5.02 APADAMTASE ALFA with CINAXADAMTASE ALFA [recombinant ADAMTS13], Powder for injection 500 I.U. with solvent, Powder for injection 1500 I.U. with solvent, Adzynma®, TAKEDA PHARMACEUTICALS AUSTRALIA PTY. LTD.

1 Purpose of submission

1.1 The Category 1 submission requested a Section 100 (Highly Specialised Drugs [HSD] Program, Public, Private hospitals and Community Access, Authority Required (Telephone/Online), listing for apadamtase alfa/cinaxadamtase alfa (recombinant ADAMTS13, herein described as rADAMTS13) enzyme replacement therapy (ERT) as a prophylactic treatment for patients with chronic, severe congenital thrombotic thrombocytopenia purpura (cTTP) who are intolerant or hypersensitive to prophylaxis with fresh frozen plasma (FFP). Listing was requested on the basis of a cost-effectiveness analysis versus on-demand FFP.

1.2 Table 1 presents the key components of the clinical issue addressed by the submission.

Table 1: **Key components of the clinical issue addressed by the submission (as stated in the submission)**

Component	Description
Population	cTTP patients who are intolerant or hypersensitive to FFP
Intervention	Prophylactic administration of rADAMTS13 40 IU/kg Q1W or Q2W
Comparator	On-demand FFP
Outcomes	TTP events, TTP manifestations, elevated LDH level, increased creatine levels, neurologic symptoms and abdominal pain.
Clinical claim	In cTTP patients who are intolerant to FFP prophylaxis, Recombinant ADAMTS13 is more effective than on-demand FFP at reducing acute TTP events.

Source: Table 1, p29 of the submission.
cTTP= congenital thrombotic thrombocytopenic purpura; FFP= fresh frozen plasma; IU= international units; LDH= lactate dehydrogenase; Q1W= once weekly; Q2W= fortnightly; TTP= thrombotic thrombocytopenic purpura.

1.3 The pre-PBAC response clarified that the submission had requested PBS listing for a limited group of cTTP patients, which the sponsor considered had a very high clinical need due to lack of alternative prophylactic options due to being unable to receive regular FFP. However, the pre-PBAC response acknowledged that, as proposed by ESC, PBAC consideration of rADAMTS13 for PBS listing in a broader population consistent with the TGA indications for rADAMTS13 would be clinically appropriate. The broader PBS listing would allow PBS prescribing of rADAMTS13 for the treatment of patients with chronic, severe cTTP for use as: 1) prophylactic enzyme replacement therapy and 2) on-demand enzyme replacement therapy.

2 Background

Registration status

2.1 rADAMTS13 was TGA registered on 8 January 2026 for treatment of ADAMTS13 deficiency in adults and children with cTTP. It can be administered either prophylactically (40 IU/kg body weight once every other week, or adjusted to 40 IU/kg once per week if required), or on-demand in the event of an acute TTP episode (with daily dosing as described in the TGA-approved PI of 40 IU/kg body weight on day 1, 20 IU/kg body weight on day 2, and 15 IU/kg body weight starting on day 3 once daily until two days after the acute event is resolved).

2.2 The requested PBS listing was narrower than the TGA indication: the submission proposed prophylactic use of rADAMTS13 in cTTP patients who are intolerant to or otherwise unsuitable for sustained FFP prophylaxis.

Medical Services Advisory Committee (MSAC)

2.3 The submission noted that a relevant application was to be considered by the Medical Services Advisory Committee (MSAC) at the April 2026 MSAC meeting (Application 1796[1]). This application was lodged by The Royal College of Pathologists of Australasia, and was titled "ADAMTS13 testing for the diagnosis of thrombotic thrombocytopenic purpura (TTP)".

For more detail on PBAC's view, see section 7 PBAC outcome.

[1] https://www.msac.gov.au/applications/1796

3 Requested listing

3.1 The requested listing and PBS restriction is presented below.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
APADAMTASE ALFA					
Apadamtase alfa, Powder for injection vial and solvent vial, 500IU	Effective Public: $[redacted] Effective Private & Community: $[redacted] Published Public: $54,120.00 Published Private & Community: $54,168.88	24	1	5	Adzynma
Apadamtase alfa, Powder for injection vial and solvent vial, 1500IU	Effective Public: $[redacted] Effective Private & Community: $[redacted] Published Public: $54,120.00 Published Private & Community: $54,168.88	8	1	5	Adzynma

Source: Table 7, p45 of the submission.

Category / Program: Section 100- Highly specialised drugs Program (Community Access)
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐
Restriction type: Authority Required (telephone/online PBS Authorities system)
Severity: Severe
Condition: Chronic, congenital thrombotic thrombocytopenic purpura (cTTP)
Indication:
Treatment Phase: Prophylactic PBS subsidised initial treatment or continued treatment
Clinical criteria:
Patient must have a diagnosis of cTTP, confirmed by appropriate testing and ADAMTS 13 activity <10%.
AND
Clinical criteria:
Patient must have experienced an intolerance to FFP or otherwise unsuitable for sustained FFP prophylaxis (e.g., due to hypersensitivity/allergic reactions, volume intolerance/overload, plasma related safety concerns, or practical/logistical barriers to frequent hospital infusions) for cTTP.
AND
Clinical criteria:
Patients ≥16 years of age must have had a Karnofsky score ≥70% and patients <16 years of age must have had a Lansky score ≥80% at the date of apadamtase initiation.
AND
Clinical criteria:
The treatment must not be used in patients with any other TTP like disorder (Micro Angiopathic Hemolytic Anemia-MAHA), including acquired or immune mediated TTP.
Treatment criteria:
Must be treated by a medical specialist, experienced in the management of haematological disorders, OR Must be treated by a medical practitioner, in consultation with a medical specialist experienced in the management of haematological disorders
Population criteria:
Not provided in the submission.
Prescribing Instructions: At the time of the authority application, prescribers should request the appropriate number of vials and number of repeats for a single dose based on the patient's weight, as per the Product Information
Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Increased maximum amounts can be requested where a patient's weight is greater than 67 kg.
Administrative Advice: Special Pricing Arrangements apply.

Category / Program: Section 100- Highly specialised drugs Program (Community Access)
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐
Restriction type: Authority Required (telephone/online PBS Authorities system)
Severity: Severe
Condition: Chronic, congenital thrombotic thrombocytopenic purpura (cTTP)
Treatment Phase: Transitioning from non-PBS to PBS subsidised treatment
Clinical criteria:
Patient must have received non- PBS treatment with this drug for this condition prior to (date of PBS listing).
AND
Clinical criteria:
Patient must have a diagnosis of cTTP, confirmed by appropriate testing.
AND
Clinical criteria:
Patient must have experienced an intolerance to FFP or otherwise unsuitable for sustained FFP prophylaxis (e.g., due to hypersensitivity/allergic reactions, volume intolerance/overload, plasma related safety concerns, or practical/logistical barriers to frequent hospital infusions) for cTTP.
AND
Clinical criteria:
Patients ≥16 years of age must have had a Karnofsky score ≥70% and patients <16 years of age must have had a Lansky score ≥80% at the date of apadamtase initiation.
AND
Clinical criteria:
The treatment must not be used in patients with any other TTP like disorder (Micro Angiopathic Hemolytic Anemia-MAHA), including acquired or immune mediated TTP.
Treatment criteria:
Must be treated by a medical specialist, experienced in the management of haematological disorders, OR Must be treated by a medical practitioner, in consultation with a medical specialist experienced in the management of haematological disorders
Population criteria:
Not provided in the submission.
Prescribing Instructions: At the time of the authority application, prescribers should request the appropriate number of vials and number of repeats for a single dose based on the patient's weight, as per the Product Information
Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Increased maximum amounts can be requested where a patient's weight is greater than 67 kg.
Administrative Advice: Special Pricing Arrangements apply.

3.2 The evaluation raised the following key issues in relation to the restriction:

- The submission proposed a general definition of the population as follows: "Patient must have experienced an intolerance to FFP or otherwise unsuitable for sustained FFP prophylaxis (e.g., due to hypersensitivity/allergic reactions, volume intolerance/overload, plasma-related safety concerns, or practical/logistical barriers to frequent hospital infusions) for cTTP". The criteria as written may result in a higher proportion of patients being considered eligible than intended.
- The submission did not propose continuation criteria but stated that continuation criteria could potentially include "treatment must demonstrate clinical benefit as determined by the discretion of the treating physician".

3.3 The ESC considered that it was not reasonable to limit rADAMTS13 to patients with cTTP who are intolerant, hypersensitive or practically/logistically unable to receive regular FFP given efficacy in the broader population (as demonstrated in Study 281102). The ESC considered that the restriction should be aligned with the TGA indication and that it should also allow for use of rADAMTS13 as on-demand treatment for patients who experience an acute event, irrespective of whether they have been treated with rADAMTS13 prophylactically. The ESC considered that this broader listing would address equity and potential leakage issues and align with the evidence.

3.4 The ESC agreed with the initial changes to the submission's requested restriction proposed by the Secretariat, including specifying that a diagnosis of severe hereditary ADAMTS13 deficiency must be confirmed by all of the following: (i) the presence of ADAMTS 13 genetic variants, (ii) the absence of ADAMTS 13 autoantibodies and (iii) ADAMTS 13 activity of less than 10%.

3.5 The requested effective ex-manufacturer price for rADAMTS13 was $[redacted] for either 500 IU x 24 vials or 1500 IU x 8 vials, corresponding to an AEMP of $[redacted] per 500 IU vial and $[redacted] per 1500 IU vial. As described in the pre-PBAC response, these prices would apply for PBS listings of rADAMTS13 for the treatment of patients with chronic, severe cTTP for use as prophylactic enzyme replacement therapy and on-demand enzyme replacement therapy consistent with the TGA-approved product information.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 cTTP (or Upshaw–Schulman syndrome or hereditary TTP) is a rare and life-threatening blood disorder. It is characterised by systemic blood clotting in small blood vessels and low platelets causing purpura (purple spots on skin). It is caused by biallelic recessive variants (genetic mutations) in the *ADAMTS13* gene, which lead to a severe deficiency of the ADAMTS13 enzyme.[2] In the absence of sufficient ADAMTS13 activity, typically

[2] Levy GG, Nichols WC, Lian EC, et al. Mutations in a member of the ADAMTS gene family cause thrombotic thrombocytopenic purpura. *Nature.* 2001;413(6855):488–94.

< 10% of normal levels, von Willebrand factor multimers accumulate and spontaneously trap flowing platelets, resulting in widespread microvascular thrombosis (clotting). The defining features of cTTP include microangiopathic haemolytic anaemia (MAHA), characterised by the mechanical destruction of red blood cells in small blood vessels, and severe thrombocytopenia (platelet count <30 x 10^9/L) caused by the consumption of platelets within clots. MAHA is characterised by low haemoglobin (median haemoglobin levels of 80–100 g/L), low haematocrit, increased lactate dehydrogenase (LDH), and the presence of fragmented red blood cells, among other signs.[3] Diagnosis of cTTP includes (i) ADAMTS13 activity <10 IU/dL, (ii) no anti-ADAMTS13 autoantibodies, and (iii) confirmatory variants in the *ADAMTS13* gene.[4]

4.2 While the occurrence of thrombocytopenia, MAHA and neurologic symptoms may begin early in childhood, in some cases, clinical diagnosis is not made until adulthood[3]. Over 60% of adults have neuropsychiatric symptoms like headaches, poor concentration and depression. Adults may rarely present with myocardial infarction, and 2% to 10% may have kidney failure.[4] Pregnancy is the most frequent trigger for adult-onset presentations in patients who have previously been asymptomatic. Acute episodes can cause symptoms and organ damage due to the widespread formation of small blood clots throughout the body. This microvascular thrombosis may result in permanent organ damage or death if untreated; neurological and renal complications are major concerns.

4.3 Untreated, cTTP has a high mortality due to acute episodes, including due to acute episodes that result in neurological and cardiac dysfunction.[5] Management of cTTP primarily comprises 2 approaches, namely[6] (1) Prophylactic treatment: a proactive approach comprising a scheduled treatment to prevent acute episodes from occurring; (2) On-demand treatment: a reactive approach comprising treatment only when an acute event occurs.

4.4 The standard of care has historically been prophylactic plasma infusions or plasma exchange therapy, using products like FFP or solvent/detergent-treated plasma (SDTP), typically administered at doses of 10–15 mL/kg every one to three weeks. Alternatively, intermediate-purity factor VIII concentrates containing ADAMTS13 may

[3] Tarasco, E; Butikofer, L; Friedman, KD et al. Annual incidence and severity of acute episodes in hereditary thrombotic thrombocytopenic purpura. *Blood.* 2021, 137, 3563–3575.

[4] van Dorland, HA, Taleghani, M., Sakai, K et al. The International Hereditary Thrombotic Thrombocytopenic Purpura Registry: Key findings at enrolment until 2017. *Haematologica*. 2019, 104, 2107–2115.

[5] Bell WR, Braine HG, Ness PM, et al. Improved survival in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Clinical experience in 108 patients. *N Engl J Med*. 1991 Aug 08;325(6):398-403.

[6] Taylor A, Scully M. Modern management of congenital thrombotic thrombocytopenic purpura (cTTP). *Hematology Am Soc Hematol Educ Program*. 2025; 2025(1):628-635.

be used (Koate, Octaplas®).[7] These treatments are usually provided in a hospital environment, enabling patient monitoring.

4.5 Allergic reactions during plasma infusion are common due to the high volume of foreign donor plasma proteins introduced over a prolonged period. While most allergic reactions to FFP are mild (predominantly urticaria), some studies have reported anaphylaxis. The rate of allergic reactions reported in the literature ranged from 9.3% to 42%, most of which were mild.[8,9,10,11,12] The reported rate of life-threatening reactions ranged from 0.3% to 1.7% in most studies, although a rate of 27% was reported in one study of severely ill cTTP patients.[12]

4.6 cTTP is extremely rare, with an estimated prevalence of 0.5-2.0/1,000,000. It accounts for approximately 2-10% of all TTP cases.[13] In large registries, the median age at diagnosis was 18 years, though 10% of patients remain undiagnosed until after the age of 40 years. There are no Australia-specific estimates for cTTP prevalence.

4.7 rADAMTS13 is an enzyme replacement therapy that mitigates ADAMTS13 enzyme deficiency. rADAMTS13 provides targeted ADAMTS13 supplementation and replenishment of plasma ADAMTS13 activity. It regulates von Willebrand factor activity by cleaving large von Willebrand factor multimers into smaller units, reducing their propensity to form microthrombi (tiny blood clots). This action reduces platelet consumption and thrombocytopenia, a key marker of disease activity in patients with cTTP. The submission stated that given the mechanism of action of rADAMTS13, there is no clinical rationale as to why the effect of rADAMTS13 would differ in patients who are tolerant of or intolerant to prophylaxis with FFP.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated on-demand FFP as the main comparator on the basis that if prophylactic treatment with FFP is not manageable, i.e. a patient is intolerant to or

[7] Zheng XL, Al-Housni Z, Cataland SR, et al. 2025 focused update of the 2020 ISTH guidelines for management of thrombotic thrombocytopenic purpura. *J Thromb Haemost*. 2025; 23(11):3711-3732.

