

CBER CMC BLA Review Memorandum

BLA STN 125795/0

ADAMTS13, recombinant-krhn

**Nobuko Katagiri, Research biologist, OPT/OPPT/DH
Chava Kimchi-Sarfaty, Research chemist, OPT/OPPT/DH
Katarzyna Jankowska, Biologist, OPT/OPPT/DH
Upendra Katneni, Staff fellow, OPT/OPPT/DH**

1. **BLA#:** STN 125795
2. **APPLICANT NAME AND LICENSE NUMBER**
Takeda Pharmaceuticals U.S.A, Inc.
U.S. License No. 1898, active
3. **PRODUCT NAME/PRODUCT TYPE**
 - a. Nonproprietary / United States Adopted Name (USAN): ADAMTS13, recombinant-krhn
 - b. Proprietary Name: ADZYNMA
 - c. Company code: TAK755 (previous codes BAX930 or SHP655)
 - d. Chemical Abstract Service (CAS) registry number: 2086325-24-6 (rADAMTS13 Q23) and 2406308-29-8 (rADAMTS13 R23)
 - e. International Nonproprietary Name (INN): Apadamtase alfa (rADAMTS13 Q23) and Cinaxadamtase alfa (rADAMTS13 R23)
4. **GENERAL DESCRIPTION OF THE FINAL PRODUCT**
 - a. Pharmacological category: not established
 - b. Dosage form: lyophilized powder for solution
 - c. Strength/Potency: single-dose vials containing nominal dosage strength of 500 IU/vial and 1500 IU/vial rADAMTS13, FRETs-VWF73 assay
 - d. Route of administration: intravenous use after reconstitution only
 - e. Indication(s): for prophylactic or on-demand enzyme replacement therapy in patients with congenital thrombotic thrombocytopenic purpura (cTTP)
5. **MAJOR MILESTONES**
 - Receipt Date: March 17, 2023
 - First Committee Meeting: April 6, 2023, 2:00 PM – 3:00 PM ET
 - Application Orientation and Dataset Walkthrough Teleconference: April 12, 2023, 3:00 PM - 4:00 PM ET
 - Filing Meeting: May 4, 2023, 2:00 PM-3:00 PM ET
 - Mid-Cycle Meeting Teleconference: July 14, 2023, 10:00 AM - 11:30 PM ET
 - Late-Cycle Meeting Teleconference: August 31, 2023, 10:30 AM - 11:30 AM ET
 - Reference Product Exclusivity Determination Board Meeting: October 25, 4:05 PM - 4:50 PM ET
 - PDUFA Action Date: November 15, 2023

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Nobuko Katagiri, Katarzyna Jankowska, Upendra Katneni, and Chava Kimchi-Sarfaty, Office of Therapeutic Products (OTP)/Office of Plasma Protein Therapeutics (OPPT)/Division of Hemostasis (DH)	Drug Substance (Section 3.2.S) Drug Product (Section 3.2.P, rADAMTS13 and Sterile Water for Injection (sWFI)) Adventitious Agents Safety Evaluation (Section 3.2.A.2) Regional Information (Section 3.2.R) Environmental Analysis (Section 1.12.14) Exclusivity Claim (Section 1.3.5.3) Reports of Bioanalytical and Analytical Methods for Human and Animal Studies (Sections 4.2.2.1 and 5.3.1.4)
Andrey Sarafanov (consult reviewer on E/L analytical methods), OTP/OPPT/DH	E/L analytical assessment (Sections 2.3.P.5.5, 3.2.S.2.2, 3.2.S.2.5.1.4, 3.2.S.6, 3.2.P.2.4.3.2, 3.2.P.3.3, 3.2.P.3.5.4, 3.2.P.5.5.2, 3.2.P.7)
Rukmini Bhardwaj (consult reviewer on E/L toxicological risk assessment), OTP/OPPT/DPT2)	E/L toxicological risk assessment (Sections 3.2.P.5.5, 1.11.1)
Zuben Sauna (consult reviewer on Immunogenicity test methods), OTP/OPPT/DH	Immunogenicity test methods (Section 5.3.1.4)

7. INTER-CENTER CONSULTS REQUESTED

Reviewer/Affiliation	Section/Topic	In agreement with consult recommendations (Yes/No)
Ila Srivastava, Center for Drug Evaluation and Research (CDER)/Office of Surveillance and Epidemiology (OSE)/ Office of Medication Error Prevention and Risk Management (OMEPRM)/ Division of Medication Error Prevention and Analysis 2 (DMEPA 2)	Human Factors Threshold/Comparability Analysis (Section 5.3.5.4) Recombinant Adamts13 Co-Packaged Combination Product (Section 3.2.R.2) Draft Labelling Text (Section 1.14.1.3)	Yes
Dunya Karimi (DHT3C/OHT3/OPEQ/CDRH)	Co-packaged transfer/delivery device (Sections 3.2.R.2, 1.11.1)	Yes

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
17 March 2023	STN 125795/0	Original BLA submission
15 May 2023	STN 125795/9 (response to 1 May 2023 IR)	CMC IR #1: Updated DP (sWFI) Stability study data
18 May 2023	STN 125795/10 (response to 2 May 2023 IR)	CMC IR #2: Updated DS Stability data
31 May 2023	STN 125795/13 (response to 4 May 2023 IR)	CMC IR #3: E/L: organic leachables in the stability study (CMC Postmarketing commitment (PMC) 2)
31 May 2023	STN 125795/13 (response to 9 May 2023 IR)	CMC IR #4: Updated DP (rADAMTS13) Stability
2 June 2023	STN 125795/15 (response to 16 May 2023 IR)	CMC IR #5: Updated DS Process and Process Validation
2 June 2023	STN 125795/15 (response to 16 May 2023 IR)	CMC IR #6: Updated i) (b) (4) testing, ii) SOPs for analytical procedures, iii) batch analysis, iv) pooling scheme
11 July 2023	STN 125795/26 (response to 26 June 2023 IR)	CMC IR #7: Updated DS and DP (rADAMTS13) stability studies (Follow-up to CMC IR ##2/4)
19 July 2023	STN 125795/27 (response to 29 June 2023 IR)	CMC IR #8: Update information on PPQ validation and (b) (4) of production campaign (CMC PMC1 additional full validation of commercial scale campaign)
19 July 2023	STN 125795/27 (response to 30 July 2023 IR)	CMC IR #9: Updated i) eCTD information, ii) deviation information
16 August 2023	STN 125795/33 (response to 8 August 2023 IR)	CMC IR #10: Updated DS and DP (rADAMTS13) Stability studies, (b) (4) (Follow-up to CMC IR #7)
01 September 2023	STN 125795/36 (response to 22 August 2023 IR)	CMC IR #11: Updated DS stability studies (b) (4)) and justification of specifications for DS and DP (rADAMTS13) (CMC PMC3/4 revision of specific activity)
08 September 2023	STN 125795/39 (response to 28 August 2023 IR)	CMC IR #12: (b) (4), nomenclature, unified amino acid number, DP lot numbering system
15 September 2023	STN 125795/42 (response to 7 September 2023 IR)	CMC IR #13: Updated information on Reference Standards or Materials and Analytical/Bioanalytical Methods
26 September 2023	STN 125795/44 (response to 11 September 2023 IR)	CMC IR #14: Update information on FRET assay in Clinical Studies
05 October 2023	STN 125795/47 (response to 27 September 2023 IR)	CMC IR #15: Regarding removal of (b) (4) from commercial DS release testing
12 October 2023	STN 125795/53 (response to 2 October 2023 IR)	CMC IR #16: Regarding INN and EPC and SOP of sampling plan for rADAMTS13 DS

13 October 2023	STN 125795/55 (response to 10 October 2023 IR)	CMC IR #17: Related to: i) reinstatement of (b) (4) in commercial DS release testing, ii) (b) (4) in Post-approval stability protocol of DS and DP and iii) reference standards
17 October 2023	STN 125795/57 (response to 11 October 2023 IR)	CMC PMC IR #1: CMC PMCs
31 October 2023	STN 125795/64 (response to 26 October 2023 IR)	CMC PMC IR #2: CMC PMCs

9. Referenced REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File, etc.)

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
IND 15219	(b) (4)		Yes	Active
DMF (b) (4)	(b) (4)	Tubular Glass Bottles	Yes	DMF is current. No DMF review required, information pertinent to container closure is provided in the BLA
DMF (b) (4)	(b) (4)	Rubber Compounds	Yes	DMF is current. No DMF review required, information pertinent to container closure is provided in the BLA
DMF (b) (4)	(b) (4)	Glassware containers for Pharmaceutical usage	Yes	DMF is current. No DMF review required, information pertinent to container closure is provided in the BLA
DMF (b) (4)	(b) (4)	(b) (4) rubber formulation/ (b) (4) Coating	Yes	DMF is current. No DMF review required, information pertinent to container closure is provided in the BLA
510(k) (b) (4)	(b) (4)	(b) (4) Winged Infusion Set with Needle Protection	Yes	Information pertinent to container closure was reviewed, assessed, and documented in the memo by CDRH in Section 3.2.P.2.4
510(k) (b) (4)	(b) (4)	(b) (4) Piston Syringes / (b) (4) and (b) (4) Insulin Syringes	Yes	Information pertinent to container closure was reviewed, assessed and documented in the memo by CDRH in Section 3.2.P.2.4
510(k) K092318	Takeda Development Center Americas, Inc. (originally submitted by Baxter Healthcare Corporation)	Baxject II Hi Flow Needleless Transfer Device	Yes	Information pertinent to container closure was reviewed, assessed, and documented in the memo by CDRH in Section 3.2.P.2.4

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

This review is an assessment of the Chemistry, Manufacturing, and Control (CMC) information in the original Biologics License Application (BLA), STN 125795/0, submitted by Takeda Pharmaceuticals U.S.A, Inc., to seek U.S. licensure for recombinant ADAMTS13 (rADAMTS13), from a Product Quality perspective.

The product is a recombinant protein of human ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin motifs 13) and its proprietary name for the U.S. market will be ADZYNMA. The active ingredient in ADZYNMA is a mixture of two variants of the protein ADAMTS13. These variants carry a single amino acid substitution at position 23. The native Q23 protein (INN: Apadamtase alfa) has a glutamine (Q) residue and the variant (INN: Cinaxadamtase alfa) R23 has an arginine (R) residue at this position.

ADZYMNA is the first recombinant product indicated for prophylactic or on-demand enzyme replacement therapy (ERT) in adult and pediatric patients with congenital thrombotic thrombocytopenic purpura (cTTP).

ADZYNMA Drug Product (DP) is a sterile, lyophilized powder for reconstitution supplied in two nominal strengths 500 IU/vial and 1500 IU/vial. The product is reconstituted in 5 mL sterile water for injection (sWFI) for intravenous administration. The Drug Substance (DS) and DP are manufactured at Takeda manufacturing facilities in (b) (4), respectively.

We present a consolidated review of all the CMC/Product Quality information provided by Takeda in the original BLA, and subsequent amendments submitted in response to the Agency's information requests (IRs). CMC reviewers concluded that the Applicant has adequately characterized the physicochemical, biochemical, and *in vitro* functional properties of ADZYNMA, and provided documented evidence that the commercial manufacturing process is adequately validated and controlled to ensure consistent manufacture of ADZYNMA DP with the intended identity, quality, purity, safety, and potency.

ADZYNMA is a co-packaged combination product. 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.

Limitations in the DS and DP control and release strategy identified during the review process will be addressed with CMC PMCs listed in section 10.A.I. APPROVAL of this memorandum.

B. RECOMMENDATION

1. APPROVAL

The CMC (Product Quality) reviewers recommend approval of this BLA under STN 125795/0.

a. List of Drug Substance and Drug Product manufacturing and testing facilities: Refer to sections 3.2.S.2.1 *Manufacturer(s)* and 3.2.P.3.1 *Manufacturer(s)* of this Review Memorandum for a complete list of manufacturing and testing facilities.

b. N/A

c. There are seven Post-Marketing Commitments (PMCs) and no Post-Marketing Requirements (PMRs), from a CMC (Product Quality) perspective for this BLA. The PMCs are stated in Amendments 57 and 64 dated October 17 and 31, 2023, respectively, as follows:

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

d. Under the provision described in Federal Register (FR) 58:38771-38773 and the 60 FR 63048-63049 publication (8 December 1995), routine lot-by-lot CBER release would not be required for ADZYMNA because it is a well-characterized recombinant product.

