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I concur with this review memo. S. Sanduja 11/07/23

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PRODUCT:	ADZYNMA™ (rADAMTS13 or TAK-755)
APPLICANT:	Takeda Pharmaceuticals U.S.A; Inc.
PROPOSED INDICATION:	Congenital thrombotic thrombocytopenic purpura (cTTP)
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EXECUTIVE SUMMARY:

ADZYNMA™ (rADAMTS13, TAK-755, BAX 930 or SHP655) is a recombinant A disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13 (rADAMTS13) enzyme, which cleaves large and ultra large von Willebrand factor (VWF) multimers in the A2 domain at the Tyr1605-Met1606 to generate smaller VWF units. The recommended maximum clinical dose level and dosing regimen for ADZYNMA™ is 40 International Units (IU)/kg weekly as prophylactic enzyme replacement therapy (ERT) for patients with congenital thrombotic thrombocytopenic purpura (cTTP). As an on-demand ERT, the recommended dose level of ADZYNMA™ is 40 IU/kg on Day 1, followed by 20 IU/kg on Day 2, and 15 IU/kg on Day 3 until two days after the acute event is resolved.

The pharmacologic activity of ADZYNMA™ was evaluated through *in vitro* and *in vivo* studies. rADAMTS13-mediated proteolysis and specificity to VWF by ADZYNMA™ were demonstrated *in vitro* using plasma from ADAMTS13 knock-out (KO) mice, healthy Sprague Dawley rats, (b) (4) guinea pigs, cynomolgus monkeys, and (b) (4) minipigs. The

ability of ADZYNMA™ to protect against TTP onset was evaluated *in vivo* following single intravenous (IV) administration of ADZYNMA™ (1, 5, 40, 80, and 200 IU/kg) in ADAMTS13 KO mice. The results showed dose-dependent protection from TTP by ADZYNMA™ with prophylactic activity similar to Octaplas (IV administration, 1 and 5 U/kg).

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

Safety of ADZYNMA™ was assessed in repeat-dose toxicology studies conducted in healthy Sprague Dawley rats and cynomolgus monkeys. No adverse findings were observed following IV administrations of ADZYNMA™ in rats at 800 or 1820 IU/kg once daily for 30 days or at 80, 200, or 400 IU/kg, every third day for 26 weeks. IV administration of ADZYNMA™ at 80, 200, or 400 IU/kg once weekly for 4 weeks or at 200 or 1790 IU/kg followed by 800 IU/kg once weekly for 4 weeks did not result in adverse findings except for several incidences of hemolytic anemia and thrombocytopenia that were attributed to cross-reactive neutralizing antibodies to endogenous monkey ADAMTS13 and were not indicative of potential toxicity of ADZYNMA™ administration to humans.

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

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

PHARMACOLOGY/TOXICOLOGY RECOMMENDATION:

There are no nonclinical deficiencies identified in this submission. There are no outstanding requests for additional nonclinical data for evaluation of ADZYNMA™. The nonclinical information provided in the BLA submission supports approval of the licensure application.

Formulation and Chemistry:

ADZYNMA™ is a sterile, lyophilized powder for reconstitution supplied in a single dose vial containing 500 or 1500 international units (IU). ADZYNMA™ final drug product (FDP) formulation is composed of sodium chloride, calcium chloride dihydrate, L-histidine, mannitol,

sucrose, and polysorbate 80. The FDP is filled in a 10 mL clear colorless glass vial. The diluent, sterile Water for Injection (sWFI), is supplied in a single-use pre-filled glass vial in a 5 mL volume. BAXJECT II Hi-Flow (BAXJECT II HF) is supplied as a reconstitution device along with an (b) (4) Syringe and a (b) (4) Winged Infusion Set as administration devices. After reconstitution, ADZYNMA™ is administered by IV injection.

Abbreviations:

ADA	Anti-drug antibody
ADAMTS13	A disintegrin and metalloproteinase with thrombospondin motifs 13
AUC	Area under the concentration-time curve
AUC24	Area under the concentration-time curve from time 0 to 24 hours
AUC72	Area under the concentration-time curve from time 0 to 72 hours
AUC last	Area under the concentration-time curve from time 0 to time of the last quantifiable concentration
C max	Maximum observed concentration
CNS	Central nervous system
cTTP	Congenital thrombotic thrombocytopenic purpura
ERT	Enzyme replacement therapy
FFP	Fresh frozen plasma
GLP	Good Laboratory Practice
ICH	International Council of Harmonization
PK	Pharmacokinetic(s)
rADAMTS13	Recombinant a disintegrin and metalloproteinase with thrombospondin motifs 13
RCo	Ristocetin cofactor activity
rVWF	Recombinant von Willebrand factor
(b) (4)	
SOC	Standard of care
T _{1/2}	Half-life
Tmax	Time of first occurrence of Cmax
TTP	Thrombotic thrombocytopenic purpura
VWF	Von Willebrand factor

Related File(s)

IND#15219: Recombinant A Disintegrin and Metalloproteinase with Thrombospondin Type-1 Motifs 13 (rADAMTS13) for the treatment, prevention, and routine prophylaxis of acute episodes of thrombotic thrombocytopenic purpura (TPP) in patients with hereditary ADAMTS13 deficiency; Takeda Development Center Americas, Inc; Active

(b) (4)

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INTRODUCTION

Target Disease: Congenital thrombotic thrombocytopenic purpura (cTTP) is an ultra-rare, life-threatening thrombotic disorder of the microcirculation caused by a severe deficiency of ADAMTS13, a plasma zinc metalloprotease which binds to and cleaves newly released ultra-large forms of VWF in the A2 domain between Tyr1605 and Met1606. Homozygous or compound heterozygous mutations in the ADAMTS13 gene result in accumulation of ultra-large VWF multimers with high platelet binding activity, resulting in spontaneous formation of widespread VWF-platelet-rich microthrombi which cause ischemic damage to multiple organs. Severe disease is characterized by <10% normal ADAMTS13 plasma activity. Currently, there is no available treatment for cTTP. Standard of care (SoC) treatment consists of ADAMTS13 replacement through on-demand or regular prophylactic infusions of FDA-approved plasma-based therapies, including fresh frozen plasma (FFP), solvent/detergent-treated plasma (S/DTP), and Factor VIII -VWF concentrates.

ADZYNMA™ is expected to act as an ERT to replace endogenous mutated ADAMTS13, allowing the breakdown of VWF multimers into small VWF fragments, preventing the formation of microthrombi, and reducing the occurrence of acute and subacute TTP episodes and TTP clinical manifestations.

Product/Chemical Structure (description obtained from Module 2.4.): ADZYNMA™ is a rADAMTS13 generated by the expression of two rADAMTS13 protein moieties expressed in Chinese Hamster Ovary (CHO) cells. One protein species, apadamase alfa, contains the native ADAMTS13 sequence. The second protein species, cinaxadamase alfa, contains a single amino acid exchange at position 23 (Q [Glutamine] to R [Arginine]) to generate the variant protein. ADZYNMA™ restores ADAMTS13 plasma zinc metalloprotease activity to bind and site-specifically cleave newly released ultra-large forms of VWF in the A2 domain between Tyr1605 and Met1606 usually anchored on the endothelial surface, reducing VWF size and adhesiveness, thereby preventing microthrombi formation.

NONCLINICAL STUDIES

Reviewer's Notes:

- *During development, ADZYNMA™ has been referred to interchangeably as rADAMTS13, TAK-755, SHP655 or BAX 930. For each nonclinical study summarized in the memo, this reviewer refers to the product as BAX 930.*
- *When referring to the dose level units of ADZYNMA™, the applicant used FRETS-U/kg, U/kg, or IU/kg interchangeably in the BLA. For this memo, this reviewer has used "IU/kg" for the dose level units.*

PHARMACOLOGY STUDIES**Summary List of Pharmacology Studies**

The following pharmacology studies were conducted to support the rationale for the administration of ADZYNMA™ to treat the proposed clinical indication.

