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Division / Office	DCEH/OCE/OTP
Committee Chair	Nobuko Katagiri, Ph.D.
Clinical Reviewer(s)	Megha Kaushal, M.D.
Project Manager	Cara Pardon, M.S.
Priority Review	Yes
Reviewer Name(s)	Jiang Hu, Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	Lin Huo, Ph.D., Team Lead, TEB2/DB/OBPV
	Lihan Yan, Ph.D., Branch Chief, TEB2/DB/OBPV
	John Scott, Ph.D., Director, DB/OBPV
Applicant	Takeda Pharmaceuticals
Established Name	ADAMTS13, recombinant-krhn
(Proposed) Trade Name	ADZYNMA
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	recombinant ADAMTS13 (rADAMTS13)
Dosage Form(s) and Route(s) of Administration	Lyophilized powder for solution for intravenous injection
Dosing Regimen	40 IU/kg BW weekly or biweekly
Indication(s) and Intended Population(s)	Prophylactic or on-demand enzyme replacement therapy (ERT) for adult and pediatric patients with congenital thrombotic thrombocytopenic purpura (cTTP)

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GLOSSARY

ADAMTS13	A Disintegrin and Metalloproteinase with Thrombospondin Motifs 13
AE	adverse event
BMI	body mass index
CI	confidence interval
cTTP	congenital thrombotic thrombocytopenic purpura
DMC	Data monitoring committee
EAS	Efficacy analysis set
ENR	Enrolled set
ER	exposure-response
ERT	enzyme replacement therapy
FAS	full analysis set
FDA	Food and Drug Administration
FTD	Fast Track Designation
FFP	fresh frozen plasma
FVIII	factor VIII
FVIII:VWF	Factor VIII: von Willebrand factor
IA	interim analysis
ICF	Informed consent form
iCSR	interim clinical study report
iTTP	immune-mediated thrombotic thrombocytopenic purpura
IV	intravenous(ly)
MFAS	modified full analysis set
PPAS	per-protocol analysis set
OD	on-demand
ODD	Orphan Drug Designation
Q1D	daily
Q1W	every week
Q2W	every 2 weeks
rADAMTS13	recombinant A Disintegrin and Metalloproteinase with Thrombospondin Motifs 13
RND	randomized analysis set
RPD	Rare Pediatric Disease
SAE	serious adverse event
SAF	safety analysis set
SD	standard deviation
SoC	standard of care
SOC	system organ class
ADZYNMA	rADAMTS13, formerly known as BAX 930
TTP	thrombotic thrombocytopenic purpura

1. EXECUTIVE SUMMARY

This original Biologics License Application (BLA) is submitted for ADZYNMA, a recombinant ADAMTS13 indicated for prophylactic or on-demand enzyme replacement therapy (ERT) in patients with severe congenital thrombotic thrombocytopenic purpura (cTTP).

The BLA is supported by data generated from a pre-planned interim analysis for Study 281102 and Study TAK-755-3002. Study 281102 was a prospective, randomized, controlled, open-label, multicenter, 2-period crossover, phase 3 study with a single-arm continuation period evaluating the safety and efficacy of ADZYNMA in the prophylactic treatment of subjects with severe cTTP as well as for on-demand (OD) treatment of acute TTP events. Subjects enrolled in the Prophylactic Cohort were randomized to receive 6 months of treatment in Period 1 with either ADZYNMA or standard of care (SoC) followed by a further 6 months of treatment in Period 2 with the alternate treatment, followed by a single arm Period 3, in which all subjects received ADZYNMA. The primary efficacy endpoint was acute TTP events focusing on the Prophylactic Cohort only.

As of the interim data cut off, zero acute TTP events occurred in 37 adult or adolescent subjects with ADZYNMA prophylaxis during the controlled comparison treatment periods, while one event occurred during SoC treatment (with a time to event resolution 14.8 days). There were no acute TTP events with ADZYNMA observed for median exposure of 7.5 months ranging from 0.1 to 22.6 months throughout the study including Period 3. In the OD Cohort, five subjects with six acute TTP events were enrolled, two subjects were randomized to ADZYNMA and three subjects were randomized to SoC treatment. Two of six events were confirmed to meet the protocol definition of acute TTP events: one event was treated with ADZYNMA the time to resolution was reported as 3 days, the other event was treated with SoC and the time to resolution was reported as 1.5 days.

The submission also includes the interim study report of Study TAK-755-3002 to support the safety of ADZYNMA. Study TAK-755-3002 was a phase 3b, prospective, open-label, multicenter, single treatment arm, continuation study of ADZYNMA in the prophylactic and on-demand treatment of subjects with severe cTTP. Currently 36 subjects (35 adults, and 1 adolescent) have received ADZYNMA up to 15.8 months with a mean duration of 6.3 months. No acute TTP events were observed. Three (8.3%) subjects experienced 3 treatment-emergent SAEs on study and none of them were considered related to ADZYNMA. No deaths were reported on study.

Overall, the statistical analyses provided adequate evidence to support the efficacy and safety of prophylaxis usage of ADZYNMA for patients with cTTP. Generalizability of prophylactic effectiveness to on-demand use is deferred to the clinical review team.

2. Clinical and Regulatory Background

ADZYNMA is recombinant “a disintegrin and metalloproteinase with thrombospondin motifs 13” (rADAMTS13) developed as a prophylactic or on demand enzyme replacement therapy (ERT) for patients with cTTP.

2.1 Disease or Health-Related Condition(s) Studied

cTTP is an ultra-rare, life-threatening, chronic, and debilitating blood clotting disorder that is caused by severe ADAMTS13 deficiency, due to mutations in the ADAMTS13 gene. The clinical presentation of cTTP lies on a spectrum of severity ranging from severe acute TTP episodes to chronic, recurring TTP manifestations which include thrombocytopenia, hemolytic activity, headache, abdominal pain, fatigue or lethargy, bruising, joint pain, muscular pain, forgetfulness, and confusion.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Currently there are no therapeutic options specifically approved for routine prophylactic treatment for cTTP.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Not applicable.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

ADZYNMA was granted Orphan Drug Designation (ODD) by the FDA in July 2008 (designations #08-2622 and #08-2652) and Fast Track Designation (FTD) in February 2017. The original IND 15219 was submitted on 30 August 2012. On 06 March 2023, ADZYNMA received Rare Pediatric Disease (RPD) designation for the treatment of cTTP (RPD-2022-685).