II. COMPLETE RESPONSE (CR)

Not applicable.

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Nobuko Katagiri, PhD / Research biologist / OTP/OPPT/DH	Concur	
Chava Kimchi-Sarfaty, PhD / Research chemist / OTP/OPPT/DH	Concur	
Katarzyna Jankowska, PhD / Biologist / OTP/OPPT/DH	Concur	
Upendra Katneni, PhD / Staff fellow / OTP/OPPT/DH	Concur	
Natalya Ananyeva, PhD / Team Lead / OTP/OPPT/DH	Concur	
Alexey Khrenov, PhD / Branch Chief / OTP/OPPT/DH/HB1	Concur	
Zuben Sauna, PhD / Division Director / OTP/OPPT/DH	Concur	

Review of CTD
Table of Contents

Module 3

3.2.S DRUG SUBSTANCE

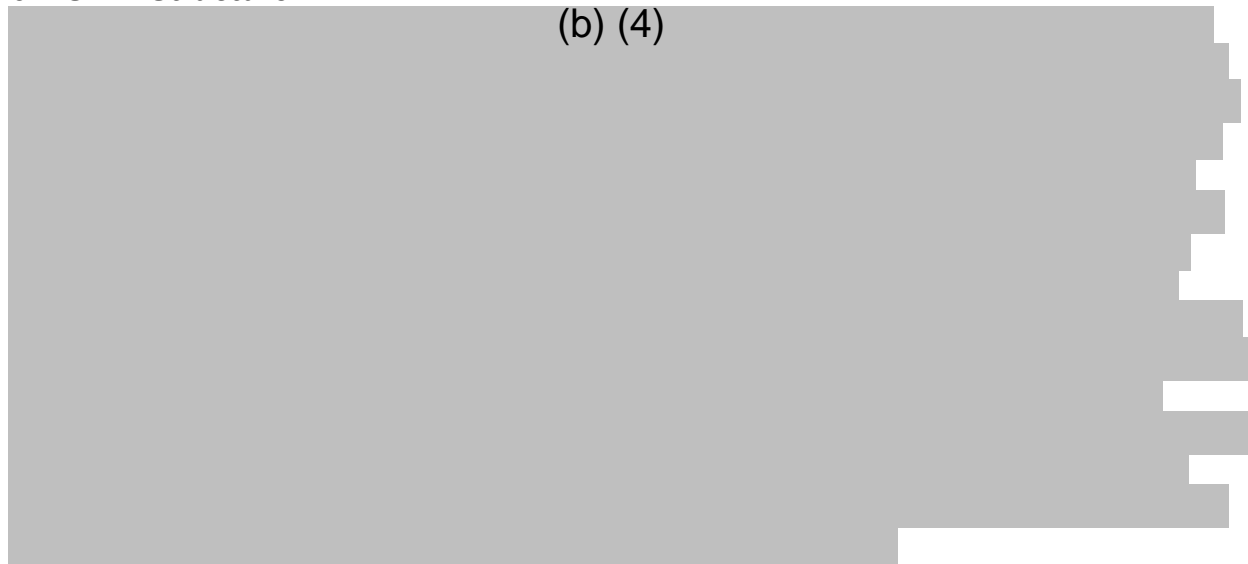
3.2.S.1 General Information

3.2.S.1.1 Nomenclature

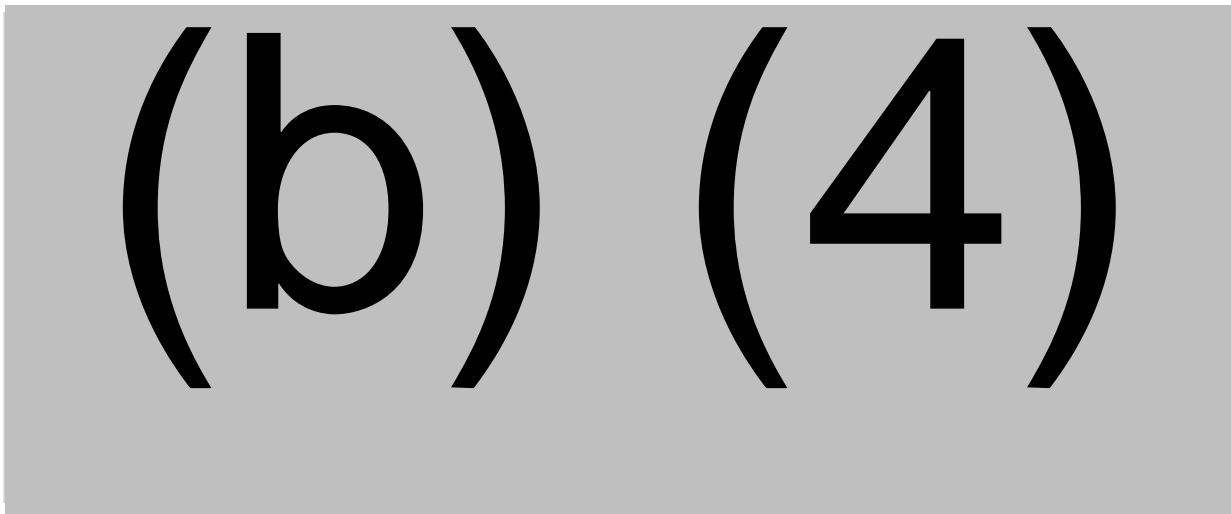
- International Non-proprietary Name (INN): Apadamtase alfa (Native rADAMTS13 Q23) and Cinaxadamtase alfa (Variant rADAMTS13 R23)
- FDA-established non-proprietary (proper) name: ADAMTS13, recombinant-krhn
- Chemical Abstract Service (CAS) registry number: 2086325-24-6 and 2406308-29-8
- Unique Ingredient Identifier (UNII): 7N28DA6HFT (ADAMTS13, recombinant mixture)
- Company Code: TAK755 (previous codes BAX930 or SHP655)

3.2.S.1.2 Structure

(b) (4)



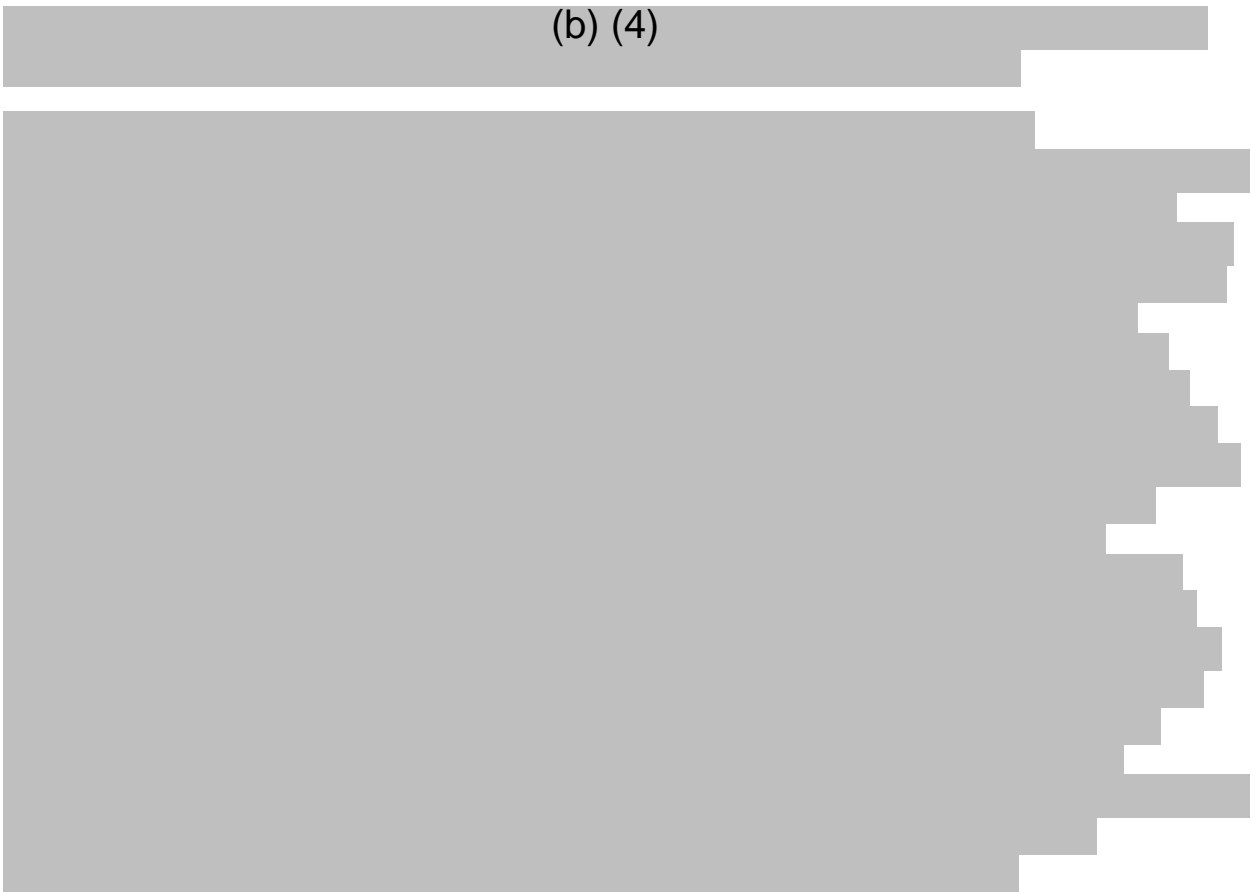


(b) (4)



55 pages have been determined to be not releasable: (b)(4)

(b) (4)



3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

ADZYNMA DP is a sterile, lyophilized powder for reconstitution for intravenous injection. It is supplied in aseptically filled single-dose vials in two nominal strengths 500 IU/vial and 1500 IU/vial. The composition of the formulation with regard to excipients prior to

lyophilization is the same for all dosage strengths. The quantity of the active ingredient, rADAMTS13 protein, varies for each dosage strength. The lyophilized DP is supplied in a clear colorless glass vial (b) (4) and reconstituted with sterile water for injection (sWFI) supplied in a single-dose glass vial (b) (4) at a nominal volume of 5 mL. The target concentration of rADAMTS13 is ensured as described in section 3.2.P.2.2.2 in this review memorandum.

The composition of the ADZYNMA DP is provided in Table 19 (modified from Table 1, Section 3.2.P.1 and Table 1, Section 3.2.P.2.2):

Table 19. Composition of ADZYNMA DP

Ingredient	Quantity per vial	Concentration after reconstitution	Quality Standard	Function
rADAMTS13	Nominal 500 IU	(b) (4)	DS release specifications	Active Ingredient
	Nominal 1500 IU			
L-Histidine	16.7 mg	(b) (4)	(b) (4)	Buffer (b) (4)
Sodium chloride	9.4 mg			Tonicity
Calcium chloride dihydrate	1.6 mg			Stabilizer
Polysorbate 80	2.7 mg			Stabilizer/Surfactant
Mannitol	161.4 mg			Bulking
Sucrose	53.8 mg			Stabilizer

Reviewers' Assessment: The information provided in Section 3.2.P.1 is sufficient to describe the DP. The active ingredient has been discussed in the review of the DS. All other components are compendial and similar to those found in the formulation of other recombinant coagulation-related protein products.

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

The active ingredient in ADZYNMA DP is DS as described in section 3.2.P.1 of this review memorandum.