In Vitro Studies

Study Number	Study Title / Publication Citation	Report Number
1	Substrate suitability evaluation of human recombinant ADAMTS13 with von Willebrand factor from different animal species	ATS0007T01

In Vivo Studies

Study Number	Study Title / Publication Citation	Report Number
2	Efficacy of prophylactic administration of BAX 930 in the rVWF-induced TTP model in ADAMTS13 KO mice	WH0610
3	Efficacy of prophylactic administration over time of BAX 930 in the rVWF-induced TTP model in ADAMTS13 KO mice	WH0211
4	Efficacy of therapeutic administration of BAX 930 in the rVWF-induced TTP model in ADAMTS13 KO mice	WH0710
5	Therapeutic efficacy of different doses of BAX 930 after single intravenous administration in rVWF-challenged ADAMTS13 KO mice as a model for TTP	248.220.5098
6	Formation and resolution of pial microvascular thrombosis in a mouse model of thrombotic thrombocytopenic purpura; Arterioscler Thromb Vasc Biol, 39(9),1817-30	Adili and Holinstat, 2019
7	Absence of exaggerated pharmacology by recombinant ADAMTS13 in the rat and monkey; Blood coagulation & Fibrinolysis, 33(1), 56-60	Rossato et al., 2022

Reviewer's Notes:

- Study 5 was reviewed but not summarized in this memo because the control mice did not develop TTP and the results of platelet and LDH assessments were highly variable, making it difficult to interpret the data.
- Studies 6 and 7 were publications submitted by the applicant and are briefly summarized as Supporting Pharmacology Studies at the end of this Section.

Overview of Pharmacology Studies

Overview of In Vitro Studies

Study # 1

Substrate suitability evaluation of human recombinant ADAMTS13 with von Willebrand factor from different animal species (Non-GLP; Study Report # ATS0007T01; Baxter Innovations GmbH, Austria)

Objective: This study evaluated the ability of human rADAMTS13 to recognize and cleave VWF in the plasma of ADAMTS13 knock-out (KO) mice and healthy Sprague Dawley rats, (b) (4) guinea pigs, Cynomolgus monkeys and minipigs.

Methods:

Purified rADAMTS13 (1, 5, and 10 U/mL] diluted in (b) (4) was incubated with plasma from ADAMTS13 KO mice, Sprague Dawley rats, (b) (4) guinea pigs, cynomolgus monkeys, and minipigs at 37°C for 24 hours. Denaturing (b) (4) was used as a negative control. The reaction was stopped by addition of (b) (4), samples were (b) (4) and the resulting (b) (4) used to detect VWF cleavage (b) (4).

Results:

Human rADAMTS13 cleaved VWF from mouse, rat, guinea pig, monkey, and minipigs plasma. Based on the (b) (4) seen on the (b) (4), the extent of cleavage varied across the species indicating differences due to (b) (4).

Overview of In Vivo Studies

Reviewer's Notes:

- *The applicant utilized a murine model of TTP to evaluate activity and safety of ADZYNMA™. ADAMTS13 KO mice contain a genetic deletion of the ADAMTS13 which results in their inability to cleave high molecular weight VWF multimers. TTP is induced by administration of a high dose [2000 Ristocetin cofactor activity (RCo/U)] of recombinant human rVWF, containing ultra-large VWF multimers. rVWF administration in ADAMTS13 KO mice results in acute and rapid onset of the cTTP-like symptoms consisting of body weight loss, severe thrombocytopenia, increase in serum LDH, and thrombotic changes in the heart. Consequently, mice develop severe thrombocytopenia and thromboembolic changes in several organs, closely mimicking clinical symptoms observed in patients with cTTP.*
- *The applicant evaluated activity of ADZYNMA™ in this model by assessing its effect on clinical pathology and histopathology parameters including platelets, % hematocrit (HCT), hemoglobin (HGB), schistocytes, lactate dehydrogenase (LDH). Specifically, the*

applicant determined the degree of protection from TTP following prophylactic or therapeutic IV administration of ADZYNMA™ through evaluation of 1) decrease in platelet count and 2) increase in LDH, both of which represent clinical parameters of TTP. Additionally, histopathology of brain, heart, kidney, liver, lungs, and macroscopic lesions was assessed to determine microthrombi formation and signs of TTP-induced tissue damage.

- RCo/U is a standard unit for the VWF activity in the VWF ristocetin cofactor activity assay, which is a measure of VWF binding to platelets (ristocetin-induced platelet aggregation).

Study #2

Efficacy of prophylactic administration of BAX 930 in the rVWF-induced TTP model in ADAMTS13 KO mice (Non-GLP; Study Report # WH0610; Baxter Innovations GmbH, Austria)

Report Number		WH0610
Date Report Signed		03/09/2011
Title		Efficacy of prophylactic administration of BAX 930 in the rVWF-induced TTP model in ADAMTS13 KO mice
GLP Status		No
Testing Facility		Baxter Innovations GmbH, Austria
Objective		To evaluate the activity of multiple dose levels of prophylactically administered BAX 930 in ADAMTS13 KO mice.
Study Animals	Strain/Breed	ADAMTS13 KO mice (B6;129x1/Sv; ADAMTS13 ^{tm1Dgi})
	Species	Mice
	Age	13-18 weeks old
	Body Weight	19.5-36.1 grams
	#/sex/group	5/sex/group
Total #		93
Test Article		BAX 930 (Lot number: A13-930-10.023)
Control Articles		<ol style="list-style-type: none"> Buffer for BAX 930 (Lot number: B-A13-930-10.022) <ul style="list-style-type: none"> ➤ Reviewer's Note: Buffer for BAX 930 contains L-histidine (b) (4), calcium chloride (b) (4), mannitol (b) (4), sucrose (b) (4), polysorbate 80 (b) (4) pH of final buffer to be pH (b) (4). It is identical to the clinical buffer, therefore, the buffer for BAX 930 will be referred to as "clinical buffer" or "BAX 930 buffer" interchangeably in all studies unless specified otherwise. Octaplas <ul style="list-style-type: none"> ➤ Reviewer's Note: Octaplas is a fresh frozen human plasma product currently used to treat TTP. This was used as a comparator for ADZYNMA™.
Route of Administration		IV
Description of the Disease/Injury Model and Implant Procedure		VWF-induced TTP disease model <ul style="list-style-type: none"> Animals were prophylactically administered BAX 930 or Octaplas immediately followed by IV injection of 2000 RCo/U rVWF to induce TTP.

Study Groups and Dose Levels	Study Group	A	B	C	D	E	F
	Test/Control Article	BAX 930 Buffer	BAX 930	BAX 930	BAX 930	BAX 930	BAX 930
	BAX 930 (IU/kg)	-	1	5	40	80	200
	Study Group	G		H		I	
	Test/Control Article	Octaplas (1U/kg)		Octaplas (5U/kg)		Untreated control	
	BAX 930 (IU/kg)	-		-		-	
Dosing Regimen	Single administration at Day 0						
Randomization	Yes; Not specified						
Description of Masking	Not provided						
Scheduled Sacrifice Time Points	24 h post-administration of rVWF						

Key Evaluations and Assessments:

- Mortality/morbidity- daily
- Clinical observations- at sacrifice
- BWs- pre-dose and at sacrifice
- Clinical pathology- at sacrifice
- Histopathology

Key Results:

- No test article related adverse findings were observed.
- BAX 930 administration resulted in dose-dependent protection against rVWF-induced TTP.
- BAX 930 administration resulted in similar or better protection against TTP compared to Octaplas.
- The minimum effective dose level (MED) of prophylactic BAX 930 to protect against TTP-related heart damage was determined as 80 IU/kg. The MED of BAX 930 to protect against kidney damage could not be determined in this study as the mean severity grade for histopathological lesions were similar across Groups B-I.