Table 1: Overview of FDA Correspondence

Date of Correspondence	Description of Correspondence	CRMTS number
6/16/2010	pre-IND Written Response	CRMTS #7462
6/20/2012	Type B Pre- IND Meeting	CRMTS #8438
11/29/2016	Type B EoP1 Meeting Minutes	CRMTS #10408
7/2/2018	Type C Written Responses- Type C Meeting Regarding Discovery of R97 Variant and Development Plans	CRMTS #11221
4/10/2019	Teleconference – Cell Line Discussion	-
7/26/2021	Type C Written Responses – Demonstration of Clinical Benefit	CRMTS #13422
12/16/2021	Type C Written Responses – Patient – Patient Reported	CRMTS #13708
1/14/2022	Type C Meeting Agency Feedback - Written Response	CRMTS #13727
4/20/2022	Type C Written Responses – Quantitative Systems Pharmacology Modelling	CRMTS #13924
12/19/2022	Response to pre-BLA Meeting Preliminary- PLI Inspection	-
1/10/2023	Type B, pre-BLA Teleconference Meeting Summary	CRMTS #14491

Source: Adapted from BLA 125795/0 Module 1.6.3: Correspondence Regarding Meetings.pdf, Table 1, page 1.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

This submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The statistical memo focuses on interim data from the ongoing pivotal phase 3 Study 281102. I will also briefly discuss the results for the ongoing phase 3b continuation Study TAK-755-3002.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The following documents in BLA 125795 were reviewed and served as the basis for this statistical memo:

- 125795/0001
 - Module 1
 - Module 2.2: Introduction
 - Module 2.5: Clinical overview
 - Module 2.7: Clinical summary
 - Module 5.3.5.1: Clinical study reports, protocols, and SAPs for Study 281102 and Study TAK-755-3002
 - Module 5.3.5.2: Clinical study reports, protocols, and SAPs for Study TAK-755-3002
 - Datasets of single studies and pooled datasets

5.3 Table of Studies/Clinical Trials

The overall ADZYNMA cTTP clinical development program comprises 3 studies: one complete study (phase 1 Study 281101) and two ongoing studies (Phase 3 pivotal Study 281102 and phase 3b Study TAK-755-3002) (Table 2).

Table 2: Summary of Clinical Studies

Study	Study Design	Dose	Primary endpoint	Number of subjects
281101 (Completed)	Phase 1, prospective, uncontrolled, open-label, multicenter, dose-escalation study evaluating the safety and PK, PD	Single dose of ADZYNMA at 5 IU/kg (n=3), 20 IU/kg (n=3), or 40 IU/kg (n=9).	Occurrence of adverse events (serious and non-serious), including the incidence of binding and inhibitory antibody formation, occurring up to 28 ± 3 days after the last investigational product infusion	15
281102 (On-going)	phase 3, prospective, randomized, controlled, open-label, multicenter, 2	40 IU/kg once every week (Q1W) or every two weeks (Q2W)	the number and incidence of acute TTP events, subacute TTP events, and	48 subjects (47 unique subjects) in the prophylactic cohort and 5 subjects (4

	period crossover study with a single arm continuation evaluating the safety and efficacy of ADZYNMA (rADAMTS13) in the prophylactic and ondemand treatment of subjects with severe cTTP		isolated TTP manifestations	unique subjects) in the on-demand cohort, 32 completed
TAK-755-3002(On-going)	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	Prophylactic: 40 IU/kg once every week (Q1W) or every two weeks (Q2W) On-demand: 40 IU/kg on Day 1; 20 IU/kg on Day 2; 15 IU/kg on Day 3 until 2 days after the acute TTP is resolved	the number and incidence of acute TTP events, subacute TTP events, and isolated TTP manifestations	planned to enroll approximately 77 eligible subjects

Source: Adapted from BLA 125795/0 Module 2.5: Clinical-overview.pdf, Table 1, page 12/77, and Module 2.7: Synopses-indiv-studies.pdf, Table 1, page 1/1.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: 281102

Study 281102 was a Phase 3, prospective, randomized, controlled, open-label, multicenter, 2 period crossover study with a single arm continuation evaluating the safety and efficacy of ADZYNMA in the prophylactic and on-demand (OD) treatment of subjects with severe cTTP.

6.1.1 Objectives

The primary objective of the study was to determine the incidence of acute TTP events in subjects with severe cTTP receiving either SoC or ADZYNMA as a prophylactic treatment.

Secondary efficacy objectives included:

- To evaluate the efficacy of ADZYNMA in the treatment of acute TTP events as measured by the 1) number of acute TTP events responding to treatment, and 2) time to resolution in both the prophylactic and the OD cohorts.
- To evaluate the incidence of isolated TTP manifestations including thrombocytopenia, MAHA, renal dysfunction, neurologic signs and symptoms, and abdominal pain in the Prophylactic Cohort.
- To evaluate the incidence of dose modification and supplemental dose for each treatment in the Prophylactic Cohort.

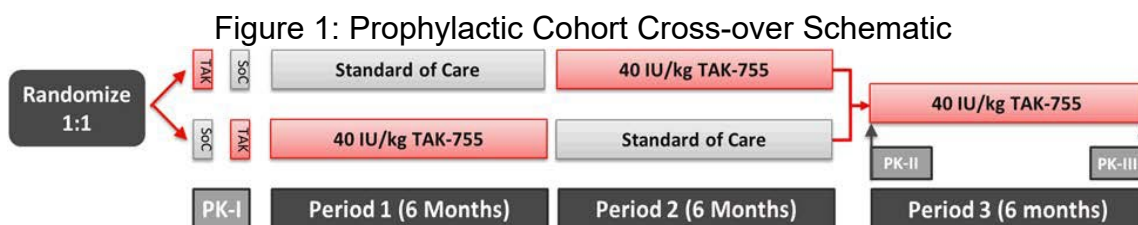
Secondary safety objectives included:

- To evaluate the safety and tolerability of ADZYNMA in terms of related adverse events (AEs) and serious adverse events (SAEs) in both the prophylactic and the OD cohorts.
- To assess the immunogenicity of ADZYNMA as measured by the incidence of binding and inhibitory antibodies to ADAMTS13 in both the prophylactic and the OD cohorts.

