Travere Therapeutics R&D Day 2020

December 9, 2020

Today's Speakers

Jonathan Hogan, M.D.
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Noah Rosenberg, M.D.
Chief Medical Officer at Travere Therapeutics

Peter Heerma
Chief Commercial Officer at Travere Therapeutics

TRAVERE™ THERAPEUTICS

Forward-Looking Statements

This presentation contains forward-looking statements, including statements about our prospects, products, growth projections, competitive position, potential regulatory filings and agency actions, and the anticipated development, timing, data readouts and therapeutic scope of programs in our clinical pipeline. These forward-looking statements may be accompanied by such words as “anticipate,” “believe,” “estimate,” “expect,” “forecast,” “intend,” “may,” “plan,” “project,” “target,” “will” and other words and terms of similar meaning. You should not place undue reliance on these statements.

These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements, including the safety and efficacy of our product candidates, product competition, market acceptance, the occurrence of adverse safety events with our products or product candidates, clinical trials risk, adverse market and economic conditions, regulatory uncertainty, our dependence on collaborations and other third parties over which we may not always have full control, failure to comply with government regulation, our ability to protect our intellectual property rights, and have sufficient rights to market our products and services together with the cost of doing so, problems with our manufacturing processes and our reliance on third parties, the potential impact of the ongoing COVID-19 pandemic, our ability to attract and retain qualified personnel, our level of indebtedness, environmental risks, change of control provisions in our collaborations and the other risks and uncertainties that are described in the Risk Factors section of our most recent annual or quarterly report and in other reports we have filed with the SEC.

These statements are based on our current beliefs and expectations and speak only as of the date of this presentation. We do not undertake any obligation to publicly update any forward-looking statements.

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Perspectives from the Nephrology Community

Rare kidney patients deserve better.

rarekidneyrevolution.com

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Bringing Travere Therapeutics to Life

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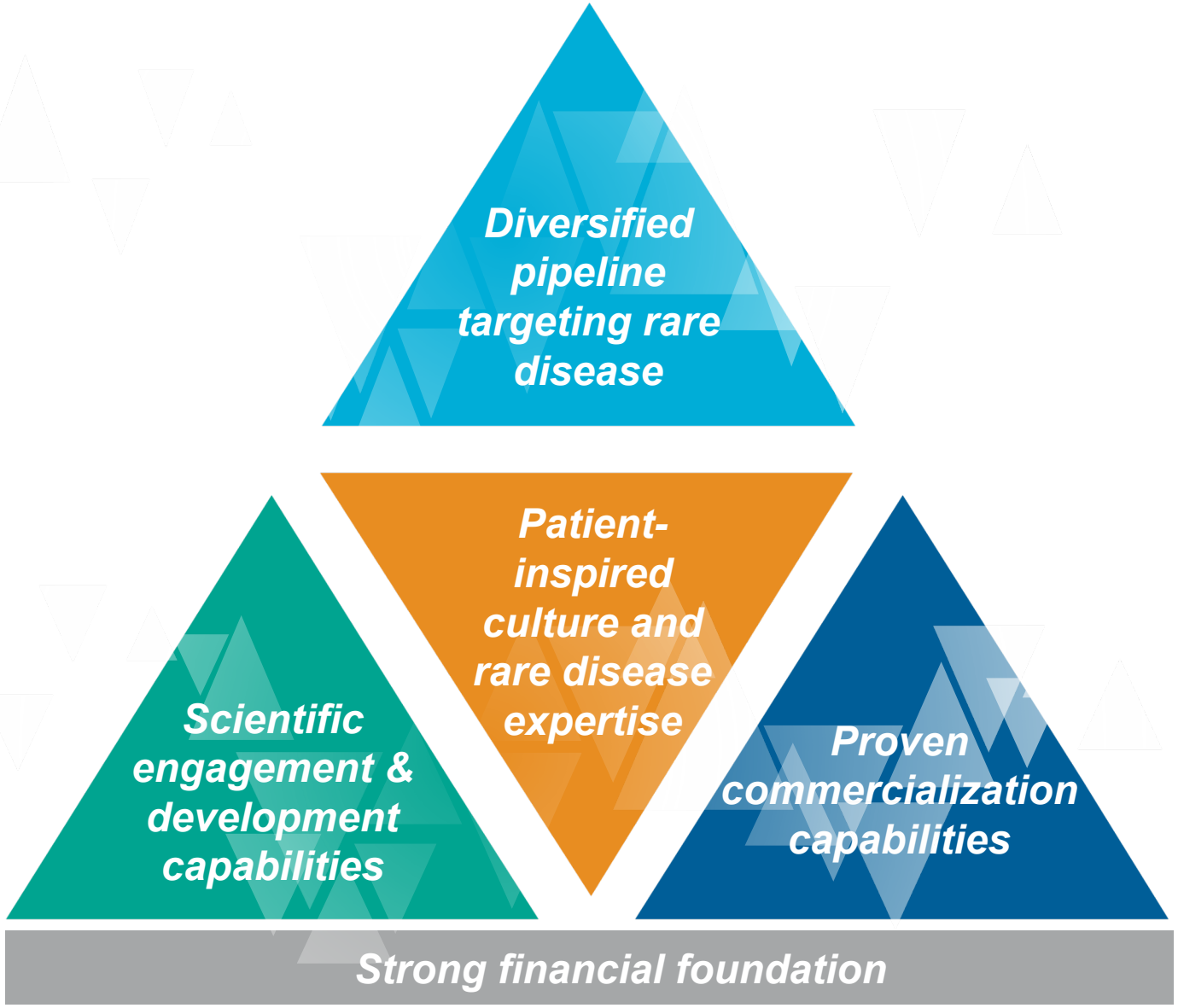
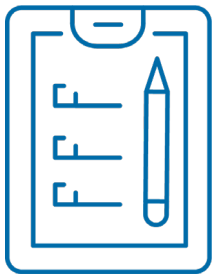
Key Strengths of Travere Therapeutics

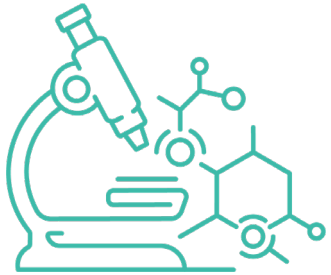


Leveraging an Established Leadership Position to Make a Difference



Driving earlier diagnosis to allow people to focus on life rather than their disease

Championing broad access to therapies and the diverse needs of people living with rare disease



Pioneering new paths to therapeutics for unmet needs in rare renal, hepatology and metabolism

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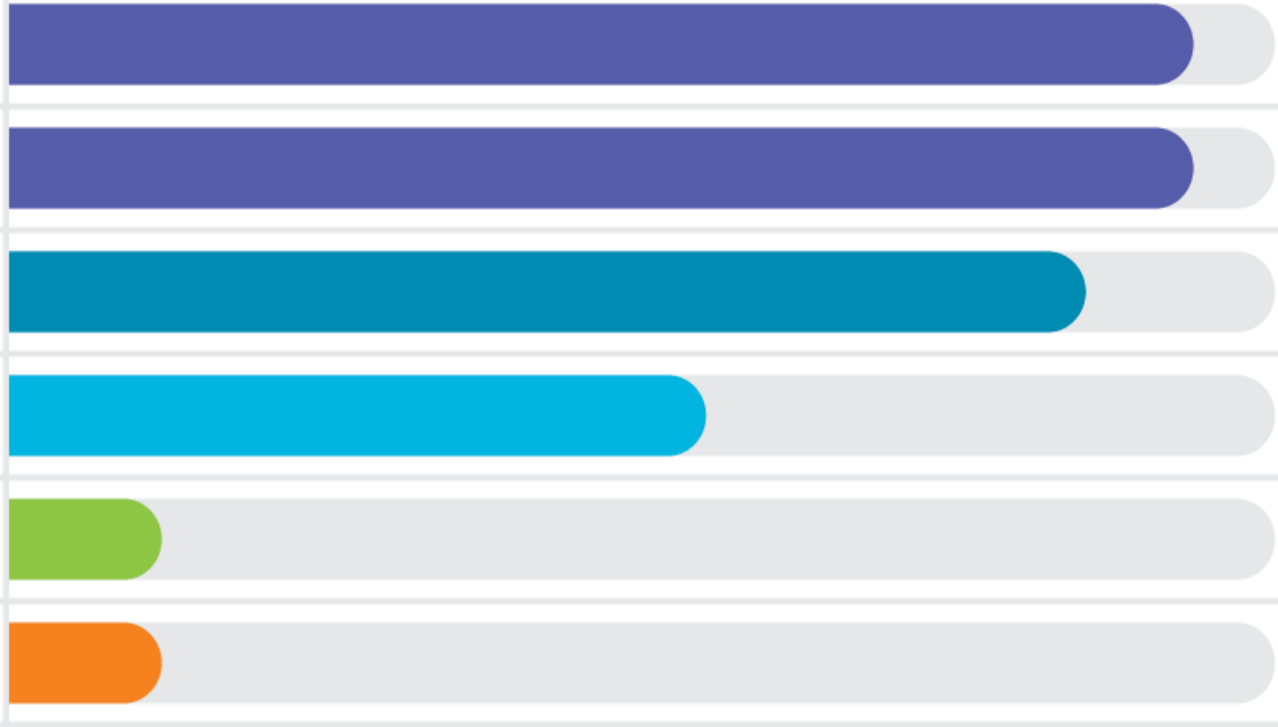
Pipeline of Potential First-in-Class Programs Targeting Rare Diseases

PROGRAM	THERAPEUTIC AREA	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3
Sparsentan	Focal Segmental Glomerulosclerosis (FSGS)				
Sparsentan	IgA Nephropathy (IgAN)				
CDCA*	Cerebrotendinous Xanthomatosis (CTX)				
TVT-058**	Classical Homocystinuria (HCU)				
NGLY1 Collaboration	NGLY1 Deficiency				
ALGS Collaboration	Alagille Syndrome (ALGS)				



*CDCA is not indicated for CTX but has received a medical necessity determination in the US by the FDA for CTX. Travere Therapeutics is conducting a Phase 3 clinical trial to examine the safety and efficacy of CDCA (Chenodal®) for the treatment of CTX.
**TVT-058 is currently in a Phase 1/2 clinical study.

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Path to Potential Breakthrough Growth for Travere Therapeutics

1Q21 Topline data from proteinuria endpoint* in DUPLEX Study in FSGS

3Q21 Topline data from proteinuria endpoint* in PROTECT Study in IgAN

2022 Potential NDA (Subpart H) and CMA filings for sparsentan in IgAN

2022 Potential commercial launch of sparsentan in IgAN

2021 Topline data from ongoing Phase 1/2 study evaluating TVT-058

2H21 Potential NDA (Subpart H) and CMA Filings for sparsentan in FSGS

2022 Potential commercial launch of sparsentan in FSGS

*Interim endpoint; confirmatory endpoint is slope of eGFR

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Patient-Inspired Urgency

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FSGS Disease State Overview

Jonathan Hogan, MD
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Perelman School of Medicine, University of Pennsylvania
Clinical Director, Penn Glomerular Center

Disclosures

Advisory board: ZyVersa Therapeutics

Consultant (last 12 months): Retrophin, GSK, Alexion, Calliditas, Aurinia, Kezar Life Sciences

Salary support for clinical trials: Retrophin, Alexion, Calliditas, Omeros, Complexa, GSK, Gilead, Boehringer Ingelheim, Regeneron, NIH

Royalties: up to date (Calcium/Phosphorous, MGRS)

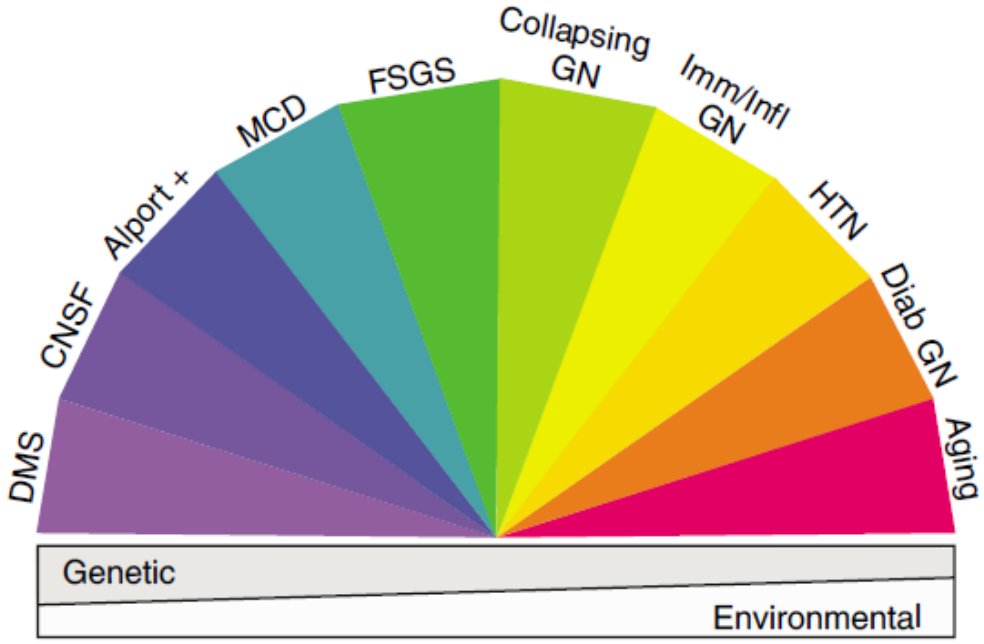
Outline

- Defining FSGS
- Epidemiology and pathophysiology of FSGS
- Impact of FSGS on kidney health
- Goals of treatment in FSGS