[8] Stubbs M, Keogh L, Gounder P, et al. Long-term follow-up outcomes in congenital thrombotic thrombocytopenic purpura. *Blood.* 2025 Nov 13;146(20):2457-2463.

[9] Blombery P, Kivivali L, Pepperell D, et al. Diagnosis and management of thrombotic thrombocytopenic purpura (TTP) in Australia: findings from the first 5 years of the Australian TTP/thrombotic microangiopathy registry. *Intern Med J.* 2016 Jan;46(1):71-9.

[10] Reutter JC, Sanders KF, Brecher ME, et al. Incidence of Allergic Reactions With Fresh Frozen Plasma or Cryo-Supernatant Plasma in the Treatment of TTP. *J. Clin. Apheresis.* 2001; 16:134–38.

[11] Shemin D, Briggs D, Greenan M. Complications of Therapeutic Plasma Exchange: A Prospective Study of 1,727 Procedures. *J. Clin. Apheresis*. 2007; 22(5):270–76

[12] Sakai K, Hamamura A, Yoshimura Y, et al. Therapeutic switch from plasma to recombinant ADAMTS13 for patients with congenital TTP from Japanese real-world data. *Blood.* 2025;145(20):2390–95.

[13] Kremer Hovinga JA, George JN. Hereditary Thrombotic Thrombocytopenic Purpura. *N Engl J Med.* 2019 Oct 24;381(17):1653-1662.

hypersensitive to FFP, in case of a serious TTP event, the patient would receive on-demand FFP or no treatment at all. The submission stated that the only available and funded prophylactic treatment is FFP and that alternative treatments (of plasma treated with solvent-detergent process, or plasma-derived factor VIII-von Willebrand factor concentrates) are not used or funded in Australia, according to local expert advice. The Pre-Sub-Committee Response (PSCR) reiterated that plasma treated with a solvent-detergent process is not available in Australia and that whilst Biostate, a plasma derived FVIII product with human von Willebrand factor is listed on the National Product Price list (NPPL), that this is not used for cTTP patients because the level of ADAMTS13 in this product is variable. To this end, the PSCR maintained that on-demand treatment with FFP is the main treatment used in patients with cTTP who cannot tolerate prophylaxis with FFP. The ESC considered that with a change in the restriction to include all patients with cTTP, that the most appropriate comparator would be FFP prophylaxis with on-demand FFP used for acute events.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician discussed the natural history of the disease, limitations associated with prophylaxis with FFP, and how rADAMTS13 would be used in practice. The clinician stated that it is very difficult to achieve the volumes required to maintain a 'safe' level of ADAMTS13 and that in young children, pregnancy (with expanded volume), and those with cardiac or renal impairment, the physical volume of FFP required is unable to be delivered. The clinician stated that any centre that does not have a blood bank facility cannot store FFP, hence FFP may not be a treatment option for rural patients or for those in remote areas. In response to the Committee's question, the clinician advised there would be no negatives from providing rADAMTS13 to patients with cTTP who are still tolerant to FFP and that the data suggests the potential for preservation of organ function in the long term and significantly improved quality of life. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this extremely rare disease. The PBAC welcomed the additional clinical advice received in response to the Committee's questions, and found this informative as it provided further comments regarding the proposed use of rADAMTS13 in Australian clinical practice.

Consumer inputs

6.2 The PBAC noted and welcomed the input from individuals (5), health care professionals (7) and organisations (2) via the Office of Health Technology Assessment Consultation Hub.

6.3 Individuals described prior adverse reactions to plasma-based treatment, including severe transfusion reactions and anaphylaxis-like events, and that rADAMTS13 had provided a more reliable and sustainable way to manage the condition.

6.4 Health care professionals stated that high volumes of FFP are required to achieve effective replacement of ADAMTS13, given that FFP contains only around 1 unit per mL, and that the volume of FFP required to achieve effective replacement is usually prohibitive, especially in neonates and infants. Without sufficient FFP to maintain ADAMTS13 levels above 10%, breakthrough episodes of TTP can occur. The input stated that this can lead to progressive organ damage, including cumulative renal impairment that ultimately requires dialysis. Health care professionals stated that "[rADAMTS13] has been shown to achieve higher ADAMTS13 levels than FFP, and maintain ADAMTS13 levels above 10% for longer. [rADAMTS13] also allows a faster increase in ADAMTS13 activity, with a much smaller volume load than FFP. This may be of particular benefit in the treatment of acute events, especially in neonates/infants where the volume load associated with the use of FFP can be problematic (as was the case in my patient)." Health care professionals cited an example of one patient who was requiring 1000 mL FFP every 2 weeks via a port. The input stated, "this was only providing about 40% of his estimated effective treatment dose, required half a day in hospital, and frequent missed days of school. Even with this protocol he suffered breakthrough episodes of TTP requiring hospital admission. Now his life has been transformed - with [rADAMTS13] he is able to give a 5 minute infusion at home via a peripheral vein, has had no breakthrough episodes, has been able to get his port removed - which has allowed him to return to contact sport which he loves. His risk of progressive kidney failure and future dialysis is now negligible, and he has freed up a fortnightly bed in the day unit."

6.5 The Thrombosis and Haemostasis Society of Australia and New Zealand, and The Royal College of Pathologists of Australia detailed the risks associated with exposure to blood products and the demand on national blood supply that would be alleviated through PBS listing of rADAMTS13. The advice also noted the likely reduction in emergency presentations, inpatient care, intensive hospital resource use and transfusion-related resource requirements.

Clinical studies and trials

6.6 The submission was based on one head-to-head randomised controlled trial (RCT) comparing prophylactic rADAMTS13 to prophylactic FFP in patients with cTTP (Study 281102) (n=48). The submission also presented 2 observational studies (Study 3002 (n=79) and Study 5002 (n=289)) of patients with cTTP as supportive evidence.

- Study 281102: This phase 3 two-period crossover open-label RCT compared prophylactic rADAMTS13 with SoC (prophylactic plasma exchange (including FFP, plasma treated with a solvent–detergent process, or plasma-derived factor VIII–von Willebrand factor concentrates)). The trial included two cohorts: A) Patients in the prophylactic cohort were randomised to: first 6 months (Period 1) of prophylactic rADAMTS13 followed by 6 months (Period 2) of prophylactic plasma

exchange therapy (n=23), or vice versa (n=25); B) Patients in the on-demand cohort were randomised to rADAMTS13 (n=3) or on-demand plasma exchange (n=3), with patients in the on-demand cohort comprising only those presenting with an acute TTP event when starting the trial.

- Study 3002: This was an open-label single-arm Phase 3b study comprised of patients on prophylactic (n=79) or on-demand (n=2) rADAMTS13. This study included a proportion of patients who continued from Study 281102. The study did not stratify event rates by FFP-intolerance status.
- Study 5002: This was a multinational, non-interventional, observational cohort study of patients with a confirmed diagnosis of cTTP who were enrolled in the United Kingdom Thrombotic Thrombocytopenic Purpura (UK TTP) Registry (N=76, 63.2% on long-term prophylaxis), the International Hereditary Thrombotic Thrombocytopenic Purpura (hTTP) Registry (N=149, 63.8% on long-term prophylaxis), and the French National Reference Center of Thrombotic Microangiopathy (CNR-MAT) Registry (N=22, 33.9% on long-term prophylaxis). The submission included this study to quantify the expected difference in event rates between prophylactic and on-demand FFP, and to contextualise the trial findings within the proposed clinical setting. This study did not present data for patients on rADAMTS13.

6.7 Details of the Study 281102 and the 2 observational studies (supportive evidence) presented in the submission are provided in Table 2.

Table 2: Trials and studies, and associated reports presented in the submission.

Trial ID	Protocol title/ Publication title	Publication citation
	Final Clinical Study Report: A phase 3, prospective, randomized, controlled, open-label, multicenter, 2 period crossover study with a single arm continuation evaluating the safety and efficacy of TAK-755 (rADAMTS13) in the prophylactic and on-demand treatment of subjects with severe congenital thrombotic thrombocytopenic purpura (cTTP, Upshaw-Schulman Syndrome [USS], hereditary thrombotic thrombocytopenic purpura [hTTP]).	December 2024
Study 281102 NCT03393975	Clinical Study Report Erratum 1: A phase 3, prospective, randomized, controlled, open-label, multicenter, 2 period crossover study with a single arm continuation evaluating the safety and efficacy of TAK-755 (rADAMTS13) in the prophylactic and on-demand treatment of subjects with severe congenital thrombotic thrombocytopenic purpura (cTTP, Upshaw-Schulman Syndrome [USS], hereditary thrombotic thrombocytopenic purpura [hTTP])	22 October 2025
	Scully M, Antun A, Cataland SR, Coppo P, Dossier C, Biebuyck N, Hassenpflug WA, Kentouche K, Knöbl P, Kremer Hovinga JA, López-Fernández MF, Matsumoto M, Ortel TL, Windyga J, Bhattacharya I, Cronin M, Li H, Mellgård B, Patel M, Patwari P, Xiao S, Zhang P and Wang LT. Recombinant ADAMTS13 in Congenital Thrombotic Thrombocytopenic Purpura.	New England Journal of Medicine 2024; 390(17): 1584-1596.

Trial ID	Protocol title/ Publication title	Publication citation
	Cataland S, Patel M, Mellgård B, Ortel T, Scully M, Wang L, Windyga J and Bhattacharya I. 2023. Pharmacokinetic Characteristics of ADAMTS13 in Patients with Congenital Thrombotic Thrombocytopenic Purpura: Interim Results from a Phase 3 Randomized, Controlled, Open-Label, Crossover Study.	Research and Practice in Thrombosis and Haemostasis 2023; Volume 7 (Suppl. 2): 100531.
	Diogo D, Zhang P, Hassenpflug WA, Mellgård B, Patwari P, Qu W and Wang LT. Mutation Analysis of the ADAMTS13 Gene in Patients with Congenital Thrombotic Thrombocytopenic Purpura from the rADAMTS13 Phase 3 Study.	Blood 2024; 144 (Supplement 1): 4002.
	Patel M, Mellgard B, Pan L, Wang LT, Xiao S and Patwari P. Pharmacodynamic Activity of Recombinant ADAMTS13 Versus Plasma-Based Therapies in Congenital Thrombotic Thrombocytopenic Purpura: interim Results of a Phase 3 Randomized, Controlled, Open-Label Study.	66th ASH Annual Meeting. Orlando. United States. 2025-12-06 to 2025-12-09. *Blood* 2024; 144: 4006.
	Scully M, Berger C, Biebuyck N, Bonanad Boix S, Dossier C, Hassenpflug WA, Kentouche K, Schaefer B, Trisolini SM, Wu R and et al. Recombinant ADAMTS13 Prophylaxis in Pediatric Patients with Congenital Thrombotic Thrombocytopenic Purpura: results from the Phase 3 Randomized, Crossover Study and the Phase 3b Continuation Study.	Blood 2024; 144 (Supplement 1): 141.
	Scully M, Biebuyck N, Coppo P, Higasa S, Ibrahimi S, Matsumoto M, Ortel TL, Windyga J, Badejo K, Mellgård B, Waliullah M, Wang LT, Xiao S, Zhang P and Patwari P. Treatment Burden during a Phase 3 Randomized, Crossover Study of Recombinant ADAMTS13 Prophylaxis and Standard of Care in Patients with Congenital Thrombotic Thrombocytopenic Purpura.	Hamostaseologie 2025; 45 (Supplementary 1): S114.
	Scully M, Ortel TL, Yu Z, Waliullah M, Zhang P, Patel M, Patwari P, Mellgard B and Wang LT. Recombinant ADAMTS13 for the Treatment of Acute TTP Events in Patients with Congenital Thrombotic Thrombocytopenic Purpura: results from the Phase 3 Randomized, Controlled, Crossover Study and the Phase 3b Continuation Study.	Blood 2023; 142: 692.
Study 3002	Clinical Study Report: A Phase 3b, prospective, open-label, multicenter, single treatment arm, continuation study of the safety and efficacy of TAK-755 (rADAMTS13, also known as BAX 930/SHP655) in the prophylactic and on-demand treatment of subjects with severe congenital thrombotic thrombocytopenic purpura (cTTP; Upshaw-Schulman Syndrome, or hereditary thrombotic thrombocytopenic purpura).	22 November 2024
	Scully M, Berger C, Biebuyck N, Bonanad Boix S, Dossier C, Hassenpflug WA, Kentouche K, Schaefer B, Trisolini SM, Wu R and et al. Recombinant ADAMTS13 Prophylaxis in Pediatric Patients with Congenital Thrombotic Thrombocytopenic Purpura: results from the Phase 3 Randomized, Crossover Study and the Phase 3b Continuation Study.	Blood 2024; 144 (Supplement 1): 141.
Study 5002	Non-interventional (observational) study report: Global Research in TTP: Characteristics, Treatment, and Disease Progression of Patients with Congenital Thrombotic Thrombocytopenic Purpura (cTTP).	8 April 2022

Source: Table 14, pp59-60 of the submission; Attachment 3 to the submission; Attachment 4 to the submission.
cTTP = congenital thrombotic thrombocytopenic purpura; hTTP= hereditary thrombotic thrombocytopenic purpura; TAK-755 = rADAMTS13; TTP = thrombotic thrombocytopenic purpura; USS= Upshaw-Schulman Syndrome.

6.8 The key features of Study 281102 are summarised in Table 3.

Table 3: Key features of the included randomised controlled trial evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Relevant outcomes [b]
rADAMTS13 vs SoC					
rADAMTS13 vs SoC [a]	Prophylactic cohort: 46 [b] rADAMTS13- SoC: 22 SoC-rADAMTS13: 26 (rADAMTS13: 45 [c]; SoC: 46) [d] OD cohort: 9	OL, R, MC, 2-period crossover, with a single arm continuation [within-patient controlled comparison]. Follow-up duration prophylactic cohort: rADAMTS13: 0.55 y (median) SoC: 0.54 y (median)	High	cTTP	Acute TTP event rate Subacute TTP event rate Isolated TTP manifestations

Source: compiled during the evaluation based on p65 of the submission, Table 15 & 16, pp115-120 of the Study 281102 CSR.
cTTP = congenital thrombotic thrombocytopenic purpura; MC = multi-centre; OD = on-demand; OL = open label; R = randomised; SoC= standard of care; TTP = thrombotic thrombocytopenic purpura: y = years.
[a] SoC comprised FFP, solvent/detergent-treated plasma (SDTP) or Factor VIII:von Willebrand Factor concentrates (FVIII:vWF)
[b] Modified full analysis set included n=46 patients of the total 48 patients (full analysis set) who were randomised. These included n=45 unique patients who were originally enrolled in the prophylactic cohort and the patients who moved to the prophylactic cohort from the on-demand cohort. It included n=1 patient who was counted twice in the prophylactic cohort. It excluded n=2 patients from the full analysis set: One was randomised to rADAMTS13-SoC sequence but received the other. Another was found to have iTTP (not cTTP) and discontinued from the trial (p115 of the Study 281102 CSR).
[c] There were n=45 patients on rADAMTS13 through the randomised Period 1 and Period 2, and in the extended single-arm Period 3 of the RCT.
[d] Exposure to each treatment was the total of exposure in Period 1 and Period 2.

