Independent Medical Education

Request for Education (RFE)

Date Issued:	June 11, 2020
RFE Requestor Information:	Sonja Boon, CHCP Manager, Medical Affairs Amicus Therapeutics Ph: 848-213-7406 Email: sboon@amicusrx.com
RFE Code:	RFE-FD-20-104
Geographic Scope:	United States
New Due Date:	July 31, 2020
Amicus IME Portal:	https://www.cybergrants.com/amicus/IME
Area of Interest:	Fabry disease
Educational Venue:	NOTE: Due to COVID-19, the format of this meeting may move to a hybrid model of part live, part virtual/streaming or all streaming depending on the status of the pandemic. Please check the ACMG website for updates, as this may impact the design of your program. If part live, part virtual/streaming • Live Breakfast Satellite Symposium at 2021 ACMG Annual Clinical Genetics Meeting • Interactive live (eg, Case-based, panel discussion, etc.) with enduring components will be considered • Accredited IME activities If virtual only: • Engaging online event • Followed by interactive enduring online component
Educational Audiences:	The education should address the needs of clinicians who have a role in the diagnosis and treatment of Fabry disease patients including but not be limited to geneticists, genetic counselors, and other healthcare professionals
Program Budget:	Single-supported and multi-supported proposals with a request amount that does not exceed $200,000 will be considered
Accreditation:	ACCME, NSGC and others as appropriate

Background and Healthcare Gap:

Fabry disease (FD) is a progressive, inherited, X-linked disorder caused by mutations in the *GLA* gene that result in deficient or absent lysosomal α-Gal A activity. Absent or deficient activity of lysosomal α-Gal A (α-Gal A) results in progressive accumulation of globotriaosylceramide (Gb3) and related glycosphingolipids within lysosomes resulting in lysosomal dysfunction. The accumulation of Gb3 substrate in Fabry disease sets off a cascade of events that impacts not only the endosomal-autophagic-lysosomal system, but also other organelles (eg, mitochondria, ER, Golgi) and overall cell function. Ultimately, this leads to organ failure particularly impacting the heart, kidneys and central and peripheral nervous systems. Although FD is X-linked, females get the disease as well and it can be equal in severity to the classic form of the disease.

More than 1000 gene mutations have been identified in patients with Fabry disease. Mutations in the *GLA* gene cause misfolding, mis-assembly, and aggregation of the α-Gal A protein in the endoplasmic reticulum (ER). Large gene rearrangements, which are easily predicted to cause deficient activity, represent less than 10% of the mutations. Many of the gene mutations are single-base substitutions, missense mutations.

Like many genetic disorders FD is heterogenous and a clear genotype-phenotype relationship can be elusive. In addition, there are a number of variants whose relation to disease pathology is unknown or not clear (variants of unknown significance - VUS). As newborn screening (NBS) becomes increasingly common in the United States, families harboring VUS are being identified more often. One example in FD of a VUS is A143T. In human studies, A143T has been associated with reduced enzymatic activity in both males and females (Dobrovolny 2005, Spada 2006, Desnick 2015, Lenders 2016, Valtola 2020), but questions surrounding its pathogenicity and clinical management persist since the residual activity remains higher than most variants causing classic disease. Interestingly, other mutations with high residual activity (e.g., P205T – 36%) are associated with a classic phenotype (Hauth 2018, Shin 2008) and residual enzyme activity is an unreliable measure of disease severity in females (Deegan 2006), highlighting that this is not the only factor determining pathogenicity.

Fabry disease phenotypes often vary greatly, even within a family with the same variant, indicating there are other factors modifying phenotypic penetrance (Schiffmann 2016). In the context of genotype-phenotype correlations, a modifier is anything that changes the probability of the genotype manifesting a disease phenotype (phenotypic penetrance). The relative impact of genetic modifiers on phenotype increases along with residual GLA enzyme activity (Schiffmann 2016). Some factors that have been shown to impact Fabry phenotypic penetrance include:

- skewed X-inactivation (Dobrovolny 2005),
- the 5' -10C>T polymorphism and other intronic variants (Desnick 2015, Oder 2018),
- polymorphisms in genes associated with inflammation, vascular wall biology, and clotting mechanisms (Altarescu 2005)
- anemia, elevated lipids, and atherosclerosis/thrombosis risk factors increase likelihood of Fabry manifestations (Koca 2019)

In summary, VUS are very challenging to interpret and predicting the future impact they may have on the health of the individual remains poorly understood.

