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Summary Basis for Regulatory Action

Date:	November 9, 2023
From:	Nobuko Katagiri, PhD, Chair of the Review Committee, office of Therapeutic Products (OTP), Office of Plasma Protein Therapeutics, Division of Hemostasis
BLA STN:	BLA 125795/0
Applicant:	Takeda Pharmaceuticals, U.S.A, Inc.
Submission Receipt Date:	March 17, 2023
PDUFA Action Due Date:	November 15, 2023
Proper Name:	ADAMTS13, recombinant-krhn
Proprietary Name:	ADZYNMA
Indication:	Prophylactic or on-demand enzyme replacement therapy (ERT) in adult and pediatric patients with congenital thrombotic thrombocytopenic purpura (cTTP)

Recommended Action: The Review Committee recommends approval of this product.

Acting Director, Office of Clinical Evaluation

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (OTP/OPPT) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	 Nobuko Katagiri, PhD, OTP/OPPT/DH Chava Kimchi-Sarfaty, PhD, OTP/OPPT/DH Katarzyna Jankowska, PhD, OTP/OPPT/DH Upendra Katneni, PhD, OTP/OPPT/DH Kula N. Jha, PhD, OCBQ/DMPQ/MRB1 Maureen DeMar, RN, OCBQ/DMPQ Salil Ghosh, PhD, OCBQ/DBSQC Esmeralda Alvarado-Facundo, PhD, OCBQ/DBSQC Brianna Davis, OCBQ/DBSQC George Kastanis, MS, OCBQ/DBSQC
Clinical • Clinical (OTP/OCE) • Postmarketing safety Pharmacovigilance review (OBPV/DPV) • BIMO	 Megha Kaushal, MD, OTP/OCE/DCEH Yeowon Kim, MD, MHS, OBPV/DPV LCDR Malcolm Nasirah, PharmD, MS, BCGP, OCBQ/DIS/BMB
Statistical • Clinical data (OBPV/DB)	 Jiang Hu, PhD, OBPV/DB Elin Cho, MS, OBPV/DB
Non-clinical/Pharmacology/Toxicology • Toxicology (Product Office) • Developmental toxicology (Product Office) • Animal pharmacology	Rukmini Bhardwaj, PhD, OTP/OPT/DPT2
Clinical Pharmacology	Xiaofei Wang, PhD, OTP/OCE/DCEGM
Labeling • Promotional (OCBQ/APLB)	Kristine Khuc, PharmD, OCBQ/APLB
Other Review(s) not captured above categories, for example: • PNR (OCBQ/APLB) • Consults	 Oluchi Elekwachi, PharmD, OCBQ/APLB Andrey Sarafanov, PhD, OTP/OPPT/DH Zuben Sauna, PhD, OTP/OPPT/DH Natalya Ananyeva, PhD, OTP/OPPT/DH Youwei Bi, PhD, CDER/OTS/OCP Da Zhang, PhD, CDER/OTS/OCP

	Guansheng Liu, PhD, CDER/OTS/OCP Selena Daniels, PharmD, CDER/OND/ODES/DCOA Jing Ju, PharmD, CDER/OND/ODES/DCOA Ila Srivastava, PharmD, CDER/OSE/OMEPRM/DMEPAII Dunya Karimi, CDRH/OPEQ/OHT3/DHT3C

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1. Introduction

The Applicant submitted an original Biologics License Application (BLA) to seek U.S. licensure for recombinant ADAMTS13 (rADAMTS13). The Applicant uses the International Nonproprietary Name, Apadamtase alfa (rADAMTS13 Q23) and Cinaxadamtase alfa (rADAMTS13 R23). The FDA-established proper name is ADAMTS13, recombinant-krhn and the proprietary name of the U.S. marketed product will be ADZYNMA. ADZYNMA is indicated for prophylactic or on-demand enzyme replacement therapy in adult and pediatric patients with congenital thrombotic thrombocytopenic purpura (cTTP).

ADZYNMA drug product (DP) is a sterile, lyophilized powder for reconstitution for intravenous injection supplied in two nominal strengths 500 IU and 1500 IU per vial. The product is reconstituted with 5 mL sterile water for injection (sWFI) for intravenous administration.

The ADZYNMA Drug Substance (DS) and DP are manufactured at Takeda manufacturing facilities in (b) (4), respectively. Chemistry, Manufacturing, and Control (CMC) reviewers concluded that the Applicant has adequately characterized the physicochemical, biochemical, and *in vitro* function properties of ADZYNMA, and provided documented evidence that the commercial manufacturing process consistently results in ADZYNMA with the intended identity and biological function.

ADZYNMA is a biologics/device co-packaged Type (b) (4) combination product. Therefore, CBER consulted the Center for Drug Evaluation Center (CDER) for an assessment of human factors (HF) threshold/comparative analysis and the Center for Devices and Radiological Health (CDRH) for the evaluation of the BAXJECT II HiFlow reconstitution device used to reconstitute ADZYNMA powder with its diluent.

This document summarizes the basis for regular approval of ADZYNMA. An interim analysis of the clinical trial supported by preclinical and pharmacokinetic (PK) studies provide the primary evidence of safety and effectiveness for prophylactic or on-demand enzyme replacement therapy in adult and pediatric patients with cTTP. Our recommendation for approval is based on the decreased incidence of acute, subacute TTP events and TTP manifestations demonstrated in the clinical trial. The risks of ADZYNMA include hypersensitivity and potential development of neutralizing antibodies.

The Applicant has provided substantial evidence of effectiveness and safety based on adequate and well controlled clinical trial supported by preclinical studies and PK studies. The review team recommends approval of this BLA. Limitations in the DS and DP release strategy identified during the review process will be addressed with CMC Post marketing Commitments (PMCs) listed in section 11.c of this document.