6.9 The population enrolled in Study 281102 did not align with the population requested in the submission. The submission argued that the trial population was relevant to the proposed listing because it was plausible that the superior outcomes observed with rADAMTS13 among patients tolerant to FFP prophylaxis would be preserved in patients who are intolerant to prophylactic FFP. The submission did not provide any clinical evidence to support generalisability of the treatment effect.

6.10 Study 281102 enrolled 8, and Study 3002 enrolled 12, paediatric patients, of which 4 were aged <6 years. Data for paediatric patients was not reported separately in Study 5002. Overall, data on the efficacy of rADAMTS13 was limited for paediatric populations.

6.11 The submission did not provide minimum clinically important differences for the outcomes presented.

Comparative effectiveness

6.12 Table 4 presents the results of Study 281102.

Table 4: Results of Study 281102 over randomised Periods 1 and 2, and non-randomised Period 3 for the whole population based on modified full analysis set (MFAS)

Outcome	Period 1 & 2				Period 3		Relative rate ratio rADAMTS13 vs SoC (95% CI); p-value
	rrADAMTS13 (n=44)		Standard of Care (n=45)		rADAMTS13 (n=44)		
	Patients with event, n/N (%) No. of events, n	AER, LS Mean (SE) [a]	Patients with event, n/N (%), No. of events, n	AER, LS Mean (SE) [a]	Patients with event, n/N (%), No. of events, n	AER, LS Mean (SE) [a]	
Primary outcome							
Acute TTP event	0	0	1/45 (2.2%), 1	0.04 (0.26) [b]	0	0	NR
Exploratory outcomes							
Isolated TTP manifestations							
Thrombocytopenia	13/44 (29.5%), 50	0.91 (0.27)	21/45 (46.7%), 89	1.62 (0.45)	11/44 (25.0%), 23	1.01 (2.66)	**0.6 (0.4, 0.8); 0.003**
MAHA	8/44 (18.2%), 23	0.38 (0.14)	12/45 (26.7%), 31	0.59 (0.20)	13/44 (29.5%), 20	0.87 (2.70)	0.6 (0.3, 1.2); 0.155
Renal dysfunction	5/44 (11.4%), 11	0.18 (0.09) [c]	2/45 (4.4%), 5	0.08 (0.05) [c]	4/44 (9.1%), 10	0.40 (1.52)	2.2 (0.5, 8.7); 0.272
Neurological symptoms events	4/44 (9.1%), 18	0.14 (0.07)	7/45 (15.6%), 28	0.23 (0.11)	9/44 (20.5%), 24	0.89 (2.35)	0.6 (0.3, 1.2); 0.138
Abdominal pain events	2/44 (4.5%), 4	0.09 (0.06)	6/45 (13.3%), 8	0.17 (0.09)	2/44 (4.5%), 4	0.17 (0.96)	0.6 (0.2, 2.0); 0.348
Other isolated TTP manifestations	5/44 (11.4%), 7	0.22 (0.10)	12/45 (26.7%), 19	0.52 (0.17)	6/44 (13.6%), 13	0.46 (1.44)	0.4 (0.2, 1.1); 0.077
Composite TTP manifestations							
Not including "Other" [d]	NR	2.56 (0.61)	NR	3.54 (0.82)	NR	2.60 (0.50)	**0.7 (0.6, 0.9); 0.017**
Including "Other" [e]	NR	2.71 (0.64)	NR	3.90 (0.90)	NR	2.90 (0.56)	**0.7 (0.5, 0.9); 0.005**
Subacute TTP events							
Subacute events	1/44 (2.3%), 1	0.04 (0.04)	6/45 (13.3%), 7	0.26 (0.11)	3/44 (6.8%),3	0.12 (0.07)	0.1 (0.0, 1.3); 0.077

Source: Developed during the evaluation from Table 26, Table 27, Table 29, Table 30 pp83-89 of the submission; Table 14.2.1.1.1, Table 14.2.2.1.21, p330, p494 of the Study 281102 CSR supplementary tables.

AER = Annualised event rate; CI = confidence interval; LS = least squares; MAHA = microangiopathic haemolytic anaemia; MFAS= modified full analysis set; n = number of patients with event; N = total patients in arm; NA= not applicable; NR = not reported; SD= standard deviation; SE= standard error; SoC= standard of care; TTP= thrombotic thrombocytopenic purpura.

Bold indicates statistically significant results.

[a] From a generalised linear mixed-effects model with a negative binomial distribution as a family and a logarithmic link function with treatment as a fixed effect, patients as a random effect, and the logarithm of follow-up time (in years) as an offset. Period (1 and 2) and sequence (rADAMTS13—SoC, SoC—rADAMTS13) were included in the model as categorical variables.

[b] Mean (SD).

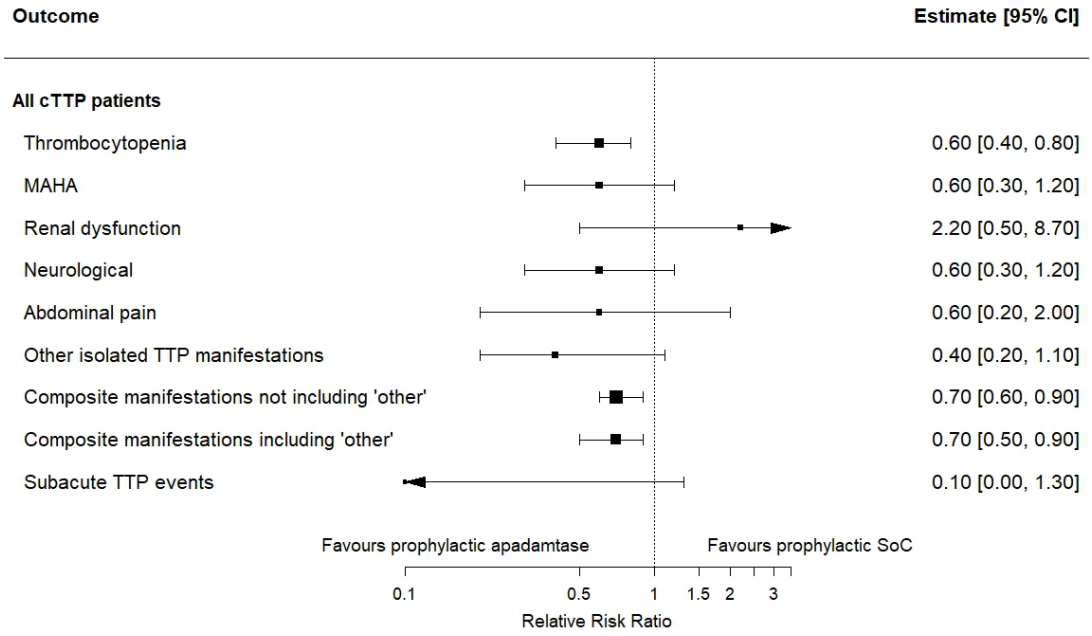
[c] Due to sparse events, the full model did not converge. Therefore, these results were from a generalised linear mixed-effects model that did not include the treatment sequence as a covariate.

[d] The composite endpoint includes the occurrence of at least one of thrombocytopenia, MAHA, neurological symptoms, renal dysfunction, or abdominal pain.

[e] This composite endpoint includes the occurrence of at least one of thrombocytopenia, MAHA, neurological symptoms, renal dysfunction, abdominal pain or other TTP manifestations.

6.13 Figure 1 presents the relative risk ratios of secondary and exploratory outcomes recorded in Period 1 and Period 2 of Study 281102, for the whole population.

Figure 1: Forest plot of relative risk ratios for annualised event rates of secondary and exploratory outcomes comparing prophylactic rADAMTS13 vs prophylactic SoC reported in Study 281102 for all patients (MFAS).



Source: Developed during the evaluation using R Studio (Package 'Metafor'), and using the model-based Relative Risk Ratios reported in the submission.
CI = confidence interval; cTTP= congenital TTP; MAHA = microangiopathic haemolytic anaemia; MFAS = modified full analysis set; SoC= standard of care; TTP= thrombotic thrombocytopenic purpura.

6.14 In Study 281102, no events for the primary efficacy outcome of acute TTP event were reported in the prophylactic rADAMTS13 arm, and one event was reported in the SoC arm. This was expected because of the short trial duration (median follow-up in Period 1 and Period 2 was 0.54 years in SoC arm and 0.55 years in the rADAMTS13 arm; median follow-up duration for Period 3 was 0.50 years). In a TTP registry with a median follow-up of 4.2 years the annual TTP event rate was less than 0.35/patient/year (Tarasco 2021).[14]

6.15 While the comparative effect was statistically significant for isolated thrombocytopenia events, statistical significance could not be established for other non-composite outcomes. Statistical significance may be difficult to establish in trials with such a small number of patients, short follow-up, and low event rates.

6.16 The submission stated that while no single manifestation defined a TTP episode in clinical practice, composite TTP manifestations provided the most representative indicator of treatment benefit. rADAMTS13 produced statistically significant reductions in both composite outcomes with and without 'other' manifestations. The ESC considered the composite endpoints were aligned with clinical practice and were reasonable. Based on the results of Study 281102 the TGA Delegate concluded that "use of Adzynma was considered superior to standard of care (SoC). There were

[14] Tarasco, E; Butikofer, L; Friedman, KD et al. Annual incidence and severity of acute episodes in hereditary thrombotic thrombocytopenic purpura. Blood. 2021, 137, 3563–3575.

significantly more thrombocytopenia event manifestations in the SoC arm than the Adzynma arm. The LS mean (SE) annualised rate of thrombocytopenia events was 0.90 (0.262) in the Adzynma arm and 1.63 (0.445) in the SoC arm, ratio (95% CI) 0.6 (0.4 to 0.8), p = 0.002. The other efficacy outcome measures, such as MAHA, neurological events and abdominal pain, although not statistically significant, also supported efficacy."

6.17 In Study 3002, there were no acute TTP events in the adults and adolescent cohort, and one acute TTP event in the paediatric cohort (annualised event rate = 0.06 (SD 0.20)).

6.18 The submission derived an estimate of the relative incidence rate for acute TTP events for patients treated with on-demand versus prophylactic plasma-based therapy from Study 5002. The submission stated that the incremental benefit of rADAMTS13 observed in the trial relative to prophylactic SoC was likely to underestimate the comparative benefit versus on-demand FFP in the proposed PBS population.

6.19 Study 5002 included results from the International hTTP registry, the CNR MAT registry and the UK Registry. The submission stated that the cohort from the International registry was deemed the most applicable to the Australian setting in terms of it representing a larger prevalent pool, international populations, use of prophylaxis and use of FFP as a treatment regimen.

6.20 Table 5 presents the incidence of acute TTP events from the International registry, comparing event rates based on the frequency of plasma therapy received.

Table 5: Efficacy results of Study 5002: Incidence of acute episodes per 1,000 Person-Years (PYs) during follow-up by prophylactic plasma-based therapy exposure (Outside of Pregnancy).

Prophylaxis timing	Regular long-term prophylaxis [A]	Regular long-term, not under prophylaxis (on-demand) [B]	Ever received prophylaxis [C]	Ever, not under prophylaxis (on-demand) [D]	Relative incidence rate ratio of on-demand vs prophylactic plasma therapy (95% CI)^	
					[E]= [B] vs [A]	[F]=[D] vs [C]
International hTTP Registry						
N	**95**	**95**	**99**	**99**		
Patients with ≥1 acute episode, n/N (%), Events, n	39/95 (41.1%), 134	14/95 (14.7%), 54	42/99 (42.4%), 137	15/99 (15.2%), 57	**3.65 (2.66, 5.0)**	**3.77 (2.77, 5.14)**
Incidence/ 1,000 PY (95% CI)	305.0 (255.5-361.2)	1112.9 (836.1, 1452.1)	301.8 (253.4-356.8)	1139.2 (862.8, 1475.9)		

Source: Table 50, p118 of the submission; Table 16, p64 of Study 5002 CSR.
CNR-MAT= French National Reference Centre of Thrombotic Microangiopathy; n = number of patients with event; N = total patients in group who received a prophylactic therapy; PY= person years; SD= standard deviation; TTP= thrombotic thrombocytopenic purpura; UCLH= University College London Hospitals.
Bold text indicated statistical significance.
[A] Acute TTP episodes recorded while patients were on regular long-term prophylaxis. Long-term prophylaxis was defined as receipt of prophylactic therapy at least once per month for a minimum of 6 months (outside of or during pregnancy).
[B] Acute TTP episodes recorded in the duration without prophylactic therapy within the group that regularly received prophylaxis (used as the on-demand comparator group against prophylactic SoC in the submission).
[C] Ever received prophylaxis with plasma-based therapy during the follow-up in the registry up.
[D] Acute episodes recorded in the duration without prophylactic therapy within the group that ever received prophylaxis.
^ Relative acute TTP event rate is the incidence rate ratio, calculated as incidence rate during on-demand treatment period/incidence rate during prophylactic treatment period. 95% CI were calculating using the following formula: $\exp(\ln(RR) \pm 1.96 \times \sqrt{((1/k1)+(1/k2))})$; where k1 represents the number of events in patients on-demand and k2 represents the number of events in patients with prophylaxis. A higher ratio indicated a higher risk of acute events when on on-demand therapy

6.21 The submission compared acute TTP event rates for patients who received regular prophylactic plasma therapy during follow-up (Column [A] in Table 5), to patients who received on-demand plasma therapy. The submission classified events as "under on-demand" as those recorded “not under prophylaxis” (Column [B] in the Table). The submission claimed that acute episodes occurred nearly 4 times more frequently during on-demand periods compared with prophylaxis using the International registry (incidence rate ratio=3.65) (Column [E] in the table).