Educational Need:

Note: It is expected that any education provider submitting a grant application conduct their own independent needs assessment when identifying gaps in patient care and learning objectives that aim to reduce those gaps

Insights from past program outcomes, a detailed literature search, and educational needs assessment have established the need to address the following practice gaps to improve the quality of care to patients with FD, especially individuals and families with VUS:

- There is a need to enhance understanding of symptom onset, severity and the clinical implications of these manifestations in patients
- There is a need for awareness of atypical FD gene variants and the interplay with phenotypic penetrance to optimize clinical decision making for patients
- There is a need to better understand when to initiate treatment (when appropriate), follow-up and/or refer patients
- There is a need, in the context of Newborn Screening (NBS), to understand evidence-based guidelines for long term monitoring to determine clinical relevance for an individual
- There is a need to understand the specific implications of VUS for genetic counseling individuals and families

Area of Interest:

Amicus is seeking grant applications for the development of an innovative, well designed initiative that that addresses the educational needs outlined above and provides outcomes important to healthcare providers. Presentations and content must be scientifically sound, fair and balanced.

Program Requirements:

The program must be accredited and fully compliant with the criteria and/or standards of commercial support for ACCME and other relevant ethical codes and regulations.

The Policy Statement and the ACCME Standards require that a Program is conducted independently and without control or influence by Amicus Therapeutics Inc. over the Program's planning, content (including selection of speakers or moderators), or execution. The Program will also be free of commercial bias for or against any product. Amicus Therapeutics Inc. support of the Program must be clearly disclosed, including any prior relationships between Institution and Amicus Therapeutics Inc., and any prior relationships between Amicus Therapeutics Inc. and the speakers selected by the Institution.

In keeping with ACCME Standards, any product discussions in the Program must be balanced, objective, accurate and scientifically rigorous. This includes discussing the limitations of data, and that unapproved drug uses are identified as such.

The accredited provider and, if applicable, educational partner(s) must have a conflict-of-interest policy in place to identify and resolve all conflicts-of-interest from faculty or staff contributing to the development of content for this activity prior to the delivery of the program.

What the Proposal should include:

Executive Summary: Highlight the key elements of the program, including the elements listed below, in a one to two-page summary.

Needs Assessment of the Gaps and Barriers: A needs assessment independently developed and validated by the accredited provider should include an understanding of the gaps and barriers of the target audiences. The needs assessment must be referenced.

Target Audience: The target audience(s) for the educational program must be defined. Provide a clear rationale of why this audience is suitable to close the healthcare gap defined in the Needs Assessment.

Audience Generation: Describe the methods that will be employed to recruit the target audience. Include a rationale for these recruitment methods. Include information regarding the size of the recruitment audience, the number of anticipated participants and the expected number of CME/CE certificates issued.

Learning Objectives: Provide clearly defined and measurable learning objectives framed as practice improvements in relation to the identified barriers and gaps.

Content Accuracy: Describe methods to ensure complete, accurate, evidence-based review of key safety data for therapeutics discussed in the activity. Explain how the content will be updated, if necessary, throughout the program.

Program Evaluation and Outcomes: Provide a description of the methods to be employed and the key measurements to be assessed in evaluating this program.

Budget: Provide a clear breakdown of the budget (using Amicus template).

Accreditation: Indicate the type(s) of Continue Education credit that this program will offer (AMA, NSGC, AOA, MOC, etc.) and the name(s) of the accredited provider.

Resolution of Conflict of Interest and Fair Balance: Outline the practices employed by your organization to ensure that conflict of interest and fair balance of content is maintained throughout this program.

Communication Plan: Discuss how the provider will keep Amicus informed of program progress.

Terms and Conditions

1) Grant applications received in response to this RFE will be reviewed in accordance with Amicus policies and guidelines.

2) All communications about this RFE must come directly to Amicus's Independent Medical Education Department via the online portal.

3) Amicus reserves the right to approve or deny applications in response to this RFE, and may cancel, in part or in its entirety, this RFE.

4) Applying for this RFE does not commit Amicus to award a grant or pay costs toward the preparation of a response to this RFE.

References

1. Dobrovolny et al. 2005 Relationship between X-inactivation and clinical involvement in Fabry heterozygotes. Eleven novel mutations in the α-galactosidase A gene in the Czech and Slovak population J Mol Med (2005) 83: 647‑654 DOI 10.1007/s00109-005-0656-2

2. Spada 2006 High Incidence of Later-Onset Fabry Disease Revealed by Newborn Screening Am. J. Hum. Genet. 2006;79:31–40

3. Desnick et al. Fabry disease: The α-galactosidase A (GLA) c.427GNA (A143T) mutation, effect of the 5′ -10CNT polymorphism doi:10.1016/j.ymgme.2014.12.067

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11. Altarescu G, Moore DF, Schiffmann R. Effect of genetic modifiers on cerebral lesions in Fabry disease. Neurology. 2005;64(12):2148-2150. doi:10.1212/01.WNL.0000166000.24321.4F

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