Study #3

Efficacy of prophylactic administration over time of BAX 930 in the rVWF-induced TTP model in ADAMTS13 KO mice (Non-GLP; Study Report # WH0211; Baxter Innovations Gmbh, Austria)

Report Number		WH0211
Date Report Signed		07/01/2011
Title		Efficacy of prophylactic administration over time of BAX 930 in the rVWF-induced TTP model in ADAMTS13 KO mice
GLP Status		No
Testing Facility		Baxter Innovations Gmbh, Austria
Objective		To evaluate the duration of prophylactic activity of BAX 930 for up to 120 hours post administration.
Study Animals	Strain/Breed	ADAMTS13 KO mice
	Species	Mice
	Age	12-18 weeks
	Body Weight	19.5-38.0 grams
	#/sex/group	5/sex/group
	Total #	81
Test Article		BAX 930 (Lot number: A13-930-10.023)
Control Article		Clinical buffer (Lot number: (b) (4))
Route of Administration		IV
Description of the Disease/Injury Model and Implant Procedure		VWF-induced TTP disease model <ul style="list-style-type: none"> Animals were prophylactically administered 200 IU/kg BAX 930 followed by IV injection of 2000 RCo/U of rVWF to induce TTP at different time intervals (5 min -120 h) post-BAX 930 administration.

Study Groups and Dose Levels	Study Group	A	B	C	D
	Test/Control Article	BAX 930 Buffer	BAX 930	BAX 930	BAX 930
	BAX 930 (IU/kg)	-	200	200	200
	Time between BAX 930 and VWF administration (TTP induction)	5 min	5 min	3h	24h
	Study Group	E	F	G	H
	Test/Control Article	Untreated control	BAX 930	BAX 930	BAX 930
	BAX 930 (IU/kg)	-	200	200	200
	Time between BAX 930 and VWF administration (TTP induction)	-	48h	72h	120h
Dosing Regimen	Single administration at Day 0				
Randomization	Yes; Not specified				
Description of Masking	Not provided				
Scheduled Sacrifice Time Points	24 h post-administration of rVWF				

Key Evaluations and Assessments:

- Mortality/morbidity- daily
- Clinical observations- daily
- BWs- pre-dose and at sacrifice
- Clinical pathology- pre-dose and at sacrifice
- Histopathology

Key Results:

- No test article related adverse findings were observed.
- BAX 930 administration was protective up to 72 hours prior to rVWF-induced TTP.
 - The protective effect of BAX 930 was lower when administered at 120 h prior to TTP induction.
 - Histopathology analysis suggested that BAX 930 was protective against TTP induced organ damage in heart only if administered within 24 hours prior to rVWF.

Study #4

Efficacy of therapeutic administration of BAX 930 in the rVWF-induced TTP model in ADAMTS13 KO mice (Non-GLP; Study Report # WH0710; Baxter Innovations Gmbh, Austria)

Report Number	WH0710					
Date Report Signed	07/01/2011					
Title	Efficacy of therapeutic administration of BAX 930 in the rVWF-induced TTP model in ADAMTS13 KO mice					
GLP Status	No					
Testing Facility	Baxter Innovations Gmbh, Austria					
Objective	To evaluate the activity of therapeutically administered BAX 930 in ADAMTS13 KO mice, rVWF-induced TTP model.					
Study Animals	Strain/Breed	ADAMTS13 KO mice				
	Species	Mice				
	Age	16 weeks old				
	Body Weight	20.8-34.4 grams				
	#/sex/group	5/sex/group				
	Total #	50				
Test Article	BAX 930 (Lot number: A13-930-10.023)					
Control Article	Clinical buffer (Lot number: (b) (4))					
Route of Administration	IV					
Description of the Disease/Injury Model and Implant Procedure	VWF-induced TTP disease model <ul style="list-style-type: none"> Animals were therapeutically administered BAX 930 (15 min-180 min) after IV injection of 2000 RCo/U of rVWF to induce TTP. 					
Study Groups and Dose Levels	Study Group	A	B	C	D	E
	Test/Control Article	BAX 930 Buffer	BAX 930	BAX 930	BAX 930	-
	BAX 930 (IU/kg)	-	200	200	200	-
	Time between VWF-induced TTP and BAX 930 administration	15 min	15 min	30 min	180 min	-
Dosing Regimen	Single administration at Day 0					
Randomization	Yes; Not specified					
Description of Masking	Not provided					
Scheduled Sacrifice Time Points	24 h post-administration of BAX 930					

Key Evaluations and Assessments:

- Mortality/morbidity- daily
- Clinical observations- daily
- BWs- pre-dose and at sacrifice
- Clinical pathology- pre-dose and at sacrifice
- Histopathology

Key Results:

- No test article-related adverse findings were observed.
- BAX 930 administration resulted in protection when administered at 15, 30 and 180 minutes post-rVWF-induced TTP, which was the last timepoint evaluated. The activity of BAX 930 decreased with increasing time interval between induction of TTP and BAX 930 dosing.
- Histopathology data suggested that BAX 930 administration was protective against TTP-induced kidney damage but not for TTP-induced heart damage.

*Supporting Pharmacology Studies:***Study #6**

Adili and Holinstat, 2019: Formation and resolution of pial microvascular thrombosis in a mouse model of thrombotic thrombocytopenic purpura; Arterioscler Thromb Vasc Biol, 39(9),1817-30

This publication demonstrated that prophylactic treatment with BAX 930 prevented the onset of the VWF-mediated pial microvascular thrombosis, and therapeutic treatment with BAX 930 resolved pre-existing or growing thrombi in the brain of ADAMTS13 KO mice following rVWF challenge.

Study #7

Rossato et al., 2022: Absence of exaggerated pharmacology by recombinant ADAMTS13 in the rat and monkey; Blood coagulation & Fibrinolysis, 33(1), 56-60

This publication demonstrated that high-dose BAX 930 administration did not increase incidence of bleeding, either alone or in combination with anticoagulants enoxaparin or acetylsalicylic-acid (ASA) in a rat tail-tip bleeding model.

SAFETY PHARMACOLOGY STUDIES**Summary List of Safety Pharmacology Studies**

The following safety pharmacology study was conducted.