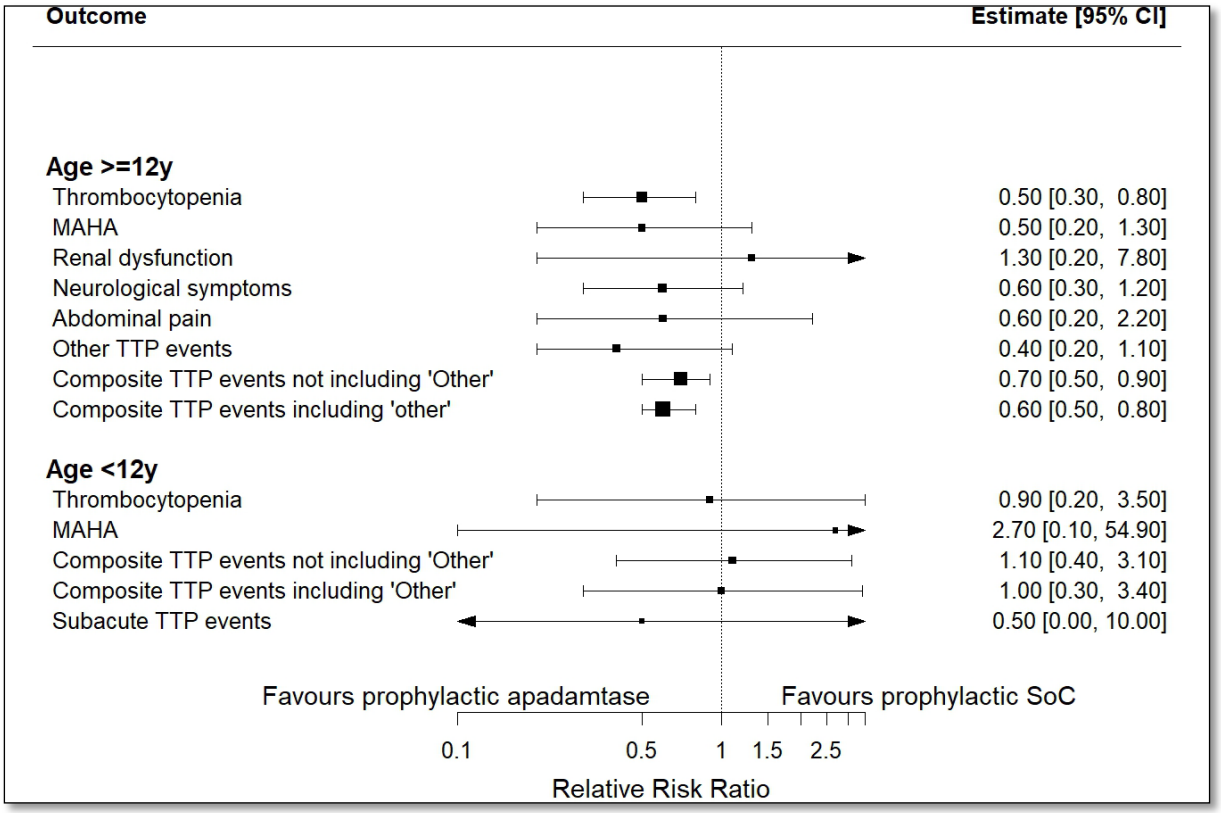
6.22 The results of Study 5002 should be interpreted considering the inherent biases associated with retrospective cohort studies including selection bias, confounding due to indication, differences in the feasibility and scope of retrospective medical-record abstraction across participating registries, and missing data. It is likely that patients classified as ever received or regularly received long-term prophylaxis had substantially different characteristics to patients classified as not having received regular prophylaxis, which would influence interpretation of the results.

Subgroup analyses

6.23 Study 281102 post-hoc subgroup analyses most relevant to the submission were stratified by age: adult and adolescent (non-paediatric) patients aged ≥ 12 years, and paediatric patients aged <12 years.

6.24 The relative annualised risk ratios for secondary and exploratory outcomes of Study 281102 in Period 1 and Period 2 by non-paediatric (≥12 years) and paediatric (<12 years) age groups are presented in Figure 2.

Figure 2: Subgroup analyses: Secondary and exploratory outcomes of Study 281102 in Period 1 and Period 2 by non-paediatric (≥12 years) and paediatric (<12 years) age groups (MFAS)



Source: developed during the evaluation from Table 26, Table 27, Table 29, Table 30, pp83-89 of the submission.
CI = confidence interval; MAHA = microangiopathic haemolytic anaemia; MFAS= modified full analysis set; TTP= thrombotic thrombocytopenic purpura.

6.25 The submission reported that analyses by non-paediatric and paediatric age categories (≥ 12 vs < 12 years) showed overall similar results to the total cohort in the RCT. The evaluation considered that results in patients aged ≥12 years were similar to those of the whole population, but results for the subgroup aged< 12 years were uncertain due to the small sample size (n=8). The evaluation considered that overall, prophylactic rADAMTS13 was likely less efficacious in paediatric patients than in adult and adolescent patients. The subgroup analyses showed the relative risk of MAHA was numerically higher in the rADAMTS13 vs SoC arm (risk ratio =2.7 (0.1, 54.9); p-value 0.461), and that of composite TTP manifestations was close to 1.0 (Figure 2).

6.26 The PSCR stated that given the small sample size that any observed differences between subgroups would likely be the result of chance rather than reflecting a true difference in treatment effect. In addition, the PSCR highlighted that the confidence intervals for paediatric patients were wide and that they overlapped with those for patients aged ≥ 12 years.

Comparative harms

6.27 Table 6 presents the adverse event profile of prophylactic rADAMTS13 and prophylactic SoC in Study 281102 and prophylactic rADAMTS13 in Study 3002.

Table 6: Safety profile of prophylactic rADAMTS13 vs prophylactic SoC in Study 281102 – Safety Analysis Set (SAF) and prophylactic rADAMTS13 in Study 3002

	Study 281102			Study 3002
	Period 1 & Period 2		Period 3	
Type of AE	rADAMTS13 (N=47)	SoC (N=48)	rADAMTS13 (N=48)	rADAMTS13 (N=75)
	n/N (%), No. of events			
Any TEAE	39/47 (83.0%), 273	44/48 (91.7%), 300	35/48 (76.1%)	66/75 (88.0%), 693
TEAE related to study procedures	1/47 (2.1%), 1 [a]	5/48 (10.4%), 7 [b]	2/48 (4.3%), 2 [c]	0
TEAE consistent with hypersensitivity reactions [d]				
Any hypersensitivity reaction	0	16/48 (33.3%), 24	0	3/75 (4.0%), 3
Allergic transfusion reaction	0	6/48 (12.5%), 7	0	NR
Rash	0	4/48 (8.3%), 5	0	1/75 (1.3%), 1
Urticaria	0	4/48 (8.3%), 6	0	1/75 (1.3%), 1
Pruritus	0	3/48 (6.3%), 3	0	1/75 (1.3%), 1
Cough	0	1/48 (2.1%), 1	0	NR
Drug hypersensitivity	0	1/48 (2.1%), 1	0	NR
Infusion-related reaction	0	1/48 (2.1%), 1	0	NR
TEAEs related to treatment	2/47 (4.3%), 8	22/48 (45.8%), 37	1/48 (2.2%), 6	6/75 (8.0%), 6
Severe TEAE related to treatment	0	1/48 (2.1%), 1	0 (0.0%)	0
Serious TEAEs	1/47 (2.1%), 1	7/48 (14.6%), 7	5 (10.9%), 6	11/75 (14.7%), 13
TEAE leading to treatment discontinuation	0	1/48 (2.1%), 1	0	0

Source: Table 39, Table 43, Table 44 p100, pp109-110 of the submission, Table 53, Table 54, Table 64 pp225-228, p251 of Study CSR; Table 14.3.1.8.1, pp3914-3916 of the Study CSR Supplementary Tables; Table 29, Table 30, Table 34, Table 35 pp94-107 of Study 3002 CSR (Interim Analysis 2).

AE= adverse events; SoC= standard of care; TEAE= Treatment-emergent adverse event.

[a] Events included iron deficiency anaemia.

[b] Events included allergic transfusion reaction, iron deficiency, syncope, pruritus, rash, and phlebitis.

[c] Events included anaemia and decreased platelet count.

[d] Identified using Standardised MedDRA Queries (SMQs) terms for "Hypersensitivity," "Anaphylactic reaction," and "Anaphylactoid shock reactions," then further narrowed to those events that occurred on the same day as a study drug infusion and were treated for an AE on the same day with a concomitant antiallergy or antipyretic medication.

[e] Included patients with any post-baseline positive binding antibodies, i.e. anti-ADAMTS13 antibodies. Absence of total binding antibodies to ADAMTS13 indicated the absence of neutralising antibodies to ADAMTS13.

[f] These were "low-titer" binding antibodies against rADAMTS13 that did not increase over time. No neutralising antibodies detected.

6.28 The submission stated that the treatment emergent adverse events (TEAEs) in Study 281102 were of mild-to-moderate severity. Study 281102 did not report any deaths across the 3 study periods. The rate of TEAEs in Study 281102 were similar to those reported in the long-term observational Study 3002 (88% of patients treated with rADAMTS13 had a TEAE in Study 3002 compared to 83% in Study 281102). A higher proportion of paediatric patients in Study 3002 had a serious TEAE (33.3%) compared to adults and adolescents (11.1%). Study 281102 reported no TEAEs in the paediatric cohort.

6.29 Patients who received prophylactic rADAMTS13 had fewer allergic reactions compared to patient who received SoC. In Study 281102, patients in the SoC arm had 24 hypersensitivity reactions, whereas patients in the rADAMTS13 arm did not report any reactions. In Study 3002, there were 3 events, all in the rollover cohort (pruritus, rash and rhinitis).

6.30 In Study 281102, TEAEs related to study procedures were numerically higher in the prophylactic SoC arm (10.4%) than the prophylactic rADAMTS13 arm (2.1%). There were no procedure-related TEAEs in the long-term observational Study 3002.

6.31 Observing the patients who received rADAMTS13 continuously from the 3 periods of Study 281102 through to Study 3002 (rollover cohort), the incidence of common TEAEs (as reported in Study 281102) likely increased over time. The rollover cohort in Study 3002 had a mean duration of exposure of 18.2 months (SD 9.8) to prophylactic rADAMTS13.

6.32 Overall, the TEAEs resulting from prophylactic rADAMTS13 exposure were likely manageable. There were no neutralising antibodies against rADAMTS13 in patients receiving rADAMTS13. However, there were 3 hypersensitivity reactions reported in the long-term follow-up data in Study 3002. Longer-term data are required to ascertain the safety of prophylactic rADAMTS13, particularly regarding the most prevalent AEs of respiratory tract infections, abdominal pain, fatigue, headaches, and hypersensitivity reactions. Longer-term data are also required to ascertain the safety of prophylactic rADAMTS13 in paediatric populations, and during pregnancy and lactation.

Benefits/harms

6.33 A summary of the comparative benefits and harms for prophylactic rADAMTS13 versus prophylactic SoC is presented in Table 7. It was not possible to present a comparative benefits and harms table for prophylactic rADAMTS13 versus on-demand SoC based on the information presented in the submission.

Table 7: Summary of comparative benefits and harms for prophylactic rADAMTS13 and prophylactic SoC reported in Period 1 and Period 2 of Study 281102

Study	rADAMTS13 n/N (%), No. of events	SoC n/N (%), No. of events	RR[a] (95% CI)[b]	Number of patients with event/100 patients		RD [c]
				rADAMTS13	SoC	
Benefits						
Secondary and exploratory outcomes						
Thrombocytopenia	13/44 (29.5), 50	21/45 (46.7), 89	**0.6 (0.4, 0.8)**	29.5	46.7	-17.2
MAHA	8/44 (18.2), 23	12/45 (26.7),31	0.6 (0.3, 1.2)	18.2	26.7	-8.5
Neurological symptoms	4/44 (9.1), 18	7/45 (15.6), 28	0.6 (0.3, 1.2)	9.1	15.6	-6.5
Renal dysfunction	5/44 (11.4), 11	2/45 (4.4), 5	2.2 (0.5, 8.7)	11.4	4.4	7
Abdominal pain	2/44 (4.5), 4	6/45 (13.3), 8	0.6 (0.2, 2.0)	4.5	13.3	-8.8
Other isolated TTP events	5/44 (11.4), 7	12/45 (26.7), 19	0.4 (0.2, 1.1)	11.4	26.7	-15.3
Subacute TTP events	1/44 (2.3), 1	6/45 (13.3), 7	0.1 (0.0, 1.3)	2.3	13.3	-11
Composite TTP events not including 'other'	24/44 (54.5), 102	27/45 (60.0), 142	**0.7 (0.6, 0.9)**	54.5	60	-5.5
Harms						
Any TEAE	39/47 (83.0%), 273	44/48 (91.7%), 300	0.93 (0.9, 1.14)	83	91.7	-8.7
SAE	1/47 (2.1%), 1	7/48 (14.6%), 7	0.15 (0.05, 3.52)	2.1	14.6	-12.5

Source: Developed during the evaluation from Table 26, Table 27, Table 29, Table 30, Table 39, Table 43, Table 44 p83-89, p100, pp109-110 of the submission; Table 14.2.1.1.1, Table 14.2.2.1.21, p330, p494 of the Study 281102 CSR supplementary tables.
CI = confidence interval; LS = least squares; MAHA = microangiopathic haemolytic anaemia; n = number of patients with event; N = total patients in the treatment arm; NR= not reported; RD = risk difference; RR = risk ratio; SAE = serious adverse event; SoC= standard of care; TTP= thrombotic thrombocytopenic purpura.
Bold indicates statistically significant results.
[a] RR was derived from the submission's estimates of relative risk ratios of annualised event rates.
[b] RR= event rate in rADAMTS13 arm/ event rate in SoC arm. 95% confidence interval calculated using the following formula: exp(ln(RR) ± 1.96 x √((1/k1)+(1/k2))); where k1 represents the number of events in patients on prophylactic rADAMTS13 and k2 represents the number of events in patients on prophylactic SoC.
[c] RD= event rate in rADAMTS13 arm - event rate in SoC arm.

6.34 On the basis of the direct comparison evidence presented by the submission, for every 100 patients with cTTP (irrespective of the FFP tolerance status) treated with prophylactic rADAMTS13 in comparison with prophylactic standard of care over a maximum duration of follow-up of 0.55 years:

- Approximately 17 fewer patients will experience thrombocytopenia.
- Approximately 5.5 patients will avoid experiencing any of the following TTP events: thrombocytopenia, microangiopathic haemolytic anaemia, renal dysfunction, a neurological symptoms event or an abdominal pain event.

Clinical claim

6.35 The submission described prophylactic rADAMTS13 as superior in terms of effectiveness compared to on-demand FFP. The evaluation considered that this claim

was likely reasonable but subject to considerable uncertainty. The key sources of uncertainty were:

- The pivotal RCT evidence compared prophylactic rADAMTS13 to prophylactic SoC (as opposed to on-demand FFP, the proposed comparator).
- The evidence to support the comparison of prophylactic FFP versus on-demand FFP was from a retrospective registry study (Study 5002).
- The pivotal RCT included cTTP patients who tolerated prophylactic FFP, and Study 5002 included cTTP patients irrespective of FFP-tolerance status.

