

**SANOFI GENZYME**  
**Rare Disease**  
**US Medical Affairs**  
**Request for Proposals**

<b>Date:</b> July 14, 2020	
<b>Disease State:</b> Fabry Disease	
<b>Therapeutic Area:</b> Rare Genetic Disease	
<b>Area of Interest:</b> Fabry Disease	
<b>Geographic Scope:</b> US	
<b>Internal Requestor Information:</b>	
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<b>Due Date:</b> September 24, 2020 5pm ET	
<b>Submission Portal:</b> <a href="https://sgrants.envisionpharma.com/vt_sgrants/">https://sgrants.envisionpharma.com/vt_sgrants/</a>	
<b>RFP Title:</b> WORLD 2021-LONGTERM CARDIAC AND RENAL OUTCOMES IN FABRY DISEASE	

## **BACKGROUND**

### **FABRY DISEASE**

Fabry disease is an X-linked lysosomal storage disorder with a prevalence significantly higher than previously thought resulting from deficiency of lysosomal  $\alpha$ -galactosidase A (GLA gene, Xq22) leading to buildup of glycosphingolipid, globotriaosylceramide (GL-3), within cells, notably endothelial cells, renal glomerular podocytes, cardiomyocytes, vascular smooth muscle cells, and neurons. Classic Fabry males exhibit extremely low to absent  $\alpha$ -Gal A activity and elevated plasma globotriaosylceramide (GL-3) and globotriaosylsphingosine (lyso-GL-3) levels. Classic Fabry disease is characterized by the pediatric onset of neuropathic pain and gastrointestinal issues differentially progressing to multi-organ involvement in both males and females with a risk of severe cardiac and/or renal involvement and endstage disease in the absence of guideline-based medical management. Patients with non-classical Fabry disease may exhibit milder reductions in  $\alpha$ -Gal A activity, a delayed onset of symptoms, slower disease progression, and a more organ-specific phenotype, in particular cardiac involvement (Hopkin et al. 2016; Ortiz et al. 2018).

### **FABRY CARDIAC AND KIDNEY DISEASE**

Cardiac disease and kidney disease are serious highly prevalent complications of Fabry disease. Evidence suggests the interplay of cardiovascular risk factors associated with Fabry chronic kidney disease and Fabry cardiac disease. Accumulation of GL-3 and Lyso-GL-3 in various

cardiac cell types leads to cardiac disease characterized by left ventricular hypertrophy, diastolic heart failure (HFpEF), hypertrophic cardiomyopathy, and cardiac arrhythmias including cardiac sudden death -- the primary cause of mortality in Fabry patients (Waldek S et al. 2009; Baig S et al. 2018). Factors associated with Fabry cardiac disease progression and outcomes include male gender, QRS duration, Mainz Severity Score Index, left ventricular mass, cardiac MRI late gadolinium enhancement, T1 mapping, and T2 mapping (Patel V et al. Heart 2015; Baig S et al. 2018; Camporeale A 2019; Augusto JB et al. 2020).

At the same time, sphingolipid deposition in renal cells, including podocytes, endothelial cells, and tubular epithelial cells, leads to podocyte dysfunction and loss, focal segmental and global glomerulosclerosis, progressive chronic kidney disease associated with albuminuria/proteinuria, and endstage kidney disease requiring dialysis and/or renal transplantation. Both baseline renal function (eGFR) and baseline level of proteinuria significantly correlate with the rate of renal function decline and renal outcomes (Schiffmann R et al. 2009; Wanner C et al. 2010). Chronic kidney disease in general is a well-established potent independent multiplier of cardiovascular risk characterized by abnormalities in endothelial function and vascular tone, progressive ventricular hypertrophy, vascular calcification, and cardiac sudden death (Go AS et al. 2004; Levey AS et al. 2011; Provenzano M et al. 2019). Contributing to Fabry cardiovascular risk is that associated with progressive Fabry kidney disease (Hopkin RJ et al. 2016; Banikazemi M et al. 2007; Talbot AS et al. 2015). Consistent with this idea, CKD stage 5 has been demonstrated to be an independent predictor of cardiovascular events including cardiac arrest, conduction defects, arrhythmias, and mortality in Fabry patients (Talbot AS et al. 2015). Such a relationship has been well-recognized in CKD irregardless of etiology although the pathogenic mechanisms remain to be more precisely defined (Turakhia MP et al. 2018).

Clinicians face significant healthcare challenges in Fabry disease from identifying, monitoring, and addressing risk factors impacting long-term cardiac outcomes and renal outcomes to the importance of implementing evidence-based long-term disease management given these considerations (Ortiz et al. 2018; Wanner C et al. 2018). Epidemiological evidence suggests that the interplay of highly prevalent Fabry cardiac and renal disease is consistent with that observed in non-Fabry CKD populations (Provenzano M et al. 2019). There is a critical need to understand risk factors and clinical characteristics associated with both Fabry cardiac and kidney disease progression including their interactions when evaluating both disease progression and evidence-based treatment response (Linhart A et al. 2020; Ortiz A et al. 2008; Wanner C et al. 2018).

## **REQUEST FOR FABRY DISEASE CME SYMPOSIUM GRANT PROPOSALS**

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

- CME live/enduring symposium at WORLD Symposium Feb 2021, San Diego (Symposium slot should be secured by grant recipient)
- Regional and/or Local distribution channels with or without enduring activity

- Accredited or Non-accredited IME activities
- Single supported and multi-supported activities
- Maximum request not to exceed \$300,000.

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. Symposium slot fee should be included and covered by the grant fees. Maximum request not to exceed \$300,000
- **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

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