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

<table>
<thead>
<tr>
<th>Timeline</th>
<th>Proposals may be submitted from March 15, 2021 until August 14, 2021. Review will be on a rolling basis.</th>
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</thead>
<tbody>
<tr>
<td>Primary Area of Focus</td>
<td>Nephrology</td>
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<tr>
<td>Therapeutic Area</td>
<td>Focal Segmental Glomerulosclerosis and/or IgA Nephropathy</td>
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<tr>
<td>Educational Format</td>
<td>Accredited innovative medical education programs designed to address knowledge and competence gaps in disease awareness. Examples include satellite symposium with enduring activities, online activities</td>
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<tr>
<td>Educational Audience</td>
<td>Primary: Nephrology&lt;br&gt;Secondary: Primary Care/Internal Medicine</td>
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<tr>
<td>Geographic Scope</td>
<td>Global</td>
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<tr>
<td>Program Cost</td>
<td>Open</td>
</tr>
<tr>
<td>Successful submission</td>
<td>See website for details</td>
</tr>
<tr>
<td>RFP Code (please reference this code in your submission)</td>
<td>RFP – FSGS IgAN 2021</td>
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<tr>
<td>Website URL</td>
<td><a href="https://travere.com/medical-education-grants/">https://travere.com/medical-education-grants/</a></td>
</tr>
<tr>
<td>Traver Contact</td>
<td><a href="mailto:medgrants@travere.com">medgrants@travere.com</a></td>
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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 mesangial 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

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/.