SANOFI GENZYME
Rare Blood Disorders
Medical Affairs
Request for Proposals

Date: May 10, 2021	
Disease State: *Acquired Thrombotic Thrombocytopenic Purpura* *(aTTP)*	
Therapeutic Area: Rare Blood Disorders	
Area of Interest: aTTP	
Geographic Scope: Global and US	
Internal Requestor Information:	
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Due Date: May 31, 2021 by no later than 5:00 PM ET	
Submission Portal: https://sgrants.envisionpharma.com/vt_sgrants/	
RFP Title: ISICEM aTTP 2021	

BACKGROUND

Acquired thrombotic thrombocytopenic purpura (aTTP) is a hematological and critical care emergency, with a 90% mortality rate if left untreated [1]. It is a thrombotic microangiopathy characterized by severe thrombocytopenia, hemolytic anemia, and a variable degree of ischemic end organ damage [2]. aTTP is caused by inhibitory autoantibodies to ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13), resulting in the impaired processing of ultra-large von Willebrand Factor (ULvWF) multimers [3]. It is an ultra-orphan disease with an annual incidence reported to be approximately 3-11 per million people [4, 5].

Many patients with aTTP require ICU admission, e.g. due to severe organ involvement or need for close surveillance, as sudden death or complications can occur at any time during the first days of treatment [1]. Differential diagnosis may be complicated, as aTTP is a member of the thrombotic microangiopathies, with a heterogeneous presentation. TMAs have a broad spectrum of overlapping clinical phenotypes, which may complicate a rapid and correct differential diagnosis [6]. The initial diagnosis of aTTP is based on clinical and laboratory findings (microangiopathic hemolytic anemia (MAHA) with schistocytes, peripheral thrombocytopenia, and variable laboratory evidence of organ involvement) [1, 6]. An ADAMTS13 assay result of <10% confirms the diagnosis of aTTP, however the ADAMTS13 activity assay is not yet widely available, and several days may elapse before the results are available. The diagnosis is urgent, as the disseminated microthromboses can result in rapidly developing multiorgan failure [1].

TTP is an emergency that requires PEX initiation together with immunosuppression (steroids and rituximab) as soon as there is a high clinical suspicion of aTTP [1]. Despite PEX and immunosuppression, patients remain at risk for significant morbidity and mortality. Up to 20% of the patients still die, with most deaths occurring within 30 days of diagnosis [7,8,9,10]. Some patients do not or only slowly respond to PEX and immunosuppression, called refractory disease, which is identified as an indicator of a poor prognosis for survival. The incidence of refractory disease is approximately 17% [10]. Up to half of the patients may suffer from disease

exacerbations shortly after stopping PEX [11], and there is a lifelong risk for relapses of the disease [12].

Due to the rarity of the disease, and the emergency-nature of aTTP, there is a need to raise awareness on the urgency to rapidly diagnose and initiate therapy in patients, particularly for ICU and emergency room physicians. In recent years, knowledge around the pathophysiology of this disease has inspired new efforts to optimize a fast differential diagnosis (e.g., ADAMTS13 testing and surrogate scoring systems) and to prevent early deaths by targeting different axis of the disease, including the incorporation of new therapies (i.e., suppression of autoantibody production, replenishing ADAMTS13, and blocking microvascular thrombosis) [13]. Recently, ISTH guidelines on the diagnosis and acute management of TTP have been recently published in an attempt to harmonize clinical practices [14,15], as well as the publication of expert statements on the ICU management for aTTP patients with thrombotic thrombocytopenic [1]. However, disease awareness is limited within ICU/ER community, and initial management practices remain very heterogeneous, so further education is needed.

REQUEST FOR aTTP IME GRANT PROPOSALS

SANOFI GENZYME is seeking proposals to close these independently defined healthcare gaps to improve clinician knowledge of new diagnosis and treatment strategies in aTTP. *Proposals can target one or multiple audiences.*

Specifically, Sanofi Genzyme will consider programs including, but not limited to, the following:

- IME Virtual live/enduring symposium at International Symposium on Intensive Care and Emergency Medicine (ISICEM) 2021
    1. For ISICEM, the 90 minute slot and slot fees have been secured by Sanofi Genzyme and fees do not need to be included in this proposal.
    2. The slot is for Wednesday Sept 1, 2021 (18.15-19.45 CET +1)
- Regional and/or Local distribution channels with enduring activity
- Accredited or Non-accredited IME activities
- Single supported and multi-supported activities
- Maximum request not to exceed $250,000

Preference will be given to proposals that recommend appropriately designed interventions that are likely to enhance a learner's knowledge of the unmet needs and employ proven strategies to overcome knowledge and performance gaps and barriers.

PROPOSALS

Proposal should include the following information

- Target Audience and Audience Generation: describe methods for reaching the target audience including description of recruitment and placement strategies to maximize participation.
- Learning Objectives and Content Accuracy: Provide clearly defined and measurable learning objectives framed as expected practice improvements in relation to the identified gaps and barriers.
- Include an overview of program content and explanation of criteria that will guide content selection, considering level of evidence and other variables. Sanofi Genzyme is committed to the highest standards in ensuring patient safety; the applicant should describe methods to ensure complete, accurate, evidence-based review of key safety data for any therapeutic

entities discussed in the activity. Explain how content will be updated, if necessary, throughout the program period, and how accuracy will be ensured.