Study Number	Study Title / Publication Citation	Report Number
8	BAX 930 Escalating dose and pilot 4-week repeated dose intravenous administration toxicity study including pharmacokinetics in the cynomolgus monkey	8234215

Overview of Safety Pharmacology Studies**Study #8**

BAX 930 4-week intravenous administration toxicity study in the cynomolgus monkey, including cardiovascular investigations, with a two-week recovery phase (GLP; Study Report # 8234215; Covance Laboratories GmbH, Germany)

Report Number		8243420
Date Report Signed		12/19/2011
Title		BAX 930 4-week IV toxicity studying Cynomolgus monkey, including cardiovascular investigations, with a two-week recovery phase
GLP Status		Yes In compliance with Organization for Economic Co-operation and Development (OECD) principles of GLP
Testing Facility		(b) (4)
Objectives		1) To evaluate the potential toxicity of BAX 930 following repeat administration for 4 weeks in Cynomolgus monkeys and 2) to evaluate the potential reversibility of any findings following a 14-day recovery period.
Study Animals	Strain/Breed	Cynomolgus
	Species	Monkeys
	Age	4-5 years old
	Body Weight	3-7 kg
	#/sex/group	5/sex/group
	Total #	40
Test Article		BAX 930 (Lot number: A13-930-10.024)
Control Article		Clinical buffer (Lot number: (b) (4))
Route of Administration		IV
Description of the Disease/Injury Model and Implant Procedure		Healthy

Study Groups and Dose Levels	Study Group	Group description	Dose Level (IU/kg)	Number of animals
	1	Control	0	5(M), 5(F)
	2	Low	80	5(M), 5(F)
	3	Intermediate	200	5(M), 5(F)
	4	High	400	5(M), 5(F)
Dosing Regimen	Repeat administration - weekly for 5 doses (Days 1, 8, 15, 22, 29)			
Randomization	Yes; Not specified			
Description of Masking	Not provided			
Scheduled Sacrifice Time Points	Main group: Day 30 Recovery group: Day 42			

Key Evaluations and Assessments:

- Mortality and morbidity- daily
- Clinical observations- daily
- BWs- pre-dose and weekly
- Ophthalmology- pre-dose, Day 30 and Day 42
- Respiratory rate- pre-dose, Days 8, 15, 22, and 42
- Electrocardiography (ECG)- pre-dose, Days 8 and 22 and week 6
- Blood pressure- twice pre-dose, Days 8, 15, and 22, and 42
- Clinical pathology-
 - Hematology and coagulation- pre-dose, Days 2, 9, 30 and 42
 - Clinical chemistry and blood gas analysis- Days 30 and 42
 - Urinalysis- pre-dose, Day 30 and 42
- Organ weights, gross pathology, and histopathology- at necropsy
- TK (BAX 930 activity)- main group only pre-dose, Days 1 and 29
- ADA (binding and neutralizing antibodies)- pre-dose, Days 14, 32, and 42

Reviewer's Note:

- *Per the study report, there were multiple deviations in cardiovascular assessments (ECG, blood pressure) due to sedation related issues or invalid recording. Therefore, these results are not summarized below.*

Key Results:

- No test article related adverse findings were observed for survival, clinical observations or body weights.
- The study pathologist attributed the following findings to the development of neutralizing ADA:
 - Slight to severe hyperpigmentation and hemorrhage of macula were noted in 1/5 Group 4 female at the end of the recovery (Day 42).
 - Thrombopenia was observed in 3/5 Group 4 female animals and 1/5 Group 3 female animals. 1/5 in Group 4 females showed hemolytic anemia, a high decrease in platelet count, bilirubinemia and LDH enzyme release.
 - Histopathology showed signs of hematopoiesis in liver and heart and proteinaceous casts in the kidneys in 1/5 in Group 4 female.

Reviewer's Comment:

➤ *This reviewer agrees with the pathologist's conclusion.*

- BAX 930 administered animals consistently showed lower BAX 930 activity at Day 29 (0.048 h* (h*U/mL/U/ Kg)) compared to Day 1(0.450 h* (h*U/mL/U/ Kg)), which was more pronounced in the high dose females.
- BAX 930 administration resulted in the development of neutralizing ADA (1/4 in Group 2, 6/7 in group 3 and 8/10 in Group 4 animals).
- The NOAEL for this study was determined to be 80 IU/kg.

PHARMACOKINETIC STUDIES**Summary List of Pharmacokinetics Studies****In Vivo Studies**

Study Number	Study Title / Publication Citation	Report Number
9	BAX 930: Pharmacokinetics in ADAMTS13 KO mice	PV2521007
10	BAX 930: Pharmacokinetics in the rat	PV2531005
11	Pharmacokinetic study of recombinant ADAMTS13 in (b) (4) minipigs	WH0411
12	Pharmacokinetic study of recombinant ADAMTS13 in (b) (4) minipigs	WH0811

Reviewer's Notes:

- *The PK profile for BAX 930 was also evaluated in Cynomolgus monkeys in Study 8 and in SD rats in Study 19 which are reviewed under "Toxicology Studies" and "Developmental and Reproductive Toxicology Studies" respectively.*
- *Study 11 was a pilot study that followed IV or (b) (4) administration of BAX 930 (200 IU/kg, IV; 1000 IU/kg, (b) (4)) in (b) (4) pigs to evaluate the PK profile of ADAMTS13. The plasma level of rADAMTS13 did not decline during the duration of the study thus leading to inaccurate estimation of terminal half-life of ADAMTS13 and the dependent parameter*

such as AUC, yielding inconclusive results. Thus, a follow up Study 12 (WH0811) was conducted.

- Study 12 is considered supportive pharmacokinetic study and is briefly summarized at the end of this Section.
- In Module 4, Section 4.2.2.1 of the BLA, the applicant also provided validation reports for i) ELISA assays used for detection of ADAMTS13 in mouse, rat, and monkey plasma and for detection of IgG antibodies to ADAMTS13 in the nonclinical studies; ii) IU/kg VWF73 assay for determination of ADAMTS13 activity in animal plasma and iii) Bethesda method for determination of neutralizing anti-ADAMTS13 antibodies. The methods used were acceptable.

Overview of Pharmacokinetic Studies

Reviewer's Comments:

- The following key parameters were assessed in each nonclinical pharmacokinetic study (Studies # 9-10 and 12):
 - $AUC_{0-t_{last}}$ (area under the concentration time curve from the time of dosing through the time that the last sample with analytically quantifiable concentration was collected)
 - AUC_{0-inf} (area under the concentration- time curve from the time of dosing through infinity)
 - Terminal HL (terminal half-life, $T_{1/2}$)
 - C_{max} (maximum concentration in plasma)
- Given that these parameters were identical for all in vivo pharmacokinetic studies, they are collectively referred to as 'PK Profile' under the nonclinical studies, as applicable.

Study #9

BAX 930: Pharmacokinetics in ADAMTS13 KO mice (GLP; Study Report # PV2521007; Baxter Innovations GmbH, Austria)

Report Number		PV2521007
Date Report Signed		10/11/2011
Title		BAX 930: Pharmacokinetics in ADAMTS13 KO mice
GLP Status		Yes In compliance with Organization for Economic Co-operation and Development (OECD) principles of GLP
Testing Facility		Baxter Innovations GmbH, Austria
Objective		To evaluate PK profile of IV administered BAX 930 at 40, 80, and 200 IU/kg in ADAMTS13 KO mice.
Study Animals	Strain/Breed	ADAMTS13 KO (B6;129 ^{(b) (4)} ; ADAMTS13 ^{tm1Dgi})
	Species	Mice
	Age	8-12 weeks
	Body Weight	18.2-32.4 grams
	#/sex/group	45/sex/group

	Total #	285		
Test Article		BAX 930 (Lot number: A13-930-10.023)		
Control Article		Clinical buffer (Lot number: (b) (4))		
Route of Administration		IV		
Description of the Disease/Injury Model and Implant Procedure		ADAMTS13 KO mice		
Study Groups and Dose Levels		Study Group	Group description	Dose Level (IU/kg)
		A	BAX 930	40
		B	BAX 930	80
		C	BAX 930	200
Dosing Regimen		Single administration at Day 0		
Randomization		Yes; Not specified		
Description of Masking		Not provided		
Scheduled Sacrifice Time Points		5 min; 3h, 6h, 10h, 14h, 24h, 30h, 38h, and 42h post-administration.		

Key Evaluations and Assessments:

- PK profile

Key Results:

- Single IV administration of BAX 930 resulted in a dose dependent increase in C_{max} .
- The $T_{1/2}$ of BAX 930 in ADAMTS13 KO mice was calculated to be 10 to 17.3 hours (Table 2).