Globally, Glomerular Disease is a Leading Cause of CKD and ESKD

- Several different diseases can result in glomerular disease
- Podocyte dysfunction caused by genetic and/or environmental factors is central to the development of glomerular disease

The spectrum of podocyte diseases



Source: Wiggins, Kidney International (2007)

What is FSGS?
Focal Segmental Glomerulosclerosis (FSGS) is a Rare Glomerular Disorder

Defined as a **histologic pattern** that is characteristic of **various underlying etiologies**[1]

Multiple classification systems:[4]

- By Histopathologic Lesion
- By Clinical Presentation (e.g. with and without Nephrotic Syndrome)
- By Limited Understanding of Biology (e.g. Primary, Genetic, Secondary, Unknown Cause)

Sclerotic lesions form that are:[3]

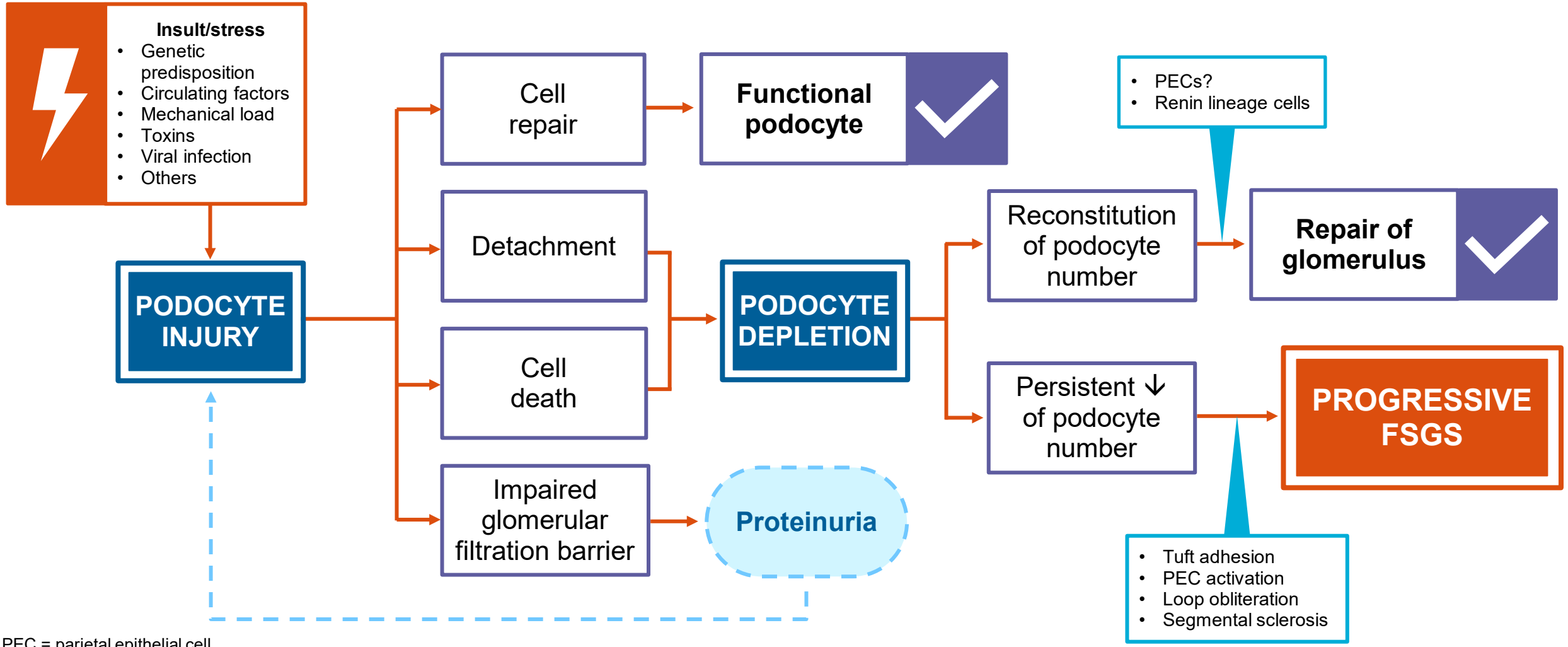
Focal
(<50% of **all glomeruli** affected)

&

Segmental
(<50% of the **glomerular tuft** affected)

1. Rosenberg AZ & Kopp JB. *Clin J Am Soc Nephrol* 2017; **12:**502–517; 2. D'Agati VD, *et al. N Engl J Med* 2011; **365:**2398–2411;
3. Jefferson JA & Shankland SJ. *Adv Chronic Kidney Dis* 2014; **21:**408–416; 4. KDIGO Clinical Practice Guideline on Glomerular Diseases (Public review draft - June 2020).
Available at: https://kdigo.org/wp-content/uploads/2017/02/KDIGO-GN-GL-Public-Review-Draft_1-June-2020.pdf [accessed September 2020]

FSGS is Caused by a Continuous and Sustained Podocyte Injury

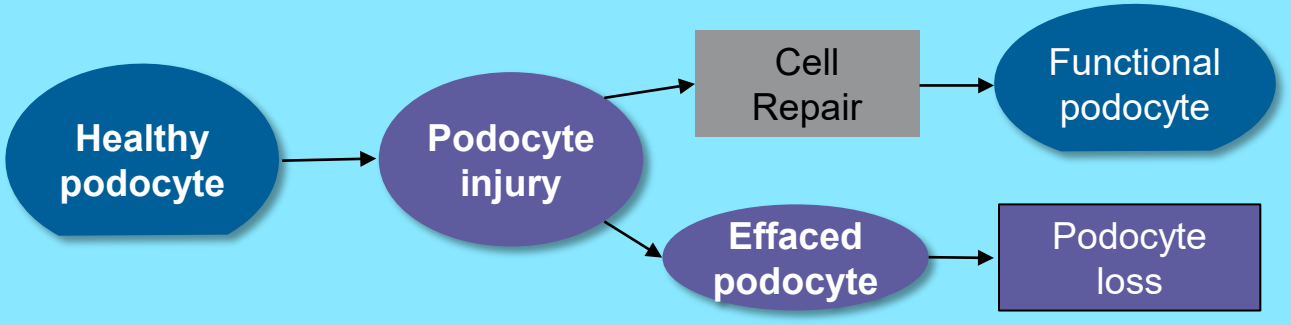


PEC = parietal epithelial cell.

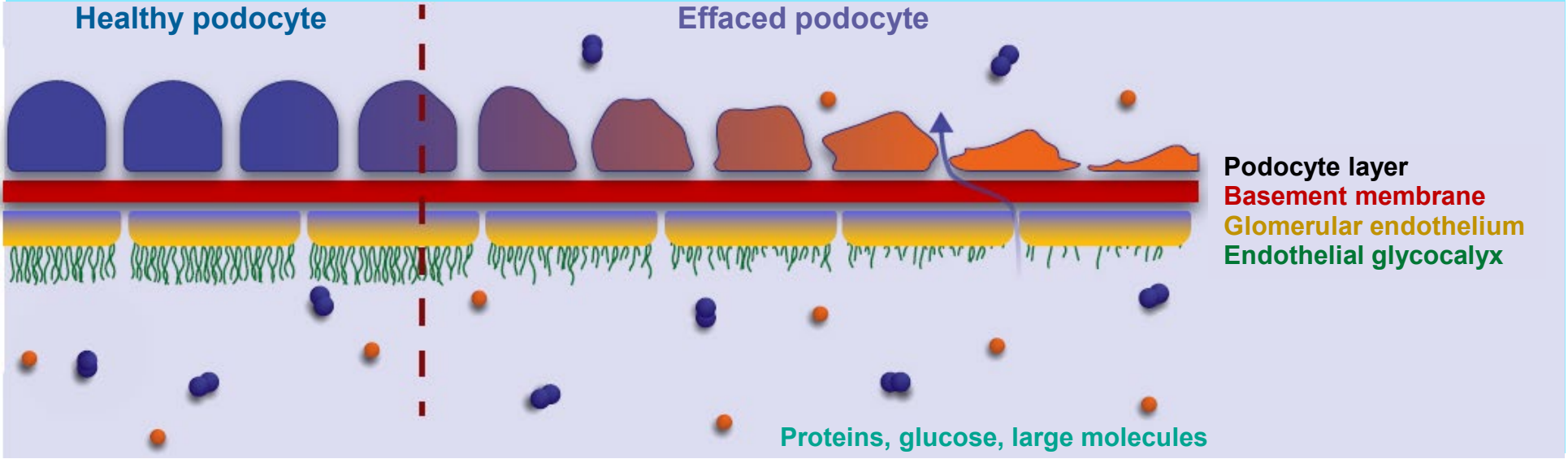
1. Jefferson JA & Shankland SJ. *Adv Chronic Kidney Dis* 2014; **21:**408–416; 2. De Vriese AS, *et al. J Am Soc Nephrol* 2018; **29:**759–774;
3. Wiggins, *et al. J Am Soc Nephrol* 2013 24(12):2081-95

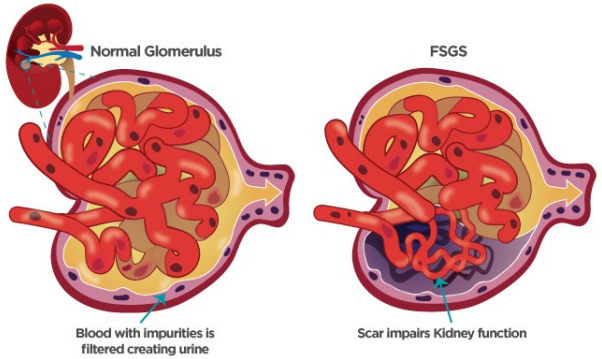
Podocyte Pathophysiology in FSGS

Podocyte injury leads to effaced podocytes and cell death



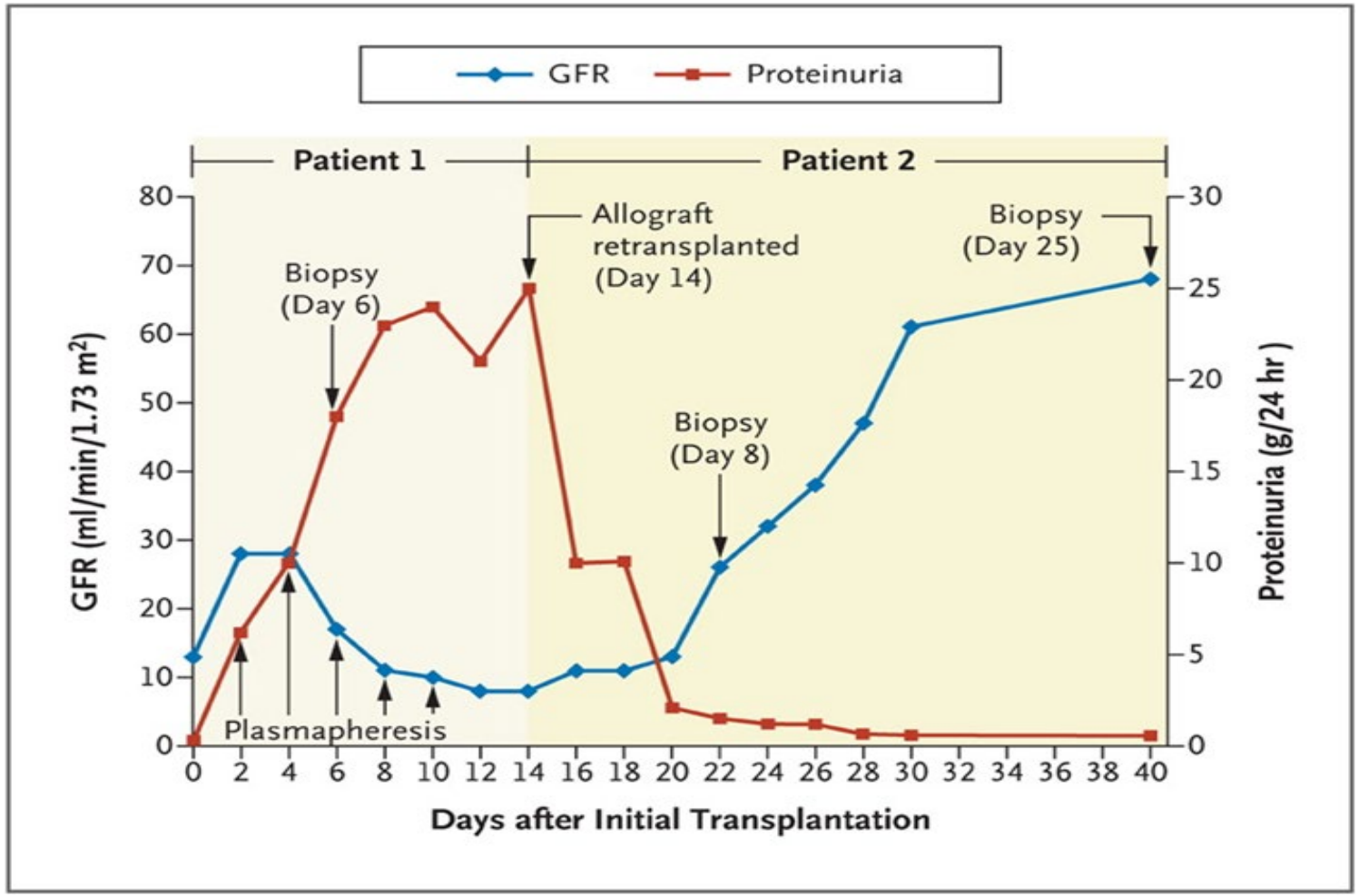
Effaced podocytes are associated with an impaired filtration barrier





1. Jefferson JA, Shankland SJ. *Adv Chronic Kidney Dis*. 2014;21(5):408-16. 2. Daehn IS. *Front. Med*. 2018;5(76), doi: 10.3389/fmed.2018.00076.