3.2.P.2.1.2 Excipients

All excipients are compendial and their specific functions are described in Table 19.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

There is no difference between clinical and commercial formulations of DP (described in section 3.2.P.1 of this memorandum). The formulation development studies and the results which led to the final formulation are summarized below:

Buffering agents and optimal pH range

To identify a suitable buffer and pH range for ADZYNMADP stability, (b) (4) buffer-pH systems were evaluated with liquid and lyophilized forms of DP. Based on the buffering capacity to maintain the best pH range for rADAMTS13 ((b) (4)), impact on the

(b) (4) and activity of rADAMTS13, and a short-term stability study (24 weeks), histidine buffer was selected as a buffering agent.

Effect of (b) (4)

Susceptibility of ADZYNMA DP to (b) (4), measured as (b) (4) was detected at above (b) (4). (b) (4) conditions of the final formulation production process were selected as (b) (4).

Effect of (b) (4) on lyophilized rADAMTS13

To identify a suitable stabilizer for ADZYNMA DP, (b) (4) potential stabilizers were tested and only calcium chloride, at as low as (b) (4) of concentration, prevented (b) (4) of rADAMTS13. In addition to calcium chloride, low concentration (b) (4) of sodium chloride had a beneficial effect of the lyophilization cake appearance. Starting with (b) (4) sugars as lyophilized cake builders and cryoprotectants, the use of mannitol and sucrose together was selected. Polysorbate 80 was essential for stabilizing the protein.

During this optimization phase, short and extended lyophilization cycles were tested together and the extended cycle was selected due to (b) (4).

Formulation robustness

Formulation robustness was tested with a (b) (4) design, covering (b) (4) range for each formulation component (b) (4) and pH between (b) (4) for (b) (4) potency levels (100 IU/mL and 300 IU/mL). During 6-month storage at elevated temperatures (20°C (b) (4)), all measured values of (b) (4) remained within the expected range although DP activity (b) (4). This exercise confirmed that all parameters remain within the acceptable ranges from the initial starting time point during 6-month storage at 5°C.

3.2.P.2.2.2 (b) (4)

The ADZYNMA (b) (4) is formulated to a target rADAMTS13 concentration of (b) (4) IU/mL (for nominal 500 IU/vial) or (b) (4) IU/mL (for nominal 1500 IU/vial) to ensure a nominal rADAMTS13 concentration of 100 IU/mL and 300 IU/mL, respectively, in the final DP. An (b) (4) of (b) (4) against the target concentration is implemented to compensate for potential rADAMTS13 activity loss during manufacturing and to ensure that the product activity specification is met. In addition to the (b) (4), the allowable (b) (4) of (b) (4) is added, as (b) (4), during the vial filling process in accordance with the (b) (4) for the nominal filling volume of 5.0 mL labeled size.

The data collected from the final formulation process show consistent DP activity results within DP specifications, and with no significant loss of rADAMTS13 activity. To ensure accurate dosing of rADAMTS13 in clinical use based on body weight, the actual rADAMTS13 activity in international units will be printed as variable text on the label of each rADAMTS13 vial and carton. The (b) (4) amount is included in the continuous

process validation program and might be adjusted as appropriate as more data becomes available during routine commercial production.

3.2.P.2.2.3 Physicochemical and Biological Properties

The physicochemical and biological properties of the ADZYNMA DP are identical to the DS formulation which was discussed in section 3.2.S of this memorandum.

3.2.P.2.3 Manufacturing Process Development

The ADZYNMA DP manufacturing process consists of the following steps: (b) (4)

, sterilizing filtration, aseptic filling of vials, and lyophilization and vial crimping.

For clinical Phase 3, the DP manufacturing process was transferred from (b) (4) facility to (b) (4) facility and the DP process was changed from “(Phase 1) Process 1” to “(Phase 3) Process A”. Changes were as follows: (b) (4)

Comparability study of analytical data between Process 1 (lot ## (b) (4)) and Process A (lot ## (b) (4)) was performed, validated, and showed that DPs manufactured by the two processes are comparable.

During Phase 3, Processes B, C, and D were introduced.

Process B: (b) (4)

Process C: (b) (4)

Process D: (b) (4)

Process D is the ADZYNMA DP process used for PPQ and for the commercial campaigns. The information regarding ADZYNMA DP lots used for the comparability studies is presented in Table 20 (adopted from Table 1, Section 3.2.P.2.3):

Table 20. ADZYNMA DP Lots Used for The Comparability Studies During Manufacturing Development

Lot Number	Dosage (IU/vial)	Batch Size Formulated BDP [kg]	Date of Manufacture	Drug Product Manufacturing Process	Lot Use
(b) (4)	1500	(b) (4)	(b) (4)	Process 1	Clinical Phase 1
	1500			Process 1	Clinical Phase 1
	1500			Process A	Clinical Phase 3
	1500			Process A	Clinical Phase 3
	500			Process B, Engineering Run (b) (4)	Engineering Run
	1500			Process B, Engineering Run (b) (4)	Engineering Run
	1500			Process A	Clinical Phase 3
	500			Process B	Clinical Phase 3
	500			Process B	Clinical Phase 3
	1500			Process B	Clinical Phase 3
	1500			Process B	Clinical Phase 3
	1500			Process C	Clinical Phase 3
	1500			Process C	Clinical Phase 3
	500			Process C	Clinical Phase 3
	500			Process D	PPQ, Commercial
	500			Process D	PPQ, Commercial
	1500			Process D	PPQ, Commercial
	1500			Process D	PPQ, Commercial

Principle of establishing control strategy based on Quality-by-Design (QbD) was the same as that for DS described in section 3.2.S.2.6 in this memorandum.

3.2.P.2.4 Container Closure System

The Container Closure System is reviewed in section 3.2.P.7.

3.2.P.2.5 Microbiological Attributes

The 10 mL glass vials used for the ADZYNMA DP are sterilized and depyrogenated in a (b) (4) sterilization (b) (4). All other process equipment, including butyl rubber lyophilization stoppers, are (b) (4) sterilized prior to use in the manufacturing process. The effectiveness of these procedures was demonstrated through sterile media fill runs simulating the manufacturing process. The integrity of the ADZYNMA DP container

closure system has been demonstrated using (b) (4) method (b) (4) test), (b) (4) Test Method, and (b) (4) Method (b) (4)). DP vials are 100% tested with the (b) (4) Method prior to release, and the identical method and equipment were used to demonstrate that shipping operations did not impact the integrity of the container closure system (refer to section 3.2.P.3.5 in this memorandum). The operations associated with container closure integrity testing have been validated.

3.2.P.2.6 Compatibility

The compatibility of the ADZYNMA DP with container closure system and the co-packaged administration devices (BAXJECT II Hi-Flow Needleless Transfer Device), (b) (4) Syringes, 25G butterfly infusion set was assessed in in-use stability study of diluent-reconstituted product. The following analytical parameters were selected for analysis based on their likelihood to be influenced by product storage in container closure, product interaction with administration devices, and by the hold time before administration: reconstitution time, appearance, (b) (4), rADAMTS13 (b) (4), rADAMTS13 activity, (b) (4), and pH. The results of the in-use studies were within the clinical specification limits demonstrating that the container closure system and administration devices are compatible with ADZYNMA DP.

Reviewers' Assessment: Adequate information has been provided with respect to the pharmaceutical development of the DP and is acceptable as submitted. The ADZYNMA DP manufacturing and composition remain unchanged since the introduction of Process D for the clinical material, and product comparability through all development stages has been sufficiently demonstrated. All steps in the manufacturing process were appropriately evaluated for adequate controls, and the compatibility of the ADZYNMA DP with container closure system during storage, reconstitution, and with infusion components has been adequately evaluated.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

ADZYNMA DP Manufacturing

Sites associated with the proposed commercial ADZYNMA DP manufacturing process are provided in Tables 21 and 22 (modified Tables 1 and 2 from Section 3.2.P.3.1).

Table 21. DP Manufacturing and Testing Sites and Responsibilities

Site Name FDA Establishment Identifier (FEI)	Address	Manufacturing or Testing Responsibilities
Takeda Manufacturing (b) (4) FEI# (b) (4)	(b) (4)	-Drug product manufacturing -Release and stability testing -Drug product primary and secondary packaging and labeling

Takeda Manufacturing (b) (4) FEI# (b) (4)	(b) (4)	Release and stability testing
(b) (4) FEI# (b) (4)	(b) (4)	Release and stability testing

Table 22. Location of DP Release and Stability Testing

Test Method	Takeda Manufacturing (b) (4)	Takeda Manufacturing (b) (4)	(b) (4)
Appearance (Lyophilized Cake; Visual Inspection)	R, S	--	--
Appearance (Reconstituted Solution; Visual Inspection)	R, S	--	--
Reconstitution Time (Visual Inspection)	R, S	--	--
pH ((b) (4))	R, S	--	--
Particulate Matters	--	--	R, S
(b) (4)	R	--	--
Residual Moisture (b) (4)	R, S	--	--
Total Protein (b) (4) ^a	--	R	--
rADAMTS13 Activity (FRETs-VWF73)	--	R, S	--
rADAMTS13 (b) (4)	--	R, S	--
(b) (4)	--	R	--
(b) (4)	R, S	--	--
Endotoxin (b) (4)	--	R, S	--
Sterility	--	R, S	--
Container Closure Integrity Test ((b) (4)) ^b	--	--	S
Polysorbate 80 ((b) (4)) ^a	R	--	--
Sodium ((b) (4)) ^a	R	--	--
Calcium ((b) (4)) ^a	R	--	--
Histidine ((b) (4)) ^a	R	--	--
Sucrose ((b) (4)) ^a	--	R	--
Mannitol (b) (4) ^a	R	--	--

R=release testing performed; S=stability testing performed

^a Test performed for release only

^b Test performed for stability only

Sterile Water for Injection, 5mL

Sites responsible for manufacturing and testing activities of the diluent are listed in Table 23 (modified from Section 3.2.P.3.1).

Table 23. sWFI DP Manufacturing and Testing Sites and Responsibilities

Site Name FDA Establishment Identifier (FEI)	Address	Manufacturing or Testing Responsibilities
(b) (4)	(b) (4)	Manufacture Release Testing

(b) (4)	(b) (4)	Stability Testing
Takeda Manufacturing (b) (4) FEI# (b) (4)	(b) (4)	Final Labeling and Packaging

3.2.P.3.2 Batch Formula

A single batch of ADZYNMA DP may be produced from a maximum of (b) (4) batches of ADZYNMA (b) (4). DP lot number contains information such as product identifier, manufacturing year, consecutive lot number, and packaging index (refer to Section 3.2.P.3.3). The quantity of active ingredient varies according to the target vial strength of the DP fill (nominal potency and additional (b) (4) of (b) (4); refer section 3.2.P.2.2.2 (b) (4) in this memorandum). The concentration of all other components in the formulation are the same for the two DP vial strengths. The typical batch size ranges from (b) (4). The formulae for both nominal 500 IU/vial and 1500 IU/vial batch sizes are provided in Table 24 (copied from Table 1, Section 3.2.P.3.2 *Batch Formula*):

Table 24. Batch Formula for ADZYNMA DP 500 IU and 1500IU Nominal Potency

Potency (Label Claim)		500 IU /vial (Nominal)	1500 IU /vial (Nominal)
Component and reference Standard	Reference	Target concentration	
rADAMTS13	(b) (4)	(4)	
Sodium chloride			
Calcium chloride dihydrate			
L-Histidine			
Mannitol			
Sucrose			
Polysorbate 80			
sWFI			

Reviewers' Assessment: The information provided in Sections 3.2.P.3.1 and 3.2.P.3.2 is acceptable as submitted.

3.2.P.3.3 Description of Manufacturing Process and 3.2.P.3.4 Controls of Critical Steps and Intermediates

The rADAMTS13 drug product is manufactured at Takeda Manufacturing site in (b) (4). The ADAMTS13 DP manufacturing process consists of the following steps:

- (b) (4)
- Step (b) (4): Sterilizing filtration,
 - Step (b) (4): Sterile filling
 - Step (b) (4): Lyophilization and crimping

The lyophilized 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 final DP is stored in the central warehouse at 2-8°C until shipment.

The Sterile Water for Injection (sWFI) drug product is prepared from Water for Injection (WFI) in (b) (4). The (b) (4) WFI is produced by (b) (4). The (b) (4) is produced from (b) (4).