2. Background

Congenital thrombotic thrombocytopenic purpura (cTTP) is a rare life-threatening thrombotic disorder caused by a deficiency of the functional ADAMTS13 due to mutations in the *ADAMTS13* gene. In the plasma, ADAMTS13 cleaves pro-thrombotic ultra-large von Willebrand Factor (UL-VWF) multimers, which spontaneously agglutinate platelets, into hemostatically active high molecular weight (HMW) VWF multimers. Severe deficiency of ADAMTS13 results in accumulation of UL-VWF multimers, leading to spontaneous formation of platelet-rich microthrombi with resultant ischemic damage to organs.

Currently, acute TTP events are treated with Fresh Frozen Plasma (FFP) or Solvent/Detergent (S/D)-treated plasma infusions. These clinical interventions have several limitations that may include prolonged and frequent plasma infusions, and potential transfusion related complications. ADZYNMA is the first recombinant ADAMTS13 product indicated for prophylactic or on-demand enzyme replacement therapy (ERT) and addresses the unmet medical needs of patients with cTTP.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. Pre-IND meeting (PTS# PS001106)	May 22, 2012
2. IND submission received (IND 15219)	August 31, 2012
3. IND allowed to proceed	September 28, 2012
4. Orphan Drug designation granted (ODD # DRU-08-2622)	August 5, 2008
5. Fast Track designation granted	February 17, 2017
6. Rare Pediatric Disease designation granted (RPD-2022-685)	March 3, 2023
7. BLA 125795/0 submission	March 17, 2023
8. BLA filed	May 16, 2023
9. Mid-Cycle communication	July 14, 2023
10. Late-Cycle meeting	August 31, 2023
11. Action Due Date	November 15, 2023

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

Description

ADZYNAMA DP is formulated as a sterile, nonpyrogenic lyophilized powder for reconstitution for intravenous injection. rADAMTS13, the active ingredient in ADZYNMA, is expressed in a Chinese Hamster Ovary (CHO) cell line and is a mixture of two amino acid variants. These variants have either a glutamine (Q) or an arginine (R) at position 97 in the rADAMTS13 protein (or position 23 in the mature protein following cleavage of the pro-peptide). The International Nonproprietary Names for the two variants are Apadamtase alfa (rADAMTS13 Q23) and Cinaxadamtase alfa (rADAMTS13 R23).

The DS is manufactured at Takeda's facility in (b) (4) . The manufacturing process of DS includes (b) (4) Satisfactory viral clearance during the manufacturing of DS is achieved by two viral inactivation/removal steps: S/D treatment and Nanofiltration.

The DP is manufactured at Takeda's facility in (b) (4) . ADZYNMA is presented in two dosage strengths, 500 IU or 1500 IU per vial. The dosage of ADZYNMA is based on ADAMTS13 potency assigned using the FRETS-VWF73 assay and a reference standard. The reference standard is a recombinant secondary reference standard (DP Lot (b) (4)), produced in-house by the Applicant and was calibrated against the WHO ADAMTS13 International Standard (IS) plasma, WHO#(b) (4). Additional ingredients in ADZYNMA include the excipients sodium chloride, calcium chloride dihydrate, L-histidine, mannitol, sucrose, and polysorbate 80.

Analytical Characterization

Analytical characterization of ADZYNMA included: i) structural and functional characterization of the active molecule in ADZYNMA (b) (4), rADAMTS13, ii) comparison of rADAMTS13 with plasma derived ADAMTS13 (pdADAMTS13) and iii) structural and functional comparison of native Q23 and variant R23 rADAMTS13.

Structural and functional characterization of mixture rADAMTS13: The Applicant conducted structural and functional characterization studies on ADZYNMA DS batch material. (b) (4) batch was used for analyses of (b) (4) . (b) (4) batches from clinical campaign (b) (4) and (b) (4) batches from process performance qualification (PPQ) campaign (b) (4) were used in other tests. These studies were carried out using the methods described in Table 2.

Table 2. Methods used for analytical characterization of rADAMTS13

(b) (4)

The mean molecular weight of rADAMTS13 was determined to be approximately 172 kDa by (b) (4) . However, due to substantial degree of (b) (4) . Structural analysis using various assays listed in Table 2 demonstrated structural similarity of rADAMTS13 between (b) (4) batches of different campaigns.

The rADAMTS13 activity during the early stages of development was measured by (b) (4) , or the (b) (4) activity using (b) (4) as a substrate. Subsequently, the Applicant validated FRETS-VWF73 assay, which uses a fluorogenic 73 amino acid VWF-peptide substrate, using samples from multiple (b) (4) batches from different campaigns and demonstrated that the FRETS-VWF73 assay is comparable to the (b) (4) analysis and (b) (4) activity assay.

Comparison of rADAMTS13 and pdADAMTS13: The Applicant demonstrated comparability between rADAMTS13 and pdADAMTS13 through (b) (4) analysis

by (b) (4) assessment by (b) (4), measuring ADAMTS13 specific activity and determination of (b) (4) and integrity of protein by (b) (4) method. The Applicant used (b) (4) pdADAMTS13 lots (purified to ~(b) (4) purity) in these analyses.

Structural and functional characterization of Q23 native and R23 variant rADAMTS13: ADZYNMA is a mixture of two molecular species; the amino acid at position 23 of the mature protein is either a Glutamine (Q) or an Arginine (R). The Applicant attempted to develop a cell line that expresses (b) (4) of ADAMTS13 using (b) (4) cell lines (b) (4) for commercial scale production. Therefore, the Applicant continued with the original CHO (b) (4) production cell line expressing a mixture of the Q23 and R23 variants of rADAMTS13. An *in-silico* assessment of immunogenicity indicated no generation of (b) (4) as a result of the amino acid substitution. As the two molecular variants Q23 and R23 (b) (4) (CHO (b) (4) cell line) using small-scale manufacturing process with some modifications compared to commercial current Good Manufacturing Practices (cGMP) manufacturing process.

The Applicant used methods depicted in Table 3 to demonstrate the comparability of the two ADAMTS13 species. As indicated in the table, the results of all assays showed that the two ADAMTS13 variants are comparable. (b) (4) studies also showed a comparable (b) (4) for both variants.

(b) (4)

The test results are consistent between the PPQ DS material, in-house reference control batch, and pdADAMTS13 sample. Overall, the characterization data provided

documented evidence that DS manufacturing consistently results in ADZYNMA DS material with the intended identity and biological function.

