Travere Therapeutics – Request for Proposals (RFP – FSGS IgAN 2021)

Timeline	Proposals may be submitted from March 15, 2021 until August 14, 2021. Review will be on a rolling basis.
Primary Area of Focus	Nephrology
Therapeutic Area	Focal Segmental Glomerulosclerosis and/or IgA Nephropathy
Educational Format	Accredited innovative medical education programs designed to address knowledge and competence gaps in disease awareness Examples include satellite symposium with enduring activities, online activities
Educational Audience	Primary: Nephrology Secondary: Primary Care/Internal Medicine
Geographic Scope	Global
Program Cost	Open
Successful submission	See website for details
RFP Code (please reference this code in your submission)	RFP – FSGS IgAN 2021
Website URL	https://travere.com/medical-education-grants/
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Clinical significance of proteinuria

Proteinuria is a marker for the presence of renal disease, mediates progressive renal dysfunction and is a strong risk factor for the development of cardiovascular disease (Topham P. *Clin Medicine* 2009;**9**:284-287). Decreasing urinary protein excretion has been shown in many glomerular diseases to slow the progression of kidney disease (Coresh J, et al. *Lancet Diabetes Endocrinol* 2019;7:115-127). What might be considered the appropriate treatment target for proteinuria varies by the glomerular disease. Changes in proteinuria may be more closely linked to better outcomes in disorders in which it represents the major pathophysiologic disturbance; for example, in podocytopathies such as FSGS, or IgAN, a mesangiopathic disease in which podocytopathic changes are a consequence of accumulation of IgA in the mesangium.

FSGS

In patients with FSGS, obtaining a partial or complete remission of proteinuria identifies those patients with better kidney outcomes, including slow progression rate and improvement in renal survival (Troyanov S, et al. *J Am Soc Nephrol* 2005; 16:1061-1068). Conventional definitions of complete (<0.3 g/g) and partial remission (<3.5 g/g and 50% reduction in proteinuria) are associated with better outcomes; however, an analysis by Troost, et al (Troost J, et al. *Clin J Am Soc Nephrol* 2018; 13:414-421) reported a novel definition of partial remission (<1.5 g/g and 40% reduction in proteinuria) associated with better long-term outcomes in patients with FSGS. Further, in a recent analysis of a randomized treatment trial of patients with steroid-resistant primary FSGS, continuous reduction in proteinuria levels, were significantly associated with improved GFR outcomes and kidney survival (Troost JP, *et al. Am J Kidney Dis* 2021; **77:** 216–225).

IgAN

Proteinuria is the single strongest modifiable prognostic indicator for disease progression in IgAN (Reich HN, *et al. J Am Soc Nephrol* 2007; **18:**3177–3183; Inker LA, *et al. Am J Kidney Dis* 2016; **68:**392–401). Reich et al (*J Am Soc Nephrol* 2007;18:3177-83) demonstrated that proteinuria exposure over

time is the strongest predictor of the rate of renal function decline and that a possible treatment target of less than 1 gram/day for proteinuria in IgAN, identified patients with better kidney outcomes; this target has been endorsed by KDIGO (draft guidelines June 2020).

Proteinuria as a validated endpoint in clinical trials

There are few clinical trials in kidney disease, especially rare glomerular disease, due to the large size, long duration and cost required to detect treatment effect in patients with CKD (Baigent C, *et al. Kidney Int* 2017; **92:**297–305). This in part is due to traditional endpoints utilized by regulatory agencies being representative of late-stage manifestations. Proteinuria and eGFR slope have been proposed as alternative early endpoints in clinical trials. These endpoints in CKD were reviewed at an NKF/FDA/EMA workshop in 2018 (Levey AS, *et al*. *Am J Kidney Dis* 2019; **75:**84–104), which concluded that early changes in albuminuria and eGFR slope meet the criteria for clinical trial endpoints. Changes in proteinuria levels are now recognized by the FDA as a valid target for clinical trials of primary glomerular diseases associated with significant proteinuria, such as FSGS and IgAN (US FDA, Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure; Accessed online at https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure [Dec 2020]).

Nephrologists could therefore benefit from evidence-based education on:

- The burden of FSGS and IgAN and unmet needs in disease management
- The pathophysiology that explains the role of proteinuria in the mechanism of disease of both FSGS and IgAN
- The importance of proteinuria in the overall management of patients with FSGS and/or IgAN
- The need to treat to proteinuric targets which have clinically meaningful outcomes
- The urgency to treat proteinuria as early as possible in the disease course

Successful proposals will follow the requirements as laid out @ https://travere.com/medical-education-grants/.