Table 2: PK parameters of IV dosed BAX 930 in ADAMTS13 KO mice

Study Group	BAX 930 (IU/kg)	AUC_{0-tlast} (h*U/mL / U/ Kg)	AUC_{0-inf} (h*U/mL / U/ Kg)	C_{max} (U/mL)	T_{1/2} (h)
A	40	0.09821	0.12036	0.478	10.0
B	80	0.12488	0.14377	1.025	15.9
C	200	0.10979	0.13074	2.440	17.3

Study #10

BAX 930: Pharmacokinetics in the rat (GLP; Study Report # PV2531005; Baxter Innovations GmbH, Austria)

Report Number		PV2531005	
Date Report Signed		11/09/2011	
Title		BAX 930: Pharmacokinetics in the rat	
GLP Status		Yes In compliance with Organization for Economic Co-operation and Development (OECD) principles of GLP	
Testing Facility		Baxter Innovations GmbH, Austria	
Objective		To evaluate PK profile of IV administered BAX 930 (80, 200 and 400 IU/kg) of in Sprague Dawley rats.	
Study Animals	Strain/Breed	Sprague Dawley	
	Species	Rats	
	Age	8-9 weeks old	
	Body Weight	237-4432 grams	
	#/sex/group	5/sex/group	
		Total #	
		34	
Test Article		BAX 930 (Lot number: A13-930-10.023)	
Control Article		Clinical buffer (Lot number: (b) (4))	
Route of Administration		IV	
Description of the Disease/Injury Model and Implant Procedure		Healthy	
Study Groups and Dose Levels		Study Group	Test article
		Dose Level (IU/kg)	
		A	BAX 930
		B	BAX 930
		C	BAX 930
Dosing Regimen		Single administration at Day 0	
Randomization		Yes; based on computer generated randomization list	
Description of Masking		Not provided	
Scheduled Sacrifice Time Points		5 min, 3h, 8h, 14h, 24h, 32h, 48h, 60h, 72h, and 80h post-administration	

Key Evaluations and Assessments:

- PK profile

Key Results:

- Single IV administration of BAX 930 resulted in a dose dependent increase in C_{max}.
- The T_{1/2} of BAX 930 in Sprague Dawley rats was calculated to be 16.7 to 25.6 hours (Table 3).

Table 3: PK parameters of IV dosed BAX 930 in healthy rats

Study Group	BAX 930 (IU/kg)	AUC _{0-tlast} (h*U/ mL / U/ Kg)	AUC _{0-inf} (h*U/ mL / U/ Kg)	C _{max} (U/mL)	T _{1/2} (h)
A	80	0.326	0.344	1.447	16.7
B	200	0.384	0.425	3.738	25.6
C	400	0.458	0.502	7.114	24.0

Supporting Pharmacokinetic Study:**Study #12**

Pharmacokinetic study of recombinant ADAMTS13 in (b) (4) Minipigs (non GLP; Study Report # WH0811; Baxter Innovations GmbH, Austria). This study followed IV or (b) (4) administration of rADAMTS13 (200 IU/Kg) in (b) (4) minipigs to evaluate its PK profile. Since the (b) (4) route is not the clinical ROA, the results from the (b) (4) ROA are not summarized here. Intravenous administration in minipigs demonstrated the median T_{max} (time to C_{max}) to be 5 min, indicating immediate bioavailability. The mean C_{max} for ADAMTS13 was 1.762 U/ml and T_{1/2} was 48.83 hours.

TOXICOLOGY STUDIES**Summary List of Toxicology Studies**

The following toxicology studies were conducted to evaluate the safety of ADZYNMA™ following administration in various animal species.

Toxicology Studies:

Study Number	Study Title / Publication Citation	Report Number
13	BAX 930 escalating dose and pilot 4-week repeated dose intravenous administration toxicity study including pharmacokinetics in the cynomolgus monkey	8234215
14	A 5-day toxicity study of BAX 930 by intravenous (bolus) injection in rats with a 2-week recovery period	527739
15	A 30-day toxicity study of SHP655 by intravenous administration in rats with a 2-week recovery period	504247
16	A 26-week toxicity study of BAX 930 by intravenous (bolus) injection in rats with a 4 week recovery period	523430
17	28-days repeated dose toxicity of BAX 930 after intravenous application with a two week recovery phase in rats	PV2511001
18	2-week intravenous toxicity study of BAX 930 in rabbits (feasibility study)	AU0112W01

Reviewer's Note:

- Studies 17 and 18 are briefly summarized as Supporting Safety Studies at the end of this Section.

Study #13

BAX 930 Escalating dose and pilot 4-week repeated dose intravenous administration toxicity study including pharmacokinetics in the cynomolgus monkey (GLP; Study Report # 8234215; (b) (4))

Report Number		8234215
Date Report Signed		12/01/2011
Title		BAX 930 Escalating dose and pilot 4-week repeated dose intravenous administration toxicity study including pharmacokinetics in the cynomolgus monkey
GLP Status		Yes In compliance with Organization for Economic Co-operation and Development (OECD) principles of GLP
Testing Facility		(b) (4)
Objective		To determine the PK profile, the NOAEL, and a suitable dose level for repeat IV administration of BAX 930 in Cynomolgus monkeys.
Study Animals	Strain/Breed	Cynomolgus
	Species	Monkeys
	Age	4-year-old
	Body Weight	3-6 kg
	#/sex/group	7/sex/group
	Total #	14
Test Article		BAX 930 (Lot number: A13-930-10.024)
Control Article		Clinical buffer (Lot number: (b) (4))
Route of Administration		IV
Description of the Disease/Injury Model and Implant Procedure		Healthy

Study Groups and Dose Levels	Dose escalation phase:				
	Study Group	Group description	Dose Level (IU/kg)	Study Day	Number of animals
	1	Test article, low	200	1	4(M), 4(F)
		Test article, high	1790	15	
	Repeat dose phase:				
	Study Group	Group description	Dose Level (IU/kg)	Study Day*	Number of animals
	1	Control article	0	24,31,38,45,52	1(M), 1(F)
	2	Test article	800	24,31,38,45,52	2(M), 2(F)
	Reviewer's Note:				
	➤ Due to the recording system used at the testing facility site (b) (4), the numbering of the days is misplaced. Therefore, the repeated dose phase starts with Day 1.				
Dosing Regimen	Single and repeat (shown above in ‘Study Groups and Dose Levels’)				
Randomization	Yes; Not specified				
Description of Masking	Not provided				
Scheduled Sacrifice Time Points	Dose escalation phase- Day 18 Repeat dose phase- Day 54				

Key Evaluations and Assessments:

- Mortality and morbidity- daily
- Clinical observations- daily
- BWs- pre-dose and weekly
- Clinical pathology
 - Dose escalation phase- pre-dose, Days 2, 14, 16, and 18
 - Repeat dose phase- pre-dose and Day 53
- Organ weights, gross pathology, and histopathology- at necropsy
- ADA-
 - Dose escalation phase- Days 14 and 18
 - Repeat dose phase- Day 54

Key Results:

- No test article related adverse findings were observed for survival, clinical observations or body weights.
- Thrombopenia, hemolytic anemia (increased reticulocyte), bilirubinemia, and generalized macroscopic skin hematoma were observed in Group 2 females. Histopathology data showed red foci in kidneys and stomach and hemorrhage in different organs. The study pathologist attributed these findings to the development of cross-reactive neutralizing ADA. ADAs were not detected in any other animals administered BAX 930 including male animals that received the same dose level of BAX 930.

Reviewer's Comment:

➤ *This reviewer agrees with pathologist's conclusion.*

- The NOAELs of BAX 930 for the dose escalation and repeat dose were determined to be 1790 IU/kg and 800 IU/kg, respectively.