6.36 The evaluation considered that the submission's claim for this population may be adequate if prophylactic rADAMTS13 is considered superior to prophylactic FFP, and prophylactic FFP is superior (or at least non-inferior) to on-demand FFP in preventing acute TTP events in the proposed population. The ESC considered the clinical claim of superior effectiveness to FFP (irrespective of the FFP tolerance status of the patient) to be reasonable.

6.37 The submission described prophylactic rADAMTS13 as having a manageable safety profile compared to on-demand FFP in cTTP patients who are intolerant to prophylactic FFP. The ESC considered a claim of non-inferior safety would be reasonable, based on the evidence presented.

6.38 The PBAC considered that prophylactic rADAMTS13 has superior comparative effectiveness and non-inferior comparative safety to prophylactic FFP.

Economic analysis

6.39 The submission presented a cost-utility analysis (CUA) comparing rADAMTS13 and on-demand FFP.

6.40 Table 8 presents the key components of the economic evaluation.

Table 8: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	rADAMTS13 vs on-demand FFP. The primary data sources were Study 281102, a randomised trial comparing prophylactic rADAMTS13 to prophylactic FFP in patients with cTTP (n=48), and extension study 3002. As Study 281102 did not provide clinical evidence for on-demand FFP, observational studies were used to inform several key inputs as described below.
Time horizon	50 years in the model base case versus 1.83 years in Study 281102. The time horizon in the model was long compared to the duration of follow-up in Study 281102 and extension Study 3002 (median 1.83 years).
Outcomes	QALYs gained, and LYs gained.
Methods used to generate results	Markov cohort-based state-transition model.
Health states	3 health states: • cTTP only; • Acute/subacute episode; • Dead. Alive health states could be: • "Without organ damage"; • "Initial organ damage" (a tunnel state representing the first occurrence of organ damage); or • "Chronic organ damage (patients remain in this substage of the model until death). Long term organ damage (LTOD) (modelled through either the initial or chronic organ damage substages) was included to capture long term consequences of disease progression. However, LTOD risk was not linked to prior acute or subacute episodes. Instead, LTOD risk was modelled as age and treatment dependent. Additionally, LTOD risk was informed by prophylaxis FFP data due to lack of on-demand FFP data. Mortality was implemented using a combination of event based (acute episodes) and health state based (organ damage) approaches.
Cycle length	6 months. Half cycle correction was applied.

Transition probabilities	• Probability of at least one acute/subacute cTTP episode:
	  ○ FFP on-demand: 100% (RR 3.65 relative to prophylaxis FFP, [calculated from Study 5002 (International hTTP Registry)]
	  ○ rADAMTS13 prophylaxis: 23.9% (RR 0.69 relative to prophylaxis FFP) [calculated from Study 281102]
	• Probability of developing organ damage:
	  ○ FFP on-demand: 1.61%-7.52% (dependent on age) [International Chart Review 2023]
	  ○ rADAMTS13: 0.13%-0.37% (dependent on age) [SEE study]
	• Probability of death given at least one acute cTTP episode: 2.17% [International Chart Review 2023]
	• Standardised Mortality Ratios:
	  ○ cTTP only (without organ damage): 1.00
	  ○ cTTP only (with initial organ damage): 6.00 [Bronnum-Hansen et al. (2001a), Bronnum-Hansen et al. (2001a), Bronnum-Hansen et al. (2001b), Neovius et al. (2014)]
	  ○ cTTP only (with chronic organ damage): 4.36 [Bronnum-Hansen et al. (2001a), Bronnum-Hansen et al. (2001a), Bronnum-Hansen et al. (2001b), Neovius et al. (2014)]
	  ○ Subacute cTTP episode only: 1.00
	
	The model applied a relative risk for incidence of acute episodes for on-demand FFP relative to ''prophylaxis FFP'' of 3.65. This was derived from patient-event rates and applied directly to a per cycle probability of acute/subacute episodes (32.6%). This was not appropriate; the estimate reflects the frequency of events rather than the probability of experiencing one event (where one patient can experience multiple episodes while others may experience none). As a result, the model generated an incorrect event risk of 100% for the on-demand FFP comparator arm, effectively assuming that all patients would experience an episode every 6-month cycle. When adjusted during the evaluation (converting 32.6%→ rate→ adjusted rate→ probability)[b],

Component	Summary
	this corresponds to an estimated per cycle risk of approximately 76%, rather than 100%. Risk of mortality from LTOD presents total weighted initial and chronic organ damage. Mortality risk from multiple conditions were added rather than averaged. This approach may overestimate mortality.
Treatment costs	6-monthly cost of prophylaxis: rADAMTS13, $80,280.91; prophylactic FFP, $0. FFP on-demand therapy cost for acute/subacute cTTP episodes (in both treatment arms): • Acute cTTP episode: $4,713[c] • Subacute cTTP episode: $1,309[d] The cost of prophylaxis FFP $12,525[e] was excluded and set to $0 when on-demand FFP was used as the comparator.
Health state costs (per cycle)	cTTP only: $643.00 (NHCDC 2022.23) Acute/subacute episodes: $2,572 (NHCDC 2022.23) • Acute cTTP episode and Subacute to Acute cTTP episode: $3,158 (NHCDC 2022.23, weighted average using AR-DRGs Q62A and Q62B. This was appropriate for thrombotic disorders. However, the use of a weighted average may underestimate costs associated with more severe presentations as high-cost cases may be diluted by less severe admissions.) • Subacute cTTP episode $643 (NHCDC 2022.23 data source was Appendix 14. NHCDC 2022-23 Non-admitted Tier 2 Version 7.0 summary). The use of non-admitted costs for subacute episodes may not fully capture cases that escalate.) With initial organ damage: + $27,200 (Kim et al., 2024[15]; Ioannides-Demos et al., 2010[16]; Deloitte, 2023[17]) With chronic organ damage: + $9,171 (Abebe et al., 2025; Deloitte, 2023) The initial and chronic organ damage were weighted averages. The submission presented an event distribution for organ damage type equalling 1.545. This was not appropriate. The reported proportions exceed 1 (as categories are not mutually exclusive), yet this was used to derive a weighted average, which assumes mutually exclusive categories, potentially resulting in double counting. AE costs: rADAMTS13, $72.19; FFP, $72.95

[15] Kim J., Neville E., et al., on behalf of the Stroke Foundation, Economic Impact of Stroke 2024. Stroke Foundation 2024. Melbourne Australia. Pages 1-115.

[16] Ioannides-Demos LL, Makarounas-Kirchmann K, et al., Cost of myocardial infarction to the Australian community: a prospective, multicentre survey. Clin Drug Investig. 2010;30(8):533-43.

[17] Deloitte (2023). Changing the chronic kidney disease landscape: The economic benefits of early detection and treatment (report commissioned by Kidney Health Australia, February 2023).

Component	Summary
Utilities	• Mapping Study 281102 EQ-5D-3L at baseline (cTTP only utility value 0.867). • Study 281102 acute and subacute utility values were defined post hoc therefore the model derived a disutility value using the midpoint utility between admission and post-discharge (0.656+0.368)/2=0.51. This was applied to the baseline utility used in McPhail & Haines (2010) of 0.8: 0.8-0.512= 0.29. This introduced uncertainty as it assumed a linear trajectory of recovery and that the midpoint adequately reflects average utility over the episode. • An assumption was made that the disutility of a subacute episode was 50% of an acute episode. The duration of the disutility, which was 16 days subacute and 46 days acute episodes (including progression from subacute to acute), was based on expert opinion. • Total QALY loss per cycle (including acute and subacute) was 0.025 for rADAMTS13, and 0.035 for on-demand FFP. • The utility LTOD weights (initial and chronic) were stroke /TIA 0.682, myocardial infarction 0.364, chronic kidney disease 0.500. Severity was not modelled for LTOD weights; the utilities applied were not in the cTTP population and utilities were averaged. • Adverse event disutilities were small, 0.00047 for rADAMTS13 and 0.00081 for on-demand FFP. The adverse event disutilities in the on-demand FFP arm were assumed to be equal to those for "prophylaxis FFP", which may not be appropriate given the increased use of therapy with prophylaxis FFP, although the impact would likely be small.

Source: Complied during the evaluation based on Table 57, pp132-133; Table 65, p145; Table 68, p148; Table 69, p149; p152; Table 78, p155; Table 79, p156; Table 92, p162; Table 93, p163; Table 98, p172; p179 of the submission; CSR Study 281102 Table 16, p118 and Table 17, p122; apadamtase alfa_cTTP_CUA_xlsm, Sheet 'HealthStateCosts', cells F45:F46.

AR-DRGs = Australian Refined Diagnosis Related Groups; CSR = Clinical Study Report; cTTP = congenital thrombotic thrombocytopenia purpura; FFP = fresh frozen plasma; ICER = incremental cost-effectiveness ratio; IPD = individual patient data; LTOD = long term organ damage; LY = life years; NHCDC = National Hospital Cost Data Collection; p.a.= per annum; PBT = Plasma based therapies (proxy for FFP); QALYs = quality adjusted life years; RR = rate ratio; SEE = structured expert elicitation; SMR = standardised mortality ratio; SoC = standard of care; TIA = Transient Ischaemic Attack; TTP = thrombotic thrombocytopenia purpura

[a] A total of 22.2% of participants were dosed Q1W, with the remaining dosed Q2W (77.8%). These values correspond to a mean dosing frequency of 0.61 per week.

[b] 32.6% (0.326) probability of ≥1 event in 6 months ("FFP prophylaxis"). 3.65 was a rate ratio, converting the probability to a rate was 76% chance of an event. (Quantities of interest were first converted to rates using the formula -ln(1-p)/t where p was the probability and t was the time frame. Then converted to 6-month probabilities using the formula 1-exp(-rt) where r was the rate and t was the time of interest)

[c] Derived from Daily dose of FFP = 704 mL; Converted to vials 295 mL (3 vials/day); Multiply by treatment duration 18 vials (3x6); 18x$261.86=$4,713.48.

[d] Derived from Daily dose of FFP = 704 mL and 352 mL (Day 2); Converted to vials 295 mL (3 vials day 1 + 2 vials day 2); Multiply by 5x$261.86=$1,309.30.

[e] PBT cost per 6-month cycle $12,524.86

Note: Clinical fresh frozen plasma (FFP), Apheresis clinical FFP, 295ml +/-10%, Australian Red Cross Lifeblood $261.86 https://www.blood.gov.au/blood-products/national-product-price-list

6.41 Table 9 summarises the acute/subacute transition probabilities used in the model and alternative values.

Table 9: Summary of transition probabilities used in the model

Parameter	Value	Source/Value	Alternative value
Risk of acute/subacute episodes per 6-month cycle: rADAMTS13			
Per cycle background risk of acute/subacute episode (prophylaxis FFP arm)	32.6%[a]	Study 281102 (IPD)	-
Relative risk of acute/subacute episode – rADAMTS13 relative to prophylaxis FFP	0.73[c]	Study 281102 (IPD)	
Per cycle risk of acute/subacute episode – rADAMTS13	23.91%	32.6% x 0.73	The estimate of 23.91% was retained as the base case. A rate-based approach gave a similar value of approximately 25%, indicating minimal impact on the estimated per cycle risk [d]
Risk of acute/subacute episodes per 6-month cycle: FFP on-demand			
Acute episode rate (per 1000 PYs) for FFP prophylaxis	305.0	International hTTP Registry in Study 5002	-
Acute episode rate (per 1000 PYs) for on-demand FFP	1,112.9	International hTTP Registry in Study 5002	-
Relative risk of acute episodes for FFP on-demand relative to FFP prophylaxis	3.65	1112.9/305.0	This was a rate ratio (not relative risk) of acute episodes for on-demand FFP relative to prophylaxis Based on rates per 1,000 person-years. The 3.65 value should be applied on the rate scale, not directly to probabilities.
Per cycle risk of acute/subacute episode – on-demand FFP	100.0%	32.6% x 3.65	32.6%x3.65=119% (this was an invalid value) and capped at 100% demonstrating the approach was inappropriate; 3.65 was the rate ratio for on-demand FFP vs prophylaxis FFP. The alternative value of 76.3% per cycle for on-demand FFP, was derived by applying the relative incidence on the rate scale and converting back to a 6-month probability [b]

Source: Table 62, p144; Table 63, p144; Table 64, p145; Table 65, p145 of the submission.
FFP = fresh frozen plasma; IPD = individual patient data; PYs = person-years
[a] Calculation: 15/46 (Periods 1 and 2 combined)
[b] Conducted during the evaluation: Prophylaxis arm 6-month probability: 15/46 = 0.326; Convert probability to rate: r=-ln(1-0.326)/0.5=0.789; Apply relative incidence for on-demand FFP vs prophylaxis FFP: r=0.789x3.65=2.879 (2.88 per year); Convert back to 6-month probability: p=1-exp(-2.879x0.5)=0.763 (76.3%)
[c] Calculation: (11/46)/(15/46) (p144 of the submission). Study duration NR, approx. 18 months (see Table 5, p24 Study 281102 (IPD)
[d] Complied during the evaluation based on prophylaxis FFP risk=32.6% per 6 months; Convert to a rate =0.789 per year; Apply treatment effect (0.73 vs prophylaxis) 0.789 x 0.73 = 0.576; Convert back to a 6-month probability ($1-e^{-0.576x0.5}$) =25%

6.42 The submission reanalysed individual patient data (IPD) from Study 281102 to recalculate the risk of acute/subacute episodes for patients on prophylactic rADAMTS13 and prophylactic FFP, based on revised definitions of acute, subacute and isolated TTP manifestations derived from a clinical advisory board meeting of UK clinicians. The evaluation considered it was unclear whether the revised definitions were applicable to Australian clinical practice. The PSCR stated that Australian clinicians have indicated that treatment pathways for cTTP are informed by British Society for Haematology guidelines (2023). "Given the similarities between the Australian and UK healthcare systems", the PSCR stated, "it is reasonable to consider

that the revised definitions defined by UK clinicians are applicable in the Australian context".

6.43 The risk of acute/subacute episodes per 6-month cycle with prophylactic FFP was 32.6%. This was derived from 15 events in 46 patients treated with prophylactic SoC over approximately 18 months, as determined from the IPD analysis of Study 281102 using the revised definitions of acute and subacute episodes.

6.44 The risk of organ damage in the model was treatment specific rather than linked to specific health states. The submission stated that there was no data that would allow health state specific LTOD risks to be parameterised in the model. The submission claimed that according to clinicians (October 2023 advisory board) and the published literature, the risk of LTOD is linked to chronically low ADAMTS13, as well as the accumulation of acute and subacute episodes, symptoms outside of an episode and whether patients receive prophylactic treatment.