The manufacturing process steps for rADAMT13 DP and SWFI along with Critical Process Parameters and In-Process Controls with the acceptable range are provided in Table 25 below.

Table 25. The Manufacturing Process Steps for rADAMT13 and SWFI DPs, Critical Process Parameters and In-Process Controls*

(b) (4)

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

*Based on data provided in eCTD sections 3.2.P.3.3 (rADAMTS13, Doc ID-000424826, Version 1.0), 3.2.P.3.3 (SWFI, Doc ID-001341135, Version 1.0), and 3.2.P.3.4 (SWFI, Doc ID-001341136, Version 1.0). Abbreviations: CPP: Critical Process Parameters; IPC: In-Process Controls; AC: Acceptance criteria; AL: Action Limit.

Reviewers' Assessment: The description of the manufacturing process and control strategy for the rADAMTS13 and SWFI drug products are acceptable as submitted.

3.2.P.3.5 Process Validation and/or Evaluation

□ Process Validation and/or Evaluation of rADAMTS13 DP

An integrated, risk-based approach was applied for validation of rADAMTS13 DP manufacturing process. The process was developed at small-scale and scaled-up to commercial scale. Characterization studies were performed at small scale or at full scale with buffer or product runs which supported the criticality assessment of critical process parameters (CPPs) and establishment of proven acceptable ranges (PAR) and normal operating ranges (NOR).

The consistency, robustness and control of full-scale manufacturing were demonstrated through the process performance qualification (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 rADAMTS13 DP from (b) (4) PPQ (b) (4) were produced at the commercial manufacturing site in accordance with a pre-approved PPQ protocol as summarized in Section 3.2.P.3.5 *Process Validation and/or Evaluation*.

Additional studies included in the PPQ runs validated the use of several (b) (4) lots, (b) (4) parameters during formulation, filling and lyophilization homogeneity, as well as processing/hold times to produce rADAMTS13 DP lots and shipping.

□ Manufacturing Process

The manufacture process validation that includes (b) (4), sterilizing filtration, aseptic filling, lyophilization, crimping and visual inspection is described in section 3.2.P.3.5 *Process Validation and/or Evaluation - Manufacturing Process*. The rADAMST13 DP manufacturing PPQ study critical process parameters (CPP), non-CPP, in-process parameters (IPC), acceptance criteria (AC) along with validation results are presented in Table 26 (modified from 3.2.P.3.5 *Process Validation and/or Evaluation - Manufacturing Process*).

(b) (4)

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

(b) (4)

Deviations that had the potential to impact product quality, process consistency or robustness have been described in Table 17, Section 3.2.P.3.5 *Process Validation and/or Evaluation - Manufacturing Process* and investigated within the appropriate quality systems and determined not to impact the results of the PPQ study.

We reviewed these deviations and concurred with Takeda's conclusion. In summary, the PPQ demonstrated that the monitored process parameters and quality attributes were within the normal operating ranges and acceptance criteria, respectively, and that the results were consistent. In addition, the (b) (4) PPQ lots have been enrolled in long-term stability studies (refer to Section 3.2.P.8.1 *Stability Summary and Conclusion* for stability data summary).

□ **Hold Times**

Hold times that were established through development and aseptic processing validation activities for each rADAMTS13 DP process are described in section 3.2.P.3.5 *Process Validation and/or Evaluation- Hold Time*. Additional qualification studies were incorporated into the drug product PPQ runs. The hold time after end of lyophilization was validated during PPQ studied using lot (b) (4) and established to be with a limit of (b) (4). All CPPs, IPCs and CQAs were within the PPQ acceptance criteria. The process time sterilizing filtration was challenged during filter validation and is described in Section 3.2.P.3.5 *Process Validation and or Evaluation-Filter Validation*.

□ **Filter Validation**

(b) (4)

(b) (4)

Further review of DP filter validation is within the responsibilities of the DMPQ reviewer.

□ **Aseptic Processing Validation**

The efficacy of aseptic process during the manufacturing of the rADAMTS13 DP was demonstrated through media fill validation. Each step of the aseptic manufacturing process (filling, lyophilization and stoppering) was validated during PPQ to ensure the sterility of rADAMTS13 DP. The results described in Section 3.2.P.3.5 *Process Validation and/or Evaluation – Aseptic Validation* support the sterility assurance for rADAMTS13 DP by aseptic processing. Detailed review of DP aseptic validation is within the responsibilities of the DMPQ reviewer.

□ **Shipping Validation**

For transportation from (b) (4) to rest of world (ROW), DP is packaged in a temperature-controlled warehouse (2-8°C) and shipped, per validated shipping methods and global SOP. The shipping validation studies demonstrated that the integrity and quality of the drug product is maintained during transportation at the recommended storage and shipping conditions. Simulated shipping studies wherein 500 IU and 1500 IU vials co-packaged in the commercial finished goods presentation and packaged with a sWFI vial, BAXJECT II HF, a syringe, an infusion set, and alcohol swabs were also conducted. This study simulated the stresses of warehouse handling, vehicle loading, and transportation by ground and air using the rADAMTS13 commercial presentation. All acceptance criteria were met, and no impact of the simulated

transportation study was observed. Detailed review of DP shipping validation is the responsibilities of the DMPQ reviewer.

❑ **Process Validation and/or Evaluation of Sterile Water for Injection**

The objective of the PPQ program for sterile water for injection (sWFI) drug product described in Section 3.2.P.3.5 *Process Validation and/or Evaluation for Sterile Water for Injection, 5 mL* was to demonstrate that the sWFI manufacturing process is capable of consistently producing drug product lots of acceptable quality. A prospective validation approach was used to demonstrate the reproducibility and consistency of the sWFI manufacturing process described in Section 3.2.P.3.3 *Description of Manufacturing Process and Process Controls – sWFI* with the container closure system described in Section 3.2.P.7 *Container Closure System - sWFI*.

The validation strategy during PPQ was to execute (b) (4) sWFI product lots manufactured and filled using commercial scale manufacturing procedures to validate the processing, filtration, filling, and testing stages of the drug product filled in glass vials and closed with a chlorobutyl rubber stopper. Validation addressed process times, lead and holding times, in-process control (IPC) and final release testing results. The validation results showed that all the tests were performed and met specifications, verifying that the process is in control and ensuring reproducibility of the batches with respect to quality.

❑ **Analysis of cumulative Extractables and Leachables**

While the main studies were performed for container closure system of DP, the evaluation of cumulative leachables, derived from multiple process components, in DP is discussed in this section to complement process validation studies. In the initial BLA submission, Takeda limited analysis of leachables in DP only to an (b) (4) assessment of the vendor-provided extractables data for selected manufacturing components that indicated low risk of leachables.

In the extractables study, organic extractables were tested (b) (4)

(b) (4)
In toxicological assessment, the HDE levels of identified (b) (4) extractables were below the respective Tolerable Daily Intake (TDI) or Threshold of Toxicological Concern (TTC) values and were concluded to be safe. Elemental leachables were not included in the assessment.

Thus, Takeda did not provide a real-time assessment of cumulative process- and storage-related leachables in DP per the (b) (4) guidelines. Additionally, the limited analysis of extractables was determined to be insufficient.

In response to CMC IR# 3 dated May 4, 2023, Takeda performed analysis of elemental leachables in the DP using PPQ lots (b) (4) after 6-months storage under long-term conditions (2-8°C), where lot (b) (4) was manufactured with the longest process hold times from multiple PPQ (b) (4) batches (Amendment 13 dated

May 31, 2023). The measurements were performed using (b) (4) and the analytical results were below the control threshold of (b) (4) of respective permitted daily exposure (PDE) levels. The CMC team has determined that the analytical methods and analytical evaluation thresholds (AET) applied for the testing of elemental leachables in the DP were adequately validated, and the levels of these compounds in DP were below AET indicating their safety.

In addition, FDA and Takeda agreed that Takeda will analyze the organic leachables in (b) (4) representative DP lots ((b) (4) (500 IU/vial) and (b) (4) (1500 IU/vial)) in the ongoing stability study at the long-term storage condition at the remaining time points until the intended DP shelf life is reached. Stability and leachables data will be provided in annual reports (AR) in 2024 and 2025, representative of the 24- and 36-months stability time points, respectively, in support of a 36-month shelf life of DP. This agreement is formalized in PMC #2 (Amendment 57 dated October 17, 2023).

The Pharmacology/Toxicology reviewer agrees with CMC's assessment and confirms that data from the real time elemental leachable study demonstrate the levels of elemental leachables in the DP to be under the safety concern threshold (SCT). Additionally, the (b) (4) toxicological assessment of cumulative extractables indicate that the levels of organic leachable are lower than the safety thresholds. Therefore, the Applicant's plan for real time assessment of organic leachables as a PMC is acceptable.

Reviewers' Assessment: Process Validation and/or Evaluation sections of DP rADAMTS13 and sWFI provide the results of detail validation of their manufacturing processes. Takeda provided PPQ protocols (Amendment 15 dated June 2, 2023, in response to CMC IR #5) and confirmed that DP PPQ batches were manufactured using the (b) (4) PPQ batches from (b) (4) campaign ((b) (4)) and no additional (b) (4) campaigns have been used yet for DP production. However, DS material covering the whole (b) (4)-PPQ campaign was used in (b) (4) batches of the DP-PPQ. This was accomplished by taking (b) (4) batches from the (b) (4) of the campaign for separate DP PPQ lots (b) (4) (Response to IR CMC #5 Q7).

The information provided in Section 3.2.S.2.5 for rADAMTS13 and SWFI DPs detailing the process validation studies and additional data submitted in response to Agency's IRs are acceptable.

The analytical methods and quantitation of the extractables and elemental leachables in DP were found validated and acceptable, and toxicological assessment concluded that their levels are below SCT. Under PMC #2, Takeda committed to perform the analysis of cumulative organic leachables from the manufacturing process and storage in (b) (4) DP lots, representative of each product strength, lot (b) (4) (500 IU/vial) and lot (b) (4) (1500 IU/vial), on stability until the end of shelf life and at the maximal in-use storage time of reconstituted product, and to perform toxicological assessment of respective leachable levels.

Overall, the rADAMTS13 PPQ studies provided documented evidence that the rADAMTS13 and SWFI DPs' manufacture processes can reproducibly process rADAMTS13 and SWFI meeting their predefined critical quality attributes. Both the routine DPs tests and the extended characterization met the PPQ acceptance criteria confirming rADAMTS13 and SWFI DPs quality and consistent process performance. Sufficient controls have been established to ensure that the manufacturing process can consistently produce high quality product and that deviations (if they occur) are identified, investigated, and controlled.

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

All excipients used in the manufacture of ADZYNMA DP are (b) (4) grade and are listed below in Table 27 (copied from Table 1, Section 3.2.P.4.1 *Specification*):

Table 27. Excipients Used in the Manufacture of ADZYNMA DP

Ingredient	Quality standard
L-Histidine	(b) (4)
Sodium chloride	
Calcium chloride dihydrate	
Polysorbate 80	
Mannitol	
Sucrose	

3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures

rADAMTS13

All excipients in rADAMTS13 DP are (b) (4) and are tested in accordance with (b) (4) and are therefore considered suitable for their intended use (as stated in Sections: 3.2.P.4.2 *Analytical Procedures rADAMTS13 (TAK-755)*, and 3.2.P.4.3 *Validation of Analytical Procedures-TAK755*).

SWFI

This section is not applicable for SWFI since the diluent, sterile Water for Injection, does not contain any excipients (3.2.P.4.2 *Analytical Procedures-SWFI*)

3.2.P.4.4 Justification of Specifications

All specifications applied to the compendial excipients are the ones provided in appropriate (b) (4).

3.2.P.4.5 Excipients of Human or Animal Origin

No excipients of human or animal origin are used in the manufacture of the ADZYNMA DP.

3.2.P.4.6 Novel Excipient

No novel excipients are used in the manufacture of the ADZYNMA DP.

Reviewers' Assessment: All excipients are (b) (4) and there are no novel excipients or those of human or animal origin. This section adequately describes the control of excipients.