Study #14

A 5 Day toxicity study of BAX 930 by intravenous (bolus) injection in rats with a 2 week recovery period (GLP; Study Report # 527739; (b) (4))

Report Number		527739
Date Report Signed		07/07/2015
Title		A 5 Day toxicity study of BAX 930 by intravenous (bolus) injection in rats with a 2 week recovery period
GLP Status		Yes In compliance with Organization for Economic Co-operation and Development (OECD) principles of GLP
Testing Facility		(b) (4)
Objectives		1) To determine the potential toxicity of repeat IV BAX 930 administration for 5 consecutive days in rats; 2) To evaluate the potential reversibility of any potential adverse findings over a two-week recovery period; and 3) To determine the toxicokinetic (TK) characteristics of BAX 930.
Study Animals	Strain/Breed	Sprague Dawley
	Species	Rat
	Age	7-8 weeks old
	Body Weight	Males (232-324 grams); females (159-256 grams)
	#/sex/group	Group 1: 18/sex/group Groups 2-4: 24/sex/group
	Total #	180
Test Article		BAX 930 (Lot number: VN930FDP12039)
Control Article		Clinical buffer (Lot number: (b) (4))
Route of Administration		IV
Description of the Disease/Injury Model and Implant Procedure		Healthy

Study Groups and Dose Levels	Study Group	Group description	Dose Level (IU/kg)
	1	Control	0
	2	BAX 930	80
	3	BAX 930	200
	4	BAX 930	400
Main group- Groups 1-4 (10/sex/group) Recovery group- Groups 1-4 (5/sex/group) TK group- Group 1 (3/sex/group), Groups 2-4 (9/sex/group)			
Dosing Regimen	Repeat- once daily for 5 days (Days 1-5)		
Randomization	Yes; based on body weight		
Description of Masking	Not provided		
Scheduled Sacrifice Time Points	Main group: Day 6 Recovery group: Day 20 TK group: Day 5 ➤ Reviewer's Note: Necropsy was not performed on animals in the TK subgroup.		

Key Evaluations and Assessments:

- Mortality and morbidity- daily
- Clinical observations- daily
- BWs- pre-dose and at sacrifice; daily (main group) and weekly (recovery group)
- Food consumption- pre-dose (weekly), daily (main group) and weekly (recovery group)
- Ophthalmic examination- pre-dose (all animals), Day 5 (Groups 1 and 4) and Day 20 (Groups 1 and 4)
- Clinical pathology-
 - Hematology and coagulation- Day 6 (main group) and Day 20 (recovery group)
 - Clinical chemistry- Day 6 (main group) and Day 20 (recovery group)
 - Urinalysis- Day 4 (main group) and Day 19 (recovery group)
- Organ weights, gross pathology and histopathology (main and recovery groups)
- TK- Days 1 and 5
- ADA- pre-dose and at sacrifice (recovery group)

Key Results:

- No test article related adverse findings or ADA development were observed.
 - One unscheduled death occurred in Group 3; per the study pathologist, this was not considered to be test article related.
- BAX 930 administration resulted in a dose dependent increase of C_0 (concentration at time zero) and $AUC_{(0-t)}$ at Day 1. Higher C_0 and $AUC_{(0-t)}$ at Day 5 compared to Day 1 suggested accumulation of BAX 930 during the dosing period.
- The NOAEL for this study was determined to be 400 IU/kg.

Study #15

A 30-day toxicity study of SHP655 by intravenous administration in rats with a 2 week recovery period (GLP; Study Report # 504247; (b) (4))

Report Number	504247		
Date Report Signed	08/14/2017		
Title	A 30-day toxicity study of SHP655 by intravenous administration in rats with a 2 week recovery period		
GLP Status	Yes In compliance with OECD principles of GLP		
Testing Facility	(b) (4)		
Objectives	1) To determine the potential toxicity of BAX 930 when given by IV administration for 30 days, 2) To evaluate the potential reversibility of any adverse findings following a 14-day recovery period; 3) To determine TK profile of BAX 930, and 4) To determine the development of binding and/or neutralizing ADAs.		
Study Animals	Strain/Breed	Sprague Dawley Crl:CD(SD)	
	Species	Rat	
	Age	8-9 weeks old	
	Body Weight	Males (270-337 grams); females (197-254 grams)	
	#/sex/group	Group 1: 18/sex/group Group 2-3: 21/sex/group	
	Total #	120	
Test Article	BAX 930 (Lot number: VNM5R002PR)		
Control Article	Clinical buffer (Lot number: not provided)		
Route of Administration	IV		
Description of the Disease/Injury Model and Implant Procedure	Healthy		
Study Groups and Dose Levels	Study Group	Group description	Dose Level (IU/kg)
	1	Control	0
	2	BAX 930	800
	3	BAX 930	1820
	Main groups- Group 1-3: 10/sex/group Recovery groups- Group 1-3: 5/sex/group TK groups- Group 1:3/sex/group and Groups 2-3: 6/sex/group		
Dosing Regimen	Repeat- once daily for 30 days (Days 1 to 30)		
Randomization	Yes; based on body weight		
Description of Masking	Not provided		
Scheduled Sacrifice Time Points	Main group: Day 31 Recovery group: Day 44 TK group: Day 30 ➤ <i>Reviewer's Note: Necropsy was not performed on animals in the TK subgroup.</i>		

Key Evaluations and Assessments:

- Mortality and morbidity- daily
- Clinical observations- daily during pre-dose, dosing and recovery
- BWs- pre-dose and recovery period (weekly), dosing period (daily)
- Food consumptions- weekly
- Ophthalmic examination- pre-dose and week 2 of recovery period for all animals and week 4 of dosing period for Groups 1 and 3
- Clinical pathology-
 - Hematology, coagulation and clinical chemistry- pre-dose, Days 29 and 42
 - Urinalysis- Days 28 and 41
- Organ weights, gross pathology, and histopathology (main and recovery groups)
- TK- Days 1 and 30
- ADA- pre-dose and Day 33

Key Results:

- No test article related adverse findings were observed.
 - Two animals in Group 3 developed a mass in the ventral cervical area and black discharge from the left eye on Day 8 and 10 respectively; one animal from Group 2 had a slight atrophy of the right retina/choroid on Day 42. Per the study director, these were not considered test article related.
- BAX 930 administration resulted in increased C_{max} (1.838-fold), and increased $AUC_{0-24\text{hours}}$ (1.740-fold) at Day 30 as compared to Day 1 indicating accumulation of BAX 930 during the dosing period.
- Few BAX 930 administered animals (1/10 animals in Group 2 and 3/10 animals in Group 3) developed neutralizing ADA.
- The NOAEL for this study was determined to be 1820 IU/kg/day.