6.1.2 Design Overview

This study was originally planned to enroll 57 eligible subjects (0 to 70 years of age) with cTTP into 2 cohorts: approximately 36 adult (≥ 18 years old) subjects and 12 adolescent (> 12 to ≤ 17 years old) or pediatric (0 to < 12 years old) subjects in the Prophylactic Cohort, and approximately 6 adult subjects and 3 adolescent or pediatric subjects in the OD cohort.

All eligible subjects were to undergo a minimum washout period of between 5 to 7 days from their last prophylactic infusion after which further screening procedures were conducted for the determination of eligibility. Subjects who met all eligibility criteria were enrolled in the Prophylactic Cohort and randomized to receive 6 months of treatment in Period 1 with either ADZYNMA or SoC followed by a further 6 months of treatment in Period 2 with the alternate treatment. The treatment order of either ADZYNMA followed by SoC or SoC followed by ADZYNMA was randomly assigned. Following the randomized crossover portion of the study, all subjects were to enter the single arm Period 3, where they were to receive ADZYNMA for a further 6 months. Figure 1 describes the schedule in the Prophylactic Cohort.



Source: Adapted from BLA 125795/0 Module 5.3.5.1/281102: report-body.pdf, Figure 1, page 36.

The total planned duration of subject participation in the Prophylactic Cohort was to be approximately 22 months.

Subjects experiencing an acute TTP event, meeting all other inclusion criteria, and entering and consenting to treatment in the study through the on-demand cohort were randomized to receive urgent treatment with either the SoC or BAX 930. Upon resolution of the acute TTP event, subjects may choose to move to the prophylaxis treatment cohort of the study or discontinue entirely. Subjects electing to move to the prophylaxis treatment cohort were to move directly to Period 1 and will not receive PK-I infusions. Subjects switching from on-demand treatment cohort to prophylaxis cohort were to receive the same treatment in Period 1 as the randomized on-demand treatment, and the alternative treatment in Period 2.

6.1.3 Population

Eligible subjects in the study were 0 through 70 years of age and had a documented diagnosis of severe hereditary ADAMTS13 deficiency, defined as:

- Confirmation by molecular genetic testing, documented in the subject history or at screening, and
- ADAMTS13 activity <10% as measured by the FRETs-VWF73 assay, documented in subject history or at screening (subjects who were currently receiving SoC prophylactic therapy may have exceeded 10% ADAMTS13 activity at screening)

For the prophylactic cohort, eligible subjects were currently on a prophylactic dosing regimen or had a documented history of at least 1 TTP event and an ability to tolerate SoC prophylactic dosing.

6.1.4 Study Treatments or Agents Mandated by the Protocol

For prophylaxis, subjects received a dose of 40 IU/kg of ADZYNMA once every 1-2 weeks. For on-demand, subjects received ADZYNMA 40 IU/kg on Day 1, 20 IU/kg on Day 2, followed by 15 IU/kg on Day 3 and daily thereafter until 2 days after the acute TTP event was resolved.

6.1.6 Sites and Centers

The study was conducted worldwide in 9 countries/regions (Australia, France, Germany, Italy, Japan, Poland, Spain, UK, and USA) at 23 centers.

6.1.7 Surveillance/Monitoring

Please refer to the clinical review.

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint

The primary efficacy endpoint was the incidence of acute TTP events among subjects receiving either ADZYNMA or SoC prophylactically during the corresponding treatment periods. The annualized incidence rate of acute TTP events reported in this memo was calculated as the number of acute TTP events during the on-treatment observation period multiplied by 12*28 divided by the duration of observation period in days.

*Reviewer's comment: All annualized event rates are based on a year of 12*28 days (pre-specified in SAP), rather than 365.25 days, resulting in approximately 10% underestimate of the annualized rates. In the relevant sections below, I included annual event rates based on both definitions.*

Secondary Efficacy Endpoints

Important secondary efficacy endpoints included:

1. Proportion of acute TTP events responding to BAX 930, defined as not requiring the use of another ADAMTS13-containing agent
2. Time to resolution of acute TTP events following initiation of treatment (for the acute TTP event) with BAX 930 or SoC agent
3. Incidence of thrombocytopenia defined as a drop-in platelet count $\geq 25\%$ of baseline or a platelet count $< 150,000/\mu\text{L}$
4. Incidence of microangiopathic hemolytic anemia defined as an elevation of LDH $> 1.5\times$ of baseline or $> 1.5\times$ ULN
5. Incidence of neurological symptoms (e.g., confusion, dysphonia, dysarthria, focal or general motor symptoms including seizures)
6. Incidence of renal dysfunction defined as an increase in serum creatinine $> 1.5\times$ baseline
7. Incidence of abdominal pain
8. Incidence of supplemental doses prompted by subacute TTP events
9. Incidence of dose modification not prompted by an acute TTP event
10. Incidence of acute TTP events while subjects are on their final dose and dosing regimen in the study

Success Criterion

No statistical hypothesis was to be tested in this study. Given that cTTP is an extremely rare disease, Study 281102 was intended to enroll a sufficient sample size to descriptively evaluate the efficacy and safety of ADZYNMA treatment, and

to allow for a controlled comparison to SoC treatment on multiple acute and subacute clinically relevant cTTP signs and symptoms.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size Determination

The sample size was not determined based on a power calculation because no statistical hypothesis testing was planned in this study.

With a consideration of 10% dropout rate, the applicant proposed to enroll 36 adult (≥ 18 years old) subjects and 12 adolescent (4 subjects age between 12 and 17) or pediatric subjects (4 subjects ages between 6- <12 , and 4 subjects age 0- <6) in the prophylaxis cohort.

Analysis Populations

The all subjects enrolled set (ENR) was to include all subjects who had signed an informed consent form (ICF).

The randomized analysis set (RND) was to include all subjects that were randomized into one of the treatment sequences for the Prophylactic Cohort or one of the treatment arms for the OD cohort.