Manufacturing process steps

The ADZYNMA manufacturing process is summarized in Table 4.

Table 4: Steps in the manufacturing process of ADZYNMA

Product	Manufacturing Steps
(b) (4)	

Description of the manufacturing process

The DS manufacturing process uses a CHO cell line grown in (b) (4). The upstream process ((b) (4) in Table 4) occurs as part of a continuous manufacturing process that lasts (b) (4).

The downstream process includes purification steps ((b) (4) in Table 4), and the resulting (b) (4) which is stored at (b) (4) until further manufacturing of the final DP at step (b) (4).

Following the rADAMTS13 DP manufacturing process (steps (b) (4) in Table 4) unlabeled vials are 100% visually inspected. During and after the packaging operation, identity tests are carried out on the labeled and packaged final product according to a statistical sampling plan. The final units are packed in shipping cartons, sealed, and labeled with product name, lot number and number of product units enclosed. The DP is stored in the central warehouse at 2-8°C until shipment.

The sWFI drug product is prepared from bulk Water for Injection (WFI).

Critical process parameters and their control

Critical process parameters (CPPs) for the manufacturing process and their acceptable ranges were initially determined during process development. The acceptance ranges were further verified and adjusted during the optimization of the process steps and production of full-scale GMP batches. These CPPs and their acceptance criteria have been justified. Process parameters deemed critical during the manufacture of ADZYNMA are shown in Table 5.

Table 5: Process parameters deemed critical for the manufacture of ADZYNMA

Process Step	Critical Process Parameter (CPP) / In-Process Control (IPC)	Limits (Acceptable Range (AR), Action Limit (AL), Acceptance Criterion (AC))
(b) (4)		

One page has been determined to be not releasable: (b)(4)

(b) (4)

Process validation for Drug Substance

(b) (4)

(b) (4)

Process validation for Drug Product

The consistency, robustness and control of full-scale manufacturing were demonstrated through the PPQ campaign in which a (b) (4) approach was used to validate both the 500 IU/vial and 1500 IU/vial dosage strengths. For each dosage strength, (b) (4) manufactured during formulation. Overall, (b) (4) full-scale batches of ADZYNMA FDP from (b) (4) PPQ (b) (4) were produced at the commercial manufacturing scale at (b) (4) facility in accordance with a pre-approved PPQ protocol.

Additional studies included in PPQ runs validated the use of several DS lots, (b) (4) parameters during formulation, filling and lyophilization (b) (4), as well as processing/hold times to produce ADZYNMA lots and shipping.

CMC Comparability Assessment

For clinical Phase 3 production process, the DP manufacturing process was transferred from a facility located at (b) (4) to the facility at (b) (4) (both in (b) (4)). Additionally, the DP process was changed from "(Phase 1) Process 1" to "(Phase 3) Process A". Changes were as follows: (b) (4) Comparability study between Process 1 and Process A showed that DP manufactured by two processes are comparable.

Processes B, C, and D were introduced during the manufacture of the lots used in the Phase 3 clinical studies. Changes implemented in these processes were:

Process B: (b) (4)

Process C: (b) (4)

Process D: (b) (4)

The compatibility of the ADZYNMA with the co-packaged administration devices (BAXJECT II Hi-Flow Needleless Transfer Device), (b) (4) Syringes, 25G butterfly infusion set and the reconstitution diluents was assessed. The results of the in-use

studies were within the clinical specification limits demonstrating that the reconstitution and administration devices are compatible with ADZYNMA.

Analytical methods for product quality

Analytical methods have been adequately validated to support quality control testing throughout the manufacturing process, release of final product, and monitoring of stability. Additional information and documentation were obtained through information requests (IRs) for clarification. The Applicant adequately addressed and resolved all the identified issues during the review process.

Impurities

Adequate removal of product and process-related impurities by the commercial manufacturing process was demonstrated during process development, process characterization studies and process validation.

Product-related impurities: ADZYNMA product-related impurities include (b) (4)

Process-related impurities: ADZYNMA process-related impurities include host cell proteins (CHO proteins), (b) (4) The Applicant measured the process-related impurity levels of the ADZYNMA DS PPQ batches using a combination of release and characterization tests. In addition, the reduction of process-related impurities was demonstrated using a (b) (4) study for the (b) (4) process and monitored during clinical manufacturing and process validation.

Host Cell Proteins (HCP): Host cell proteins, the impurities consisting of proteins other than rADAMTS13 produced by the CHO host cells, are measured using CHO Protein (b) (4) and monitored during rADAMTS13 (b) (4) batch release specification using an in-house (b) (4) assay with the HCP release limit of (b) (4).

As part of extended characterization studies, the (b) (4)

(b) (4)

(b) (4)

Detergents: (b) (4) detergents, (b) (4) are added during S/D treatment step. The effective and consistent removal of these (b) (4) detergents was demonstrated during the PPQ studies. These detergents are classified as CPPs and are monitored during the (b) (4) Process of (b) (4). Mean level of (b) (4) was reduced by more than (b) (4) log reduction at (b) (4) step (Step (b) (4), Table 4) and (b) (4) were < LOQ. All PPQ batches met the acceptance criteria.

Other impurities: (b) (4)

Microbial Contaminants: The potential microbial contaminants include bacterial endotoxin and viable microorganisms. Endotoxin is routinely measured as a part of ADZYNMA (b) (4) release testing per a (b) (4) test method and the release specification is (b) (4). Bioburden is also monitored during (b) (4) manufacture as IPC with action limit of (b) (4) and measured in all DP batches prior to release with the release specification of (b) (4).

The information provided related to ADZYNMA product- and process-related impurities is acceptable as submitted. The ADZYNMA manufacturing process adequately clears and controls the levels of product- and process-related impurities.