3.2.P.5 Control of Drug Product

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

Analytical data were generated from (b) (4) DP lots including (b) (4) lots manufactured with Process C manufacturing process ((b) (4) lots of 1500 IU/vial potency and (b) (4) lots of 500 IU/vial potency used in Clinical Phase 3 trials) and (b) (4) lots manufactured from the PPQ campaign (Process D, (b) (4) lots of 1500 IU/vial potency and (b) (4) lots of 500 IU/vial potency). All the above referenced DP lots were manufactured using (b) (4) batches manufactured from 2019 and 2020 (b) (4) campaigns at the (b) (4) manufacturing facility. Takeda defined DP specifications in accordance with (b) (4) and applicable (b) (4) requirements (b) (4). The proposed parameters and their specifications are reflective of product quality requirements. Acceptance criteria are based on the manufacturing process development experience, process validation data, release and ongoing stability data, and the intrinsic variability of analytical methods. Table 28 summarizes the details of commercial release and stability specifications and their justification for DP (based on Sections "3.2.P.5.1 Specifications" and "3.2.P.5.6 Justification of Specifications").

Table 28. Summary of DP Release and Stability Specifications and Their Justification

Attribute Category	Test: Method	Acceptance Criteria		Justification
		Release	Stability	
General Properties	Appearance (Lyophilized cake): Visual Inspection	Compact, white lyophilized cake	Same as release	Specification based on (b) (4) requirements (b) (4)
	Appearance (Reconstituted solution): Visual Inspection	Clear, colorless solution, free from visible particles	Same as release	Specification based on (b) (4) requirements (b) (4)
	Reconstitution time: Visual Inspection	(b) (4)	Same as release	Observed maximum reconstitution time plus 3-fold standard deviation
	pH: (b) (4)	7.0 (b) (4)	Same as release	Test method based on (b) (4) requirements (b) (4)
	Particulate matters	(b) (4)	Same as release	Test method based on (b) (4) requirements (b) (4)
	(b) (4)	(b) (4)	N/T ¹	Limit for (b) (4) is set per (b) (4) guidelines (b) (4)
	Residual moisture: (b) (4)	(b) (4)	Same as release	Measured according to (b) (4). A worst-case prediction (upper 99% confidence interval) from

				regression model was set as upper specification limit
Content	Total Protein: (b) (4) method	Report results as (b) (4)	N/T	Protein concentration is determined by (b) (4) and used for calculation of Specific Activity
Potency	rADAMTS13 Activity: FRETs-VWF73 assay	500 IU/Vial: (b) (4) IU/mL 1500 IU/Vial: (b) (4) IU/mL	Same as release	Specification limits were normalized for vial potency and calculated using (b) (4) Standard Deviations" formula ²
	Specific rADAMTS13 Activity: (b) (4)	(b) (4) IU/mg	Same as release	Specification limits were calculated using (b) (4) Standard Deviations" formula ²
Identity	rADAMTS13 (b) (4)	500 IU/Vial: (b) (4) 1500 IU/Vial: (b) (4)	Same as release	Specification limits were normalized for vial potency and calculated using (b) (4) Standard Deviations" formula ²
	(b) (4)	(b) (4)	Same as release	(b) (4)
Purity and Impurities	(b) (4)	(b) (4)	Same as release	The specification limit was proposed based on release data from (b) (4) lots; one limit is set for release and shelf-life specification ³
Microbiological Quality	Endotoxin	(b) (4)	Same as release	Testing is performed according to (b) (4) requirements ((b) (4))
	Sterility	Sterile	Same as release	Specification is based on (b) (4) requirements ((b) (4))
	Container Closure Integrity: (b) (4) Method	Not applicable	Report results (b) (4)	Testing is performed according to (b) (4) requirements ((b) (4))
Other Characteristics	Polysorbate 80: (b) (4)	(b) (4)	N/T	Specification limit was set to be (b) (4) of the target concentration ((b) (4))
	Sodium: (b) (4)	(b) (4)	N/T	Specification limit was set to be (b) (4) of the target concentration ((b) (4))
	Calcium: (b) (4)	(b) (4)	N/T	Specification limit was set to be (b) (4) of the target concentration ((b) (4))

	Histidine: (b) (4)	(b) (4)	N/T	Specification limit was set to be (b) (4) of the target concentration ((b) (4))
	Sucrose: (b) (4) Method	(b) (4)	N/T	Specification limit was set to be (b) (4) of the target concentration ((b) (4))
	Mannitol: (b) (4)	(b) (4)	N/T	Specification limit was set to be (b) (4) of the target concentration ((b) (4)

¹ Not tested in stability program

² Takeda identified 2 groups of data in change-point analysis – group 1 with lower activity and group 2 with higher activity. Lower specification limit was calculated using the mean of group 1 minus (b) (4) fold the (b) (4) standard deviation. Similarly, upper specification limit was calculated using the mean of group 2 plus (b) (4) fold (b) (4) standard deviation (please see relevant discussion below)

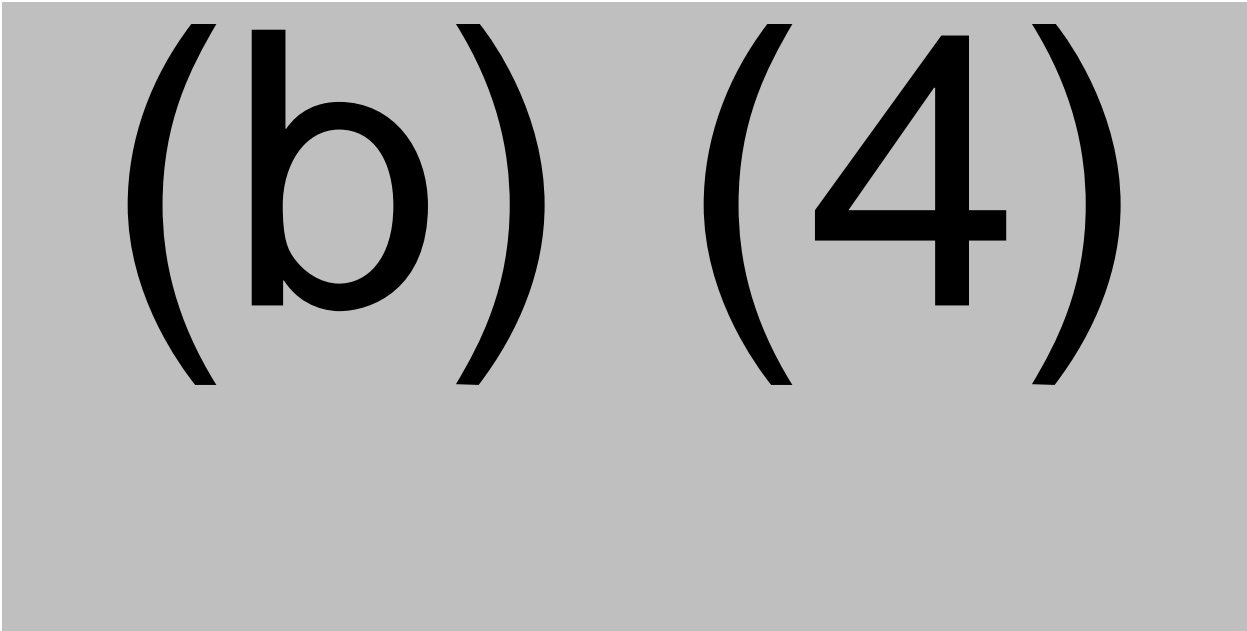
³ Takeda stated it will re-evaluate the specification limits for (b) (4) when more release data is available

⁴ (b) (4)

⁵ (b) (4)

Testing for Container Closure Integrity was not included as a release test for the batches used in the Clinical Phase studies. This parameter was included as a release test for the commercial batches. Takeda updated the specifications for reconstitution time, rADAMTS13 activity, Specific rADAMTS13 activity, and rADAMTS13 (b) (4). These modifications represent tightening of specifications to narrower ranges based on manufacturing experience.

While analyzing data for setting specifications, Takeda noticed a shift in the observed data for rADAMTS13 activity, specific rADAMTS13 activity and rADAMTS13 (b) (4) levels determined by (b) (4) of DP in change-point analysis, which resulted in two groups of data with respect to specific activity values (Figure 7, copied from Section “3.2.P.5.6 Justification of Specifications”).



These differences corresponded to the observed differences in the Specific Activity data between (b) (4) batches from 2019 and 2020 campaigns manufactured in the (b) (4) facility (refer to review of sections “3.2.S.4.1 *Specifications*” and “3.2.S.4.5 *Justification of Specifications*” for additional information). Due to the change-point in data, Takeda used the “(b) (4) Standard Deviations” formula in the calculation of acceptance criteria for release and stability specifications for rADAMTS13 activity, Specific Activity, and (b) (4) (Table 11 in this memorandum). However, the review team had concerns that this approach allows excessively wide ranges and requested Takeda to reanalyze data by performing the calculations using “(b) (4) Mean (b) (4) Standard Deviations” formula (CMC IR #11 dated August 22, 2023). The reanalysis with this formula resulted in a tighter specification range of (b) (4) compared to that previously proposed by Takeda ((b) (4)) for Specific Activity. Takeda proposed keeping the wider DP Specific Activity specification limits ((b) (4)) until the completion of real time stability studies at the intended storage condition (30 month at 5°C and 6 months at 30°C) when additional data become available for both the clinical and PPQ DP lots placed on stability program. These data can then be used to reassess the specification limits for Specific Activity. (Amendment # 38). Per PMC # 5 (refer to Section 10.B.I.c for complete text of PMCs), Takeda will propose amended interim rADAMTS13 DP Specific Activity release and stability acceptance criteria following the completion of ongoing stability studies of PPQ DP lots at long-term storage conditions. Per PMC # 6, Takeda will propose an additional amended interim rADAMTS13 DP Specific Activity release and stability acceptance criteria following the availability of a minimum of 12 months stability data for DP lots manufactured from (b) (4) batches of (b) (4) campaigns. In addition to DP PPQ lots, DP lots included in this analysis will be representative of both dosage strengths (500 and 1500 IU/vial) and (b) (4) campaigns (total (b) (4) DP lots). Per PMC # 7, Takeda will propose final rADAMTS13 Specific Activity release and stability acceptance criteria for DP following the availability of 36 months stability data for DP lots manufactured from (b) (4) and the planned (b) (4) campaign under PMC #1.

Reviewers’ Assessment: Takeda proposed commercial release specifications based on product quality requirements reflective of product CQAs and established acceptance criteria which are based on the manufacturing process development experience, process validation data, release and ongoing stability data, and the intrinsic variability of analytical methods. For select parameters, Takeda tightened specifications compared to clinical specifications that we consider as improvement. Statistical methods employed in the specification setting strategy are appropriate except for the rADAMTS13 Specific Activity parameter. Per PMC ## 5, 6 and 7, Takeda and FDA agreed to continue with the current limits for rADAMTS13 Specific Activity ((b) (4)) until stability data for PPQ DP lots and DP lots manufactured from additional commercial scale campaigns from (b) (4) facility becomes available to reanalyze the specification. The revised specification for Specific Activity will be communicated to the FDA as PASs. The current proposed specifications for DP are acceptable.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

DBSQC reviewers are responsible for the review of all rADAMTS13 DP release analytical procedures and method validations, except for:

- Potency- rADAMTS13 Activity (FRETS-VWF73)
- Identity - (b) (4)
- Specific rADAMTS13 Activity
- Purity/Impurities - (b) (4)

The DBSQC reviewers concluded the analytical methods and their validations and/or qualifications reviewed for rADAMTS13 DP release testing were found to be adequate for their intended use and their rationale is included in an independent review memo.

The analytical procedures for rADAMTS13 DP release testing reviewed by OPPT/DH CMC reviewers are the (b) (4) release testing (for description and validation, refer to (b) (4) sections 3.2.S.4.2 and 3.2.S.4.3 of this memorandum and are listed in Table 29 (modified from 3.2.P.5.2 *Analytical Procedures – Introduction*, and 3.2.P.5.3 *Validation of Analytical Procedures – Introduction*).