The safety analysis set (SAF) was to include all subjects who received at least 1 dose of ADZYNMA or SoC treatment after randomization.

The full analysis set (FAS) was to include all subjects with a confirmed cTTP diagnosis who received at least 1 dose of ADZYNMA or SoC treatment after randomization.

The modified full analysis set (MFAS) was to include all subjects who were included in the FAS with the following modifications:

- For subjects enrolled prior to the study hold in November 2017, if ADZYNMA was the randomized treatment for Period 1 and they were instead treated on SoC because ADZYNMA was not available, the subjects were to be excluded from MFAS.
- For subjects enrolled prior to the study hold in November 2017, if SoC was the randomized treatment for Period 1 and were treated on SoC beyond the 6-month period specified in the protocol because ADZYNMA was not available, only the efficacy data for Period 1 collected prior to the Month 6 visit was to be used in the MFAS-based efficacy analysis. The period over which the endpoint was to be evaluated was between the first dose date and the date of the Month 6 visit for Period 1. Data in Period 2 and beyond was also to be included in the MFAS-based efficacy analyses.

The per-protocol analysis set (PPAS) was to include all subjects in the MFAS who had no major protocol deviations, defined as major if they were considered

to have had an influence on the efficacy outcome, PK outcome, or the treatment of the subject.

Primary Efficacy Analyses

Efficacy analyses were performed separately for Prophylactic Cohort and OD Cohort. Descriptive statistics were planned for the primary efficacy endpoint, i.e., the incidence rate of acute TTP events based on the MFAS. Sensitivity analyses were performed over the FAS, PPAS, and SAF. All confidence intervals (CIs) were to be 2-sided 95% CIs, unless stated otherwise. No control of study-wide Type I error was to be implemented.

The primary estimation method for the annualized acute TTP rate would be model based. Specifically, the acute TTP event rate would be assumed to follow a negative binomial distribution, and the mean acute TTP rate would be estimated using a generalized linear mixed -effects model (GLMM) with a negative binomial distribution as a family and a logarithmic link function (the default) with treatment as a fixed effect, subject as a random effect, and the logarithm of follow-up time (in years) as an offset. Period (1 and 2) and sequence (ADZYNMA – SoC, Soc – ADZYNMA) would be included in the model as categorical variables. On the other hand, if no events are observed, the GLMM model would not be fitted, only the descriptive statistics on TTP event rates would be reported.

Interim Analysis

For the efficacy analysis for the prophylactic cohort, one interim analysis (with interim clinical study report) was scheduled to be performed after 30 subjects in the prophylactic cohort complete the study. The current application is based on data accumulated at the interim data cutoff when 32 subjects in the prophylactic cohort had completed the study.

Secondary Efficacy Analysis

Analyses of the secondary endpoints related to incidence rate would be performed similarly as that for the acute TTP events. Kaplan-Meier estimates of the median time to resolution would be presented for the time to resolution of acute TTP secondary endpoint.

No multiplicity adjustment to control Type I error was planned in the study. Therefore, all analyses are considered as descriptive.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

A total of 64 subjects were enrolled and screened and 10 subjects were screen failures. Forty-eight subjects in the total Prophylactic Cohort and 5 subjects in the OD Cohort were randomized to treatment, and all randomized subjects received

at least 1 dose of either ADZYNMA or SoC. A summary of the analysis populations is provided in Table 3.

Table 3: Analysis Populations

	Prophylactic	OD
Number of Subjects Enrolled	59	5
RND/SAF	48	5
FAS	47	5
MFAS	46	5
PPAS	42	4

Source: Adapted from BLA 125795/0 Module 5.3.5.1/281102: report-body.pdf, Table 15, page 124.

6.1.10.1.1 Demographics

Demographic characteristics are summarized by SAF in Table 4. The mean (SD) age was 31.0 (16.69) years for all subjects in the Prophylactic Cohort and 25.0 (7.28) years for all subjects who began the study in the OD Cohort. There were 20 male and 28 female subjects in the Prophylactic Cohort and 3 male and 2 female subjects in the OD Cohort; the majority of subjects were White and not Hispanic or Latino for both the Prophylactic and OD Cohorts. There were 36 adults with a median (range) age of 38.0 (18, 68) years for the Prophylactic Cohort; all 5 subjects in the OD Cohort were adults with a median (range) age of 20.0 (20, 36) years.

Table 4: Demographics by Treatment Cohort (SAF)

	ADZYNMA – SoC (Prophylactic)	Soc – ADZYNMA (Prophylactic)	Total (Prophyl actic)	ADZYNMA (OD)	Soc (OD)	Total (OD)
N	21	27	48	2	3	5
Age (years)						
Mean	33.5	29.1	31.0	N/A	28.3	25.0
SD	16.51	16.89	16.69	N/A	8.02	7.28
Median	42.0	27.0	32.5	N/A	29.0	20.0
Min, Max	3, 54	5, 68	3, 68	20, 20	20,36	20, 36
Age group, n(%)						
< 6 years	3 (14.3)	1 (3.7)	4 (8.3)	0	0	0
6 to <12 years	1 (4.8)	3 (11.1)	4 (8.3)	0	0	0
12 to < 18 years	1 (4.8)	3 (11.1)	4 (8.3)	0	0	0
≥ 18 years	16 (76.2)	20 (74.1)	36 (75.0)	2 (100)	3 (100)	5 (100)
Sex, n(%)						
Female	12 (57.1)	16 (59.3)	28 (58.3)	1 (50.0)	1 (33.3)	2 (40.0)