A Picture is Worth…



Gallon L et al. NEJM 2012

Epidemiology

FSGS is the leading glomerular cause of ESKD in the United States[1]

FSGS global incidence is estimated as[2]

0.1/100,000 in children

0.8/100,000 in adults

Incidence of primary FSGS has increased by

3- to 13-fold

during the last 20-30 years[3]

Incidence in adults is almost **equal** to that of **IgA nephropathy** and **twice** that of **membranous glomerulonephritis**[3]

Relative to other glomerular diseases, the **prevalence** of FSGS appears to be **increasing**[1]

Of all nephrotic syndrome cases, FSGS is the cause in:

~20% of children

40% of adults

Biopsy results for evaluation of idiopathic nephrotic syndrome have shown that FSGS is seen in up to **80%** in African American patients[3]

1. Kitiyakara C, et al. *Sem Nephrol.* 2003;23 (2):172-182. 2. McGrogan A *et al. Nephrol Dial Transplant.* 2011;26: 414–430. 3. Korbet SM. *J Am Soc Nephrol.* 2012; 23:1769–1776.

Unmet Needs in FSGS

50% of patients with **severe nephrotic syndrome** progress to **renal failure** at **1,000 days** after diagnosis[1]

FSGS is associated with a **50% risk** for **end-stage kidney disease (ESKD)** within **5 years of diagnosis** if patients do not achieve **partial or complete remission**[2]

47% of children[1,3]

38% of adults

Do not respond to currently available therapies[2]

Current therapeutic strategies are **limited** and include ACE-I's, ARBs, calcineurin inhibitors and steroids. There remains an **unmet need** for treatment options approved specifically for FSGS.

ACE-I = Angiotensin-converting enzyme inhibitor; ARB = Angiotensin II receptor blocker.

1. Gipson D. *Semin Nephrol.* 2016; 36(6):453-459. 2. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. *Kidney Inter., Suppl*. 2012; 2: 139–274. 3.Gipson D, et al. *Pediatr Nephrol.* 2006;21:344–349.

Why is it important to treat FSGS-associated glomerular disease? Treating FSGS-Associated Glomerular Disease is Important in Slowing the Progression to ESKD[1]

The severity of proteinuria is associated with risk of developing ESKD[2]

Non-nephrotic proteinuria
<15% of patients progress to ESKD in 10 years

→

Nephrotic proteinuria (>3 g/24 h)
≥50% of patients progress to ESKD in 5–10 years

→

Massive proteinuria (>10–14 g/24 h)
2–3 years = average time to ESKD

Patients with FSGS and persistent proteinuria are at increased risk of **progressive CKD** and **CV morbidity/mortality**

Remission of proteinuria is widely regarded as beneficial in slowing the progression of FSGS[3]

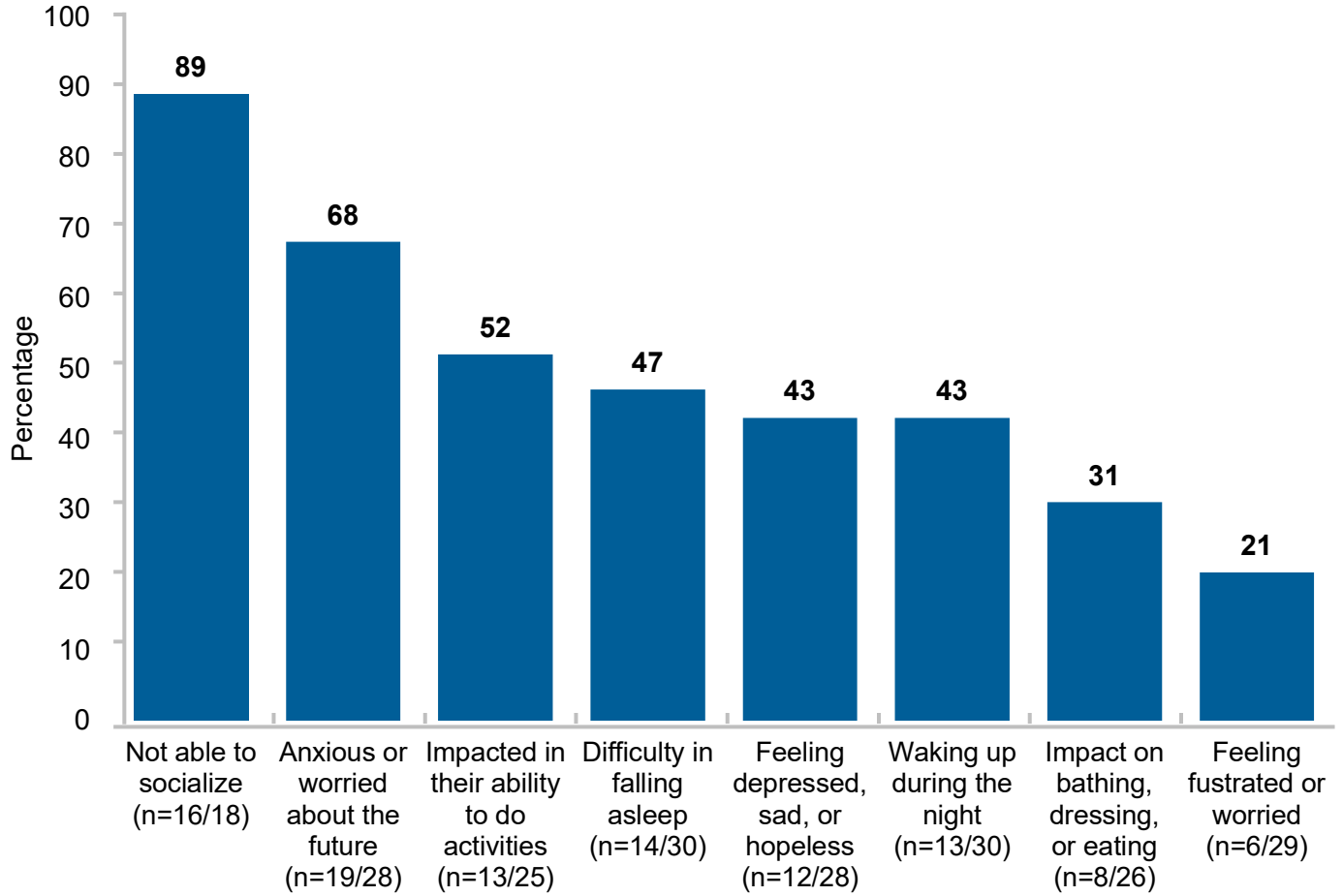
The short-term goal of therapy is to induce a **complete or partial remission of proteinuria**

CKD = chronic kidney disease; CV = cardiovascular; ESKD = end-stage kidney disease.

1. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. *Kidney Int Suppl* 2012; **2:**139–274;
2. Korbet SM. *J Am Soc Nephrol* 2012; **23:**1769–1776; 3. D'Agati VD, *et al. N Engl J Med* 2011; **365:**2398–2411.

Patient Reported Outcomes in FSGS

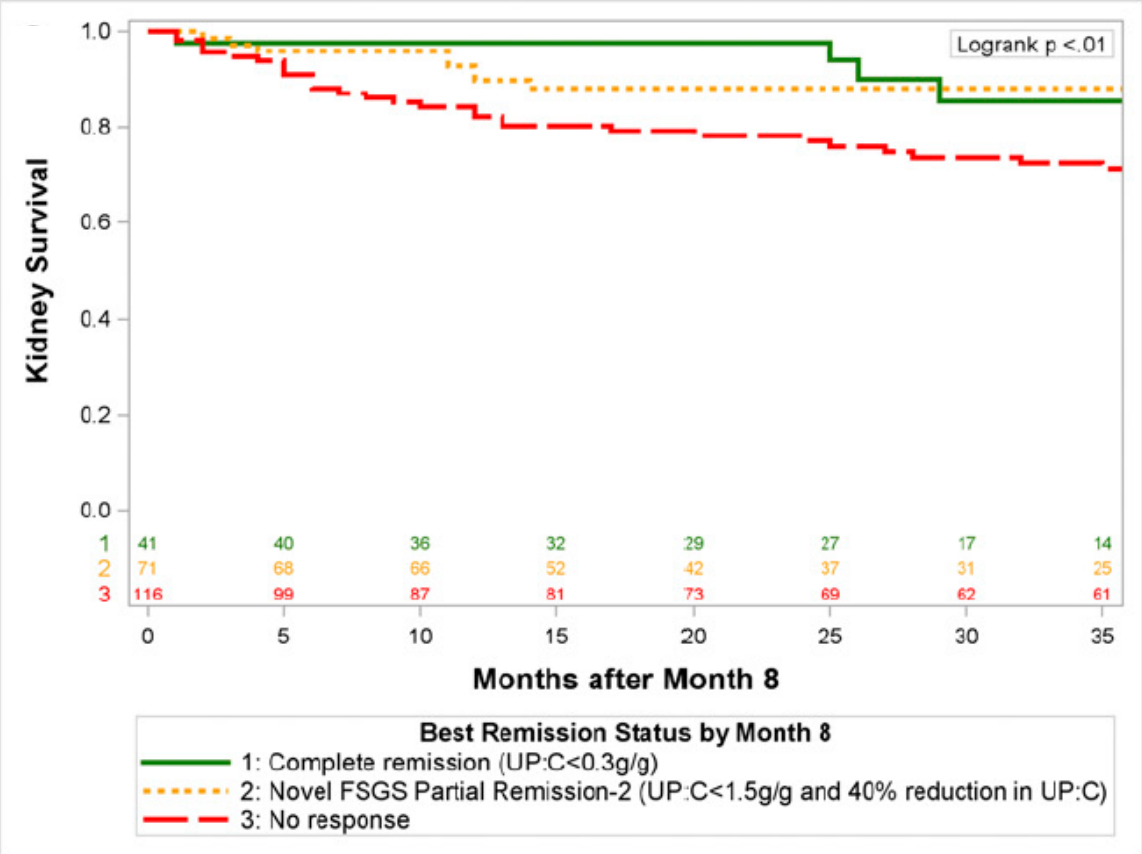
- Equally important goal of treatment: Alleviating symptoms
- Generic PRO Instruments: PedsQL, SF-36, PROMIS
- FSGS-Specific Instruments: FSGS Symptom Diary and FSGS Symptom Impact Questionnaire



PedsQL = Pediatric Quality of Life Inventory; PRO = patient reported outcome; PROMIS = Patient Reported Outcomes Measurement Information System.

Mathias SD, *et al.* *Am J Kidney Disease*, 2017: **70**:532-540.

FSGS Partial Remission of Proteinuria Endpoint - a Robust Correlate of Kidney Survival in Patients with Primary FSGS



Data from five independent cohorts totaling 466 patients with primary FSGS were analyzed and established that achieving a modified partial remission of proteinuria endpoint of <1.5 g/g accompanied with at least a 40% reduction in proteinuria was a robust correlate of kidney survival

UP/C = urinary protein-to-creatinine ratio.

Troost JP, *et al*. *Clin J Am Soc Nephrol* 2018; **13:**414–421.