Table 29. Overview of Drug Product Analytical Procedures Reviewed by CMC Reviewers

Attribute Category	Test	Method	Method Reference Section	Validation Reference
Potency	rADAMTS13 Activity (FRETS-VWF73)	(b) (4)	3.2.S.4.2 – Analytical Procedures - rADAMTS13 Activity	3.2.S.4.3 - Validation of Analytical Procedures - rADAMTS13 Activity
	Specific rADAMTS13 Activity	Calculation	3.2.S.4.2 – Analytical Procedures - Introduction	3.2.S.4.3 - Validation of Analytical Procedures - Introduction
Identity	(b) (4)	(b) (4)	3.2.S.4.2 – Analytical Procedures – (b) (4)	3.2.S.4.3 - Validation of Analytical Procedures - (b) (4)
Purity and Impurities	(b) (4)	(b) (4)	3.2.S.4.2 – Analytical Procedures - (b) (4)	3.2.S.4.3 – Validation of Analytical Procedures - (b) (4) and this section

The analytical procedure for the determination of (b) (4) in rADAMTS13 by (b) (4) was validated for 500 IU/vial and 1500 IU/vial of rADAMTS13 DP concentrations. This analytical procedure is classified as Testing of Impurities - Quantitation according to (b) (4).

The (b) (4) method was validated for accuracy, repeatability, intermediate precision, specificity, LOQ, linearity, range, and robustness. The validation results are summarized in Section 3.2.P.5.3 *Validation of Analytical Procedures - (b) (4) rADAMTS13 (TAK-755)*. The results showed that the analytical procedure for the determination of (b) (4) in rADAMTS13 DP by (b) (4) has met the acceptance criteria established in the validation protocol; thus, the analytical procedure is suitable for its intended purpose.

Reviewers' Assessment: The analytical procedures and validation studies for the determination of rADAMTS13 activity (FRET-VWF73), Specific Activity, Identity via (b) (4) and (b) (4) in rADAMTS13 DP by (b) (4) were reviewed and evaluated in (b) (4) sections of this memorandum, all meet the acceptance criteria established in the validation protocol and are suitable for their intended purpose to control DP quality. The analytical procedures and method validations review by CMC reviewers (listed in Table 28) are acceptable as submitted.

sWFI

All the analytical procedures used in the release and stability testing of the diluent, sterile Water for Injection, are based on the (b) (4) for sterile Water for Injection (Section 3.2.P.5.2 *Analytical Procedures Sterile Water for Injection, 5 mL*). Therefore, validation of the analytical method was not warranted (3.2.P.5.3 *Validation of Analytical Procedures- Sterile Water for Injection, 5 mL*).

Reviewers' Assessment: The provided validation is acceptable as submitted.

3.2.P.5.4 Batch Analyses

Batch analyses data were provided including recent data in Amendment 27 dated July 19, 2023, covering all ADZYNMA DP lots manufactured over the development thus far. Table 30 contains a list of all ADZYNMA DP batches manufactured in (b) (4), according to Process D that is currently used for commercial production (adopted from Table 1, Section 3.2.P.5.4 *Batch Analyses*):

Table 30. Overview of ADZYNMA DP Lots

Lot Number	Nominal Vial Strength	Date of Manufacturing	Number of Vials	DS Batch Number	Lot Use
(b) (4)	500	(b) (4)			Clinical, Stability, PPQ
	500				Clinical, PPQ
	500				Clinical, Stability, PPQ
	1500				Clinical, Stability, PPQ
	1500				Clinical, Stability, PPQ

Lot Number	Nominal Vial Strength	Date of Manufacturing	Number of Vials	DS Batch Number	Lot Use
				(b) (4)	
(b) (4)	1500	(b) (4)	(b) (4)		Clinical
	500				Clinical, Stability

^a These two DP lots were manufactured by the commercial process using the remaining clinical (b) (4) and PPQ (b) (4) lots.

3.2.P.5.5 Characterization of Impurities

No additional impurities arise from the DP process. The product-related impurities in ADZYNMA DP are the same as those found in the (b) (4) and described in section 3.2.S.3.2 *Impurities* in this memorandum. Only (b) (4) excipients are used for DP (refer to 3.2.P.2.1.2 *Excipients* in this memorandum). Review of extractables and leachables is described in sections 3.2.P.3.5 *Process Validation and/or Evaluation* and 3.2.P.7 *Container Closure System* in this memorandum.

Reviewers' Assessment: The information and data described in Section 3.2.P.5 demonstrate that adequate controls are in place to ensure the safety, efficacy, and quality of the ADZYNMA DP. Takeda provided all available lot release information from seven Process D DP lots ((b) (4)) including (b) (4) PPQ DP lots manufactured from (b) (4) PPQ campaign. All ADZYNMA PPQ DP batches met all release specification acceptance criteria. The batch analysis data support the consistency of ADZYNMA Process D for DP manufacturing. Sufficient manufacturing experience and appropriate statistical methods were used to justify the specifications used to ensure the quality of the ADZYNMA DP.

3.2.P.6 Reference Standards or Materials

The reference standards are the same as those used for the ADZYNMA (b) (4).

3.2.P.7 Container Closure System

The primary container closure of rADAMTS13 DP consists of a 10 mL colorless Type (b) (4) glass vial (for both 500 and 1500 IU/vial potencies and meets (b) (4) requirements) with a 20 mm butyl rubber stopper having (b) (4) lamination on the plug and top and (b) (4) coating on the sealing surfaces (meets (b) (4) requirements) and an aluminum crimp seal (meets (b) (4) requirements). Specifications of glass vial, rubber stopper, crimp cap and drawings of the container closure system are provided in eCTD Section "3.2.P.7 *Container Closure System*".

An extractables study (by Takeda) was performed only for organic compounds from the stopper. These results and toxicological assessment revealed no individual organic extractable to be above the corresponding tolerable daily intake (TDI) suggesting minimal toxicological concern (refer to section 3.2.P.3.5 in this memorandum). However, both organic and elemental E/L for the whole container closure system were not assessed. This deficiency will be addressed under PMC #2 as described in section 3.2.P.3.5, *Analysis of cumulative Extractables and Leachables*.

The biological reactivity of the rubber stopper was tested per (b) (4) requirements and found to be negative (details are included in eCTD Section “3.2.P.2.4 *Container Closure System*”). Integrity of container closure system is validated by using (b) (4) (details are included in Section “3.2.P.2.5 *Microbiological Attributes*”).

Takeda performed DP stability studies using the same container closure system that is used for the final DP to assess compatibility of DP with the container closure system. These studies showed that the DP remained stable in the container closure system under long-term storage conditions (please refer to review of Section “3.2.P.8 *Stability*”). Further, stability study data indicated the photosensitive nature of the DP when stored in unprotected container closure system. Subsequently, Takeda included a precautionary statement regarding the photosensitivity of the DP in the Prescribing Information and carton label. This was verified during the labeling review. Finally, the ability of container closure system to protect the DP from the physical stresses of shipping are validated by simulated shipping studies (details are included in eCTD Section 3.2.P.3.5 *Process Validation and/or Evaluation* (Shipping Validation)).

Reviewers’ Assessment: The information provided for DP container closure system is acceptable from a Product Reviewer perspective. The in-depth analysis of this information is reflected in the memorandum of the DMPQ reviewer who confirmed its acceptability. For more detailed analysis of cumulative leachables, please refer to Section 3.2.P.3.5 Process Validation and/or Evaluation of this memorandum.

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

For the DP, Takeda proposed a shelf-life of 36 months at $5\pm3^{\circ}\text{C}$ including 6 months at $30^{(b)(4)}\text{C}/$ (b) (4). Following storage at $30^{(b)(4)}\text{C}/$ (b) (4) (will be referred to as Room Temperature (RT) in this review memorandum), DP cannot be returned to the refrigerator ($5\pm3^{\circ}\text{C}$) to complete the 36 months shelf life. For the reconstituted product, Takeda proposed a shelf-life of 3 hours at RT. In support of the proposed shelf-life periods, Takeda performed: i) Primary long-term stability studies with DP up to 36 months followed by testing of reconstituted DP (with sWFI) for up to $^{(b)(4)}$ hours, ii) Photostability studies to evaluate the light sensitivity of DP, iii) Temperature cycling studies to simulate temperature excursions that DP might be exposed to during manufacturing, sample handling, shipping and storage, and iv) (b) (4) studies to verify the stability-indicating capacity of the test methods. Samples used for stability studies were stored in the same container closure system as the DP. The

acceptance criteria used for stability studies were same as those used for Clinical Phase 3 DP release testing. Takeda updated acceptance criteria of select parameters (primarily tightened specifications) for commercial release testing (reviewed under Sections 3.2.P.5.1 *Specification* and 3.2.P.5.6 *Justification of Specification*).

Primary long-term stability studies were performed at the following conditions: i) $5\pm 3^{\circ}\text{C}$ for 36 months, ii) $5\pm 3^{\circ}\text{C}$ for 30 months followed by $30^{\circ}\text{C}/\text{(b) (4)}$ for 6 months, iii) $30^{\circ}\text{C}/\text{(b) (4)}$ for 36 months and iv) (b) (4) for 6 months.

Additionally, product stability studies following reconstitution with sWFI were performed at RT for up to (b) (4) hours. For these studies, data from (b) (4) PPQ (data up to 18 months) and (b) (4) clinical (data up to 36 months) DP lots were provided. Table 31 summarizes the details of DP lots included in the primary long-term stability studies (adapted from Table 1 in Sections 3.2.P.8.1. *Stability Summary and Conclusion* and 3.2.P.5.4 *Batch Analyses*).

Table 31. DP lots Included in Stability Studies

Lot Number	Lot Use	Lot Size (No. of Vials)	Potency (IU/Vial)	Date of Manufacture	Data Availability (up to Months)
(b) (4)	PPQ, primary long-term and (b) (4)	(b) (4)	500	(b) (4)	18
	PPQ, primary long-term, (b) (4) and photostability		500		18
	PPQ, primary long-term and (b) (4)		1500		18
	PPQ, primary long-term, (b) (4), photostability and (b) (4)		1500		18
	Clinical, primary long-term and (b) (4)		500		36
	Clinical, primary long-term and (b) (4)		1500		36
	Clinical and primary long-term		1500		36

The parameters tested in the Primary long-term studies included appearance (lyophilized cake and reconstituted solution), reconstitution time, pH value, rADAMTS13 activity, rADAMTS13 Specific Activity, rADAMTS13 (b) (4) , (b) (4) , particulate matters, sterility, endotoxins, container closure integrity and residual moisture. At the time of initial BLA submission (March 17, 2023), (b) (4) was validated for the analysis of (b) (4) , but not (b) (4) . For measuring ADAMTS13 activity and (b) (4) , a validated in-house recombinant reference standard, was used in the assays (see Section 3.2.S.5 *Reference Standards or Materials*). Samples were scheduled to be tested for the above parameters at 0, 3, 6, 9, 12, 18, 24, 30 and 36 months as applicable per the protocol ((b) (4) particulate matters, sterility, container closure integrity and endotoxins were tested at select time-points only). Results for the available time points for all DP lots in all stability

studies met the acceptance criteria. For DP lots stored at 30^{(b) (4)} °C/ (b) (4) for (b) (4) months, an increase in (b) (4) levels (b) (4), acceptance criterion is (b) (4) towards later points ((b) (4) months) was observed for several lots including (b) (4). However, storage at 30^{(b) (4)} °C/ (b) (4) for (b) (4) months is not the proposed long-term storage condition and duration for the DP by Takeda. These studies are ongoing for PPQ lots, which will continue to be monitored through (b) (4) months.