Study #16

A 26 week toxicity study of BAX 930 by intravenous (bolus) injection in rats with a 4 week recovery period (GLP; Study Report # 523430; (b) (4))

Report Number		523430
Date Report Signed		12/30/2013
Title		A 26 week toxicity study of BAX 930 by intravenous (bolus) injection in rats with a 4 week recovery period
GLP Status		Yes In compliance with Organization for Economic Co-operation and Development (OECD) principles of GLP
Testing Facility		(b) (4)
Objectives		1) To determine the potential toxicity of repeat IV administration of BAX 930 every 3 days for 26 weeks in rats; 2) To determine recovery from any potential adverse findings following a 4-week recovery period; 3) To determine TK characteristics of BAX 930, and 4) To evaluate the development of binding and/or neutralizing ADA.
Study Animals	Strain/Breed	Sprague Dawley
	Species	Rats
	Age	7-8 weeks old
	Body Weight	Males (239-325 grams); females (158-243 grams)

	#/sex/group	Group 1: 28/sex/group Groups 2-4: 31/sex/group		
	Total #	242		
Test Article		BAX 930 (Lot number: VNM5M001A and VN930FDP12038)		
Control Article		Clinical buffer (Lot number: (b) (4))		
Route of Administration		IV		
Description of the Disease/Injury Model and Implant Procedure		Healthy		
Study Groups and Dose Levels		Study Group	Group description	Dose Level (IU/kg)
		1	Control	0
		2	BAX 930	80
		3	BAX 930	200
		4	BAX 930	400
		Main groups- Group 1-4: 15/sex/group Recovery groups- Group 1-4: 5/sex/group TK groups- Group 1:3/sex/group and Groups 2-3: 6/sex/group		
Dosing Regimen		Repeat- once every 3 days over a period of 26 weeks (61 total administrations)		
Randomization		Yes; based on computer-based randomization list		
Description of Masking		Not provided		
Scheduled Sacrifice Time Points		Main group: Day 184 Recovery group: Day 211		

Key Evaluations and Assessments:

- Mortality and morbidity- daily
- Clinical observations- daily
- BWs- twice weekly during pre-dose and recovery and each day of BAX 930 administration
- Food consumption- pre-dose and weekly
- Ophthalmic examination- pre-dose and Day 91, 182 and 210 for Groups 1 and 4
- Clinical pathology-
 - Hematology, coagulation and clinical chemistry- Day 91, 182 and 210 and at sacrifice
 - Urinalysis- Day 91, 182 and 210
- Sperm evaluation (motility and morphology)- Days 184 and 211
- Organ weights, gross pathology, and histopathology (Groups 1 and 4 main and recovery)- Days 184 and 211
- TK- Days 1, 91 and 181
- ADA- pre-dose, Day 91, 182 and 210

Key Results:

- No test article related adverse findings were observed. However, several unscheduled deaths were reported (2/62 in Group 4 and 1/62 rats in Groups 2 and 3 each); per the study director, these were not considered test article related.
- BAX 930 administration resulted in dose-dependent increases in C_{\max} and $AUC_{0-72\text{hours}}$ at Day 1. Increased C_{\max} and $AUC_{0-72\text{hours}}$ at Days 91 and 181 compared to Day 1 suggested accumulation of BAX 930 during the dosing period.
- Few BAX 930 administered animals (2/10 in Group 4 and 1/10 in Group 3) developed binding ADAs but not neutralizing ADAs.
- The NOAEL for this study was determined to be 400 IU/kg once every 3 days for 61 administrations.

*Supporting Safety Studies:***Study #17****28-days Repeated dose toxicity of BAX 930 after intravenous application with a two-week recovery phase in rats** (GLP; Study Report # PV2511001; Baxter Innovations GmbH, Austria)

This study evaluated 28-day-repeat IV administration (once every 3 days for 10 doses) of BAX 930 (80, 400 or 800 IU/kg) in Sprague Dawley rats with a two-week recovery phase to assess the safety of BAX 930. The results showed no test article related adverse findings. BAX 930 administration resulted in dose-dependent increase of C_{\max} and $AUC_{0-72\text{hours}}$ at Day 1. The results were similar at Day 28 suggesting no accumulation of BAX 930 with 3 days dosing intervals for the duration of the dosing period. Few BAX 930 dosed animals from all three dose levels developed binding and neutralizing ADA. The NOAEL for this study was determined to be 800 IU/kg once every 3 days for 10 administrations.

Study #18**2-Week intravenous toxicity study of BAX 930 in rabbits** (Feasibility Study) (non GLP; Study Report # AU0112W01; Baxter Innovations GmbH, Austria)

This study evaluated repeat IV BAX 930 administration (80, 400 or 800 IU/kg) in (b) (4) rabbits to determine the suitability of the species for safety evaluation. However, the results showed lack of BAX 930 activity and adverse findings related to clinical pathology and histology of the heart due to the development of cross-reactive ADA. Therefore, rabbits were not considered a suitable species for safety evaluation for ADZYNMA™. This reviewer agrees with the applicant's position based on the review of the data.

Developmental and Reproductive Toxicology Studies:

Study Number	Study Title / Publication Citation	Report Number
19	BAX 930: A reproductive toxicity and placental transfer feasibility study in rats	495388
20	A female fertility and embryo-fetal development study of BAX 930 by intravenous (bolus) injection in rats	497081
21	A pre and post-natal study of BAX 930 by intravenous administration in rats	496821

Study #19

BAX 930: A reproductive toxicity and placental transfer feasibility study in rats (non GLP; Study Report # 495388; (b) (4))

Report Number		495388	
Date Report Signed		01/18/2011	
Title		BAX 930: A reproductive toxicity and placental transfer feasibility study in rats	
GLP Status		No	
Testing Facility		(b) (4)	
Objective		To evaluate the placental transfer of BAX 930 following a single IV administration on Day 21 of gestation in Sprague Dawley rats.	
Study Animals	Strain/Breed	Sprague Dawley	
	Species	Rat	
	Age	~ 9 weeks old	
	Body Weight	Females (205-255 grams)	
	#/sex/group	6 females/group	
		Total #	12
Test Article		BAX 930 (Lot number: ORAM 09002#07)	
Control Article		Clinical buffer (Lot number: (b) (4))	
Route of Administration		IV	
Description of the Disease/Injury Model and Implant Procedure		Healthy pregnant rats	
Study Groups and Dose Levels		Study Group	Treatment (IU/kg)
		1	Control, 0
		2	BAX 930, 3200
Dosing Regimen		Single administration at gestation Day 21	
Randomization		Yes; Not specified	
Description of Masking		Not provided	
Scheduled Sacrifice Time Points		30 min post administration	

Key Evaluations and Assessments:

- Mortality and morbidity- daily
- Clinical observations- daily
- BWs- Days 4, 6-18, 20 and 21
- BAX 930 levels in maternal and fetal serum- Day 21

Key Results:

- No test article related adverse findings were observed.
- Single IV administration of 3200 IU/kg BAX 930 to pregnant Sprague-Dawley rats resulted in incomplete placental transfer.
 - 0.6% of ADAMTS13 detected in maternal serum (19.62 µg/ml to 37.09 µg/ml) was detected in fetal serum (0.01 µg/ml to 0.12 µg/ml) on Day 21 of gestation IU/kg.

Reviewer's Comment:

- Per the applicant, the poor placental transfer of ADAMTS13 was due to the high MW of ADAMTS13 (176 kD) and is within the range of what has been reported for placental transfer studies with other similar products with molecular weights (MW) > 0.5 kD. This reviewer agrees with the applicant's conclusion.