Male	9 (42.9)	11 (40.7)	20 (41.7)	1 (50.0)	2 (66.7)	3 (60.0)
Ethnicity, n(%)						
Hispanic or Latino	1 (4.8)	0	1 (2.1)	0	0	0
Not Hispanic or Latino	16 (76.2)	23 (85.2)	39 (81.3)	2 (100)	3 (100)	5 (100)
Not reported	4 (19.0)	4 (14.8)	8 (16.7)	0	0	0
Race, n(%)						
Asian	2 (9.5)	3 (11.1)	5 (10.4)	1 (50.0)	0	1 (20.0)
Black	0	1 (3.7)	1 (2.1)	0	0	0
White	15 (71.4)	17 (63.0)	32 (66.7)	1 (50.0)	2 (66.7)	3 (60.0)
Multiple	0	1 (3.7)	1 (2.1)	0	1 (33.3)	1 (20.0)
N/A	4 (19.0)	5 (18.5)	9 (18.8)	0	0	0
Height (cm)						
Mean (SD)	159.62 (24.28)	162.92 (16.44)	161.48 (20.08)	156.5 (10.61)	175.33 (13.32)	167.80 (14.94)
Weight (kg)						
Mean (SD)	68.30 (25.97)	65.06 (17.87)	66.48 (21.59)	55.9 (12.87)	67.87 (5.45)	63.08 (9.96)
BMI (kg/m ²)						
Mean (SD)	25.46 (5.82)	24.09 (4.73)	24.69 (5.22)	22.62 (2.18)	22.18 (2.10)	22.36 (1.86)

Source: Adapted from BLA 125795/0 Module 5.3.5.1/281102: report-body.pdf, Table 16, page 127.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 5 summarizes cTTP treatment history for SAF. The majority of subjects in both the Prophylactic (47 subjects, 97.9%) and OD Cohorts (4 subjects, 80.0%) had received a prior treatment for cTTP, which was primarily fresh frozen plasma (FFP) (33 subjects [68.8%] and 2 subjects [40.0%], respectively). Investigators reported an acute event in the 12 months prior to screening in eight subjects in the Prophylactic Cohort and one subject in the OD Cohort.

Table 5: cTTP History by Treatment Cohort (SAF)

	ADZYNMA – SoC	Soc – ADZYNMA	Total prophylac tic	ADZYN MA, OD	Soc, OD	Total OD
N	21	27	48	2	3	5
Any cTTP treatment, n(%)	21 (100)	26 (96.3)	47 (97.9)	2 (100)	2 (66.7)	4 (80.0)
cTTP Pre- Study Treatments, n(%)	21 (100)	26 (96.3)	47 (97.9)	2 (100)	2 (66.7)	4 (80.0)
FFP, n (%)	16 (76.2)	17 (63.0)	33 (68.8)	1 (50.0)	1 (33.3)	2 (40.0)
Solvent/Deter gent Treated Plasma, n(%)	5 (23.8)	6 (22.2)	11 (22.9)	0	1 (33.3)	1 (20.0)
FVIII-VWF Concentrates, n(%)	0	3 (11.1)	3 (6.3)	1 (50.0)	0	1 (20.0)
History of Acute TTP Events (in the Past 12 Months)						
Yes	5 (23.8)	3 (11.1)	8 (16.7)	0	1 (33.3)	1 (20.0)
No	16 (76.2)	24 (88.9)	40 (83.3)	2 (100)	2 (66.7)	4 (80.0)
History of Subacute TTP Events (in the Past 12 Months)						
Yes	2 (9.5)	3 (11.1)	5 (10.4)	1 (50.0)	0	1 (20.0)
No	19 (90.5)	24 (88.9)	43 (89.6)	1 (50.0)	3 (100)	4 (80.0)

Source: Adapted from BLA 125795/0 Module 5.3.5.1/281102: report-body.pdf, Table 18, page 132.

Medical history is summarized for the SAF by treatment cohort and SOC in Table 6, sorted by descending order of frequency in the Prophylactic Cohort. The majority of subjects in both the Prophylactic (93.8%) and OD (60.0%) Cohorts had at least one medical condition before enrolling in the study. The most common congenital, familial, and genetic disorder was congenital thrombocytopenia (14 subjects in the Prophylactic Cohort and 1 subject in the OD Cohort).

Table 6: Medical History by Treatment Cohort and System Organ Class (SAF)

	ADZYNMA – SoC	Soc – ADZYNMA	Total Prophylac tic	ADZYN MA, OD	Soc, OD	Total OD
N	21	27	48	2	3	5
Any Medical History	20 (95.2)	25 (92.6)	45 (93.8)	1 (50.0)	2 (66.7)	3 (60.0)
Nervous system disorders	15 (71.4)	11 (40.7)	26 (54.2)	0	1 (33.3)	1 (20.0)
Surgical and medical procedures	14 (66.7)	6 (22.2)	20 (41.7)	0	1 (33.3)	1 (20.0)
Congenital, familial, and genetic disorders	7 (33.3)	11 (40.7)	18 (37.5)	0	1 (33.3)	1 (20.0)
Vascular disorders	6 (28.6)	8 (29.6)	14 (29.2)	0	0	0
Metabolism and nutrition disorders	4 (19.0)	9 (33.3)	13 (27.1)	0	0	0
Renal and urinary disorders	5 (23.8)	8 (29.6)	13 (27.1)	0	1 (33.3)	1 (20.0)
Infections and infestations	5 (23.8)	6 (22.2)	11 (22.9)	0	0	0
Blood and lymphatic system disorders	5 (23.8)	6 (22.2)	11 (22.9)	0	1 (33.3)	1 (20.0)
Gastrointestin al disorders	5 (23.8)	4 (14.8)	9 (18.8)	1 (50.0)	1 (33.3)	1 (20.0)
Psychiatric disorders	4 (19.0)	5 (18.5)	9 (18.8)	0	1 (33.3)	1 (20.0)

Source: Adapted from BLA 125795/0 Module 5.3.5.1/281102: report-body.pdf, Table 19, page 135.

6.1.10.1.3 Subject Disposition

Disposition of subjects in the Prophylactic Cohort is presented in Table 7. As of the IA data cut-off date (12 Aug 2022), enrollment of all age groups of the Prophylactic Cohort is complete; 32 subjects in the Prophylactic Cohort (66.7% [32/48] of subjects randomized, 16 subjects each in the ADZYNMA - SoC and the SoC - ADZYNMA sequences) have completed the study, and 36 (75%) subjects have completed Periods 1 and 2. Among 32 subjects who have completed the study, 29 (80.6%) are adult subjects (≥ 18 year old) and 3 (75.0%)

are adolescent subjects (12 to <18 years old) as of the interim data cutoff. There are 14 (29.2%) subjects, primarily younger pediatric subjects, still on study in the Prophylactic Cohort.