Treatment Strategies for FSGS

- In the absence of an approved therapy specifically indicated for FSGS, current treatment strategies are limited to:
  - Renin-angiotensin system blockade (ACEIs, ARBs, MRBs)
  - Blood pressure control
  - Immunosuppression (in cases of proposed “primary/idiopathic” FSGS)
  - Extracorporeal therapies: Plasma exchange therapy, LDL apharesis
  - Management of complications of CKD and nephrotic syndrome
    - Lipid lowering agents
    - Diuretics
    - Anticoagulation in some cases

Conclusions

- FSGS is a histologic pattern associated caused by podocyte injury, which ultimately results in impaired glomerular filtration barrier function and proteinuria
- FSGS is an important cause of chronic kidney disease and end stage kidney disease
- The pathogenesis of FSGS is heterogeneous, involving genetic causes, “secondary” stresses, and circulating factors
- The main goal of treatment in FSGS is to reduce proteinuria (complete remission, FSGS partial remission of proteinuria) in order to improve long-term kidney outcomes
- Treatment of FSGS depends on the underlying pathogenesis, and may involve renin-angiotensin system blockade and immunosuppressive agents
- There remains a significant unmet need for safe and effective treatments for FSGS

Sparsentan - A Potential First-in-Class Molecule

Bill Rote, PhD – Head of Research and Development

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FSGS and IgAN Share Common Renal Injury Pathways

Kidney injury in FSGS

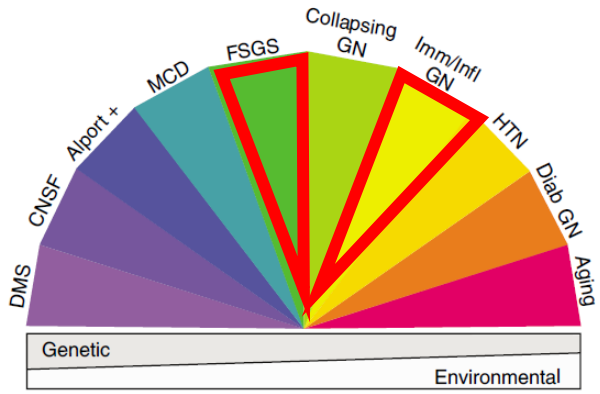
Factors affecting podocyte structural integrity

Podocyte Pathology

Proteinuria

Glomerulosclerosis

Tubulointerstitial Fibrosis



Kidney Failure = Transplant/ Dialysis

Kidney injury in IgAN

Formation of glomerular deposition of immune complexes with hypogalactosylated IgA

Mesangial Cell Activation

Glomerular Inflammation

Proteinuria

Hematuria

Glomerulosclerosis

Tubulointerstitial Fibrosis

Source: Wiggins, Kidney International (2007)

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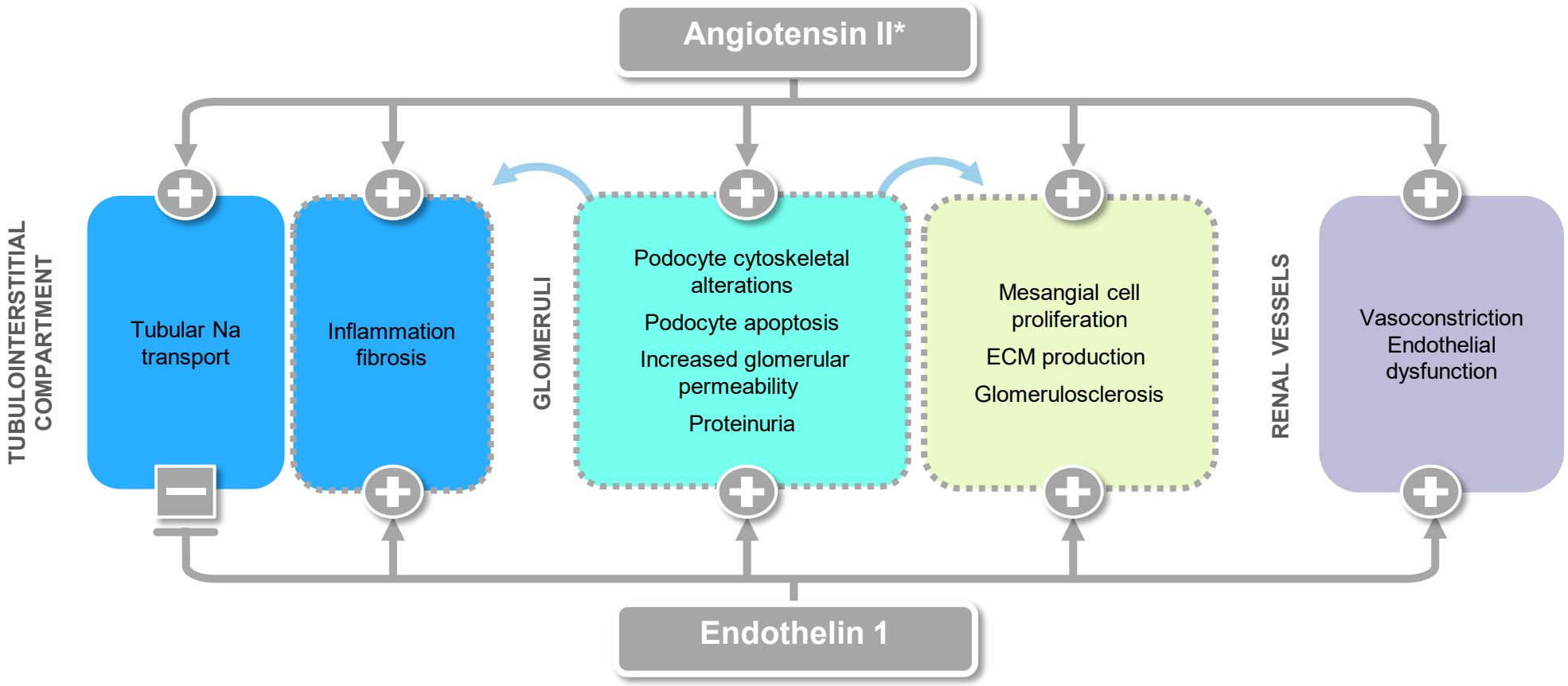
Endothelin 1 and Angiotensin II Signaling Pathways Play Fundamental Roles in Several Kidney Diseases



*Also applies to aldosterone. Image adapted from Komers R. et al. *Am J Physiol Regul Integr Comp Physiol.* 2016;310:R877–R884.
ECM, extracellular matrix; ERA, endothelin receptor antagonist; FSGS, focal segmental glomerulosclerosis; IgAN, immunoglobulin A nephropathy; RAAS, renin-angiotensin-aldosterone system.

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Sparsentan is a Potential First-in-Class Molecule Designed to Selectively Inhibit the Endothelin Receptor and Angiotensin II Receptor

- Sparsentan is an investigational product candidate designed to inhibit both endothelin receptor type A (ET_A) and angiotensin II receptor type 1 (AT_1)[1-3]
- Distinct selectivity profile: high affinity selective antagonist at both the ET_A and AT_1 receptors; highly selective ET_A/ET_B
- Has shown nephroprotective properties across pre-clinical studies in both FSGS and IgAN
- Sparsentan has been granted orphan drug designation for the treatment of FSGS by the FDA and European Commission

Source: 1. Kowala MC, et al. *J Pharmacol Exp Ther*. 2004;309:275–284., 2. Komers R, et al. *Am J Physiol Regul Integr Comp Physiol.* 2016: 310 (10): R877-884., 3. Benigni A, et al. *Pediatr Nephrol* 2020. https://doi.org/10.1007/s00467-020-04518-2

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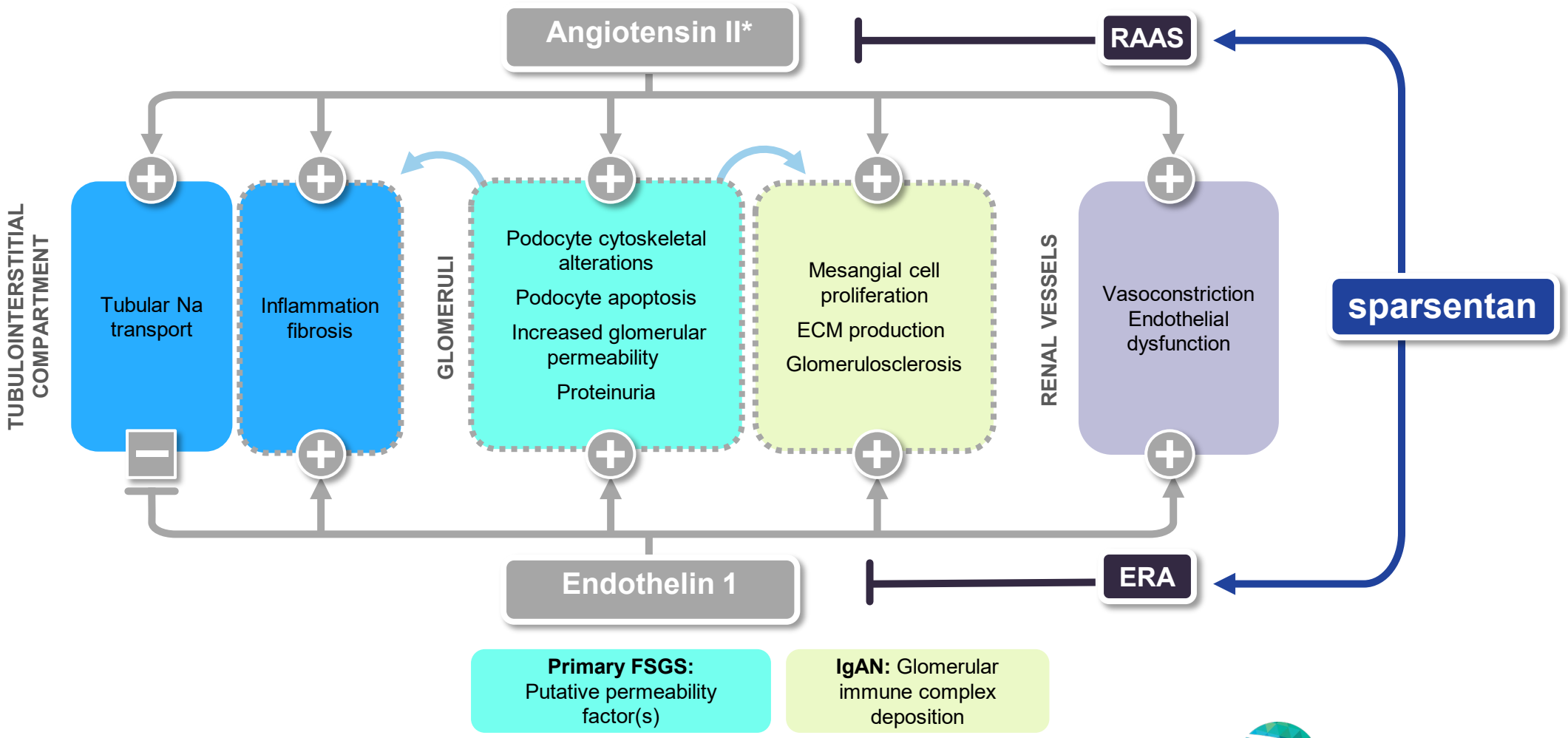
Sparsentan Acts by Inhibiting the Signaling Pathways Present in FSGS and IgAN



*Also applies to aldosterone. Image adapted from Komers R. et al. *Am J Physiol Regul Integr Comp Physiol.* 2016;310:R877–R884.
ECM, extracellular matrix; ERA, endothelin receptor antagonist; RAAS, renin-angiotensin-aldosterone system.

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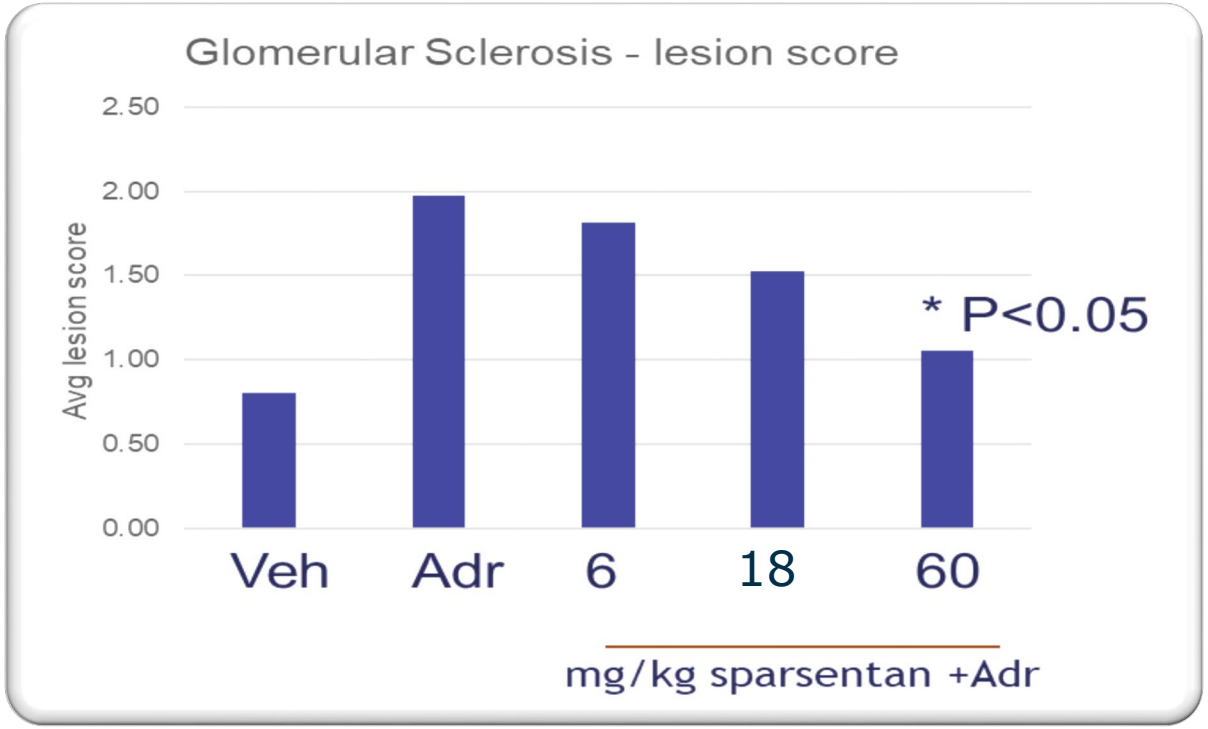
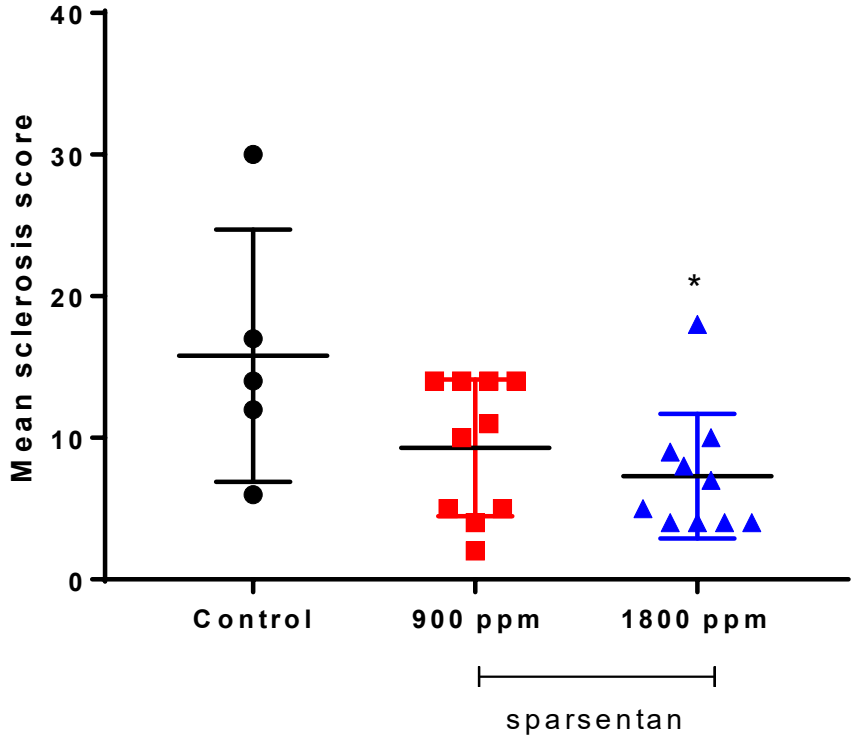
Preclinical Demonstration of Prevention of Glomerulosclerosis