6.45 The ESC noted that the undiscounted life years gained in the model were largely driven by treatment-specific LTOD risks (stroke, MI, CKD). The ESC considered that if patients are adherent to weekly or twice weekly rADAMTS13 that very few events and very little organ damage should occur, whereas for patients who can't have FFP at all and for the majority of patients where sufficient volume of FFP cannot be administered to keep ADAMTS13 at 10% or more, that the cumulative risk of LTOD would be high. On that basis, the ESC considered that there would likely be differences in LTOD risk based on treatment, but that a 20% risk for rADAMTS13 versus 100% risk for FFP on-demand by age 80 years was optimistic and favoured rADAMTS13.

6.46 The ESC noted that mortality from LTOD events was estimated by adding Standardised Mortality Ratios (SMRs) derived from external, non-cTTP cardiovascular populations for stroke, MI, CKD. The ESC considered that this likely resulted in double-counting of mortality risk as these conditions are not mutually exclusive. The pre-PBAC response acknowledged an element of double-counting in the submission base case and provided a revised model that allowed for flexibility to consider a non-overlapping LTOD distribution (standardised to sum to 100%) and an option to use the highest SMR/cost in an overlapping LTOD distribution.

6.47 The submission assigned a disutility to acute and subacute episodes of 0.29 and 0.14 respectively. Utility values from Study 281102 were not used in the model, as there were insufficient QoL data (One patient in the prophylaxis FFP arm and none in the rADAMTS13 arm had an acute TTP event.)

6.48 The total QALY loss due to acute and subacute episodes per 6-monthly cycle was 0.025 for rADAMTS13 and 0.035 for on-demand FFP.

6.49 Table 10 presents the results of the stepped economic evaluation.

Table 10: **Results of the stepped economic evaluation**

Step and component	rADAMTS13	On-demand FFP	Increment
Step 1: Trial-based costs and outcomes			
Costs	$[redacted]	$7,288	$[redacted]
LYG	0.9990	0.9952	0.0038
Incremental cost/LYG gained			$[redacted][1]
Step 2: Time horizon extended to lifetime (50 years)			
Costs	$[redacted]	$264,797	$[redacted]
LYG	36.1839	15.8260	20.3580
Incremental cost/LYG gained			$[redacted][2]
Step 3: Discounting (5%) included			
Costs	$[redacted]	$151,388	$[redacted]
LYG	15.9187	9.8861	6.0326
Incremental cost/LYG gained			$[redacted][3]
Step 4: Incorporation of medical resource costs			
Costs	$[redacted]	$286,898	$[redacted]
LYG	15.9187	9.8861	6.0326
Incremental cost/LYG gained			$[redacted][3]
Step 5: Utility weights applied			
Costs	$[redacted]	$281,168	$[redacted]
QALYs	12.7342	7.0583	5.6760
Incremental cost/QALY gained (base case)			**$[redacted][3]**

Source: Complied during the evaluation from apadamtase alfa_cTTP_CUA_xlsm
FFP = fresh frozen plasma; LYG = life years gained; QALY = quality-adjusted life-years.
Note: Costs decreased following reintroduction of the organ damage health state due to changes in cost allocation rather than the application of utility weights alone.
The redacted values correspond to the following ranges:
[1] *> $1,055,000*
[2] *$255,000 to < $355,000*
[3] *$355,000 to < $455,000*

6.50 The ICER was mainly driven by extending the time horizon to a lifetime horizon.

6.51 The results should be considered with caution because a gain of 20 life years (as calculated in step 2) was optimistic. Also, the increase in the ICER after discounting, alongside the reduction in life years gained (LYG) (from 20.36 to 6.03 LYG) indicated the modelled survival benefit was concentrated in later years, reinforcing that cost-effectiveness was driven by long term extrapolation rather than short-term observed outcomes.

6.52 Table 11 summarises the key drivers of the model.

Table 11: Key drivers of the model

Description	Method/Value	Impact Base case: $[redacted][1]/QALY gained.
Transition probability	Risk of organ damage	Moderate, favours rADAMTS13. Changing the Risk of organ damage for rADAMTS13 (SEE Study) to International Chart Review (2023) increased the ICER to $[redacted][2]/QALY gained ([redacted]%).
Transition probability	Risk of acute/subacute episodes for on-demand FFP	Moderate, favours rADAMTS13. Reducing the risk of acute/subacute episodes for on-demand FFP (100% to 76.3%) increased the ICER to $[redacted][2]/QALY gained ([redacted]%).
Time Horizon	50 years	Moderate, favours rADAMTS13. Setting the time horizon to 20 years increased the ICER to $[redacted][2]/QALY gained ([redacted]%).

Source: Table 98, pp172-173 of the submission and complied during the evaluation from Apadamtase alfa_cTTP_CUA_xlsm.
FFP = Fresh frozen plasma; ICER = Incremental cost-effectiveness ratio; LTOD = Long term organ damage; QALY = Quality adjusted life years.
The redacted values correspond to the following ranges:
[1] *$355,000 to < $455,000*
[2] *$455,000 to < $555,000*

6.53 Table 12 presents the key sensitivity analyses including the scenario analysis provided in the Pre-Sub-Committee Response.

Table 12: Results of the sensitivity analyses in the submission, the evaluation and scenario analysis from Pre-Sub-Committee Response

Parameter (base case value/source/assumption)	Incremental cost	Incremental QALYs	ICER	% change to ICER
Base case	**$[redacted]**	**5.6760**	**$[redacted][1]**	
Mortality risk from an acute cTTP episode (3.65%), changed to International Chart Review 2023 (2.17%)	$[redacted]	5.0677	$[redacted][2]	[redacted]%
Baseline proportion of chronic organ damage (9.5%) changed to 100%	$[redacted]	4.3447	$[redacted][1]	[redacted]%
Probability of acute/subacute episodes – per cycle (rADAMTS13: 23.91%; on-demand FFP: 100%) changed to 23.91% vs 83.15% (lower 95% CI vs prophylaxis FFP)	$[redacted]	5.1573	$[redacted][1]	[redacted]%
Risk of organ damage – rADAMTS13 (SEE Study) changed to International Chart Review (2023)	$[redacted]	3.8861	$[redacted][2]	[redacted]%
Risk of organ damage – on-demand FFP (International Chart Review (2023)) changed to UK-UCLH Chart Review (5009) - Overall	$[redacted]	6.5058	$[redacted][3]	-[redacted]%
Time horizon (50 years)				
• 10 years	$[redacted]	1.3840	$[redacted][4]	[redacted]%
• 20 years	$[redacted]	3.1652	$[redacted][2]	[redacted]%
• 30 years	$[redacted]	4.5144	$[redacted][1]	[redacted]%
• 40 years	$[redacted]	5.3005	$[redacted][1]	[redacted]%
Discount rate for costs and outcomes (5% pa.)				
• 0%	$[redacted]	17.4513	$[redacted][3]	-[redacted]%
• 3.5%	$[redacted]	7.6161	$[redacted][1]	-[redacted]%
Background risk of acute/subacute episodes (100% changed to 76.3%)	$[redacted]	4.9205	$[redacted][2]	[redacted]%
Subacute mortality increased from 0% (base case) to 5%	$[redacted]	5.5115	$[redacted][3]	-[redacted]%
Subacute mortality increased from 0% (base case) to 10%	$[redacted]	4.9874	$[redacted][3]	-[redacted]%
Broader TGA indication scenario (rADAMTS13 vs FFP prophylaxis)	$[redacted]	2.8418	$[redacted][5]	[redacted]%

Source: Table 98, pp172-173 of the submission and complied during the evaluation from Apadamtase alfa_cTTP_CUA_xlsm,and from Table 2, Pre-Sub-Committee Response.

cTTP = Congenital Thrombotic Thrombocytopenic Purpura; FFP = Fresh frozen plasma; ICER = incremental cost-effectiveness ratio; pa = per annum; QALY = quality adjusted life year

The redacted values correspond to the following ranges:

[1] *$355,000 to < $455,000*

[2] *$455,000 to < $555,000*

[3] *$255,000 to < $355,000*

[4] *$755,000 to < $855,000*

[5] *$655,000 to < $755,000*

6.54 As requested by the evaluation, the PSCR provided a scenario analysis evaluating rADAMTS13 prophylaxis versus FFP prophylaxis across the broader cTTP population. This is included in Table 12. Additional sensitivity analyses requested by the ESC based on the PSCR scenario analysis are included in Table 13.

Table 13: Results of the sensitivity analyses – ESC analyses - Broader TGA indication scenario (vs FFP prophylaxis)

	Parameter (base case value/source/assumption)	Incremental cost	Incremental QALYs	ICER
	Base case	$[redacted]	2.8418	$[redacted][1]
A	Mortality risk Acute cTTP episode (3.65%), changed to International Chart Review 2023 (2.17%)	$[redacted]	2.5374	$[redacted][2]
B	Risk of LT organ damage – rADAMTS13 (SEE Study), changed to International Chart Review (2023)	$[redacted]	1.0443	$[redacted][3]
	Time horizon (50 years)			
C1	• 10 years	$[redacted]	0.4412	$[redacted][3]
C2	• 20 years	$[redacted]	1.1896	$[redacted][3]
C3	• 30 years	$[redacted]	1.9598	$[redacted][4]
	Acute event disutility (-0.29), +/- 20%, i.e.			
D1	• -0.35	$[redacted]	2.8634	$[redacted][1]
D2	• -0.23	$[redacted]	2.8201	$[redacted][1]
	Baseline cTTP utility (0.867), changed +/- 10%, i.e.			
E1	• 0.78	$[redacted]	2.5740	$[redacted][2]
E2	• 0.95	$[redacted]	2.9170	$[redacted][1]
	Subacute disutility fraction (50%), changed to:			
F1	• 25%	$[redacted]	2.8073	$[redacted][1]
F2	• 75%	$[redacted]	2.8762	$[redacted][1]
G	Distribution of LTOD events to a ceiling of 100% (155%)	$[redacted]	2.5088	$[redacted][2]
	Assume a proportion of subacute episodes treated in inpatient setting (100% outpatient)			
H1	• 10% inpatient	$[redacted]	2.8418	$[redacted][1]
H2	• 25% inpatient	$[redacted]	2.8418	$[redacted][1]

Source: Compiled during preparation of the ESC Advice

cTTP = Congenital Thrombotic Thrombocytopenic Purpura; FFP = Fresh frozen plasma; ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year: LTOD = long-term organ damage

The redacted values correspond to the following ranges:

[1] *$655,000 to < $755,000*

[2] *$755,000 to < $855,000*

[3] *> $1,055,000*

[4] *$855,000 to < $955,000*

6.55 The ESC considered the revised model a more plausible basis for decision making, as it aligned directly with the available head-to-head trial data and accepted clinical practice guidelines. However, the ESC noted that the scenario analysis retained the optimistic assumptions around LTOD risk and mortality rates. Specifically, the ESC

noted that the PSCR model likely overestimated LTOD-related mortality by inappropriately double-counting the risk of death for patients who develop multiple types of organ damage, resulting in a total weighted distribution of 155%. The ESC noted that normalising these weights to 100% increased the ICER to $755,000 to < $855,000 per QALY. The ESC considered that distribution of LTOD mortality rates to a maximum ceiling of 100% should form a revised base case. The ESC considered that a revised base case should also incorporate a less optimistic assumption regarding the risk of LTOD.

6.56 As requested by the ESC, the pre-PBAC response provided a scenario analysis for the patient population aligned with the TGA indication, that is the scenario presented in the PSCR with FFP prophylaxis as the comparator was extended to include costs for on-demand rADAMTS13 for acute and subacute cTTP events. On-demand dosing was as per the approved PI (40 IU/kg on day 1, 20 IU/kg on day 2, and 15 IU/kg on day 3 onwards, see paragraph 2.1), with subacute dosing based on Study 281102 where investigators could elect to treat subacute manifestations with 1 or 2 additional daily doses of 40 IU/kg. This increased the ICER to $655,000 to < $755,000/QALY compared with $655,000 to < $755,000/QALY in the PSCR scenario. The analysis estimated each acute episode would require 5.84 500 IU vials and 4.37 1500 IU vials of rADAMTS13 corresponding to a cost of $[redacted]. For subacute episodes, the analysis estimated a requirement of 1.82 500 IU vials and 2.39 1500 IU vials of rADAMTS13 corresponding to a cost of $[redacted]. The analysis assumed that patients who discontinued rADAMTS13 prophylaxis would use FFP as on-demand treatment. The pre-PBAC response model was not evaluated.

Drug cost/patient

6.57 Table 14 presents the drug cost per patient.

Table 14: Drug cost per patient

	rADAMTS13 (administered as a prophylactic treatment)	**On-demand FFP (cost applied in both treatment arms)**
	Economic model and financial estimates	**Economic model and financial estimates**
Dose	40 IU/kg 22% once weekly 78% every second week Average doses per week = 0.61	Acute: 704 mL per day for 6 days Subacute: 704 mL on day one, 352 mL on day two
Mean weight	66.5 kg	-
Cost per patient	$[redacted] per year	$4,713.48 per acute episode $1,309.30 per subacute episode

Source: Table 62, Table 84, Table 85 of submission

Estimated PBS usage & financial implications

6.58 This submission was not considered by the DUSC. The submission used a prevalence-based epidemiological approach to estimate utilisation. The inputs used in the submission were not consistent with the proposed population in that the dosage was based on the weight of adult patients, which was likely an overestimate.

6.59 Table 15 presents the key inputs and data sources used to estimate the financial impact.

Table 15: Key inputs for financial estimates - Epidemiological Approach

Parameter	Value	Source	Comment
Population: cTTP			
cTTP prevalence	0.86 per 100,000,000	Du et al. (2024)	Likely underestimated. Sensitivity analysis provided in the submission were based on Norway estimate (3.1/1,000,000). The PSCR and pre-PBAC response argued that the Norway estimate was likely inflated and not representative of prevalence due to a high incidence of the ADAMTS13 mutation c.4143_4144dupA.
FFP intolerant	65.8%	Reutter et al. (2001)	Uncertain estimate. Based on small sample evidence (Reutters 2001) using outdated definitions of intolerance and FFP management, which would now likely include management of reactions (slower infusion, premed prednisolone or antihistamines[18]) rather than true FFP ineligibility. Restriction also allows use in patients practically/logistically unable to receive regular FFP.
% Treatment Uptake Rate	Yr 1: [redacted]% Yr 2: [redacted]% Yr 3: [redacted]% Yr 4: [redacted]% Yr 5: [redacted]% Yr 6: [redacted]%	Submission assumption	This was high uptake however probably reasonable. The submission stated that the majority of patients in Australia have been grandfathered ([redacted][1] with [redacted][1] pending). The submission stated that the program has been running for 12 months.
Proposed Medicine: rADAMTS13			
Compliance	99.68%	Study 281102	
Patient weight	Mean (SD) weight 66.48 kg (21.59)	Study 281102	Based on mean weight in Study 281102 where most patients were aged over 18 years. Individual patient weights were not provided therefore the financials do not account for variability in dosing for very low or very high body weights.
rADAMTS13 dose	40 IU/kg Q1W or Q2W	Australian PI	
rADAMTS13 percentage of patients on weekly dosing	22%	Study 281102	
rADAMTS13 percentage of patients on fortnightly dosing	78%	Study 281102	
rADAMTS13 1500IU vials per dose	1.6065	Weighted average across the population	This was consistent with the economic evaluation

[18] Australian Red Cross Lifeblood. (accessed April 2026) Management of suspected reactions. https://www.lifeblood.com.au/health-professionals/clinical-practice/adverse-events/management-of-suspected-reactions

Parameter	Value	Source	Comment
rADAMTS13 500IU vials per dose	0.9999	Weighted average across the population	This was consistent with the economic evaluation.
rADAMTS13 for grandfathering	[redacted][1] patients ([redacted][1] pending)	Presented in the submission	
MBS item 82215 (Nurse practitioner)	$88.90	MBS online (schedule fee)	
MBS item 14245 Infusion for at least 2 hours)	$114.30	MBS online (schedule fee)	

Source: Complied during the evaluation from Table 100, p182; Table 101, p183; Table 102, p184; Table 103, p185 Table 104, p187 of the submission; apadamtase alfa_BIM

CSR = clinical study report; cTTP = congenital thrombotic thrombocytopenic purpura; Copay = patient copayment; FFP = Fresh frozen plasma; MBS = Medicare benefits schedule; NR = Not reported; IU = international units; PBS = Pharmaceutical Benefits Scheme; PI = Product Information; Q1W = one per week; Q2W = once per fortnight; RPBS = Repatriation Pharmaceutical Benefits Scheme; SD = standard deviation.