Specification for final drug product

The Applicant defined DP specifications in accordance with applicable pharmacopoeia requirements (USP) and International Council for Harmonization of Technical Requirements for Registration for Pharmaceuticals for Human Use (ICH) Guideline Q6B. The proposed acceptance criteria are based on the manufacturing process development and clinical use experience, release and stability data of final DP and the intrinsic variability of analytical methods. The release and stability specifications listed in Table 6 are considered adequate to confirm product quality and manufacturing consistency.

Table 6. Release and stability specifications for final drug product

Attribute Category	Test: Method (Applicable USP General Chapter)	Acceptance Criteria	
		Release	Stability
General Properties	Appearance (Lyophilized cake): Visual Inspection ((b) (4))	Compact, white lyophilized cake	Same as release
	Appearance (Reconstituted solution): Visual Inspection ((b) (4))	Clear, colorless solution, free from visible particles	Same as release

	Reconstitution time: Visual Inspection	(b) (4)	Same as release
	pH: (b) (4)	7.0(b) (4)	Same as release
	Particulate matters ((b) (4))	(b) (4)	Same as release
	(b) (4)	(b) (4)	Not tested (N/T)
	Residual moisture: (b) (4)	(b) (4)	Same as release
Content	Total Protein: (b) (4)	Report results as (b) (4)	N/T
Potency	rADAMTS13 Activity: FRETS-VWF73 assay	500 IU/Vial: (b) (4) IU/mL 1500 IU/Vial: (b) (4) IU/mL	Same as release
	Specific rADAMTS13 Activity: (b) (4)	(b) (4)	Same as release
Identity	rADAMTS13 (b) (4)	500 IU/Vial: (b) (4) 1500 IU/Vial: (b) (4)	Same as release
	(b) (4)	(b) (4)	Same as release
Purity and Impurities	(b) (4)	(b) (4)	Same as release
Microbiological Quality	Endotoxin: (b) (4)	(b) (4)	Same as release
	Sterility ((b) (4))	Sterile	Same as release
	Container Closure Integrity: (b) (4)	Report results as (b) (4)	Report results
Other Characteristics	Polysorbate 80: (b) (4)	(b) (4)	N/T
	Sodium: (b) (4)	(b) (4)	N/T
	Calcium: (b) (4)	(b) (4)	N/T
	Histidine: (b) (4)	(b) (4)	N/T
	Sucrose: (b) (4)	(b) (4)	N/T
	Mannitol: (b) (4)	(b) (4)	N/T

Stability Studies

The stability study program for ADZYNMA DS and DP followed ICH guidelines and included primary long-term, temperature cycling and forced degradation studies. The available stability data showed no adverse trends at long-term storage conditions and supports the following proposed shelf-life periods:

1. ADZYNMA DS – (b) (4) when stored at the long-term storage temperature of (b) (4)
2. ADZYNMA DP – 36 months at +5±3°C including 6 months at +30(b) (4)°C/ (b) (4) Relative Humidity (RH) (after storage at +30°C, the product must not be returned to the refrigerator to extend the storage duration)
3. ADZYNMA reconstituted DP – Should be used immediately or within 3 hours after reconstitution

Results from forced degradation studies demonstrated that analytical methods used for ADZYNMA (b) (4) DP release and stability testing can detect quality changes in the event of manufacturing process or storage condition excursions.

Combination product

ADZYNMA is a co-packaged combination product consisting of three different constituent parts: lyophilized powder of rADAMTS13 in a product vial, sWFI in a separate vial and a transfer device (BAXJECT II HiFlow device with a Luer-lock syringe and a (b) (4) winged infusion set). CDRH and CDER were consulted for the evaluation of the BAXJECT II HiFlow device and the HF threshold/comparative analysis respectively. The use of the combination product is supported by the following:

• BAXJECT II HiFlow device, Luer-lock syringe, and (b) (4) winged infusion set have been cleared under 510(k) [510(k) ## K092318, (b) (4) , and (b) (4) , respectively] and CE marked.

• To support use of the BAXJECT II HiFlow transfer device with Luer-lock syringe and (b) (4) winged infusion set with ADZYNMA, the Applicant submitted a use-related risk assessment, a risk management report, the instructions for use of the device, a threshold analysis, and a design traceability matrix. In addition, a device compatibility study was provided. The CDRH consult reviewer concluded that the data from these assessments/studies support the use of the BAXJECT II HiFlow reconstitution device and does not have adverse impact on the quality of ADZYNMA DP.

• The CDER consult reviewer reviewed the information related to device used for the reconstitution of ADZYNMA in terms of the HF threshold/comparative analysis under IND 15219. Based on the evaluation, the CDER consult reviewer agreed with the revisions in the Instruction-For-Use made by the Applicant and recommended that submission of additional HF data was not required.

Evaluation of product safety with respect to Adventitious Agents

ADZYNMA's manufacturing process employs facility and procedural controls, control of raw materials used in the process and various filtration steps to minimize the entry and control microbial load in the process stream. In-process and (b) (4) testing is performed to monitor the level of adventitious agents in and around the process stream. No human or animal origin components, raw materials or ingredients are used in the ADZYNMA manufacturing process, except for CHO cells. Downstream manufacturing process employs two viral inactivation/removal steps: S/D treatment and 20 nm Nanofiltration (Steps (b) (4) , Table 4). Additionally, viral removal also occurs during (b) (4) (Step (b) (4), Table 4) which contributes to the viral safety of product. Thereafter, the product is sterile filtered and then aseptic filling is performed. The final release tests include those for sterility and endotoxin.

The Applicant evaluated viral inactivation/clearance steps using scaled-down models under worst case conditions. A panel of model viruses were used to determine the log reduction of virus (LRV) for each of the relevant purification steps. (b) (4) model viruses were selected based on differences in size, resistance to physicochemical impacts, genome type, and envelope coat. They are (b) (4) The Applicant determined the sample virus titer by (b) (4). Mean reduction factors for individual steps ranged from (b) (4) log reduction, and the overall reduction factor for each virus ranged from (b) (4). These results (Table 7) are sufficient to support the effectiveness of viral clearance in the commercial manufacturing process.