- Educational Methods: Sanofi Genzyme supports the ACCME guidance for educational methods to be clearly designed to address the knowledge, competence and/or performance gaps that may underlie an identified healthcare gap. Your proposal should demonstrate an understanding of instructional design as it relates to the gaps in the knowledge, competence, or performance of the targeted audience. Educational methods and design should be based on current literature in CME best practice and consistent with ACCME accreditation criteria, as applicable. Preference will be given to applications that utilize methods that have been shown to result in practice improvements, and/or with data on the effectiveness of other programs of the same type.
- Faculty Recruitment and Development: Provide Information on the expected qualifications of contributors and description of methods to ensure recruitment of course directors and faculty who meet the qualifications. Explain any methods that will be used to ensure that faculty are fully trained in the program expectations and any skills that may be needed to ensure effective delivery of intended education.
- Program Evaluation and Outcomes: Provide a description of the approach to evaluate the reach and quality of program delivery; methods for monitoring individual activities and for ensuring ongoing quality improvements.

Preference will be given to programs with Objectives and Outcomes Plans with objective measures of changes in knowledge, and/or additional measures of improvements in competence, performance, patient health, population health, and/or system improvements, as aligned with the design of the intervention.

- Budget: Include a detailed budget with rationale and breakdown of costs, per unit, and description of each budget line item. In addition, please include any registrations fees paid by the learner, and how the fees will be applied. The 90-minute symposium slot fee for ISICEM will be covered by Sanofi Genzyme and should not be included in the proposal.
- Accreditation: If proposal involves an accredited program, the accreditation must be provided by an appropriate accrediting body and fully compliant with the accrediting body's criteria and applicable government guidelines and regulations.
- Fair Balance: The proposal should briefly describe methods for ensuring fair and balanced content, identification and resolution of conflict of interest, in alignment with applicable ACCME criteria.
- Communication and Publication Plan: Provide a description of how the provider will keep Sanofi Genzyme informed of progress. If applicable, include description of how the results of this educational intervention will be presented, published or disseminated.

REFERENCES

[1] Azoulay E, Bauer PR, Mariotte E, et al. Expert statement on the ICU management of patients with thrombotic thrombocytopenic purpura. Intensive Care Med. 2019 Nov;45(11):1518-1539
[2] Sadler JE. Von Willebrand factor, ADAMTS13, and thrombotic thrombocytopenic purpura. Blood 2008; 112: 11-8
[3] Sadler JE. Pathophysiology of thrombotic thrombocytopenic purpura. Blood 2017;130:1181-8
[4] Miller DP, Kaye JA, Shea K, et al. Incidence of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome. Epidemiology 2004;15:208-15.
[5] Reese JA, Muthurajah DS, Kremer Hovinga JA, Vesely SK, Terrell DR, George JN. Children and adults with thrombotic thrombocytopenic purpura associated with severe, acquired Adamts13 deficiency: comparison of incidence, demographic and clinical features. Pediatr Blood Cancer 2013;60:1676-82.

[6] Scully M, Hunt BJ, Benjamin S, et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol 2012;158:323-35
[7] Benhamou Y, Assie C, Boelle PY, et al. Development and validation of a predictive model for death in acquired severe ADAMTS13 deficiency-associated idiopathic thrombotic thrombocytopenic purpura: the French TMA Reference Center experience. Haematologica 2012;97:1181-6.
[8] Chaturvedi S, Bhatia N. Predictors of survival in thrombotic thrombocytopenic purpura. Haematologica 2013;98:e58.
[9] Goel R, King KE, Takemoto CM, Ness PM, Tobian AA. Prognostic risk-stratified score for predicting mortality in hospitalized patients with thrombotic thrombocytopenic purpura: nationally representative data from 2007 to 2012. Transfusion 2016.
[10] Benhamou Y, Boelle PY, Baudin B, et al. Cardiac troponin-I on diagnosis predicts early death and refractoriness in acquired thrombotic thrombocytopenic purpura. Experience of the French Thrombotic Microangiopathies Reference Center. J Thromb Haemost 2015;13:293-302.
[11] Coppo P, Veyradier A. Press Med. 2012; 41 (3 Pt2): e163-76
[12] Falter T, Alber KJ, Scharrer I. Long term outcome and sequelae in patients after acute thrombotic thrombocytopenic purpura episodes. Hamostaseologie 2013;33:113-20.
[13] Coppo P, Cuker A, George JN. Res Pract Thromb Haemost. 2019;3(1):26-37
[14] Zheng XL, Vesely SK, Cataland SR, Coppo P, Geldziler B, Iorio A, Matsumoto M, Mustafa RA, Pai M, Rock G, Russell L, Tarawneh R, Valdes J, Peyvandi F. ISTH guidelines for the diagnosis of thrombotic thrombocytopenic purpura. J Thromb Haemost. 2020 Oct;18(10):2486-2495.
[15] Zheng XL, Vesely SK, Cataland SR, Coppo P, Geldziler B, Iorio A, Matsumoto M, Mustafa RA, Pai M, Rock G, Russell L, Tarawneh R, Valdes J, Peyvandi F. ISTH guidelines for treatment of thrombotic thrombocytopenic purpura. J Thromb Haemost. 2020 Oct;18(10):2496-2502.