FSGS Rat Model



IgAN gddY Mouse Model



Source: Adriamycin rat FSGS model: RE-021-Report0034-PHARM; gddY Model: RE-021-Report054-2018-PHARM; presented as e-poster ERA-EDTA 2020

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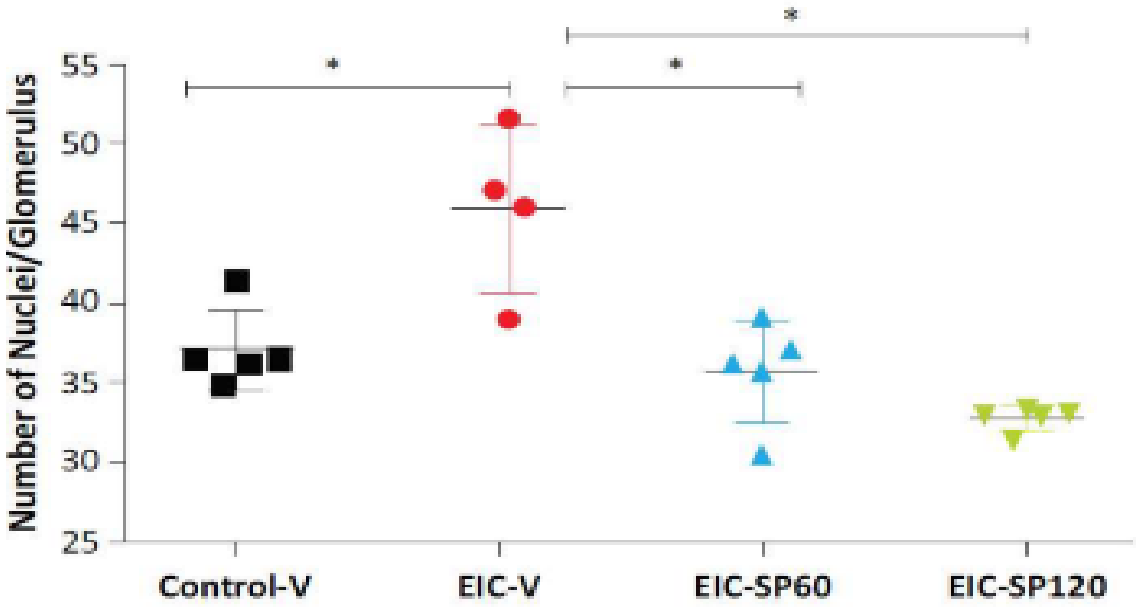
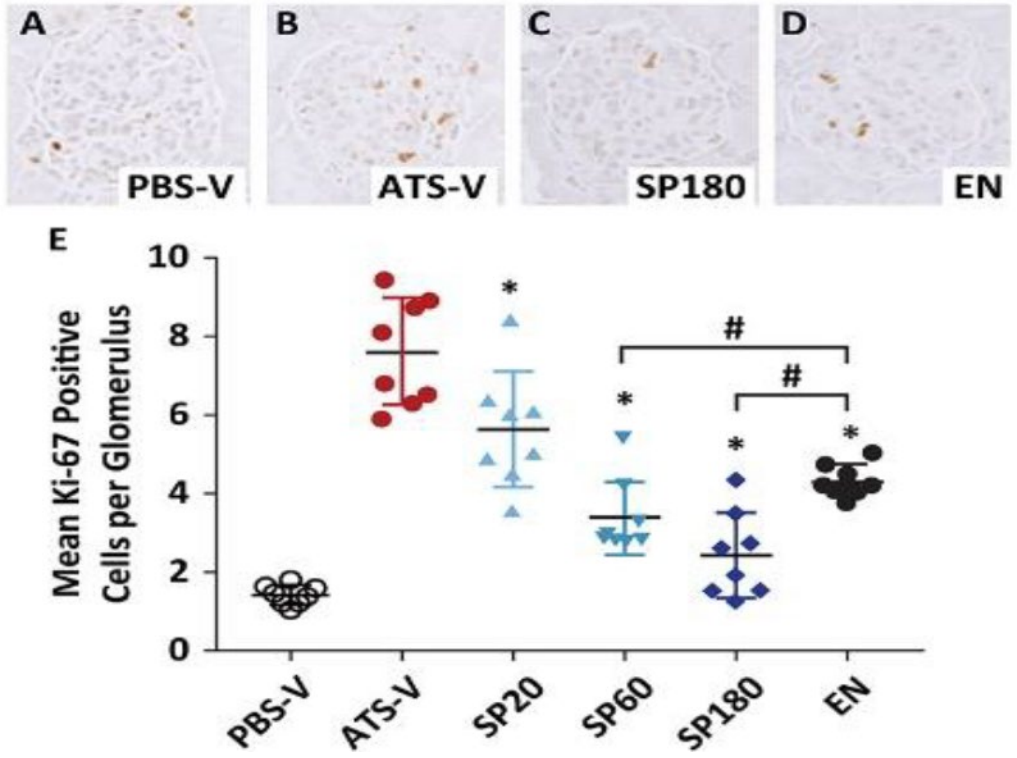
Preclinical Demonstration of Prevention of Mesangial Cell Proliferation

Engineered Immune Complex (EIC) - induced IgAN Model



Anti-Thy1 Model



Source: EIC Model: RE-021-Report004-2018-PHARM; presented as poster WCN 2019
Anti-Thy1 Model: Jenkinson, et.al. (2018) 15th International Symposium on IgA Nephropathy, Buenos Aires. Argentina

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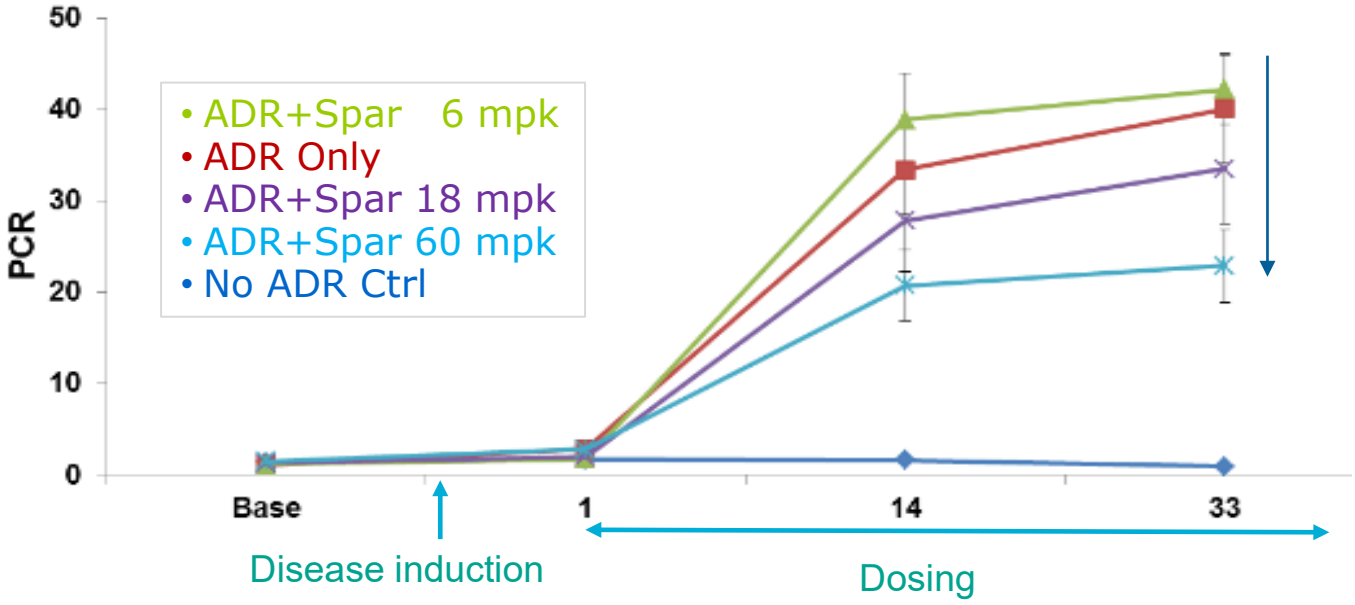
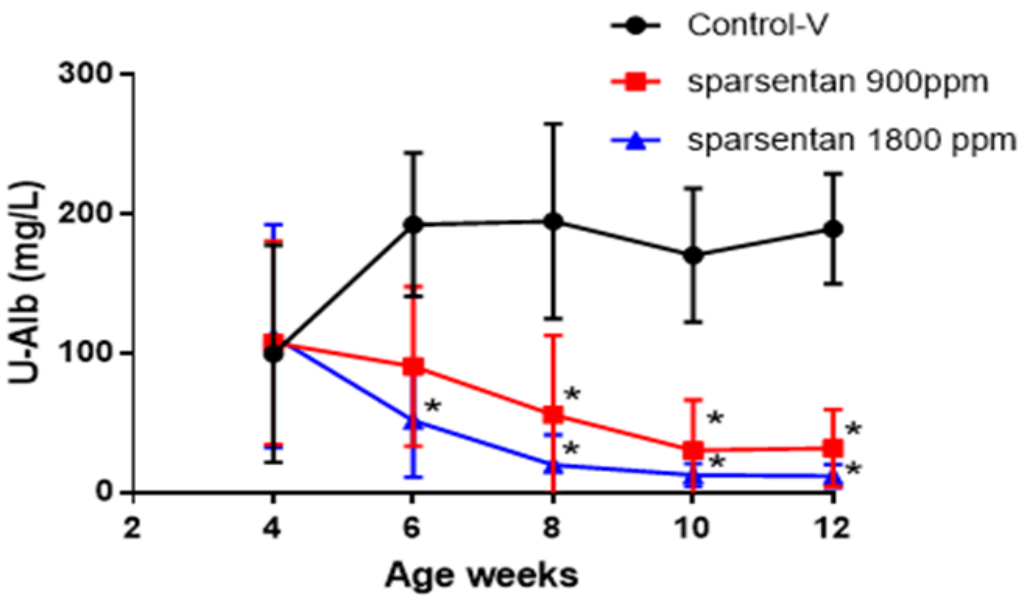
Preclinical Demonstration of Proteinuria Reduction

FSGS Rat Model



IgAN gddY Mouse Model



Source: Adriamycin rat FSGS model: RE-021-Report0034-PHARM; gddY Model: RE-021-Report054-2018-PHARM; presented as e-poster ERA-EDTA 2020

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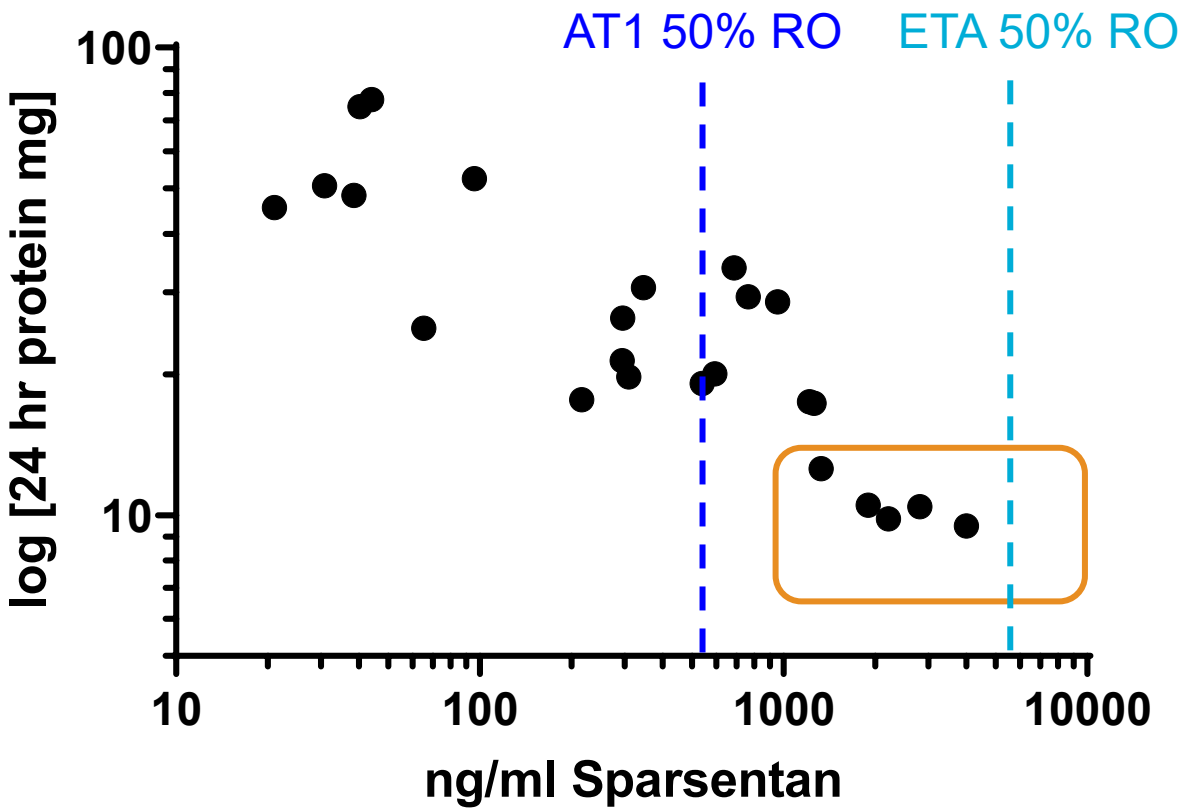
Inhibition of Both AT_1 and ET_a Together Results in Further Proteinuria Reduction in Rat Models