Table 7. Total virus reduction factors (log_{10}) achieved by the ADZYNMA manufacturing process

(b) (4)

b. Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for the ADZYNMA DS and DP were found to be adequate for their intended use.

c. CBER Lot Release

Under the provision described in 60 FR 63048-63049 publication (8 December 1995), routine lot-to-lot release by CBER is not required for ADZYNMA because it is a well-characterized therapeutic recombinant product. Thus, ADZYNMA is not subject to CBER Lot Release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of ADZYNMA, activities performed, and inspectional histories are provided in Table 8.

Table 8. Manufacturing Facilities for ADZYNMA (rADAMTS13)

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification /Results
Takeda Manufacturing (b) (4)	(b) (4)	(b) (4)	Waiver	(b) (4) Surveillance

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification /Results
(b) (4) *DS manufacturing*				ORA/OBPO VAI
Takeda Manufacturing (b) (4) *DP manufacturing; DP release testing; DP packaging and labeling; sWFI labeling and packaging; final packaging of co-packaged combination product*	(b) (4)	(b) (4)	Waiver	(b) (4) Surveillance ORA/OBPO VAI
Takeda Manufacturing (b) (4) *DP release testing*	(b) (4)	(b) (4)	Waiver	(b) (4), (b) (3) (A) GMP inspection (b) (4), (b) (3) (A) Satisfactory (b) (4) Surveillance ORA/OBPO VAI
(b) (4) *DP release testing*	(b) (4)	(b) (4)	Waiver	(b) (4), (b) (3) (A) GMP inspection (b) (4), (b) (3) (A) Satisfactory
(b) (4) *sWFI (Co-packaged Diluent) Manufacture*	(b) (4)	(b) (4)	Waiver	(b) (4), (b) (3) (A) GMP Inspection (b) (4), (b) (3) (A) Satisfactory (b) (4) Surveillance ORA/OBPO VAI

(b) (4), (b) (3) (A) known as (b) (4), (b) (3) (A); Office of Biological Products Operations (OBPO); Office of Regulatory Affairs (ORA); Voluntary Action Indicated (VAI)

ORA/OBPO performed the most recent FDA surveillance inspection of Takeda Manufacturing (b) (4) from (b) (4). All inspectional issues were resolved, and the inspection was classified as VAI.

ORA/OBPO performed the most recent surveillance inspection of Takeda Manufacturing (b) (4) in (b) (4) from (b) (4). All inspectional issues were resolved, and the inspection was classified as VAI.

An inspection of Takeda Manufacturing (b) (4) in (b) (4) was performed by (b) (4) regulatory authority, (b) (4), (b) (3) (A) from (b) (4), (b) (3) (A). The inspection report was made available to the FDA via the Mutual Recognition Agreement (MRA). (b) (4), (b) (3) (A) issued a Certificate of GMP Compliance of a Manufacturer. The FDA agreed with (b) (4), (b) (3) (A)' conclusion that the firm complied for the level of manufacturing. ORA/OBPO conducted a surveillance inspection of the facility from (b) (4) . All inspectional issues were resolved, and the inspection was classified as VAI.

An inspection of (b) (4) was performed by (b) (4), (b) (3) (A) from (b) (4), (b) (3) (A) . The inspection report was made available to the FDA via the MRA. (b) (4), (b) (3) (A) issued a Certificate of GMP Compliance of a Manufacturer. The FDA agreed with (b) (4), (b) (3) (A)' conclusion that the firm complied for the level of manufacturing.

The (b) (4), (b) (3) (A) conducted an inspection of (b) (4) from (b) (4), (b) (3) (A) . A Certificate of GMP Compliance of a Manufacturer was issued. The FDA agreed with the inspectorate's conclusion that the firm complied for the level of manufacturing. ORA/OBPO conducted a surveillance inspection of this manufacturing site from (b) (4) . All inspectional issues were resolved, and the inspection was classified as VAI.

e. Container/Closure System

rADAMTS13 is a co-packaged combination product that contains one vial of rADAMTS13 DP lyophilized powder (500 or 1500 IU/vial), one vial of 5 mL diluent (sWFI), one reconstitution device, one 10 mL or 20 mL syringe (for 500 IU or 1500 IU, respectively), one needle infusion set, and two alcohol swabs.

The rADAMTS13 lyophilized DP is filled in a 10 mL colorless Type (b) (4) borosilicate glass vial with a 20 mm (b) (4) laminated butyl rubber stopper with (b) (4) coating on sealing surfaces, and an aluminum crimp seal containing a polypropylene flip-off disk. The rADAMTS13 DP vials, rubber stoppers, and crimp seals are manufactured by (b) (4) , and (b) (4) , respectively. Takeda Manufacturing (b) (4) performed the container closure integrity testing (CCIT) at the (b) (4) facility, employing the (b) (4) test methods; all acceptance criteria were met.

The sWFI diluent is filled in a (b) (4) clear Type (b) (4) glass vial, with a chlorobutyl ((b) (4)) or bromobutyl ((b) (4)) rubber stopper, and a 20 mm diameter aluminum crimp cap. The diluent vials and chlorobutyl stoppers are manufactured by (b) (4) and (b) (4) , respectively. The bromobutyl stoppers and aluminum crimp caps are manufactured by (b) (4) performed the CCIT at the (b) (4) facility, employing the (b) (4) test method; all acceptance criteria were met.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

The pharmacologic activity of ADZYNMA was evaluated through *in vitro* and *in vivo* studies. rADAMTS13-mediated proteolysis and specificity to VWF by ADZYNMA were demonstrated *in vitro* using plasma from ADAMTS13 knock-out (KO) mice, healthy Sprague Dawley rats, (b) (4) guinea pigs, cynomolgus monkeys, and (b) (4) minipigs. The ability of ADZYNMA to protect against TTP onset was evaluated *in vivo* following single intravenous (IV) administration of ADZYNMA (1, 5, 40, 80, and 200 IU/kg) in ADAMTS13 KO mice. The results showed dose-dependent protection from TTP by ADZYNMA with prophylactic activity similar to Octaplas (IV administration, 1 and 5 U/kg).

