7) Dated 10 Oct 2023
12 Oct 2023	Takeda Pharmaceuticals	STN 125795/0.54	Module 1.11.3, Response to FDA Request for Information (Clinical IR 8) Dated 11 Oct 2023
20 Oct 2023	Takeda Pharmaceuticals	STN 125795/0.60	Module 1.16.1, Risk Management Plan v2.3