The redacted values correspond to the following ranges:

[1] *< 500*

6.60 Table presents the estimated use and financial implications (effective price of rADAMTS13).

Table 16: Estimated use and financial implications in the submission

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Treated patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
1500 IU scripts (max qty=8)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
500 IU scripts (max qty=24)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total scripts	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Cost to PBS/RPBS (before copays)	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Total impact of copayments	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted]	-$[redacted][3]
Net financial implications						
Cost to PBS/RPBS	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Total costs to MBS[a]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Total costs to the PBS/RPBS/MBS	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]

Source: Complied during the evaluation from Table 103, p185; Table 104, p487 of the submission; apadamtase alfa_BIM; apadamtase alfa

IU = international units; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

a MBS items included: MBS item 82215: Nurse practitioner – at least 40 minutes; and MBS item 14245: Infusion at least 2 hours duration (S100)

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *$0 to < $10 million*

[3] *net cost saving*

6.61 The total net cost to the PBS/RPBS/MBS of listing rADAMTS13 was estimated to be $0 to < $10 million in Year 6, and a total of $10 million to < $20 million over the first 6 years of listing. The ESC noted that this cost was heavily driven by the assumption that 65.8% of patients are FFP-intolerant. The ESC considered this assumption to be highly uncertain, as it was based on a small, older study of patients undergoing high-volume plasma exchange, and not the prophylactic schedules used in Australia. The ESC noted that if the FFP-intolerance restriction was removed, that the cost to PBS/RPBS would increase by 52% to $20 million to < $30 million over 6 years.

6.62 The submission conducted a literature review to identify studies that estimated the incidence of cTTP in Australia. The prevalence of cTTP was assumed to be 0.86 cases per million population, based on estimates reported by Du et al. (2024). A scenario analysis was conducted using a Norwegian estimate (3.1 per million), which would allow upward adjustment for improved detection of cTTP. The PSCR stated, "the five-year report of the Australian TTP Registry, which recorded 57 cases of 'true TTP' between June 2009 and October 2014 (Blombery 2016)" provides additional context. The PSCR stated, "This cohort included both cTTP and iTTP patients, and as a result the registry data was not adequate to derive prevalence estimates for cTTP on its own. When applying the commonly cited assumption that 5% of all TTP cases are attributable to cTTP, this results in prevalence estimates that are significantly lower than other estimates reported in the literature (von Krogh 2016; Du 2024), thereby limiting the use of this data for the budget impact modelling. However, this supports the conclusion that the true prevalence estimate in Australia is likely closer to the French than the Norwegian estimates. Therefore, a prevalence of 0.86 cases per million was considered the most appropriate input for estimating budget impact and PBS financial implications".

6.63 The submission proposed that the patient population eligible for rADAMTS13 were those unable to tolerate ongoing treatment with FFP. The financial estimates assumed 65.8% of patients were intolerant to FFP. This was a key driver of the financial estimates and was uncertain. The estimate of 65.8% was based on Reutter et al. (2001). In this study, all patients received FFP or cryosupernatant plasma (CPP): 27 of 41 patients (65.8%) experienced at least one allergic reaction and all received large volume daily plasma exchange using exclusively FFP or CPP. However, one allergic reaction may not represent intolerance or inability to continue lifelong FFP. In addition, the use of daily plasma exchange may have resulted in a higher incidence of intolerance than prophylactic FFP schedules used in Australia. The requested restriction also proposed that patients practically/logistically unable to receive regular FFP would be able to receive rADAMTS13. A sensitivity analysis assuming FFP intolerance of 100% (i.e. removing the requirement to be FFP intolerant) is presented in Table 17 below.

6.64 No costs associated with allergic reaction medications or monitoring were included in the financial estimates. The cost of ADAMTS13 activity testing for the diagnosis of TTP as per MSAC application 1796 was not included. The PSCR stated that the requested PBS listing of rADAMTS13 is not expected to change current diagnostic pathways for cTTP as "patients will undergo testing regardless of treatment choice".

6.65 The submission stated that a substantial proportion of diagnosed patients have already commenced treatment with rADAMTS13 on a compassionate access scheme (grandfathered < 500/< 500 ([redacted]%)) and that an additional < 500 patients have requested treatment (application pending).

6.66 Sensitivity analyses are presented in Table 17.

Table 17: Sensitivity analyses on the net financial impact to the PBS/RPBS

Year	2027	2028	2029	2030	2031	2032	% change
Base case (cost to PBS/RPBS after copayments)	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	0%
Prevalence (base case: 0.8 per /1,000,000)							
cTTP prevalence set to the Norway estimate (3.1 per million inhabitants)	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	+[redacted]%
Proportion Australian patients with FFP intolerance (base case: 65.8%)							
FFP intolerance set to 100%	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	+[redacted]%

Source: Table 105, p188 of the submission
cTTP = congenital thrombotic thrombocytopenic purpura; FFP = fresh frozen plasma; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.
The redacted values correspond to the following ranges:
[1] *$0 to < $10 million*

6.67 The pre-PBAC response presented an estimate of the financial impact of listing rADAMTS13 for all patients irrespective of FFP intolerance, and including use of on-demand rADAMTS13 for acute and sub-acute events. The response estimated a total cost to the PBS/RPBS of $20 million to < $30 million over the first 6 years of listing (see Table 18). A summary of the presented scenario is provided below:

- For prophylactic use, the analysis assumed that rADAMTS13 would be used in the full TGA population, with assumptions aligned with the sensitivity analysis where FFP intolerance is set to 100% in Table 17 above.
- For on-demand use, the analysis assumed an average 0.73 acute and 3.82 subacute cTTP episodes per year in patients treated prophylactically with rADAMTS13, corresponding to an additional 1.54 PBS scripts per patient per year of 1500 IU vials, and 1.40 PBS scripts per patient per year of 500 IU vials for on-demand use.
- The analysis assumed an expected utilisation of 12.4% in a private/community setting and 87.6% in a public setting for the purposes of calculating the DPMQ, consistent with the submission's estimates for prophylactic use. The same proportions were applied to prophylactic and on-demand use, however it was noted that the cost of rADAMTS13 as on-demand treatment of acute episodes in public hospitals will not be borne by the PBS. As such, the estimated costs to the PBS for on-demand use shown in Table 18 are overestimated as the public hospital use was not removed from the estimates. These costs should have been presented as a separate line item in the financial estimates.
- The analysis assumed cost-offsets for FFP prophylaxis for the estimated 34.2% of the eligible population who are FFP tolerant (i.e. 100% - 65.8%) however the costs could not be verified.

Table 18: Net financial impact from the pre-PBAC response including prophylactic and on-demand use

Year	2027	2028	2029	2030	2031	2032
PBS/RPBS - prophylaxis[a]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
PBS/RPBS - acute/subacute[b]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
MBS[c]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]

Source: Table 1, pre-PBAC response

a. Prophylactic rADAMTS13: FFP intolerance set to 100% with dosing assumptions as per Table 15.

b.On-demand rADAMTS13: Based on an average 0.73 acute and 3.82 subacute cTTP episodes per year in patients treated prophylactically with rADAMTS13 corresponding to an additional 1.54 PBS scripts per patient per year of 1500 IU vials, and 1.40 PBS scripts per patient per year of 500 IU vials.

c. MBS: Cost offset for reduced administration costs (infusion MBS 14245 and nursing practitioner MBS 82215) for prophylaxis with fresh frozen plasma.

MBS = Medicare Benefits Scheme, PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

The redacted values correspond to the following ranges:

[1] $0 to < $10 million

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC recommended a Section 100 (Highly Specialised Drugs Program) listing of recombinant ADAMTS13 (rADAMTS13) enzyme replacement therapy for prophylactic and on-demand treatment of patients with chronic, severe congenital thrombotic thrombocytopenia purpura (cTTP). While the submission requested a listing restricted to cTTP patients who are intolerant to or who are otherwise unable to receive prophylaxis with fresh frozen plasma (FFP), the PBAC considered that it would be reasonable to allow all patients with cTTP to access prophylactic and on-demand treatment with rADAMTS13 in line with the approved TGA indication where PBS eligibility criteria are met. The PBAC was satisfied that rADAMTS13 provides, for some patients, a reduction in thrombocytopenia and other manifestations of TTP, compared with FFP. The PBAC considered that in the context of an extremely rare and life-threatening disease with high unmet clinical need, that the cost-effectiveness of rADAMTS13 would be acceptable at the price requested. The PBAC noted that consumer input supported the recommended PBS listing which is broader than the population initially requested by the sponsor.

7.2 The PBAC noted and welcomed the input from health care professionals, individuals and medical organisations who supported the listing of rADAMTS13. The input described the high clinical need for effective therapies for patients with cTTP and the potential risks associated with exposure to blood products. The input stated that the volume of FFP required to maintain ADAMTS13 at levels high enough to prevent acute and subacute events cannot be delivered for many patients, and that rural and remote patients can only access FFP in locations that have a blood bank facility. The PBAC also recognised that rADAMTS13 may provide benefit in the treatment of acute events, especially in young children where delivery of the volume load associated with the use of FFP can be problematic.

7.3 The PBAC noted most acute episodes of the disease lead to hospitalisation. The Committee noted that the chronic complications of the disease are broad ranging and

include, stroke, TIAs, memory loss, cognitive issues, chronic kidney injury and cardiac issues. The PBAC noted that FFP is the only treatment used for patients with cTTP in Australia and considered prophylactic FFP to be the appropriate comparator for prophylactic rADAMTS13.

7.4 The PBAC noted that rADAMTS13 resulted in a statistically significant reduction in both the number of thrombocytopenia events and the number of composite manifestations of TTP compared to standard of care (which included FFP) in Study 281102. The PBAC considered prophylaxis with rADAMTS13 to be superior in terms of efficacy compared to prophylaxis with FFP.

7.5 The PBAC noted that patients who received prophylactic rADAMTS13 in Study 281102 and extension Study 3002, had fewer hypersensitivity reactions compared to patients who received SoC in Study 281102. Longer-term data are required to ascertain the safety of prophylactic rADAMTS13, particularly regarding the most prevalent AEs of respiratory tract infections, abdominal pain, fatigue, headaches, and hypersensitivity reactions. Longer-term data are also required to ascertain the safety of prophylactic rADAMTS13 in paediatric populations, and during pregnancy and lactation.

7.6 The PBAC considered that a claim of non-inferior comparative safety of rADAMTS13 was reasonable compared to prophylaxis with FFP.

7.7 The PBAC noted that the submission had requested a listing for prophylactic use of rADAMTS13 for patients intolerant, hypersensitive or otherwise unsuitable to receive prophylactic treatment with FFP based on the rationale that this subpopulation has the highest clinical need. The PBAC considered there to be significant limitations associated with the use of FFP, as detailed by the clinician in the sponsor hearing. The PBAC considered that prophylaxis with FFP would not be a viable treatment option for a significant proportion of patients, due to the difficulty in administering the high volume of FFP required and in the context of ongoing risk of hypersensitivity reactions to FFP. Further, the PBAC considered that it would be difficult to define a patient population who were tolerant of and suitable to receive regular prophylaxis with FFP and on that basis that a recommendation aligned with the TGA-approved indication would be more appropriate. The PBAC considered this broader listing would address equity and potential leakage issues.

7.8 The PBAC noted that the TGA had approved rADAMTS13 for both prophylaxis and on-demand treatment of acute TTP episodes. The PBAC considered that prophylaxis with rADAMTS13 would reduce the risk of acute events, and it would be reasonable for clinicians to be able to treat acute episodes with additional doses of rADAMTS13 in line with the dosing recommendations in the TGA-approved PI. The PBAC noted that the pre-PBAC response indicated that the sponsor was open to a whole of population restriction.

7.9 The PBAC noted that a revised economic model submitted with the PSCR provided a scenario analysis evaluating rADAMTS13 prophylaxis versus FFP prophylaxis across the broader cTTP population. The ESC had however, considered the economic model to be unreliable for decision making. The PBAC noted the sponsor had provided a second

scenario analysis in their pre-PBAC response for prophylactic and on-demand use of rADAMTS13. The PBAC noted the cumulative disease complications (paragraph 7.3) and associated treatments including dialysis and liver and renal transplants have a substantial impact on quality of life and survival, although, reflecting the rarity of the condition, acknowledged the paucity of data available to reliably model long-term outcomes. Given this, the PBAC considered that revising the model structure or inputs is unlikely to adequately resolve the uncertainty associated with the modelled outcomes.

7.10 The PBAC reflected on previous determinations made for other rare diseases where there was significant unmet clinical need. The PBAC compared the available evidence, nature of the benefits, ICERs, numbers of patients expected to be treated, and the cost per patient per year for rADAMTS13 at the proposed price, with previous recommendations for other high-cost treatments for rare diseases. The PBAC considered that in the context of this extremely rare and life-threatening disease with high clinical need, it was satisfied that rADAMTS13 for prophylactic and on-demand use would be acceptably cost-effective at the price requested.

7.11 The PBAC noted that the requested vial prices for on-demand use were consistent with the requested prices for prophylactic use.