For Temperature cycling studies, Takeda subjected (b) (4) select PPQ DP lots (Table 31) to various (b) (4) (detailed in Table 9 of Section 3.2.P.8.1 *Stability Summary and Conclusion*) and then stored samples at 5±3°C or 30^{(b) (4)} °C/ (b) (4) for 36 months. Following initial testing, samples are scheduled for evaluation at 3-month time point and then (b) (4) up to 36 months. Stability after reconstitution was scheduled to be evaluated at time 0 and after 36 months storage. The parameters tested in these studies were same as those tested in Primary long-term stability studies. Results from the available time-points (up to 12 months) for both DP lots met the acceptance criteria and showed no adverse trends. These studies are ongoing and will continue to be monitored through 36 months.

Photostability studies were performed with (b) (4) select PPQ DP lots (Table 31). In these studies, light sensitivity of DP was evaluated by (b) (4)

(b) (4)

These results indicated that the DP is photosensitive, and that the carton provides adequate protection from light exposure.

(b) (4) studies were performed with (b) (4) clinical and (b) (4) PPQ DP lots (Table 31) by (b) (4)

(b) (4)

Results from these completed studies confirmed that analytical methods can be used to control product stability. (b) (4) resulted in decreased activity, increased (b) (4) and the appearance of (b) (4). (b) (4) treatment of DP samples resulted in change of appearance and decrease in Specific Activity and a slight increase in (b) (4). Light exposure resulted in decrease of Specific Activity, increase in (b) (4) and

increased (b) (4). Other stress conditions did not show significant effects on the investigated parameters of the DP.

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

Takeda commits to complete the ongoing stability studies with PPQ DP lots per the protocols provided in Section 3.2.P.8.1 Stability Summary and Conclusion. Further, Takeda commits to place (b) (4) of DP in the stability program (b) (4) at the combined storage conditions of $5\pm3^{\circ}\text{C}$ for 30 months followed by $30^{(b)(4)}\text{C}/(b) (4)$ for 6 months according to the Post-approval Stability Protocol provided in Section 3.2.P.8.2. Post-approval Stability Protocol and Stability Commitment. In the Post-approval Stability Protocol, Takeda removed (b) (4) from the tested parameters citing that evaluation of rADAMTS13 (b) (4) by (b) (4) is sufficient to ensure the identity of rADAMTS13 and reasoning that (b) (4) serves the purpose of controlling impurities. However, the current (b) (4) method is not validated to study (b) (4). Takeda has committed to reinstate the (b) (4) in Post-approval Stability Protocol until current (b) (4) method and/or (b) (4) based methods are evaluated for their applicability in quantitation of (b) (4) (Amendment ## 34 dated August 16, 2023 and 55 dated October 10, 2023). The method validation and changes in tests used in the stability studies will be submitted as a Prior Approval Supplement. In addition, data from the stability studies will be provided (b) (4) in (b) (4) reports and the FDA will be informed of any confirmed out-of-specification results within the licensed shelf-life and storage conditions.

Reviewers' Assessment: The provided DP stability information from primary long-term and supportive stability studies is acceptable. The primary long-term stability studies are ongoing and 36-month data from (b) (4) clinical DP lots supports the proposed shelf-life period of 36 months at $5\pm3^{\circ}\text{C}$ including 6 months at $30^{(b)(4)}\text{C}/(b) (4)$. Data from (b) (4) PPQ DP lots for up to 18 months met acceptance criteria. Further, data from (b) (4) studies confirmed the stability indicating ability of the analytical methods. CMC reviewers noted that Takeda excluded (b) (4) from the tested parameters of Post-approval Stability Protocol. CMC reviewers communicated this limitation and obtained commitment from Takeda to reinstate the (b) (4) test in post-approval stability protocol until an alternative method is adequately validated for the quantitation of degradation protein products. Takeda updated relevant Sections accordingly (in amendment # 55 dated October 10, 2023).

3.2.P. Drug Product (sWFI)

Each vial of the rADAMTS13 DP (500 and 1500 IU) is supplied with 5 mL (nominal volume) of sterile water for injection (sWFI) in a single-use (b) (4) Type (b) (4) glass vial (6 mL) with chlorobutyl or bromobutyl rubber stopper and aluminum crimp cap for reconstitution. The proposed shelf life of sWFI packaged with the final DP (rADAMTS13) is 60 months when stored at not more than 30°C and unfrozen. Table 32 summarizes the details of commercial release and stability specifications for sWFI (based on information in Section 3.2.P.5.1 *Specifications*). The specifications were in accordance with the applicable (b) (4) guideline and requirements of the (b) (4) for sWFI, (b) (4) for sterilized water for

injections and parenteral preparations and (b) (4) for sWFI.

Table 32. Release and Stability Specifications for DP (sWFI)

Test	Acceptance Criterion	
	Release	Stability
Appearance	Colorless, clear liquid	Same as release
(b) (4)	(b) (4)	Same as release
		Same as release
		Same as release
		Same as release
		Same as release
		Not tested
		Same as release
		Same as release
		Same as release
		Same as release
		Same as release
		Same as release
Sterility	Sterile	Same as release
Bacterial endotoxins	(b) (4)	Same as release
Extractable volume	(b) (4)	Same as release

Takeda performed stability studies with sWFI in vials with chlorobutyl rubber stopper at storage temperatures of 5±3°C (5°C), (b) (4) and 30 (b) (4) (30°C) for 60 months. (b) (4) lots of sWFI were tested at each of the storage conditions and samples were tested at 0, 3, 6, 9, 12, 18, 24, 36, 48 and 60 months. Data was provided for up to 60 months for all studies and all lots complied with the specifications at all time-points and storage conditions. For the sWFI packaged with bromobutyl rubber stopper, Takeda initiated stability studies with (b) (4) lots, each at 30 (b) (4) (30°C) for 60 months to mimic worst-case long-term storage conditions and (b) (4) for 6 months to mimic accelerated storage conditions. Available data from these studies (24 months and 6 months for 30°C and (b) (4) storage conditions, respectively) met specifications at all time-points. Takeda commits to place (b) (4) commercial lot of sWFI in stability studies (b) (4) at 30°C for 60 months (b) (4) the filling sizes of (b) (4) vials according to the stability testing schedule provided in Section 3.2.P.8.2 *Post-approval Stability Protocols*

and Stability Commitment- Sterile Water for Injection, 5 mL. Takeda stated similarity of the container closure system for justifying the inclusion of (b) (4) filling sizes in stability studies for the diluent for this (5 mL) and other (b) (4) products. No stability study will be initiated if the manufacturing of the diluent is not performed in that year.

Reviewers' Assessment: The information provided for sWFI is satisfactory as submitted.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

CBER/OCBQ/Division of Manufacturing and Product Quality (DMPQ) CMC reviewers are responsible for the review of all facilities and equipment information.

3.2.A.2 Adventitious Agents Safety Evaluation

Takeda based the ADZYNMA adventitious agents safety plan on (b) (4) guidelines. Takeda's safety plan includes facility/procedural controls, absence of animal-derived raw materials during establishment of MCB, cell bank testing for adventitious agents, including risk assessment of TSE agents, testing of (b) (4) samples, and viral clearance studies of the purification process.

□ Viral Clearance Studies

Takeda assessed the (b) (4) manufacturing process for clearance of adventitious viral agents by testing samples pulled from established scaled-down models under worst-case conditions. Takeda evaluated (b) (4) downstream manufacturing unit operations for viral clearance capacity using (b) (4) studies: (i) Solvent/ detergent treatment for viral inactivation of enveloped viruses; (ii) 20 nm nanofiltration for viral removal of non-enveloped and enveloped viruses; (iii) (b) (4) were tested. A panel of model viruses was used to determine the log reduction of virus (LRV) for each of the purification steps. (b) (4) model viruses were selected based on (b) (4)




Table 33 Mean Reduction Factors at (b) (4) rADAMTS13^{(b) (4)} Manufacturing Steps

(b) (4)

Reviewers' Assessment: The provided adventitious agent safety valuation and viral clearance study information is acceptable as submitted. Using (b) (4) and a linear down-scale model, Takeda has provided documented evidence that the at-scale^{(b) (4)} manufacturing process can inactivate and effectively clear enveloped and non-enveloped viruses from representative rADAMTS13^{(b) (4)} material and ensure product safety over the established resin lifetime.

3.2.A.3 Novel Excipients

Not applicable.

3.2.R Regional Information (USA)

❑ Executed Batch Records

The submission includes all ADZYNMA^{(b) (4)}/DP master records. The executed batch records from^{(b) (4)} validation^{(b) (4)} batch per step (from PPQ campaign (b) (4)) and DP lot (# (b) (4)) were provided.

❑ Method Validation Package

In Section 3.2.R.1 *Batch Records*, Takeda provided a summary of method validation protocols and reports. Responsibility of CBER/OCBQ/DBSQC CMC reviewers in review of analytical methods validation are described in sections 3.2.S.4.2 and 3.2.S.4.3, and 3.2.P.5.2 and 3.2.P.5.3 of this memorandum.

❑ Combination Products

ADZYNMA DP (vial of lyophilized powder for reconstitution) is co-packaged as a biologics-device combination product with a BAXJECT II Hi-Flow needleless transfer device (Baxter (manufactured specifically for Takeda)), a (b) (4) Luer-lock syringe, 10 mL or 20 mL ((b) (4)), and a (b) (4) winged infusion set with needle protection ((b) (4)). BAXJECT II Hi-Flow, Luer-lock syringe, and (b) (4) winged infusion set

received 510(k) clearance from CDRH under K092318 (October 30, 2009), (b) (4) (August 16, 2007), and (b) (4) (February 5, 2014), respectively. All components are commercially available.

The Center for Devices and Radiological Health (CDRH), Office of Product Evaluation and Quality (OPEQ), Office of Health Technology 3 (OHT3) evaluated the Baxject II Hi Flow Needleless Transfer Device, (b) (4) syringe, (b) (4) winged infusion set, and an alcohol pad used to reconstitute ADZYNMA powder with its diluent and inject the solution (ICCR# (b) (4)). All devices are legally marketed. Three are 510(k) cleared and the fourth, an alcohol pad, is a pre-amendment device. The device constituents are intended to be co-packaged with the drug vial and will not be integrated with the device prior to use. As such, re-evaluation of essential performance requirements is not needed. A labeling review was conducted which ensured no discrepancies with the cleared indications for use in the respective 510(k)s. The CDRH reviewer concluded that device constituent parts of the combination product are acceptable as submitted.

The Center for Drug Evaluation and Research (CDER), Office of Surveillance and Epidemiology (OSE), Office of Medication Error Prevention and Risk Management (OMEPRM), Division of Medication Error Prevention and Analysis 2 (DMEPA 2) evaluated human factors threshold/comparative analysis reports including use-related risk analysis (URRA) and comparative analyses in Section 5.3.5.4 *Other Study Reports*, draft *Instructions for Use* (IFU) and labels to determine whether Takeda needs to submit the results of a human factors (HF) validation study (under an inter-center consult, ICCR# (b) (4)).

During pre-BLA stage, the DMEPA reviewer concluded: (i) some descriptions in the draft IFU are acceptable only if the intended users are healthcare professionals (HCPs), ii) all remaining tasks evaluated in the URRA appear to be comprehensive and appropriate based on the proposed user interface design and intended use of this product, (iii) comparative analyses with the co-packaged devices for RIXUBIS are acceptable and no differences were identified in the results of the physical comparison, comparative task analysis, and labeling comparison. The DMEPA reviewer recommended that the results of a HF validation study do not need to be submitted to support the BLA marketing application. This determination is based on Takeda's claim that i) the size of the filter in the transfer device has an imperceptibly small impact in aspiration force required to withdraw the mixed drug from the device, and ii) intended users are licensed HCPs. This information was verified again during the BLA review, and no changes were identified.

Reviewers' Assessment: The information provided in Section 3.2.R *Regional Information – Medical Devices* is acceptable as submitted. Takeda provided adequate descriptions for each component of the co-packaged biologics-device combination product.

We requested a consult review from CDRH (ICCR# (b) (4)) to evaluate whether the device components of the co-packaged combination product are compatible and suitable for safe and effective reconstitution and administration of rADAMTS DP to

cTTP patients. The CDRH consult review provided feedback that they have no concerns regarding the use of the co-packaged reconstitution device with the biologic. The physicochemical compatibility of reconstituted ADZYNMA DP is evaluated under section 3.2.P.2.6 *Compatibility* of this review memorandum.