- In vitro receptor binding in Rats
  - AT1 Ki = 11 nM
  - ETA Ki = 110 nM
- Sparsentan circulates bound to protein, hence 10x Ki concentration results in ~50% receptor occupancy
- **Maximum efficacy is observed with significant inhibition of ETA receptors**

Source: RE-021-0045; RE-021-0057, RE-021-Report003-2018-PHARM; RE-021-Report007-2018-BIOA

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The Clinical Path to Shaping the Treatment Paradigm for FSGS

Noah Rosenberg, MD – Chief Medical Officer

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Overview of Sparsentan Clinical Programs for FSGS

DUET: Randomized, double-blind, safety and efficacy study of sparsentan in primary or genetic FSGS

duet

Phase 2 study
sparsentan vs irbesartan
8-week blinded trial followed by an open-label extension period

DUPLEX: Study of sparsentan in patients with primary or genetic FSGS

duplex

Phase 3 study
sparsentan vs irbesartan
108-week blinded treatment period with 4 weeks of off-treatment follow-up and followed by an open-label extension period

DUPLEX clinicaltrials.gov ID: NCT03493685; DUPLEX clinicaltrialsregister.eu number: 2016-005141-23.
Komers R, et al. Kidney Int Rep 2020; **5:**494–502; DUPLEX Protocol ID: 021FSGS16010.

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Phase 2 DUET Study of Sparsentan in FSGS

A Phase 2, randomized, double-blind, parallel-group, active-controlled study of the efficacy and safety of sparsentan for the treatment of primary or genetic FSGS

Hypothesis

Dual blockade of ETA and AT1 receptors (sparsentan) in patients with primary or genetic FSGS reduces proteinuria to a greater extent compared with the blockade of AT1 receptor alone (irbesartan)

Objectives

To evaluate the efficacy and safety of sparsentan, compared with irbesartan, to reduce proteinuria in patients with primary or genetic FSGS during an 8-week, double-blind study period and an open-label extension

AT1 = angiotensin II receptor type 1; ETA = endothelin receptor type A.
Trachtman H, et al. J Am Soc Nephrol 2018; **29:**2745–2754; DUET ClinicalTrials.gov Identifier: NCT01613118.

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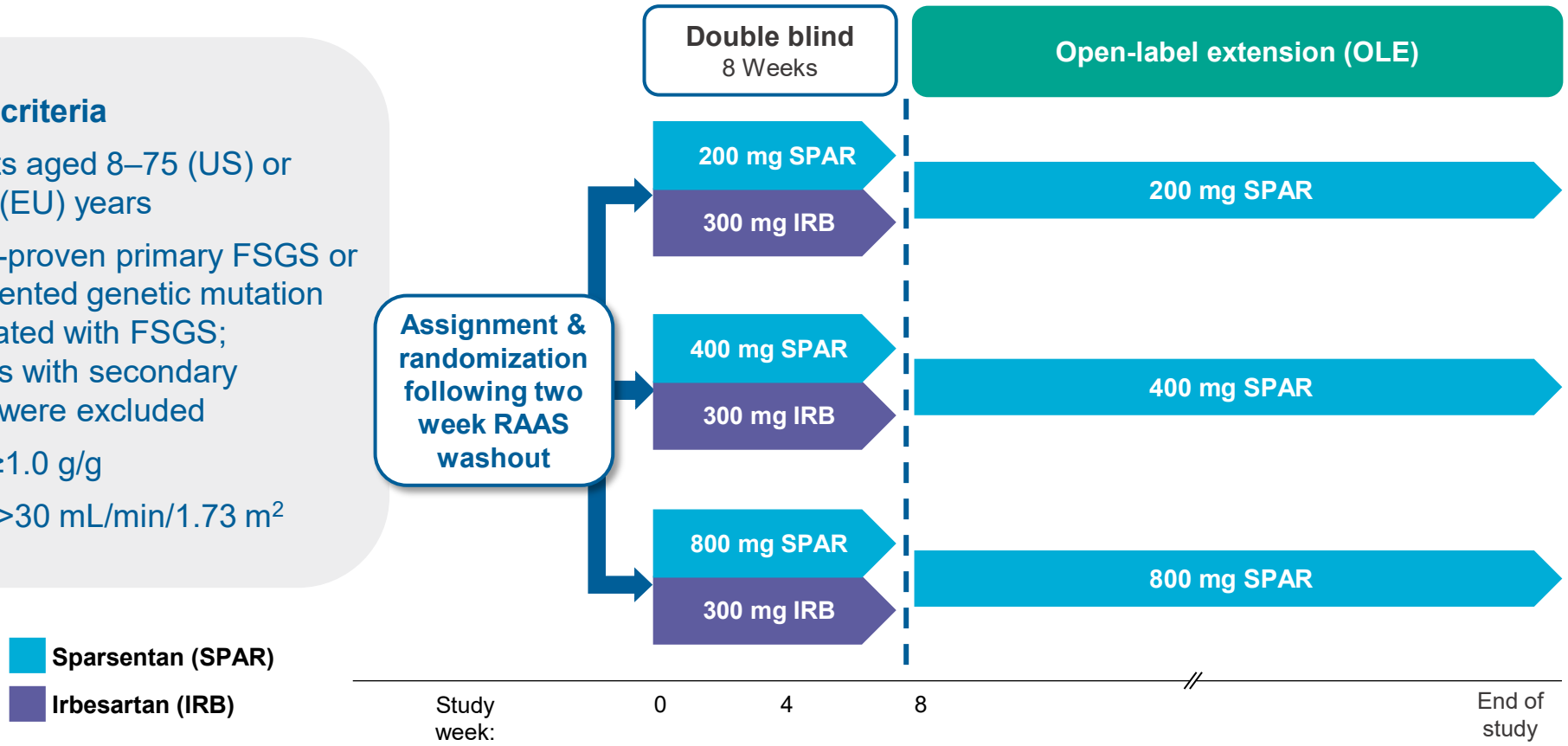
Phase 2 DUET Study: Trial Design

Selection criteria

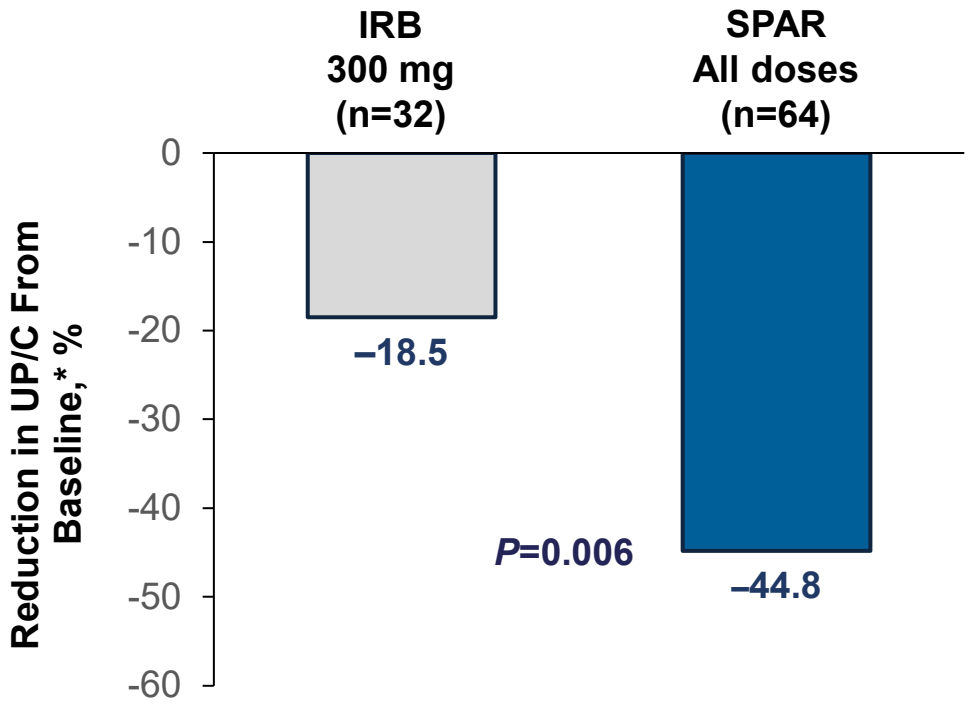
- Patients aged 8–75 (US) or 18–75 (EU) years
- Biopsy-proven primary FSGS or documented genetic mutation associated with FSGS; patients with secondary FSGS were excluded
- UP/C ≥1.0 g/g
- eGFR >30 mL/min/1.73 m^2



*After 2 weeks' RAAS inhibitor washout. Patients were assigned to dose cohort, then randomized to sparsentan or irbesartan within the dose cohort. Study drug administered orally, once daily. Patients who weighed ≤50 kg received half of the daily dose of sparsentan or irbesartan according to the assigned dose cohort.
eGFR = estimated glomerular filtration rate; IRB = irbesartan; SPAR = sparsentan; RAAS = renin–angiotensin–aldosterone system; UP/C = urinary protein-to-creatinine ratio.
Trachtman H, et al. *J Am Soc Nephrol* 2018; 29:2745–2754; DUET ClinicalTrials.gov Identifier: NCT01613118.

TRAVERE™ THERAPEUTICS

Phase 2 DUET Study: Overall Sparsentan Treatment Group Met Primary Endpoint; More Than Doubled Reduction of Proteinuria vs. Irbesartan



Significant reduction in proteinuria after 8 weeks of sparsentan vs irbesartan treatment in primary and genetic FSGS patients

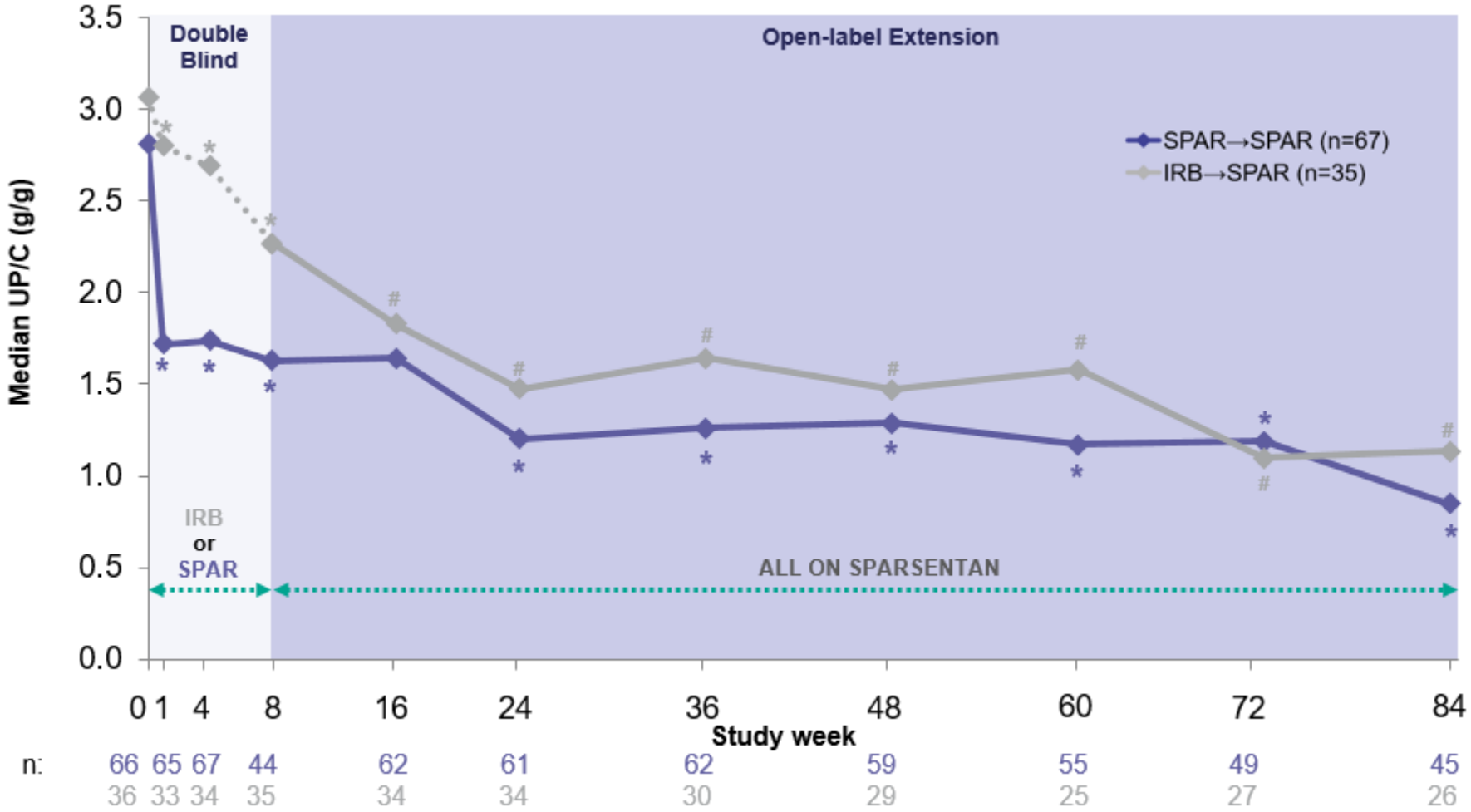
TEAE	Patients with TEAEs During the Double-Blind Period, %	
	IRB (n = 36)	SPAR, All Doses (n = 73)
Any	72.2	76.7
Drug-related	36.1	43.8
Serious	2.8	2.7
Leading to dose change or interruption	8.3	23.3
Leading to drug discontinuation	2.8	4.1
Leading to study withdrawal	2.8	2.7
Death	0	0