PK assessments were performed following single IV administration of ADZYNMA in ADAMTS13 KO mice, healthy Sprague Dawley rats, and cynomolgus monkeys at doses levels up to 40, 80, 200, 400, 800, and 1790 IU/kg. The mean terminal half-life ($T_{1/2}$) of ADZYNMA were calculated as 10-17.3 hours in mice, 16.7-24.0 hours in rats, and 24.6-27.9 hours in monkeys.

Safety of ADZYNMA was assessed in repeat-dose toxicology studies conducted in healthy Sprague Dawley rats and cynomolgus monkeys. No adverse findings were observed following IV administrations of ADZYNMA in rats at 800 or 1820 IU/kg once daily for 30 days or at 80, 200, or 400 IU/kg, every third day for 26 weeks. IV administration of ADZYNMA at 80, 200, or 400 IU/kg once weekly for 4 weeks or at 200 or 1790 IU/kg followed by 800 IU/kg once weekly for 4 weeks did not result in adverse findings except for several incidences of hemolytic anemia and thrombocytopenia that were attributed to cross-reactive neutralizing antibodies to endogenous monkey ADAMS13 and were not indicative of potential toxicity of ADZYNMA administration to humans.

Potential for ADZYNMA to cause developmental and reproductive toxicity was evaluated in healthy Sprague Dawley rats. Placental transfer was examined in pregnant rats after a single IV administration of ADZYNMA at 3200 IU/kg on gestation day (GD) 21. In a female fertility and embryo-fetal development study in rats, ADZYNMA was IV administered at 80, 200, or 400 IU/kg, every third day for 2 weeks before mating, throughout mating, and up to approximately Day 16 of gestation. In a pre- and post-natal study in female rats, ADZYNMA was IV administered at 80, 200, or 400 IU/kg every three days from GD Day 6 to approximately Day 21 of lactation. Based on these studies, ADZYNMA was not associated with any adverse treatment-related effects on fertility, pregnancy performance, fetal development, or offspring health.

Genotoxicity and carcinogenicity studies were not conducted with ADZYNMA. These studies are not warranted based on the product and its nonclinical safety profile.

5. Clinical Pharmacology

The clinical pharmacology section of this BLA includes 3 clinical studies in subjects with cTTP: one completed Phase 1 study (Study 281101) and 2 ongoing Phase 3 studies (pivotal Study 281102 and continuation Study TAK-755-3002 [hereafter Study 3002]). The Applicant also developed population PK and exposure-response models, as well as a quantitative systems pharmacology (QSP) model to provide supportive evidence for approval.

The key clinical pharmacology findings are summarized as following:

General PK Profile: Following IV administration of ADZYNMA, both ADAMTS13 antigen and activity followed bi-exponential PK profiles. PK characteristics of ADAMTS13 antigen and activity following ADZYNMA IV administration were similar. C_{max} of ADAMTS13 antigen and activity was achieved immediately after the end of infusion. At the dose of 40 IU/kg, the mean values of C_{max} for ADAMTS13 antigen and activity were 0.84 µg/mL and 1.15 IU/mL, respectively. Mean $AUC_{0\text{-}288h}$ were 38.97 µg*h/mL and 52.81 IU*h/mL for ADAMTS13 antigen and activity, respectively. Mean incremental recovery (IR) for ADAMTS13 antigen and activity was 0.03 (µg/mL)/(µg/kg) and 0.03 (IU/mL)/(IU/kg), respectively. Mean clearance (CL) was 0.05 L/h for both ADAMTS13 antigen and activity.

ADZYNMA produced from DS that were manufactured at two sites ((b) (4) (commercial)) were evaluated in the clinical development. The PK of ADZYNMA manufactured at the two sites were comparable.

PK Comparison between ADZYNMA and Standard of Care (SoC): ADZYNMA IV administration at 40 IU/kg resulted in approximately 4- to 5-fold higher ADAMTS13 activity exposures (C_{max}, AUC) and lower inter-subject variability when compared to plasma-based therapies. Mean time duration above 10% ADAMTS13 activity and average ADAMTS13 activity (average concentration, C_{ave}) were both approximately 3-to 4-fold higher following ADZYNMA IV administration for rADAMTS13 compared to pdADAMTS13.

Dose Proportionality: Following single-dose IV administration of ADZYNMA at 5 IU/kg, 20 IU/kg, and 40 IU/kg to adults and adolescents, dose-related increases in individual ADAMTS13 activity were observed and reached a maximum at approximately 1 hour post-infusion or earlier. ADZYNMA PK was approximately dose proportional between 20 and 40 IU/kg.

PK Over Time: The PK profile of ADAMTS 13 activity following ADZYNMA administration is time independent.

Intrinsic Factors Impacting ADZYNMA PK Profiles (PK in Specific Populations): No intrinsic factors such as age, gender, race, baseline estimated glomerular filtration rate (eGFR), and baseline bilirubin were identified as covariates impacting ADZYNMA PK. Therefore, no dose adjustment in the cTTP patient population beyond body weight-based dosing. ADAMTS13 activity were generally similar across the age groups (<6, 6 to <12, 12 to <18, and ≥18 years). The results from popPK analysis also showed that age did not significantly impact the PK of ADAMTS13 activity and overall ER relationship. The

weight-based dosing effectively compensates for the majority of observed drug exposure variations across different age groups.

Pharmacodynamics: VWF antigen and VWF:ristocetin cofactor activity (VWF:RCo) were used to assess VWF platelet binding activity. Following IV doses of ADZYNMA at the recommended dose, both VWF antigen and VWF:Rco transiently decreased for 1 to 2 days with a 15% to 25% change from baseline.

Exposure-Response Relationships: The relationships between ADAMTS13 activity and the likelihood of isolated TTP manifestations, including composite TTP manifestation endpoints, after administering treatment (ADZYNMA vs. SoC) were evaluated. The exposure-response (E-R) analysis results showed a noteworthy therapeutic impact of ADZYNMA compared to the SoC. The E-R analysis results indicated that average level of ADAMTS13 activity (C_{ave}) significantly decreases the risk of thrombocytopenia and microangiopathic hemolytic anemia (MAHA) in a concentration-dependent manner across different age groups, including adults, adolescents, and pediatrics. In addition, the results from the QSP model also provided confirmative evidence to support the use of ADZYNMA in subjects with cTTP.