Table 7: Subject Disposition for Prophylactic Cohort

	ADZYNMA - SoC	SoC - ADZYNMA	Total
Number of Subjects Enrolled	-	-	59
Screen failures	-	-	10
Withdrew	-	-	1
Randomized to treatment	22	26	48
Entered Period 1	22	25	47
Entered Period 2	19	23	42
Entered Period 3	18	18	36*

*: Thirty-five subjects in MFAS entered Period 3 from Prophylactic Cohort and one subject ((b) (6)) entered Period 3 but was excluded from MFAS.

Source: Adapted from BLA 125795/0 Module 5.3.5.1/281102: report-body.pdf, Table 11, page 114.

Disposition of subjects for the OD Cohort is presented in Table 8. Two subjects were randomized to receive ADZYNMA without moving to the Prophylactic Cohort. Three subjects were randomized to receive SoC and moved to the Prophylactic Cohort after completing OD treatment. One subject (Subject ((b) (6))) has discontinued the study from the Prophylactic Cohort due to PI decision following an allergic reaction to the SoC treatment. The other two subjects are still on-study in the Prophylactic Cohort.

Table 8: Subject Disposition for On-Demand Cohort

	ADZYNMA	SoC	Total
Number of Subjects Enrolled	-	-	5
Screen failures	-	-	0
Randomized to treatment	2	3	5
Number of Subjects that Received OD Treatment	2	3	5
Completed Study in OD Cohort	2	0	2
Moved to Prophylactic Cohort and Still on Study	0	2	2
Moved to Prophylactic Cohort and Discontinued Study	0	1	1

Source: Adapted from BLA 125795/0 Module 5.3.5.1/281102: report-body.pdf, Table 12, page 116.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

No acute TTP events occurred in 37 adult or adolescent subjects while receiving ADZYNMA prophylaxis during the cross-over treatment period and throughout the duration of the study including in 35 subjects in Period 3 at the time of IA data cutoff. The longest duration of ADZYNMA exposure was 22.6 months.

One acute TTP event occurred in 1 adult subject (Subject (b) (6)) while receiving SoC (FFP) prophylactically during the cross-over treatment Period 1. The event was confirmed to be an acute event by laboratory abnormalities. There were no acute events in pediatric subjects. All sensitivity analyses showed similar results in FAS, PPAS, and SAF. Table 9 below summarizes the statistics of acute TTP events.

Table 9: Summary of Acute TTP Events by Study Period in the Prophylactic Cohort - MFAS (Age ≥12 Years)

	SoC Period 1 and 2 (N=38)	ADZYNMA Period 1 and 2 (N=37)	ADZYNMA Period 3 (N=35)
Number of subjects with acute TTP event	1	0	0
Number of acute TTP events	1	0	0
Annualized acute TTP event rate mean (SD)*	0.05 (0.28)	0 (0)	0 (0)
Duration of observation period in years (SD)*	0.54 (0.113)	0.53 (0.106)	0.58 (0.219)
Annualized acute TTP event rate mean (SD)**	0.05 (0.304)	0 (0)	0 (0)
Duration of observation period in years (SD)**	0.50 (0.104)	0.48 (0.098)	0.53 (0.202)

*: with the definition of one year as 12*28 days

**: with the definition of one year as 365.25 days

Source: Adapted from BLA 125795/0 Module 5.3.5.1/281102: report-body.pdf, Table 21, page 141, and the 125795/0/0050 Module 1: clinical-information-amendment-ad-hoc-combined-tables.pdf, page 1.

Remark: Because of the sparse number of events, only descriptive statistics on acute event rates are reported.

The incidences of subacute TTP events in Prophylactic Cohort are summarized in Table 10. No subacute TTP event occurred in subjects while receiving ADZYNMA during Periods 1 and 2, while five subacute TTP events occurred in four subjects receiving SoC. There were two subacute TTP events occurring in two subjects with ADZYNMA treatment in Period 3.

Table 10: Summary of subacute TTP Events* by Study Period in the Prophylactic Cohort - MFAS (Age ≥12 Years)

	SoC Period 1 and 2 (N=38)	ADZYNMA Period 1 and 2 (N=37)	ADZYNMA Period 3 (N=35)
Number of subjects with event	4	0	2
Number of events	5	0	2
Annualized event rate mean (SD)**	0.25 (0.778)	0 (0)	0.07 (0.291)
Duration of observation period in years (SD)**	0.54 (0.113)	0.53 (0.106)	0.58 (0.219)
Annualized event rate mean (SD)***	0.27 (0.836)	0 (0)	0.08 (0.317)
Duration of observation period in years (SD)***	0.50 (0.104)	0.48 (0.098)	0.53 (0.202)

*: Subacute events were defined by a thrombocytopenia event or a microangiopathic hemolytic anemia event; and organ-specific signs and symptoms including but not limited to renal dysfunction events, neurological symptoms events, fever, fatigue/lethargy, and/or abdominal pain.

** : with the definition of one year as 12*28 days

***: with the definition of one year as 365.25 days

Source: Adapted from BLA 125795/0 Module 5.3.5.1/281102: report-body.pdf, Table 30, Page 171.

6.1.11.2 Analyses of Secondary Endpoints

Proportion of acute TTP events responding to ADZYNMA treatment

A total of five subjects were enrolled in the OD Cohort, two subjects were randomized to receive ADZYNMA and three subjects were randomized to receive SoC treatment. A total of six acute TTP events occurred in these five subjects, as one subject (Subject (b) (6)) receiving SoC treatment in the OD Cohort experienced two acute events.

Only one acute TTP event treated with ADZYNMA in the OD Cohort was confirmed to meet the protocol definition of an acute event (Subject (b) (6)). The acute TTP event was resolved. Another acute event treated with ADZYNMA in the OD Cohort was not confirmed by the central laboratory as an acute event (Subject (b) (6)), and therefore is not included in this endpoint analysis, although it met the criteria for being resolved by ADZYNMA treatment.

Time to Resolution of Acute TTP Events

In the Prophylactic Cohort, one subject receiving SoC had an acute TTP event (Subject (b) (6)); this event was reported as resolved after 14.8 days.