Similar incidence of TEAEs between irbesartan and sparsentan-treated patients

*Geometric least squares mean reduction. P values from analysis of covariance. Analyses based on the efficacy evaluable set. UP/C based on 24-hour urine. Individual dose cohorts showed clear signals of relative improvement, but did not reach statistical significance; H Trachtman, *et al. J Am Soc Nephrol* 2018; 29:2745–2754. Loreto G, *et al. ERA-EDTA* 2017 Oral presentation TO042

TRAVERE™ THERAPEUTICS

Phase 2 DUET Study: Sustained Long-Term Proteinuria Reduction over 84 Weeks

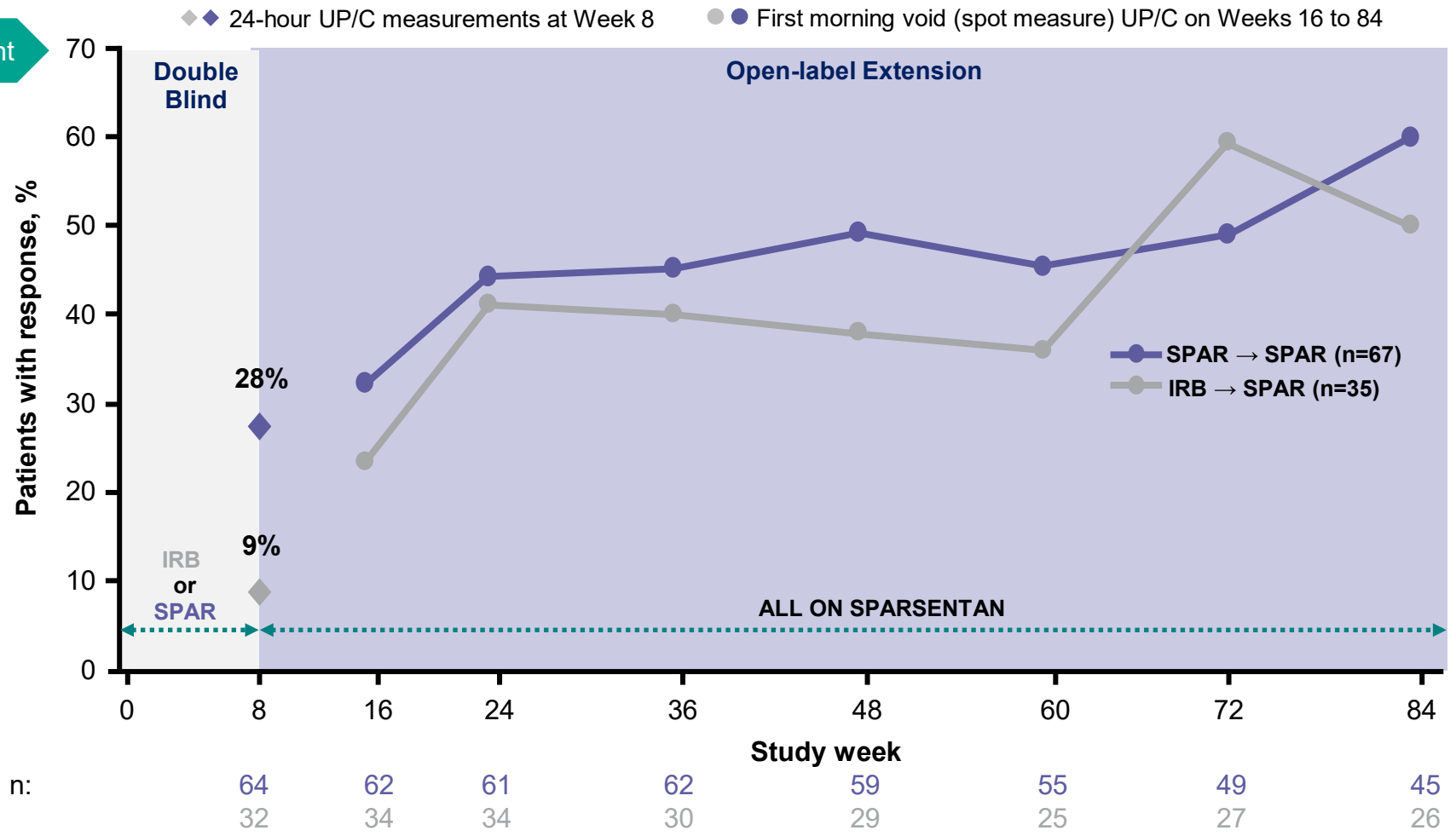


95% confidence interval of the mean change from baseline (* Week 0; # Week 8) excludes 0.
Based on the full analysis set. UP/C based on first morning void.
UP/C = urinary protein-to-creatinine ratio; OLE = open-label extension

TRAVERE™ THERAPEUTICS

Phase 2 DUET Study: Promising Proportion of Patients Achieved FSGS Partial Remission Endpoint (FPRE)

Secondary Endpoint



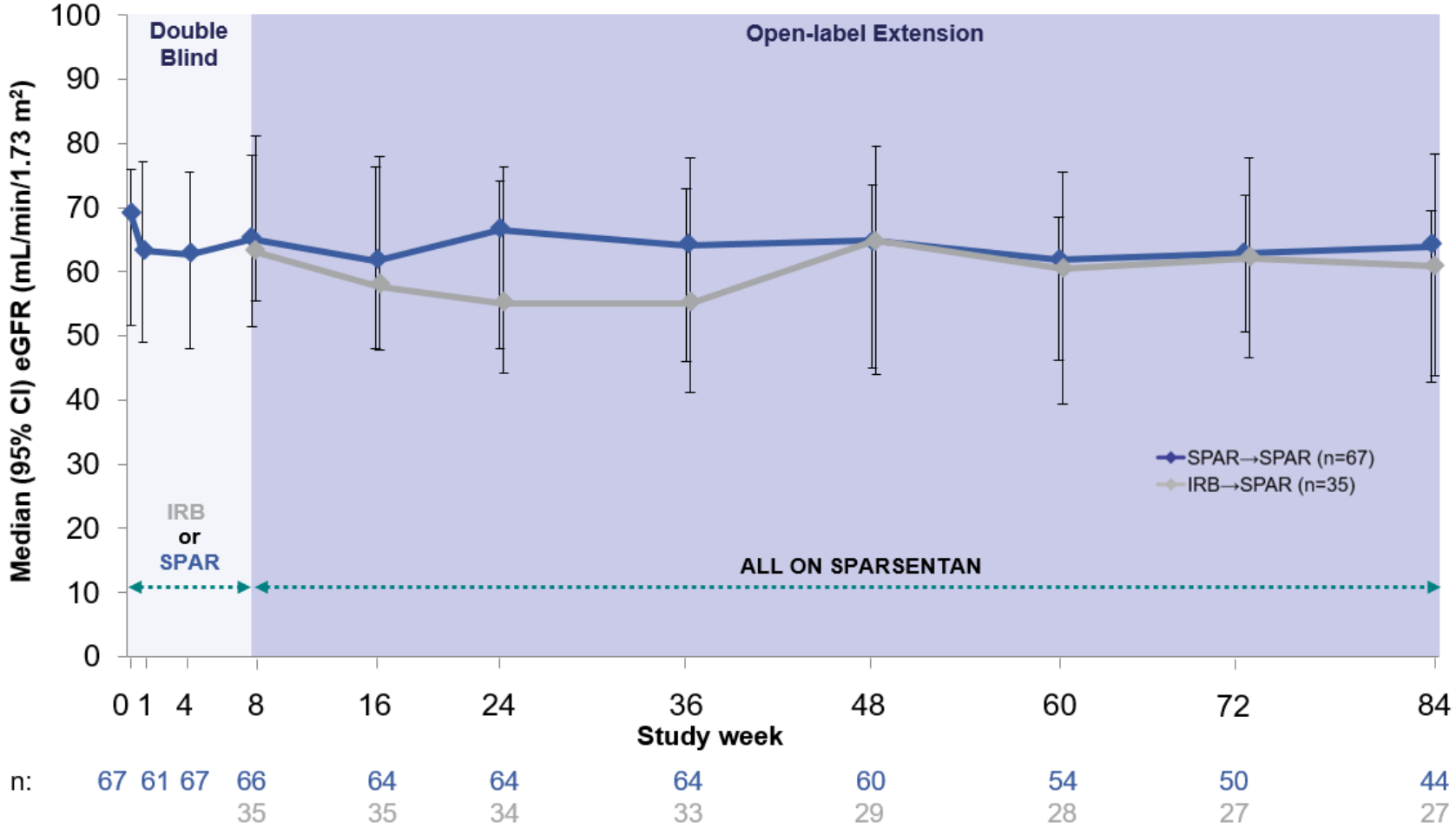
p<0.04

An increasing proportion of patients achieved FPRE with ongoing sparsentan treatment in the OLE

FPRE is defined as UP/C ≤1.5 g/g and >40% reduction in UP/C from baseline. Baseline in the double-blind period defined as Week 0; baseline for the open-label period defined as last observation before start of open-label sparsentan treatment (i.e.Week 8). Data for Week 8 are based on the EES. Data for Weeks 16 to 84 are based on the full analysis set. EES = efficacy evaluable set; FPRE = FSGS partial remission endpoint; IRB:SPAR = patients randomized to irbesartan who then transitioned to sparsentan in the OLE; OLE = open-label extension; SPAR:SPAR = patients randomized to sparsentan who also received sparsentan in the OLE; UP/C = urinary protein-to-creatinine ratio. 1. Hogan J, et al. *J Am Soc Nephrol* 2018; 29:61 (Abstract FR-OR087); 2. Trachtman H, et al. *J Am Soc Nephrol* 2018; 29:2745–2754; DUET ClinicalTrials.gov Identifier: NCT01613118.

TRAVERE™ THERAPEUTICS

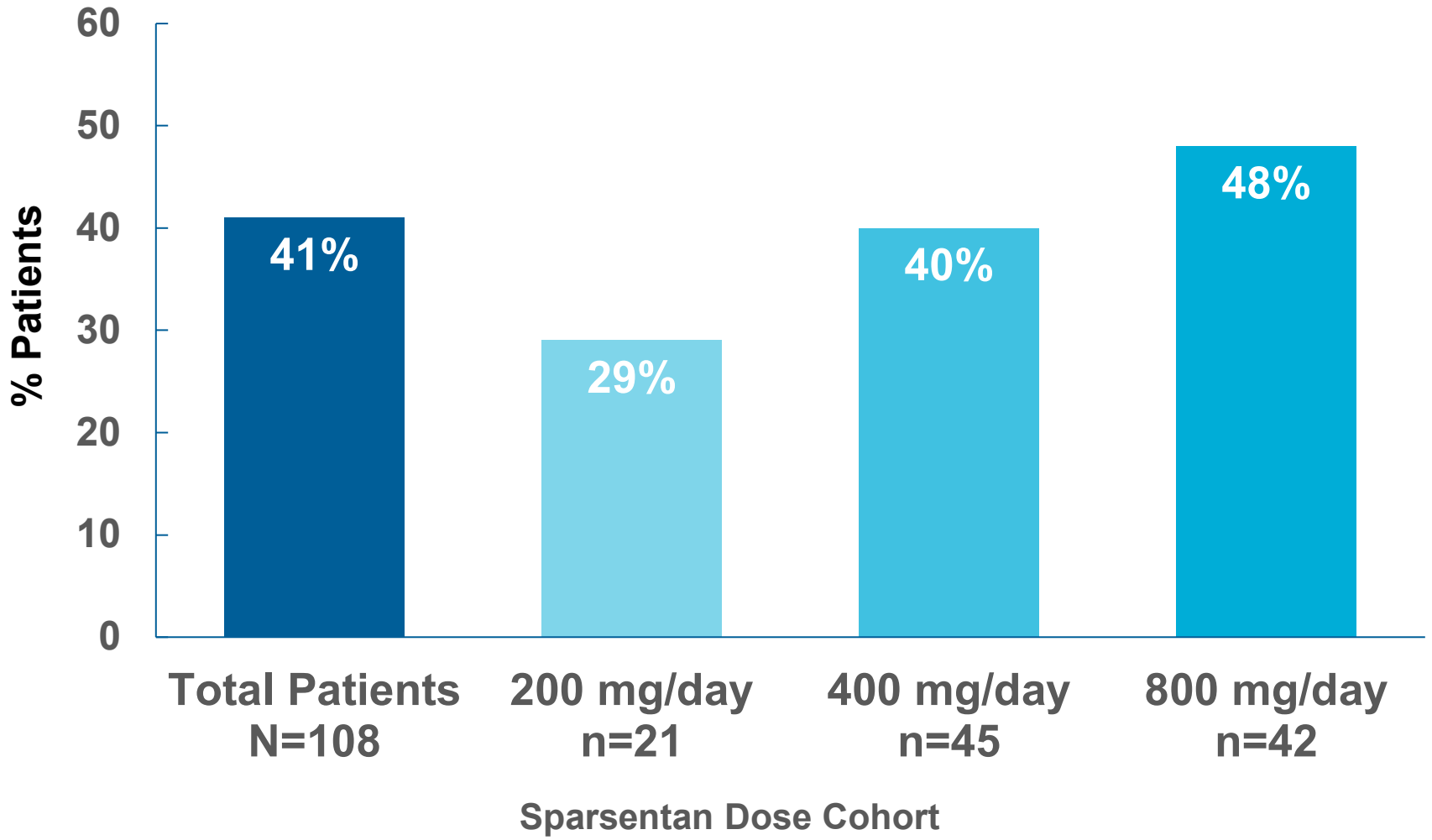
Phase 2 DUET Study: eGFR Remained Stable in Sparsentan-Treated Patients Over 84 Weeks