7.12 The PBAC noted the patient population is small and well defined. The PBAC noted that the Medical Services Advisory Committee (MSAC) had considered and supported the creation of a new Medicare Benefits Schedule item for ADAMTS13 activity, anti-ADAMTS13 autoantibody and ADAMTS13 genetic testing for the diagnosis of TTP (MSAC Application 1796). The PBAC advised it would be appropriate for severe hereditary ADAMTS 13 deficiency to be confirmed by all of the following (i) the presence of ADAMTS 13 genetic variants, (ii) the absence of ADAMTS 13 autoantibodies and (iii) ADAMTS 13 activity of less than 10%.

7.13 The PBAC considered it would be appropriate to allow for patients with a confirmed diagnosis of cTTP who have been receiving rADAMTS13 under an access program to be grandfathered if PBS criteria are met. The PBAC noted that under the proposed restriction, a grandfathered patient would be able to transition to PBS subsidised treatment through the initial treatment phase.

7.14 The PBAC noted the cost to PBS/RPBS for listing rADAMTS13 was estimated to be approximately $30 million to < $40 million over the first 6 years of listing as shown in Table 18 and described in paragraph 6.67.

7.15 In relation to the restriction:

- The PBAC noted that the volume of FFP required to achieve effective replacement of ADAMTS13 is usually prohibitive in neonates and infants considered it would be appropriate for the listing to be age-agnostic.
- The PBAC considered that it would be appropriate for a patient to have had a Karnofsky score of at least 70% if aged 16 years or older, or a Lansky score of at

least 80% if aged less than 16 years, at treatment initiation to be eligible for treatment with rADAMTS13.

- For prophylactic treatment, the PBAC considered that a S100 Highly Specialised Drugs (HSD) Program Public/Private hospitals listing would be appropriate for initial treatment and continuing prophylactic treatment.
- For on-demand treatment, a S100 HSD Program Public/Private hospitals listing would be appropriate.
- The PBAC considered that an Authority Required listing, submitted in writing or electronically through the Online PBS Authorities (OPA) system, is appropriate for initial prophylactic and on-demand therapy (once per episode). For continuing prophylactic therapy and additional doses for on-demand treatment, the PBAC considered that an Authority Required (telephone/electronic) listing is appropriate.
- The PBAC noted that consistent with usual arrangements, rADAMTS13 will not be PBS-subsidised if it is prescribed to an in-patient in a public hospital setting.
- The PBAC considered that rADAMTS13 should be prescribed by a haematologist.
- The PBAC noted that the approved Product Information stated that rADAMTS13 should be administered prophylactically every second week, or adjusted to every week based on prior prophylactic dosing regimen or clinical response), also based on patient's body weight. The PBAC considered it would be reasonable to allow clinicians to request an appropriate number of vials for 4 weeks of treatment under the initial and continuing treatment phases for prophylactic rADAMTS13 taking into account variations in patient body weight and dosing regimens.
- The PBAC noted the pre-PBAC response suggested sub-acute manifestations could be managed by administration of an additional 1 or 2 daily doses of rADAMTS13. The PBAC considered that the restriction should allow clinicians to request additional quantities of rADAMTS13 to treat sub-acute events.

7.16 The PBAC considered that rADAMTS13 should be exempt from the Early Supply rule given that it follows a variable, weight-based dosage regimen, and the Early Supply rule does not apply to prescriptions generated by hospitals.

7.17 The PBAC advised that rADAMTS13 should not be treated as interchangeable with any other drugs under Section 101 (3BA) of the *National Health Act 1953*.

7.18 The PBAC advised that rADAMTS13 is not suitable for prescribing by nurse practitioners.

7.19 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for rADAMTS13:

a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over alternative therapies, on the basis of the clinically relevant reduction in thrombocytopenia and other manifestations of TTP observed in

Study 281102;

b) The treatment is expected to address a high and urgent unmet clinical need given the limitations of existing therapy with FFP, and the significant long-term consequences of inadequate levels of ADAMTS13;

c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.

7.20 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Initial & grandfather prophylactic treatment

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
Recombinant ADAMTS-13					
Recombinant ADAMTS-13 500 units injection [1 vial] (&) inert substance diluent [5 mL vial], 1 pack	NEW (Public) NEW (Private)	1	1	5	Adzynma
Recombinant ADAMTS-13 1500 units injection [1 vial] (&) inert substance diluent [5 mL vial], 1 pack	NEW (Public) NEW (Private)	1	1	5	

Concept ID		**Category / Program:** ☒ Section 100 – Highly Specialised Drugs Program – Public and Private Hospitals
		Prescriber type: ☒ Medical Practitioners
		Benefit type: ☒ Authority Required in writing only via OPA HPOS upload/Post)
Prescribing rule level		**Administrative Advice:** Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
		Administrative Advice: The Karnofsky Performance Score is available at: https://oncologypro.esmo.org/oncology-in-practice/practice-tools/performance-scales www.mdcalc.com/calc/3168/karnofsky-performance-status-scale

		Administrative Advice: The Lansky Performance Score is available at: www.mdcalc.com/calc/3176/lansky-play-performace-scale-pediatric-functional-status
		Administrative Advice: No increase in the maximum number of repeats may be authorised.
		Administrative Advice: Special Pricing Arrangements apply
Restriction Summary [new1] / Treatment of Concept: [new1A]		
		Episodicity: Chronic
		Severity: Severe
		Condition: Congenital thrombotic thrombocytopenic purpura (cTTP)
		Indication: Chronic severe congenital thrombotic thrombocytopenic purpura (cTTP)
		Treatment Phase Prophylactic enzyme replacement therapy - Initial treatment
		Clinical criteria:
		Patient must have a diagnosis–of severe hereditary ADAMTS-13 deficiency, confirmed by all of the following: (i) presence of ADAMTS-13 genetic variants, (ii) absence of ADAMTS-13 autoantibodies and (iii) ADAMTS-13 activity of less than 10%
		AND
		Clinical criteria:
		Patient must have had a Karnofsky score of at least 70% if aged at least 16 years at treatment initiation with this drug **OR**
		Patient must have had a Lansky score of at least 80% if aged less than 16 years at treatment initiation with this drug
		Treatment criteria:
		Patient must not be undergoing PBS-subsidised treatment with this drug for any other thrombotic microangiopathy such as acquired or immune related TTP or atypical haemolytic uraemic syndrome (aHUS).
		Treatment criteria:
		Patient must be undergoing PBS-subsidised treatment with this drug as prophylactic enzyme replacement therapy.
		Treatment criteria:
		Must be treated by a haematologist
		Prescribing Instruction: This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting.
		Prescribing Instruction: At the time of authority application, medical practitioners must request the appropriate number of vials to provide sufficient drug for 4 weeks of treatment and up to 5 repeats, according to the patient's weight and the specified dosage in the Therapeutic Goods Administration (TGA) approved Product Information (PI). An appropriate amount of drug (maximum quantity in units) may require prescribing both strengths. Consider strengths and combinations that minimise drug wastage. A separate authority prescription form must be completed for each strength requested.
		Prescribing Instruction: Confirmation of eligibility for treatment with diagnostic reports including ADAMTS-13 genetic testing must be documented in the patient's medical records.
		Prescribing Instructions: The authority application must be made via the Online PBS Authorities System, or in writing via HPOS form upload or mail.

	Prescribing Instruction: If the application is submitted through HPOS form upload or mail, it must include: (1) details of the proposed prescription; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).

Continuing prophylactic treatment

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
Recombinant ADAMTS-13					
Recombinant ADAMTS-13 500 units injection [1 vial] (&) inert substance diluent [5 mL vial], 1 pack	NEW (Public) NEW (Private)	1	1	5	Adzynma
Recombinant ADAMTS-13 1500 units injection [1 vial] (&) inert substance diluent [5 mL vial], 1 pack	NEW (Public) NEW (Private)	1	1	5	

Concept ID		**Category / Program:** ☒ Section 100 – Highly Specialised Drugs Program – Public and Private Hospitals
		Prescriber type: ☒ Medical Practitioners
		Benefit type: ☒ Authority Required (telephone/online PBS Authorities system)
Prescribing rule level		**Administrative Advice:** Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
		Administrative Advice: The Karnofsky Performance Score is available at: https://oncologypro.esmo.org/oncology-in-practice/practice-tools/performance-scales www.mdcalc.com/calc/3168/karnofsky-performance-status-scale
		Administrative Advice: The Lansky Performance Score is available at: www.mdcalc.com/calc/3176/lansky-play-performace-scale-pediatric-functional-status
		Administrative Advice: No increase in the maximum number of repeats may be authorised.
		Administrative Advice: Special Pricing Arrangements apply
Restriction Summary [new2] / Treatment of Concept: [new2A]		
		Episodicity: Chronic
		Severity: Severe
		Condition: Congenital thrombotic thrombocytopenic purpura (cTTP)
		Indication: Chronic severe congenital thrombotic thrombocytopenic purpura (cTTP)
		Treatment Phase: Prophylactic enzyme replacement therapy- Continuing treatment
		Clinical criteria:
		Patient must have previously received PBS-subsidised treatment with this drug for this condition
		AND
		Clinical criteria:
		Patient must continue to demonstrate clinical benefit as assessed by the treating clinician.
		Treatment criteria:

	Patient must not be undergoing PBS-subsidised treatment with this drug for any other thrombotic microangiopathy such as acquired or immune related TTP or atypical haemolytic uraemic syndrome (aHUS).
	Treatment criteria:
	Patient must be undergoing PBS-subsidised treatment with this drug as prophylactic enzyme replacement therapy.
	Treatment criteria:
	Must be treated by a haematologist
	Prescribing Instruction: This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting.
	Prescribing Instruction: At the time of authority application, medical practitioners must request the appropriate number of vials to provide sufficient drug for 4 weeks of treatment and up to 5 repeats, according to the patient's weight and the specified dosage in the Therapeutic Goods Administration (TGA) approved Product Information (PI). An appropriate amount of drug (maximum quantity in units) may require prescribing both strengths. Consider strengths and combinations that minimise drug wastage. A separate authority prescription form must be completed for each strength requested.

On-demand treatment

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
Recombinant ADAMTS-13					
Recombinant ADAMTS-13 500 units injection [1 vial] (&) inert substance diluent [5 mL vial], 1 pack	NEW (Public) NEW (Private)	1	1	0	Adzynma
Recombinant ADAMTS-13 1500 units injection [1 vial] (&) inert substance diluent [5 mL vial], 1 pack	NEW (Public) NEW (Private)	1	1	0	

Concept ID		**Category / Program:** ☒ Section 100 – Highly Specialised Drugs Program – Public and Private Hospitals
		Prescriber type: ☒ Medical Practitioners
		Benefit type: ☒ Authority Required in writing only via OPA/post/HPOS upload)
Prescribing rule level		**Administrative Advice:** The Karnofsky Performance Score is available at: https://oncologypro.esmo.org/oncology-in-practice/practice-tools/performance-scales www.mdcalc.com/calc/3168/karnofsky-performance-status-scale
		Administrative Advice: The Lansky Performance Score is available at: www.mdcalc.com/calc/3176/lansky-play-performace-scale-pediatric-functional-status
		Administrative Advice: No increase in the maximum number of repeats may be authorised.
		Administrative Advice: Special Pricing Arrangements apply
Restriction Summary [new1] / Treatment of Concept: [new1A]		
		Severity: Severe
		Condition: Congenital thrombotic thrombocytopenic purpura (cTTP)
		Indication: Chronic severe congenital thrombotic thrombocytopenic purpura (cTTP)
		Treatment Phase: On demand enzyme replacement therapy
		Clinical criteria:
		Patient must have a diagnosis of severe hereditary ADAMTS-13 deficiency, confirmed by all of the following: (i) presence of ADAMTS-13 genetic variants, (ii) absence of ADAMTS-13 autoantibodies and (iii) ADAMTS-13 activity of less than 10%
		AND
		Clinical criteria:
		Patient must have had a Karnofsky score of at least 70% if aged at least 16 years at treatment initiation with this drug **OR**
		Patient must have had a Lansky score of at least 80% if aged less than 16 years at treatment initiation with this drug
		Treatment criteria:
		Patient must not be undergoing PBS-subsidised treatment with this drug for any other thrombotic microangiopathy such as acquired or immune related TTP or atypical haemolytic uraemic syndrome (aHUS).
		Treatment criteria:
		Patient must be undergoing PBS-subsidised treatment with this drug as on demand therapy to manage an acute TTP episode.

	Treatment criteria:
	Must be treated by a haematologist
	Prescribing Instruction: This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting.
	Prescribing Instruction: At the time of authority application, medical practitioners must request the appropriate number and strength of vials, to provide sufficient drug until 2 days after the resolution of the acute event, according to the patient's weight and the specified dosage in the Therapeutic Goods Administration (TGA) approved Product Information (PI). An appropriate amount of drug (maximum quantity in units) may require prescribing both strengths. Consider strengths and combinations that minimise drug wastage. A separate authority prescription form must be completed for each strength requested.
	Prescribing Instruction: Confirmation of eligibility for treatment with diagnostic reports including ADAMTS-13 genetic testing must be documented in the patient's medical records.
	Prescribing Instructions: The authority application must be made via the Online PBS Authorities System, or in writing via HPOS form upload or mail.
	Prescribing Instructions: If the application is submitted through HPOS form upload or mail, it must include: (i) details of the proposed prescription; and (ii) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
	Prescribing Instruction: To manage an acute TTP episode, patients are eligible for one on-demand therapy authority approval per episode under the 'on demand enzyme replacement therapy' restriction. Where additional doses are clinically required during the same episode, these must be prescribed under the 'Additional Doses-on demand enzyme replacement therapy ' restriction, which is also applicable to that episode.
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
	Indication: Chronic severe congenital thrombotic thrombocytopenic purpura (cTTP)
	Treatment Phase: Additional doses **-** On demand enzyme replacement therapy
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition under the 'on demand enzyme replacement therapy' restriction to manage the current acute TTP episode.
	AND

	Clinical criteria:
	Patient must have received an insufficient number of doses with this drug for the current acute TTP episode to resolve.
	Treatment criteria:
	Patient must not be undergoing PBS-subsidised treatment with this drug for any other thrombotic microangiopathy such as acquired or immune related TTP or atypical haemolytic uraemic syndrome (aHUS).
	Treatment criteria:
	Must be treated by a haematologist,
	Prescribing Instruction: This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting.
	Prescribing Instruction: At the time of authority application, the prescriber must request the appropriate number and strength of vials, to provide sufficient drug to complete treatment until 2 days after resolution of the acute or subacute event, according to the patient's weight and the specified dosage in the Therapeutic Goods Administration (TGA) approved Product Information (PI). An appropriate amount of drug (maximum quantity in units) may require prescribing both strengths. Consider strengths and combinations that minimise drug wastage. A separate authority prescription form must be completed for each strength requested.
	Prescribing Instruction: To manage an acute TTP episode, patients are eligible for one on-demand therapy authority approval per episode under the 'on demand enzyme replacement therapy' restriction. Where additional doses are clinically required during the same episode, these must be prescribed under the 'Additional Doses-on demand enzyme replacement therapy ' restriction, which is also applicable to that episode.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.