Immunogenicity:
No cTTP patients tested positive for neutralizing antibodies against ADAMTS13. Thirteen (one in Study 281102 and 12 in Study 3002) of 67 patients treated prophylactically with ADZYNMA with confirmed cTTP tested positive for low-titer binding antibodies against ADAMTS13 with no observable clinical impact on the safety or efficacy of ADZYNMA, and no increase in antibody titers over time. No obvious clinical impact was observed. Because of the low occurrence of anti-drug antibody (ADA), the effect of these antibodies on the PK, PD, safety, and/or efficacy of rADAMTS13 products is unknown.
There are no data on immunogenicity in previously untreated patients (subjects naïve to plasma-based products), therefore, the risk of immunogenicity for naïve subjects to this drug product is unknown.

6. Clinical/Statistical

The clinical review team's recommendation for regular approval of ADZYNMA for prophylactic or on-demand enzyme replacement therapy in adult and pediatric patients with congenital TTP is based on the interim analysis of Study TAK-755-281102.

a. Clinical Program

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. The median age of patients was 32.5 years (range 3-58 years). Adult and pediatric subjects enrolled in the Prophylactic Cohort were 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, 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, 37 subjects in the Prophylactic Cohort were efficacy evaluable and 31 completed the study. Zero acute TTP events occurred with ADZYNMA prophylaxis during the controlled comparison treatment periods, while one event occurred during SoC treatment (with a time to event resolution of 14.8 days). 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. Four of six events were adjudicated to meet the protocol definition of acute TTP events: one event was treated with ADZYNMA and the time to resolution was reported as 3 days, the four other events were treated with SoC and the time to resolution was 1.5- 5 days.

The basis of FDA's conclusion of substantial evidence of effectiveness is based on this adequate and well controlled clinical trial, supported by the clinical investigation of PK and preclinical studies, with clinically meaningful benefit as evidenced by a decrease in the incidence of acute TTP events during the evaluable period. Therefore, the evidence supports regular approval for ADZYNMA.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring (BIMO) Clinical Investigator (CI) inspection assignments were issued for one foreign and three domestic clinical study sites that participated in the conduct of protocol *TAK-755-3002*. The inspections did not reveal substantive issues that impact the data submitted in this BLA.

c. Pediatrics

This application is exempt from Pediatric Research Equity Act (PREA) because it is intended for a biologic product for which Orphan Designation has been granted. The results of the interim analysis from Study TAK-755-281102 provides evidence of clinical benefit in the pediatric population.

d. Other Special Populations

The efficacy of ADZYNMA has not been studied in any other special populations.

7. Safety and Pharmacovigilance

The safety of ADZYNMA was evaluated in a total of 48 subjects. The safety dataset included all subjects who received at least one dose of ADZYNMA. There were no deaths related to ADZYNMA. The most frequent (>5% of subjects) adverse reactions were headache, diarrhea, migraine, abdominal pain, nausea, upper respiratory tract infection, dizziness, and vomiting. There were no anaphylactic or allergic reactions while on ADZYNMA. Neutralizing antibodies were not reported in the cTTP clinical trials. One subject had binding antibodies against the study drug at baseline and no increase in titer was observed. Two additional subjects had transient low titer anti-CHO antibodies at a single time point with subsequent negative results. The risk of hypersensitivity and potential risk of immunogenicity will be conveyed in the USPI.

There is no post-marketing safety data available for ADZYNMA. Review of the available clinical data did not identify any safety concerns which would necessitate a Risk Evaluation and Mitigation Strategy (REMS) or a Post-marketing Requirement (PMR) study that is specifically designed to evaluate a particular safety issue as a primary endpoint. Thirteen (one in Study 281102 and 12 in the ongoing continuation study 3002) subjects treated prophylactically with ADZYNMA with confirmed cTTP tested positive for

low-titer binding antibodies against ADAMTS13; the clinical significance of non-neutralizing ADAMTS13 antibodies is unknown at this time. The Applicant will conduct routine pharmacovigilance in accordance with 21 CFR 600.80 and enhanced pharmacovigilance with a follow-up questionnaire for all AEs involving the development of antibodies to ADAMTS13 for a period of 3 years post-licensure, as outlined in the Applicant's *Core Risk Management Plan, version 2.3*. The ongoing Phase 3 studies, including Study 3002, will yield additional efficacy and safety data for ADZYNMA.

8. Labeling

The proposed proprietary name, ADZYNMA, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on June 5, 2023, and was found acceptable. CBER communicated the acceptability of the proprietary name to the Applicant on June 15, 2023. The proper name suffix, -krhn, was designated on September 05, 2023, making (*ADAMTS13, recombinant-krhn*) the proper name.

The APLB reviewed the proposed prescribing information, patient package insert, instructions for use, package and container labels on September 5, 2023, and found them acceptable from a promotional and comprehension perspective.

9. Advisory Committee Meeting

No advisory committee meeting was held because review of information submitted in the BLA did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

10. Other Relevant Regulatory Issues

ADZYNMA has received Orphan Drug, Fast Track, and Rare Pediatric Disease Designations and this submission was granted priority review and a rare pediatric disease priority review voucher.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The Applicant has provided substantial evidence of effectiveness and safety based on an adequate and well controlled clinical trial, supported by preclinical studies. The Applicant has provided evidence of a clinically meaningful benefit in reduction of acute TTP events and demonstrated efficacy with OD treatment of acute TTP events in children and adults with congenital TTP.

The Applicant has met the statutory requirements for regulatory approval and the review team recommends regular approval of ADZYNMA, for prophylactic or on-demand enzyme replacement therapy in adult and pediatric patients with congenital thrombotic thrombocytopenic purpura (cTTP).

b. Benefit/Risk Assessment

ADZYNMA has demonstrated a clinically meaningful benefit in reduction of acute TTP, subacute, and isolated TTP events and demonstrated efficacy with OD treatment of acute TTP events in children and adults with congenital TTP.

