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Newcastle University

Health Technology Briefing
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Apadamtase alfa for treating acute thrombotic thrombocytopenic purpura (TTP) episodes associated with congenital TTP (cTTP) and long-term prophylaxis in patients with congenital ADAMTS-13 deficiency

Company/Developer	Takeda UK Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 22741	NICE ID: 9978	UKPS ID: 664931

Licensing and Market Availability Plans

Currently in phase II/III trials.

Summary

Apadamtase alfa is currently in clinical development for treating thrombotic thrombocytopenic purpura (TTP) episodes associated with congenital TTP (cTTP) and long-term prophylaxis in patients with congenital ADAMTS-13 deficiency. Congenital ADAMTS-13 occurs when genetic mutations lead to low levels of the ADAMTS-13 enzyme (a protein). This condition is characterised by recurrent episodes of acute (sudden onset) TTP - a rare, serious blood disease, and sub-acute manifestations in the intervening periods. It typically presents either in infancy or later in life, particularly in pregnancy. Major manifestations may include a severe decrease in the number of blood platelets (thrombocytopenia), abnormal destruction of red blood cells (hemolytic anemia), and disturbances in the nervous system and other organs occur due to small clots that form in the smallest arteries. There is a need for treatments that directly increase ADAMTS-13 levels. Since apadamtase alfa replaces ADAMTS-13, it may prevent/control TTP flare-ups.

Apadamtase alfa is a lab-made replacement therapy for the ADAMTS-13, which is involved in the regulation of blood clotting. By replacing ADAMTS-13, apadamtase alfa may prevent or control acute TTP events. In a phase III trial, apadamtase alfa will be administered via intravenous infusion (IV). Current standard of care involves burdensome plasma infusions. If licensed, apadamtase alfa will offer an additional treatment option which directly addresses the underlying mechanism of disease for patients with TTP who currently have few well-tolerated therapies available.

Proposed Indication

Patients with thrombotic thrombocytopenic purpura (TPP) episodes associated with congenital TTP (cTTP) and long-term prophylaxis in patients with congenital ADAMTS-13 deficiency.[1]

Technology

Description

Apadamtase alfa (TAK-755; BAX 930; rADAMTS13; SHP-655; recombinant ADAMTS-13) is a recombinant [lab-made] form of the distntegrin and metalloproteinase enzyme with a thrombospondin type 1 motif, member 13 (ADAMTS-13) enzyme, which is involved in regulation of blood clotting.[2] The ADAMTS-13 enzyme breaks up another blood protein called von Willebrand factor that forms blood clots by clumping together with platelets.[3]

Apadamtase alfa is currently in clinical development for TTP episodes associated with congenital TTP (cTTP) and long-term prophylaxis in patients with congenital ADAMTS-13 deficiency. In the phase III trial, apadamtase alfa will be administered via intravenous infusion (IV). Participants in the prophylaxis cohort will receive 40 international units (IU) per kilogram of apadamtase alfa ORT during periods one and two and switch to apadamtase alfa SIN during period three for six months once or twice per week. In the on-demand cohort, participants will receive daily IV dose of apadamtase alfa.[1]

Key Innovation

The most common treatment option for TTP is therapy with fresh frozen plasma, with the aim to replace the ADAMTS-13 enzyme in the patient's plasma. However, plasma therapies have limitations. Some subjects do not respond and are refractory to plasma therapies. Others receive only transient benefits following plasma therapies and experience relapse. TTP relapse rates following plasma exchange are reported to be 36-37% and may be even higher in survivors with low ADAMTS-13 activity levels. Therefore, there is a need for more therapeutic options that mechanistically support ADAMTS-13 activity for the treatment of TTP.[4] Apadamtase alfa is a medicine that replaces ADAMTS-13 and thus may prevent or control TTP flare-ups, called acute TTP events.[5] If licensed, apadamtase alfa will offer an additional treatment option for patients with TTP who currently have few well-tolerated therapies available.

Regulatory & Development Status

Apadamtase alfa does not currently have Marketing Authorisation in the EU/UK for any indication.

Apadamtase alfa is in phase II development for acquired TTP (aTTP).[6]

Patient Group

Disease Area and Clinical Need

Congenital ADAMTS-13 deficiency is a rare disease that leads to recurrent episodes of acute TTP.[7] TTP is a rare, serious blood disease.[8] Congenital TTP is caused by deficiency of an enzyme called ADAMTS-13 which breaks down large von Willebrand factor multimers. When ADAMTS-13 levels are very low, the ultra-large von Willebrand factor multimers can cause a thrombotic microangiopathy that is, damage to small blood vessels in vital organs (typically the brain, the heart, and kidneys).[9] Major manifestations may include a severe decrease in the number of blood platelets (thrombocytopenia), abnormal destruction of red blood cells (hemolytic anemia) and disturbances in the nervous system and other organs occur as a result of small clots that form in the smallest arteries. The thrombocytopenia and hemolytic anemia are a