We requested a consult review from CDER (ICCR# (b) (4)) to evaluate whether Takeda needs to submit the results of a HF validation study. The CDER consult reviewer provided feedback that the results of HF study are not needed unless there is any modification in the combination product user interface or intended users. It was confirmed by Takeda that there are no changes in the product user interface or intended users who are licensed HCPs.

❑ **Comparability Protocols**

Not applicable. Section 3.2.S.2.6 contains comparability studies performed during product development upon the changes in manufacturing process or manufacturing site.

Other eCTD Modules

Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

In *Section 1.12.14 Environmental Analysis*, Takeda claims categorical exclusion from preparation of an environmental assessment for ADZYNMA under 21 CFR 25.31(c), as the ADZYNMA product represents a recombinant version of naturally occurring plasma-derived endogenous ADAMTS13.

Reviewers' Assessment: Takeda's claim for categorical exclusion from preparing an environmental assessment is valid as ADZYNMA is comprised of naturally occurring amino acids, it is unlikely that approval of this product would significantly alter the concentration or distribution of proteins, product metabolites, or degradation products in the environment. This claim is acceptable.

B. Reference Product Designation Request

In *Section 1.3.5.3 Exclusivity Claim*, Takeda claims the following exclusivity:

- i) Orphan Drug Exclusivity: A seven-year period of marketing exclusivity based upon orphan drug designation #08-2622 and 08-2652 per 21 CFR 316.31. Takeda's request for orphan drug designation of rADAMTS13 was granted for prevention of thrombotic thrombocytopenic purpura including its congenital, acquired idiopathic, and secondary forms on July 29, 2008.
- ii) New Chemical Entity Exclusivity: Takeda requested the twelve-year reference-product exclusivity provided in 42 U.S.C. § 262(k)(7)(A) and the four-year period of reference-product exclusivity under 42 U.S.C. § 262(k)(7)(B), for first licensure of a reference product under 42 U.S.C. § 262(a). This request was recommended to the CBER Reference Product Exclusivity Board, and the final determination of product exclusivity will be made by the Board.

Reviewers' Assessment: The provided reference product designation information is acceptable as submitted. From a CMC (Product Quality) perspective, we recommend a reference product exclusivity period for ADZYNMA (pending licensure). ADZYNMA would be the first licensed recombinant product indicated for prophylactic or on demand enzyme replacement therapy in patients with cTTP. The CBER Reference Product Exclusivity Determination Board (RPEDB) determined that the Applicant does not manufacture a structurally similar product and the reference product exclusivity was supported. Reference product exclusivity period expiry dates will be determined after the approval.

C. Labeling Review

❑ Full Prescribing Information (PI):

In Section 1.14 *Draft Labeling*, Takeda provided draft *Prescribing Information* (PI) and *Instructions for Use* (IFU) documents.

We reviewed the CMC-related information from a Product Quality perspective. Our proposed edits and comments were communicated to Takeda by the Regulatory Project Manager on October 11, 2023. "Dosage Forms and Strengths (section 3)", "Description (section 11)" and "How Supplied/Storage and Handling (section 16)" in Full PI are acceptable in the final version (Amendment 67 received November 6, 2023).

❑ Carton and Container Label:

In Section 1.14 *Draft Labeling*, Takeda provided draft vial labels (ADZYNMA and sWFI) and carton labels information. We reviewed the CMC-related information from a Product Quality perspective. Our proposed edits and comments were communicated to Takeda and the labels received on October 20, 2023 were found acceptable.

Modules 4 and 5

❑ Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints

FRETs-VWF73 assay

The FRETs-VWF73 assay monitors the fluorescence signal during the cleavage of the synthetic substrate FRETs-VWF73 (which contains the cleavage site of VWF) by ADAMTS13 as described in Sections 3.2.S.4.2 *Analytical* and 3.2.S.5. *Reference Standards*.

Section 4.2.2.1 Analytical Methods and Validation Reports (FRET assay)

The method for the determination of ADAMTS13 activity in animal plasma by the FRETs-VWF73 assay during the nonclinical (animal) studies was validated as summarized in two Study Reports.

1. Study Report OR-13-00589-01-VB.01 demonstrated that the FRETs-VWF73 assay performed according to SOP OR13-00589 is suitable for the determination of

ADAMTS13 activity in plasma from ADAMTS13 (b) (4) mice, rats and (b) (4) monkeys for preclinical purposes. The assay was validated for accuracy, precision, specificity, linearity, range, and robustness.

2. The objective of Validation Report S01-102-02-VR was to prove reliability of the analytical results obtained with the FRET-VWF73 assay for the determination of ADAMTS13 (recombinantly derived) activity in rat plasma samples as well as in formulation samples obtained from preclinical studies. The assay was validated for calibration curves, specificity, accuracy, precision, linearity, selectivity (Matrix effect), and range. The formulation samples were tested for accuracy, precision, and range.

Reviewers' Assessment: The analytical procedure for the determination of rADAMTS13 activity in animal plasma by FRET-VWF73 assay met the acceptance criteria for all validation parameters established in the validation protocol. The method validation results demonstrate that the assay has the appropriate specificity, accuracy, precision, linearity, and range to be suitable for its intended use. The validation studies were performed on appropriate numbers of samples. We conclude that the analytical procedure is appropriate for its intended purpose and the results obtained with this method in animal studies are valid.

Section 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies (FRET Assay)

The method for the determination of ADAMTS13 activity in human plasma by the FRET-VWF73 assay during the clinical phase studies was validated in several independent Study Reports.

1. The objective of Validation Study OR-13-00589-02-VB.01 was to demonstrate that the FRET-VWF73 assay performed according to SOP OR-13-00589 is suitable for the determination of ADAMTS13 activity in human cTTP plasma samples for clinical purposes. The method was validated for selectivity (matrix effect), accuracy, precision, calibration curve, linearity, range, quantitation limit, (b) (4) and stability of sample and reagent. Specificity was not addressed because FRET substrate is specifically cleaved by ADAMTS13 and no other enzyme in plasma was identified to be able to cleave the VWF73 substrate. The validation was performed on the (b) (4) in the range of (b) (4) (the (b) (4) measurable FRET-VWF73 activity). The requirements and acceptance criteria for measurement of rADAMTS13 activity in human cTTP plasma samples, which were defined in the validation protocol, were fulfilled.
2. Validation Study S01 -097-02-VR was performed to prove reliability of the analytical results obtained in the FRET-VWF73 assay for the determination of ADAMTS13 (plasmatic and recombinantly derived) activity in human plasma samples obtained from study participants treated with rADAMTS13 and their standard-of-care plasma product (plasma-based therapies) during the clinical Phase 3 study conducted in cTTP patients. The method was validated for calibration curve (WHO Plasma Standard and (b) (4)), specificity, linearity of standards (WHO and (b) (4)) and

selectivity (Matrix effect). The plasma samples were validated for accuracy, precision, range, robustness, and limit of quantification ((b) (4)). The method is (b) (4)

(b) (4) plasma samples from cTTP subjects with severe deficiency of ADAMTS13 activity showed the ADAMTS13 activities (tested by the FRETs-VWF73 assay) <LLOQ (Lower Limit of Quantification) or near the LOQ ((b) (4)). In cases where activity levels of untreated baseline plasma samples were >LLOQ, the resulting background values were (b) (4). Overall, all the requirements and acceptance criteria defined in the validation protocol were fulfilled.

3. The objective of Validation Study S01-147-02-VR was to investigate potential interference of (b) (4) in the FRETs-VWF73 assay for the determination of ADAMTS13 activity in human plasma samples obtained from study participants treated with rADAMTS13 and their standard-of-care plasma product during the clinical Phase 3 study conducted in cTTP patients. Samples were (b) (4)

(b) (4) and results of ADAMTS13-VWF73 activity, a threshold between (b) (4) samples was determined.

4. The objective of Validation Study FHSOP-31-0023-TI00I-06-VR.01 was to increase the sensitivity of the assay and introduce a LLOQ below (b) (4). Samples for plasmatic and for recombinant ADAMTS13 protein at levels below (b) (4) were tested to demonstrate suitability of the assay. The results showed that the LLOQ can be set to (b) (4) as all validation parameters fulfilled the acceptance criteria for inter- and intra- assay precision and accuracy.
5. The objective of Study A12198M-TAK-755 was to validate the FRETs-VWF73 assay for the determination of ADAMTS13 Activity in human plasma ((b) (4) plasma) at (b) (4). A quantitative assay was successfully validated for a run size of up to (b) (4) samples per (b) (4) (analyzed in (b) (4) and inclusive of a Calibration curve, Quality Controls (QC's) and study samples). Samples were measured against a reference standard of (b) (4) calibrated against the WHO first international plasma standard for ADAMTS13. The (b) (4) was also monitored. Overall, method was validated for human plasma reference standard calibration, WHO verification of TAK-755, inter and intra-assay accuracy, precision and range of quantification, system suitability, selectivity (matrix interference), (b) (4) linearity and hook effect, stability, and cross validation.

Reviewers' Assessment: The analytical procedure for the determination of ADAMTS13 activity in human plasma by the FRET-S-VWF73 assay met the acceptance criteria for all validation parameters established in the validation protocol. The validation studies were performed on appropriate numbers of samples. The method validation study results demonstrate that the assay has the appropriate accuracy, precision (intermediate; repeatability), linearity, and range to be suitable for its intended use. The results from cTTP studies indicate that FRET-VWF73 assay is specific to measure rADAMTS13 activity in cTTP disease population under validated assay condition.

In response to CMC IR#14 dated September 11, 2023, Takeda provided clarification about the method specificity, clinical studies and the standards used in nonclinical and clinical studies (Amendment #44 dated September 26, 2023). Takeda explained that the FRET-S-VWF73 substrate, (b) (4)

(b) (4) is specifically optimized to be cleaved by ADAMTS13. (b) (4)

To distinguish between recombinant and plasmatic ADAMTS13 activities, (b) (4)

(b) (4). In response to CMC IR# 17, Takeda amended Section 3.2.S.5 Reference Standards to include the recommended detailed information regarding the use of different reference standards in nonclinical and clinical studies (Amendment 55 dated October 13, 2023). Overall, we conclude that the analytical procedure, FRET-S-VWF73 assay, is appropriate for its intended purpose and the results obtained with this method in clinical studies are valid.

❑ **ADAMTS13 (b) (4) for the Quantitation of ADAMTS13 (b) (4) in Human Plasma**

Section 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

The method for the determination of ADAMTS13 (b) (4) in human plasma by (b) (4) assay during the clinical phase studies was validated in several independent study reports.

1. The objective of Validation Study OR-13-00662-01-VB.01 was to demonstrate that the ADAMTS13 (b) (4) assay when performed according to SOP OR-13-00662 is suitable for the determination of ADAMTS13 (b) (4) in human cTTP plasma samples in clinical Phase 1 study. The method was validated for selectivity (matrix effect), accuracy, precision, calibration curve, linearity, range, (b) (4) integrity, and stability of sample and reagent. Specificity was not addressed since the (b) (4) used in the assay specifically (b) (4)

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

(b) (4)

Reviewers' Assessment: The analytical procedure for the determination of ADAMTS13 (b) (4) in human plasma by (b) (4) ADAMTS13 (b) (4) assay met the acceptance criteria for all tested validation parameters established in the validation protocol. The validation studies were performed on appropriate numbers of samples. The method validation study results demonstrate that the assay has the appropriate accuracy, precision, linearity, and range to be suitable for its intended use. We conclude that the analytical procedure (b) (4) ADAMTS13 (b) (4) is suitable for its intended purpose and that the results obtained in clinical studies with the use of this method are reliable.

❑ **Analytical procedures and validation of analytical procedures for assessment of (b) (4) to ADAMTS13**

Takeda provided method validation reports for the immunogenicity assessment (detection of (b) (4)) of ADZYNMA.

(b) (4)

2 pages have been determined to be not releasable: (b)(4)