The most commonly reported adverse reactions included headache, diarrhea, migraine, abdominal pain, nausea, upper respiratory tract infection, dizziness, and vomiting. No neutralizing antibodies were reported following administration of ADZYNMA. The risks of ADZYNMA include hypersensitivity and potential for immunogenicity.

This application has provided substantial evidence of effectiveness and safety of ADZYNMA in adults and pediatric patients with congenital TTP. The overall benefit-risk profile favors approval of ADZYNMA for prophylactic or on-demand enzyme replacement therapy in adult and pediatric patients with congenital thrombotic thrombocytopenic purpura (cTTP).

c. Recommendation for Postmarketing Activities

The review team determined that ADZYNMA does not require a PMR safety study or a REMS. Additionally, there are no agreed upon Post-marketing Commitments (PMCs) for safety studies. The Applicant will conduct routine and enhanced pharmacovigilance activities as outlined in the *Core Risk Management Plan, version 2.3*. Regarding the latter, the Applicant will be required to conduct enhanced pharmacovigilance activities for AEs involving the development of antibodies to ADAMTS13 for a period of 3 years post-licensure. Enhanced pharmacovigilance activities will consist of 1) expedited reporting of all AEs involving the development of antibodies to ADAMTS13, regardless of label status or seriousness; 2) the Applicant's assessment of antibody development to ADZYNMA, with a subgroup analysis of this risk among treatment-naïve patients, in periodic safety reports; and 3) the use of a targeted data collection tool for all AEs involving the development of antibodies to ADAMTS13.

In STN 125795.0058 and STN 125795.0065 (received October 17 and 31, 2023), the Applicant agreed to seven non-section 506B PMCs:

CMC PMC 1

Takeda commits to perform and provide data from (b) (4) This will include:

a. (b) (4) to monitor the potential occurrence of any (b) (4),
b. monitoring process parameters and in-process controls, and
c. release and stability testing of (b) (4) and Drug Product (DP) lots manufactured from DS batches derived from the (b) (4)

The results will be submitted as a "Postmarketing Study Commitment – Final Study Report" by August, 31, 2027.

Final Study Report Submission: August 31, 2027

CMC PMC 2

Takeda commits to perform the analysis of cumulative organic leachables from the manufacturing process and storage in (b) (4) Drug Product (DP) lots representative of each product strength, lot (b) (4) (500 IU/vial) and lot (b) (4) (1500 IU/vial), at the remaining stability study time points under the long-term storage condition at 2°C to 8°C until the intended DP shelf life of 36 months is reached and at the maximal in-use

storage time of reconstituted product until administration to patient, and to perform toxicological assessment of respective leachable levels.

The results will be submitted in the 2024 and 2025 Annual Reports for the 24-month and 36-month time points, respectively.

CMC PMC 3
Takeda commits to reanalyze the (b) (4) release data for (b) (4) from (b) (4) additional (b) (4) campaigns: (b) (4) at the (b) (4) facility and perform statistical analysis of data and propose amended interim rADAMTS13 (b) (4) release and stability acceptance criteria for (b) (4). The results will be submitted as a Prior Approval Supplement (PAS) specifying the submission in fulfillment as a ”Postmarketing Study Commitment – Final Study Report” by January 31, 2024.

Final Study Report Submission: January 31, 2024

CMC PMC 4
Takeda commits to reanalyze the (b) (4) data for (b) (4) following the completion of the (b) (4) campaign to be produced no later than 2026 at the (b) (4) facility. Data analysis will include release and stability data generated on (b) (4) batches manufactured at the (b) (4) facility and placed on stability prior to the 2026 (b) (4) campaign; release data from the 2026 (b) (4) campaign; 12 months stability from the same 2026 (b) (4) campaign; and statistical analysis of all data from batches manufactured at this facility and propose amended final rADAMTS13 (b) (4) release and stability acceptance criteria for (b) (4). The results will be submitted as a PAS, specifying submission in fulfillment of a ”Postmarketing Study Commitment – Final Study Report” by August 31, 2027.

Final Study Report Submission: August 31, 2027

CMC PMC 5
Takeda commits to reanalyze Drug Product (DP) data for Specific Activity upon completion of stability studies for PPQ DP lots at the intended stability storage conditions (36 months at 2-8°C including 6 months at +30°C) and propose amended interim rADAMTS13 Specific Activity release and stability acceptance criteria for DP. The results will be submitted as a Prior Approval Supplement (PAS) specifying the submission in fulfillment of “Postmarketing Study Commitment – Final Study Report” by January 31, 2025.

Final Study Report Submission: January 31, 2025

CMC PMC 6
Takeda commits to reanalyze Drug Product (DP) release and stability data for Specific Activity once a minimum of 12 months stability data have been generated from specified DP lots as follows. Analysis will incorporate additional release and stability data from (b) (4) DP lots (consisting of (b) (4) 500 IU/vial and (b) (4) 1500 IU/vial) manufactured from each of the following (b) (4). If appropriate, Takeda will propose amended interim rADAMTS13 Specific Activity release and stability

acceptance criteria for DP. The results will be submitted as a Prior Approval Supplement (PAS) specifying the submission in fulfillment of “Postmarketing Study Commitment – Final Study Report” by December 31, 2025.

Final Study Report Submission: December 31, 2025

CMC PMC 7

Takeda commits to reanalyze Drug Product (DP) data for Specific Activity upon completion of stability studies for DP lots manufactured from the (b) (4) campaigns under PMC 3, specifically those DP lots manufactured from the (b) (4) campaigns, at the intended stability storage conditions (36 months at 2-8°C including 6 months at +30°C) and propose amended final rADAMTS13 Specific Activity release and stability acceptance criteria for DP, if appropriate. The results will be submitted as a Prior Approval Supplement (PAS) specifying the submission in fulfillment of “Postmarketing Study Commitment – Final Study Report” by June 30, 2030.

Final Study Report Submission: June 30, 2030