result of these small clots in the blood vessels of many organs, which potentially block the normal flow of blood through the vessels. Disturbances affecting the nervous system may include headaches, mental changes, confusion, speech abnormalities, slight or partial paralysis (paresis), seizures or coma. Fever, blood plasma proteins in the urine (proteinuria), and red blood cells in the urine (hematuria) may also occur. Affected individuals also exhibit red rash-like areas of skin or patches of purplish discoloration (purpura) resulting from abnormal bleeding into the mucous membranes (the thin, moist layer lining the body's cavities) and into the skin that can be a sign of low platelets. Additional features of TTP can include abnormally heavy bleeding (hemorrhaging), weakness, fatigue, lack of colour (pallor) and abdominal pain with nausea and vomiting. In half of individuals with TTP, increased levels of a chemical compound known as creatinine are found in the blood.[8] TTP can be either congenital or acquired. Acquired TTP is more common than the congenital type. Congenital form of TTP results from mutations to the gene coding for ADAMTS-13.[10] It typically appears either in infancy or later in life, particularly in pregnancy.[11] The deficiency of ADAMTS-13 activity alone does not cause clinically apparent TTP. Individuals with hereditary ADAMTS-13 deficiency remain asymptomatic until a triggering event such as an infection or pregnancy occurs.[10]

TTP has an annual incidence of between 1.2 to 11 cases per million in the UK and is more common in females than males. There are between 100 and 150 cases of TTP per year. Relapses have been reported in 30% to 40% of patients.[9] In England, in 2020-21, thrombotic microangiopathy (ICD10: M31.1), which is a pattern of damage that can occur in the smallest blood vessels inside many of body's vital organs – most commonly the kidney and brain,[12] resulted in 1,439 finished consultant episodes (FCESs), 963 of which resulted in day cases, and 1,425 in FCE bed days.[13] The population likely to be eligible to receive apadamtase alfa could not be estimated from available published sources.

Recommended Treatment Options

Treatment for cTTP is focused on replenishing ADAMTS-13 levels. This can be achieved using therapeutic plasma exchange in an acute episode but this is rarely required as an ongoing treatment approach. Instead, infusion of ADAMTS13-rich blood products is more frequently used and, although a number of products including cryosupernatant, whole blood, and cryoprecipitate have historically been used, the most common treatment is fresh-frozen plasma (FFP) infusion. In the United Kingdom, intermediate purity factor VIII concentrate (BPL 8Y) is also used, a virally inactivated plasma-derived factor VIII product containing ADAMTS-13.[14]

Clinical Trial Information

Trial	NCT03393975; A Phase 3, Prospective, Randomized, Controlled, Open-label, Multicenter, 2 Period Crossover Study With a Single Arm Continuation Evaluating the Safety And Efficacy of BAX 930 (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]) **Phase III –** Recruiting **Location(s):** 6 EU countries, UK, USA, Switzerland and Japan **Primary completion date:** November, 2023
Trial Design	Randomised, crossover assignment, open-label
Population	N=57 (estimated); participants aged 0 to 70 years who have a documented diagnosis of severe hereditary ADAMTS13 deficiency

Intervention(s)	• Prophylaxis cohort: IV infusions of 40 IU/kg apadamtase alfa ORT during period 1 and period 2 and switch to BAX 930 SIN during period 3 for six months once in a week or twice in a week • On-demand cohort: daily IV dose of apadamtase alfa
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: number of acute TTP events (time frame: throughout the study period of approximately 70 months) See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	NCT04683003; EudraCT 2020-003348-10; 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) **Phase III –** Recruiting **Location(s):** 6 EU countries, UK, USA, Switzerland and Japan **Primary completion date:** August, 2026
Trial Design	Non-randomised, parallel assignment, open-label
Population	N=77 (estimated); participants aged 0 to 70 years who have completed NCT03393975 study in the prophylactic cohort
Intervention(s)	• Prophylaxis cohort: IV infusions of 40 IU/kg apadamtase alfa once every week or once every other week for the duration of the study (approximately 3 years, or until commercial availability of investigational product (IP) in the country, or decision not to launch in the country, whichever occurs first). Participants joining from an Expanded Access Program may continue to follow their previous dosing regimen. • On-demand cohort: IV infusion of 40 IU/kg followed by 20 IU/kg on day 2 and then 15 IU/kg daily until 2 days after the acute TTP event has resolved (approximately one month)
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: incidence of related treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) (time frame: throughout the study period of approximately 6 years) See trial record for full list of other outcomes
Results (efficacy)	-

Results (safety)	-

Estimated Cost

The cost of apadamtase alfa is not yet known.

Relevant Guidance

NICE Guidance

No relevant guidance identified.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- International Society on Thrombosis and Haemostasis (ISTH). ISTH guidelines for the diagnosis of thrombotic thrombocytopenic purpura. 2020.[15]
- International Society on Thrombosis and Haemostasis (ISTH). ISTH guidelines for treatment of thrombotic thrombocytopenic purpura. 2020.[16]
- British Society for Haematology. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. 2012.[17]

Additional Information

References

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