In the OD Cohort, one confirmed acute TTP event was treated with SoC (Subject (b) (6)); the time to resolution was reported as 1.5 days. One confirmed acute event (Subject (b) (6)) was treated with ADZYNMA, and the reported time to resolution of the acute TTP event was 3.0 days.

Incidence of Isolated TTP Manifestations During Prophylaxis

The incidences of TTP clinical signs and symptoms, including manifestations of thrombocytopenia, MAHA, renal dysfunction, neurologic symptoms (e.g., headache and migraine), and abdominal pain during the prophylactic treatment Periods 1, 2, and 3, were analyzed with negative binomial regression models. The model-based estimate of mean annualized incidence rate of TTP manifestations in adult and adolescent subjects in the MFAS is presented in Table 11 for each treatment for the Prophylactic Cohort specifically during Period 1 and Period 2, as well as the ratio of the 2 treatment incidence rates accompanied by 95% CI and 2-sided nominal p-value.

Table 11: Analysis of Annualized Event Rates of TTP Manifestations for Periods 1 and 2 in the Prophylactic Cohort - MFAS (Age ≥ 12 Years)*

Event	ADZYNMA (N=37)	SoC (N=38)	Ratio (95% CI)
Thrombocytopenia events	0.81 (0.279)	1.87 (0.577)	0.4 (0.3, 0.7)
Microangiopathic hemolytic anemia events	0.29 (0.141)	0.8 (0.264)	0.4 (0.1, 1.1)
Renal dysfunction events	0.11 (0.085)**	0.08 (0.063)**	1.4 (0.2, 8.0)
Neurological symptoms events	0.19 (0.101)	0.31 (0.154)	0.6 (0.3, 1.2)
Abdominal Pain events	0.12 (0.074)	0.18 (0.102)	0.6 (0.2, 2.3)
Other Isolated TTP manifestations	0.34 (0.138)	0.88 (0.264)	0.4 (0.2, 0.9)

*: Calculated from a generalized linear mixed-effects model with a negative binomial distribution as a family and a logarithmic link function with treatment as a fixed effect, subject as a random effect, and the logarithm of follow-up time (in years) as an offset. Period (1 and 2) and sequence (TAK-755 - SoC, SoC - TAK-755) were included in the model as categorical variables. One year is defined as 365.25 days.

** : Due to sparse events, the full model did not converge. Therefore, these results are from a generalized linear mixed effects model that did not include the treatment sequence as a covariate.

Source: Adapted from BLA 125795/0 Module 5.3.5.1/281102: report-body.pdf, Table 24, page 156.

Incidence of Thrombocytopenia Manifestations

The incidence of thrombocytopenia manifestations was defined as a drop in platelet count of $\geq 25\%$ of baseline or a platelet count $< 150,000/\mu\text{L}$.

In Periods 1 and 2, 19 out of 38 subjects experienced a total of 75 thrombocytopenia manifestations while receiving SoC, with a mean (SD) annualized event rate of 4.44 (6.312); 9 out of 37 subjects experienced a total of 30 thrombocytopenia manifestations while receiving ADZYNMA treatment, with a mean (SD) annualized event rate of 2.0 (4.706). In Period 3, 9 out of 35 subjects experienced 16 thrombocytopenia manifestations while receiving ADZYNMA treatment, with a mean (SD) annualized event rate of 1.57 (4.893).

Incidence of Microangiopathic Hemolytic Anemia Manifestations (MAHA)

The incidence of MAHA manifestations was defined as an elevation of LDH $> 1.5\times$ baseline or LDH $> 1.5\times$ ULN.

IN Periods 1 and 2, 11 out of 38 subjects experienced a total of 20 events of MAHA while receiving SoC, with a mean (SD) annualized event rate of 1.47 (3.274). Five out of 37 subjects experienced 7 events of MAHA while receiving ADZYNMA with a mean (SD) annualized event rate of 0.38 (1.028). In Period 3, 1 out of 35 subjects experienced 3 events of MAHA while receiving ADZYNMA treatment, with a mean (SD) annualized event rate of 0.58 (0.901).

Incidence of Neurological Symptom Manifestations

In Periods 1 and 2, 7 out of 38 subjects experienced 29 neurological symptom manifestations while receiving SoC, with a mean (SD) annualized event rate of 1.46 (4.472); 4 out of 37 subjects experienced 18 neurological symptom manifestations while receiving ADZYNMA, with a mean (SD) annualized event rate of 0.96 (3.494). In Period 3, 8 out of 35 subjects experienced 23 neurological symptom manifestations while receiving ADZYNMA, with a mean (SD) annualized event rate of 1.15 (2.812).

Incidence of Renal Dysfunction Manifestations

In Periods 1 and 2, 2 out of 38 subjects experienced a total of 5 renal dysfunction manifestations while receiving SoC, with a mean (SD) annualized event rate of 0.26 (1.158); 3 out of 37 subjects experienced 8 renal dysfunction manifestations while receiving ADZYNMA treatment, with a mean (SD) annualized event rate of 0.45 (1.687). In Period 3, 1 out of 35 subjects experienced 3 renal dysfunction manifestations while receiving ADZYNMA treatment, with a mean (SD) annualized event rate of 0.07 (0.411).

Incidence of Abdominal Pain Manifestations

In Periods 1 and 2, 5 out of 38 subjects experienced 7 abdominal pain manifestations while receiving SoC, with a mean (SD) annualized event rate of 0.37 (1.022); 2 out of 37 subjects experienced 4 abdominal pain manifestations while receiving ADZYNMA, with a mean (SD) annualized event rate of 0.21 (0.904). In Period 3, 2 out of 35 subjects experienced 4 abdominal pain manifestations while receiving ADZYNMA, with a mean (SD) annualized event rate of 0.23 (1.162).

Incidence of Other TTP Manifestations

In Periods 1 and 2, 14 out of 38 adult and adolescent subjects experienced 24 “Other” TTP manifestations while receiving SoC, with a mean (SD) annualized event rate of 1.27 (2.205); 6 out of 37 subjects experienced 9 “Other” TTP manifestations while receiving ADZYNMA, with a mean (SD) annualized event rate of 0.48 (1.277). In Period 3, 4 out of 35 subjects experienced 9 TTP manifestations while receiving ADZYNMA, with a mean (SD) annualized event rate of 0.39 (1.516).