Study #20

Female fertility and embryo-fetal development study of BAX 930 by intravenous (Bolus) injection in rats (GLP; Study Report # 497081; (b) (4))

Report Number		497081		
Date Report Signed		4/22/2015		
Title		Female fertility and embryo-fetal development study of BAX 930 by intravenous (bolus) injection in rats		
GLP Status		Yes In compliance with OECD principles of GLP		
Testing Facility		(b) (4)		
Objective(s)		To determine the effects of the BAX 930 on female fertility and pregnancy following IV administration to females for 2 weeks prior to mating, throughout mating, and up to gestation day 16.		
Study Animals	Strain/Breed	Sprague Dawley		
	Species	Rat		
	Age	6-7 weeks old		
	Body Weight	Males (201-245 grams); females (125-169 grams)		
	#/sex/group	20/sex/group		
Total #		124		
Test Article		BAX 930 (Lot number: VNM5M001A and VN930FDP12039)		
Control Article		Clinical buffer (Lot number: (b) (4))		
Route of Administration		IV		
Description of the Disease/Injury Model and Implant Procedure		Healthy		
Study Groups and Dose Levels		Study Group	Test Item	Dose Level (IU/kg)
		1	Control	0
		2	BAX 930	80
		3	BAX 930	200
		4	BAX 930	400
		N=20 for all groups		
Dosing Regimen		Repeat- once every 3 days for two weeks		
Randomization		Yes; Not specified		
Description of Masking		Not provided		
Scheduled Sacrifice Time Points		Day 20 of gestation		

Key Evaluations and Assessments:

- Mortality and morbidity- daily
- Clinical observations- weekly
- BWs- daily
- Food consumption- pre-dose, weekly during pre-mating, daily post-mating
- Oestrous cycles- daily for 2 weeks prior to mating
- Clinical pathology (hematology and LDH only)- at sacrifice
- Pregnancy performance assessments- at sacrifice
 - Gravid uterus weights
 - Ovarian/uterine examinations
 - Corpora lutea
 - Total implantation sites
 - Early and late embryonic deaths
 - Live and dead fetuses
- Embryo-fetal development- at sacrifice
 - BWs
 - Sex
 - Visceral examination
 - Skeletal examination
- TK- Days 22, 31/34 (**Note:** Per the study report, animals were assessed either on Day 31 or 34)
- ADA- pre-dose and at sacrifice

Key Results:

- No test article related adverse findings were observed with mating performance, fertility, estrous cycles, pregnancy performance, corpora lutea graviditatis, total implant sites, liver implants, uterus weights, and mean fetal weights in any study groups.
- No fetal or embryonic abnormalities were observed.
- BAX 930 administration resulted in dose-dependent increase in AUC_{0-t} at Day 22 and Day 31/34.
- Group mean platelet levels were 17%, 13%, and 30% higher (Group 2, 3 and 4 respectively) compared to Group 1 at the end of the study. Additionally, mean LDH was 12% lower in Group 4 compared to Group 1.
- The NOAEL for this study was determined to be 400 IU/kg/dose.

Study #21

A pre and post natal study of BAX 930 by intravenous administration in rats (GLP; Study Report # 496821; (b) (4))

Report Number	496821
Date Report Signed	06/30/2015
Title	A pre and post natal study of BAX 930 by intravenous administration in Rats
GLP Status	Yes In compliance with OECD principles of GLP
Testing Facility	(b) (4)

Objective		To detect any effects of IV ADAMTS13 administration on the implantation/pregnancy/parturient/lactation of F0 dams and the development of the conceptus and offspring to sexual maturity.		
Study Animals	Strain/Breed	Sprague Dawley		
	Species	Rat		
	Age	9-10 weeks old		
	Body Weight	Males (not specified); females (210-360 grams)		
	#/sex/group	Not specified		
	Total #	≥144 Males (n ≥48 and no more than 2 females were mated by any one male) and 96 females		
Test Article		BAX 930 (Lot number: VN930FDP12038)		
Control Article		Clinical buffer (Lot number: (b) (4))		
Route of Administration		IV		
Description of the Disease/Injury Model and Implant Procedure		Healthy		
Study Groups and Dose Levels		<u>F0 dams</u>		
		Study Group	BAX 930 Dose Level (IU/kg)	Animal Numbers
		1	0	1-24
		2	80	25-48
		3	200	49-72
		4	400	73-96
		<u>F1 generation</u>		
		Study Group	F1 Male Numbers	F1 Female Numbers
		1	101-124	201-224
		2	125-148	225-248
		3	149-172	249-272
		4	173-196	273-296
		When F1 was sexually matured, they were mated to generate F2 offspring.		
Dosing Regimen		F0 dams: Day 6 of gestation followed by repeat dosing once every 3 days for two weeks		
Randomization		Yes; Not specified		
Description of Masking		Not provided		
Scheduled Sacrifice Time Points		F0 dams- post weaning of litters (Day 21 of lactation) F1 and F2 offspring- after litters reach Day 14 of lactation		

Key Evaluations and Assessments:

- Mortality and morbidity- daily
- Clinical observations- pre-dose and weekly
- BWs-
 - F0 dams- pre-dose and daily
 - F1- weekly
- Food consumption- daily
- Reproductive indices (fertility, gestation, birth, live birth, viability, lactation and overall survival)
- F1 Post-natal assessments-
 - Physical maturation- Day 1 (Pinna detachment), Day 7 (Upper incisor eruption), and Day 11 (Eye opening)
 - Sensory function assessments- Day 11 (Negative geotaxis), Day 16 (Auditory function), and Day 18 (Visual function)
 - Selection and weaning- Day 2
 - Sexual maturation- Day 28 (females), Day 35 (males)
 - Post weaning functional development- Day 35 (Rota-rod test), Day 40 (Multiple Y water maze test), and Day 42 (Open field test)
 - Reproduction (fertility index)
- Clinical pathology- F0 dams (hematology and LDH)- at sacrifice
- ADA-
 - F0 dams- pre-dose, prior to 5th dose and at sacrifice
 - F1- at sacrifice
- TK-
 - F0 dams- at 1st, 5th, and final BAX 930 administrations

Key Results:

- F0 dams- No test article-related adverse findings were observed for any study parameters.
- F1- No test article-related adverse findings were observed except two deaths in animals which were not test article-related.
- No ADAs were detected in the F0 generation.
- The maternal and reproductive NOAELs were determined to be 400 IU/kg, the highest dose level evaluated in the study.

Genotoxicity Studies: No genotoxicity studies were conducted with BAX 930.

Carcinogenicity/Tumorigenicity Studies: No carcinogenicity studies were conducted with BAX 930.

Other Safety/Toxicology Studies

Study Number	Study Title / Publication Citation	Report Number
22	Investigation of local tolerance of BAX 930 in rabbits	PV2541101
23	A single-dose irritation study of TAK-755 by subcutaneous injection in rabbits	L11910M-SHP655

Reviewer's Note:

- Study 23 followed SC administration of BAX 930 (300 IU/Kg) in (b) (4) rabbits to evaluate potential irritation. Since the SC route is not the clinical ROA, this study has been reviewed but is not summarized in this memo.

Study #22

Investigation of local tolerance of BAX 930 in rabbits (GLP; Study Report # PV2541101; Baxter AG, Austria)

- This study followed a single BAX 930 administration via multiple ROAs (IV, IA and periventricular [PV]) in (b) (4) rabbits to determine the local tolerance/irritation. Injection volumes for IV and IA was 5 ml and PV was 0.5 ml. All animals survived until scheduled sacrifice timepoints and there were no test article related adverse findings observed for any study parameters during macroscopic and microscopic examinations. This study was not considered a pivotal study to inform the safety of BAX 930 since the safety of IV BAX 930 administration was demonstrated in rats and monkeys and rabbit was determined an unsuitable species for BAX 930 toxicology assessments.

APPLICANT'S PROPOSED LABEL

Section 8 ('Use in Specific Populations') complies with 21 CFR 201.56(d)(1), 201.57(c)(9) and 201.57(c)(14); minor edits will be recommended.

Section 13.1 ('Carcinogenesis, Mutagenesis, Impairment of Fertility') is generally acceptable, but edits to make the statements more concise will be recommended.

Information from the nonclinical toxicology studies that are not necessary to inform clinical use of the product in Section 13.2 ('Animal Toxicology and/or Pharmacology') will be recommended for deletion.

CONCLUSION OF NONCLINICAL STUDIES

Review of the nonclinical studies did not identify any safety concerns that could not be addressed in the product label. The nonclinical data support approval of the license application.

KEY WORDS

ADAMTS13, TAK-755, BAX 930, mice, rats, monkeys, cTTP, pharmacokinetic, toxicity, intravenous, immunogenicity, pharmacology, ADA, SHP655, clinical pathology