Remark: *It should be noted the model-based estimates were different from the non-model based estimates. The model-based results are from a generalized linear mixed-effects model assuming a negative binomial distribution and*

logarithmic link function with treatment, period, and sequence as fixed effects, subject as a random effect, and the logarithm of follow-up time (in years) as an offset. Given the complex study design and right-skewed, over-dispersed data, with potential influence of confounders and outliers, the applicant believes that the model-based approach for estimating and comparing treatment arm event rates provides more robust estimates of the mean over the non-model-based approach. I agree in general an appropriately specified model would yield more robust estimates. At the time of this writing, there is ongoing review of a response to an Information Request from the applicant related to the accuracy of their model construction and assumptions. The final Prescribing Information will reflect updated model estimates if necessary. Overall, the treatment effects were consistent between the two estimation approaches despite the differences in individual group estimates.

Incidence of Supplemental Doses Prompted by Subacute TTP Events

In Periods 1 and 2, there were no supplemental doses prompted by subacute TTP events in subjects receiving ADZYNMA prophylaxis compared to a total of six supplemental doses in two subjects receiving SoC to treat two subacute TTP events. In Period 3, one subject receiving ADZYNMA prophylaxis was administered four supplemental doses to treat one subacute event. All of the supplemental doses prompted by subacute TTP events occurred in adult subjects.

Incidence of Dose Modifications Not Prompted by an Acute TTP Event During Prophylaxis

There were no dose modifications prompted by an acute TTP event during this study.

Incidence of Acute TTP Events While on Final Dose and Dosing Regimen

There were no acute TTP events from any subjects within the final dose and dosing regimen period while receiving ADZYNMA.

6.1.11.3 Subpopulation Analyses

The applicant provided subgroup analyses of acute TTP events by age group, race, sex and geographical region in the submission. Since only one acute TTP event observed in the study, most subgroups yield zero acute TTP events and subgroup analyses will unlikely provide meaningful information. Therefore, these subgroup analyses are not reported in detail in this memo.

6.1.11.4 Dropouts and/or Discontinuations

Two subjects have discontinued the study: one subject in the Prophylactic Cohort discontinued the study because it was determined that the subject was an immune-mediated TTP (iTTP) patient (and not a cTTP patient).

Another subject completed treatment in the OD Cohort and moved to the Prophylactic Cohort. This subject then discontinued the study from the Prophylactic Cohort due to PI decision following an allergic reaction to the SoC treatment. Therefore, this subject is counted as discontinuing the study in both the OD and Prophylactic Cohorts. This same subject later reenrolled in the study to the Prophylactic Cohort receiving different SoC (FVIII instead of S/D plasma) and was assigned a new subject number; data for this person are presented as 2 unique subjects throughout this CSR.

6.1.12 Safety Analyses

6.1.12.3 Deaths

No death occurred in this study.

6.1.12.4 Nonfatal Serious Adverse Events

During Periods 1 and 2, one Serious Adverse Events (SAEs) were reported for 1 (2.2%) subject while receiving ADZYNMA and 11 SAEs were reported for 7 (15.9%) subjects while receiving SoC. One SAE of pyrexia was considered possibly related to SoC. No SAEs were considered related to ADZYNMA.

There were 2 SAEs that were not treatment-emergent: one subject had an allergic reaction to FFP infusion and another subject had trigeminal neuralgia that resulted in hospitalization.

6.1.12.5 Adverse Events of Special Interest (AESI)

There were no AESIs identified in the study.

6.1.12.7 Dropouts and/or Discontinuations

6.2 Trial #2: TAK-755-3002

Study TAK-755-3002 was a Phase 3b, prospective, open-label, multicenter, single treatment arm, continuation study of the safety and efficacy of ADZYNMA in the prophylactic and on-demand treatment of subjects with severe cTTP. This study planned to enroll approximately 77 eligible subjects and is ongoing. As of the date for this interim analysis (12 Aug 2022), 47 subjects were enrolled and 36 had been treated with ADZYNMA up to 15.8 months with a mean duration as 6.3 months. No acute TTP events were reported in any subjects while receiving ADZYNMA prophylactic treatment as of the IA data cutoff date. No deaths occurred. There were 3 SAEs with 3 subjects and none of these SAEs were considered related to ADZYNMA.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

This statistical review memo focuses on the efficacy analysis and safety analysis of the pivotal phase 3 Study 281102. The phase 3b Study TAK-755-3002 is also reviewed for safety.

According to the current interim report of Study 281102, zero acute TTP events occurred in 37 adult or adolescent subjects with ADZYNMA prophylaxis during the controlled comparison treatment periods, while one event occurred during SoC treatment (with a time to event resolution 14.8 days). There were no acute TTP events with ADZYNMA observed for up to 22.6 months throughout the study including Period 3. In the OD Cohort, five subjects with six acute TTP events were enrolled, two subjects were randomized to ADZYNMA and 3 subjects were randomized to SoC treatment. Two of six events were confirmed to meet the protocol definition of acute TTP events: one event (Subject (b) (6)) was treated with ADZYNMA the time to resolution was reported as 3 days, and the other event was treated with SoC and the time to resolution was reported as 1.5 days (Subject (b) (6)).

The safety of ADZYNMA was supported by both Study 281102 and Study TAK-755-3002. At the time of the IA cutoff date, 48 subjects had been exposed to ADZYNMA up to 22.6 months, with a mean (SD) exposure of 11.48 (6.3) months in Study 281102, and 36 had received ADZYNMA up to 15.8 months with a mean duration as 6.3 months in phase 3b Study TAK-755-3002. No acute TTP event was observed. No deaths occurred. No serious safety concern was issued. No SAEs in either study were considered related to ADZYNMA.

10.2 Conclusions and Recommendations

The statistical analysis of Study 281102 provides statistical evidence to support the efficacy of ADZYNMA as a ERT treatment for prophylactic for subject with cTTP. I defer to the clinical reviewer on the generalizability of prophylactic effectiveness to on-demand use and the acceptability of the safety profile of ADZYNMA.