Based on the full analysis set. 95% CIs were calculated for the median value at each time point. Note: There were 9 study withdrawals due to renal causes during the follow-up period, including 1 case of end-stage renal disease.
CI = confidence interval; eGFR = estimated glomerular filtration rate; IRB:SPAR = patients randomized to irbesartan who then transitioned to sparsentan in the OLE; OLE = open-label extension; SPAR:SPAR = patients randomized to sparsentan who also received sparsentan in the OLE.
Hogan J, et al. Long-Term Effects of Sparsentan, a Dual Angiotensin and Endothelin Receptor Antagonist in Primary FSGS: Interim 84-Week Analysis of the DUET Trial (Abstract FR-OR087). *J Am Soc Nephrol*. 2018;29:61. Accessed at https://www.asn-online.org/education/kidneyweek/archives

TRAVERE™ THERAPEUTICS

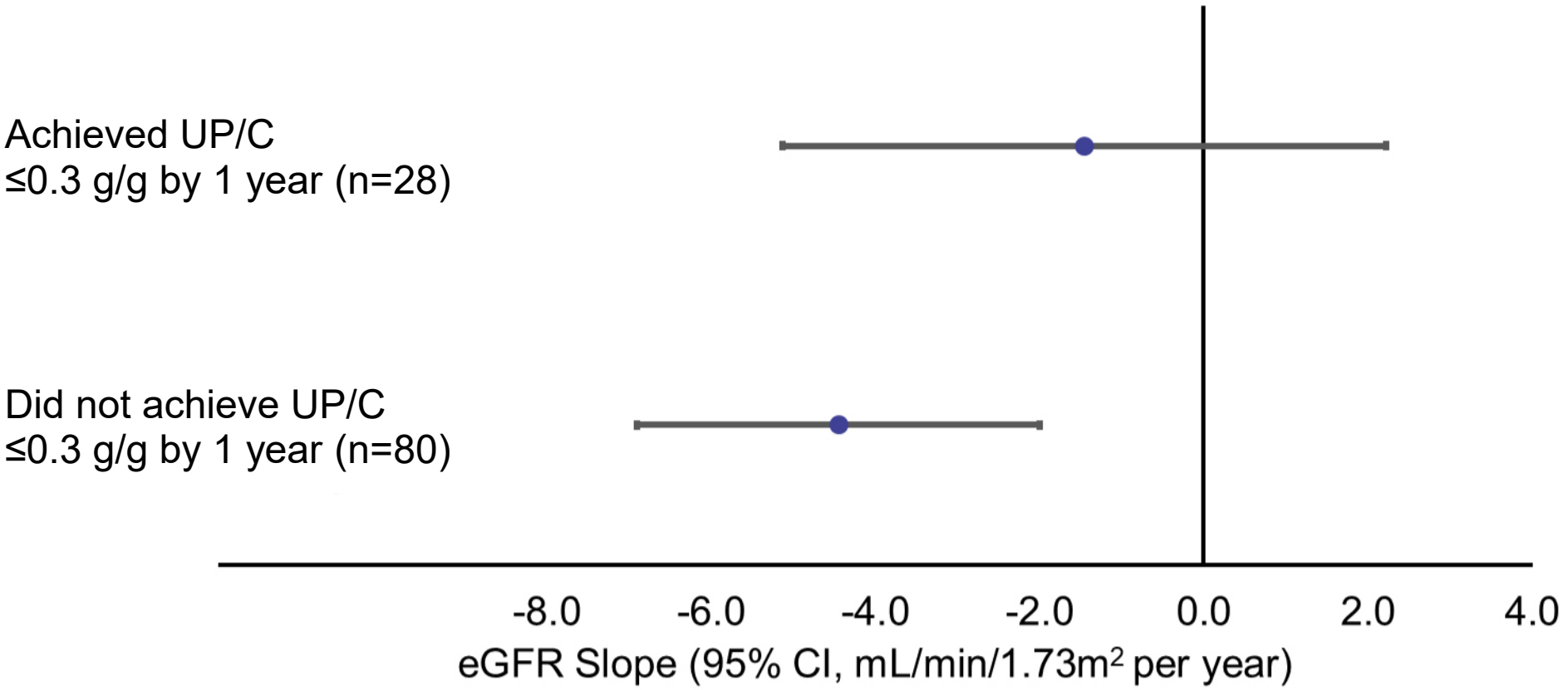
Phase 2 DUET Study: Post hoc analysis – A High Percentage of Patients Achieved UP/C ≤0.3 g/g at Any Visit in a Dose-related Manner



Hogan J, *et al*. ASN 2020 [oral presentation]
109 patients were randomized in DUET; 108 patients received at least one dose of sparsentan and were eligible for evaluation of UP/C while on sparsentan.

TRAVERE™ THERAPEUTICS

Achieving Complete Remission With Sparsentan in the First Year was Associated With Slower eGFR Decline Over Two Years



Hogan J, *et al*. ASN 2020 [oral presentation]

TRAVERE™ THERAPEUTICS

A Closer Look at Edema in DUET

TEAEs with Incidence >5%	Patients n (%)			
	Irbesartan		Sparsentan	
	All	Drug Related	All	Drug Related
Headache	7 (19.4)	1 (2.8)	14 (19.2)	**9 (12.3)**
Hypotension/orthostatic hypotension	3 (8.3)	3 (8.3)	12 (16.4)	**11 (15.1)**
Dizziness	4 (11.1)	3 (8.3)	10 (13.7)	**8 (11.0)**
Edema/edema peripheral	1 (2.8)	0	9 (12.3)	**2 (2.7)**
Nausea	3 (8.3)	0	9 (12.3)	**6 (8.2)**
Diarrhea	1 (2.8)	0	6 (8.2)	**2 (2.7)**
Vomiting	1 (2.8)	0	6 (8.2)	**4 (5.5)**
Upper abdominal pain	2 (5.6)	0	4 (5.5)	**2 (2.7)**
Cough	2 (5.6)	0	3 (4.1)	**0**
Fatigue	4 (11.1)	1 (2.8)	3 (4.1)	**2 (2.7)**
Nasal congestion	4 (11.1)	0	2 (2.7)	**0**
Upper respiratory tract infection	2 (5.6)	0	2 (2.7)	**0**
Hyperkalemia	2 (5.6)	2 (5.6)	1 (1.4)	**1 (1.4)**
Muscle spasms	2 (5.6)	0	0	**0**

- Edema is common in people living with FSGS
- Adverse event of interest given potential ERA class effect
- Treatment related edema events in DUET were well managed with diuretics
- OLE findings are consistent with double blind portion of study

TRAVERE™ THERAPEUTICS

Leveraging Our Learnings in DUET to Design Pivotal DUPLEX Study

UP/C inclusion criteria from 1.0g/g to 1.5g/g to allow all patients to be eligible for FPRE endpoint

Evaluating the FPRE endpoint after 36-weeks of treatment

Target dose of 800mg of sparsentan with two-week dose titration schedule

Confirmatory eGFR endpoint after 108 weeks of treatment

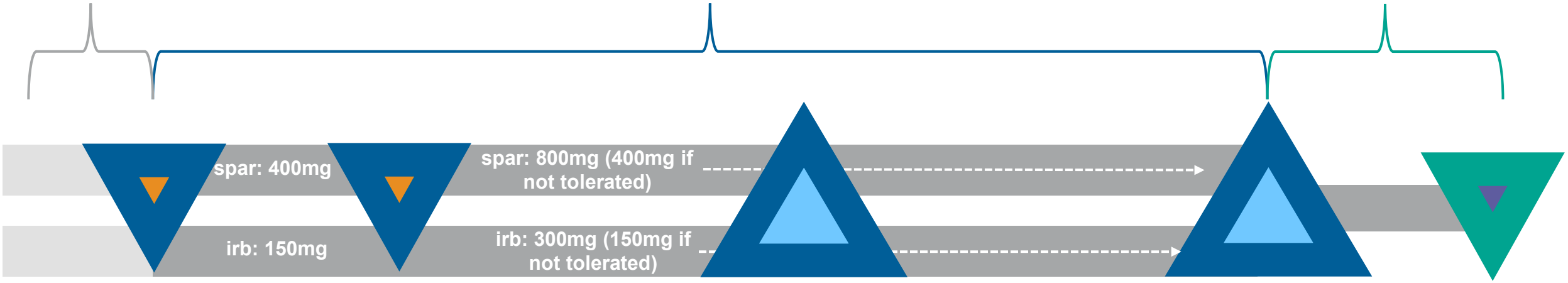
TRAVERE™ THERAPEUTICS

Phase 3 DUPLEX Study Designed to Support NDA & CMA Submissions for FSGS

Washout
2 weeks
no RAAS inhibitors

Double-Blind Treatment Period
108 Weeks

Cessation of Treatment
4 Weeks
No sparsentan or irbesartan



DAY 1
- Baseline
- UP/C, eGFR
- Randomize 1:1
- Initial dose

WEEK 2
Achieve target dose of 800mg sparsentan or 300mg irbesartan

WEEK 36
Interim analysis of FPRE endpoint
~190 patients

WEEK 108
End of treatment, primary endpoint of change in slope of eGFR endpoint from ~300 subjects

WEEK 112
End of study

- **More than 90% powered to detect difference in FPRE response**
- **90% powered to detect low single digit difference in eGFR slope b/t sparsentan and irbesartan arms after 108wks**

TRAVERE™ THERAPEUTICS

Enrollment Complete; On Track for Topline Interim Data in February 2021

- DUPLEX achieved randomization of 300th patient and completed new patient enrollment
- DUPLEX has completed four independent data monitoring committee assessments of safety with recommendations for study to proceed as planned
- Sample size reassessment completed - no increase in sample size recommended
- Initial baseline characteristics supporting the interim assessment are in-line with expectations and the DUET/NEPTUNE databases used to design DUPLEX
  - No clinically meaningful difference in the baseline distribution of UP/C compared to DUET
  - Blinded baseline range of eGFR is consistent with DUET
  - Blinded variability in-line with expectations
- Topline data from interim proteinuria analysis are anticipated in February 2021

TRAVERE™ THERAPEUTICS

UNIVERSITY OF LEICESTER

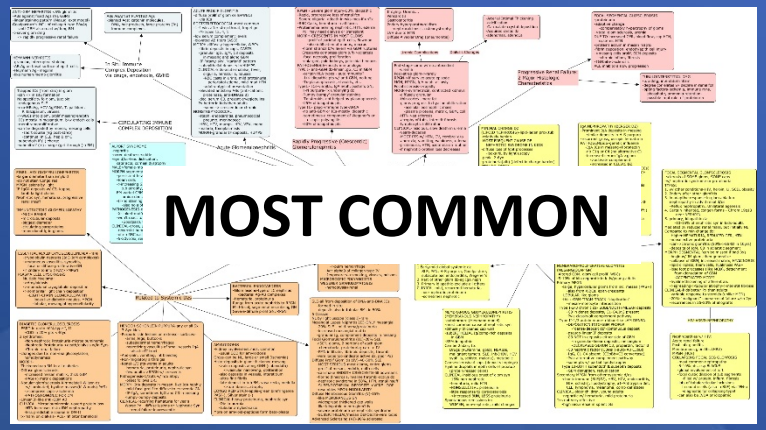
Leicester IgA Nephropathy Research Group

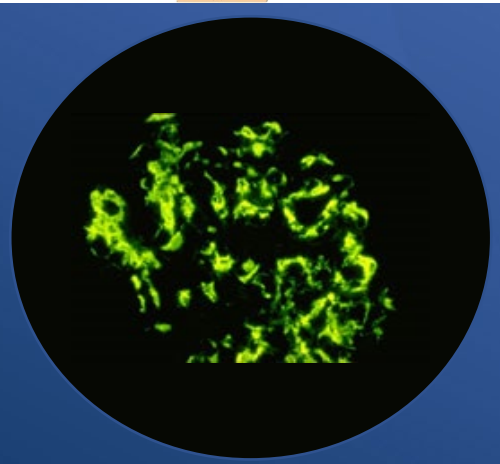
IgA nephropathy: where are we in 2020 and where is the unmet need?

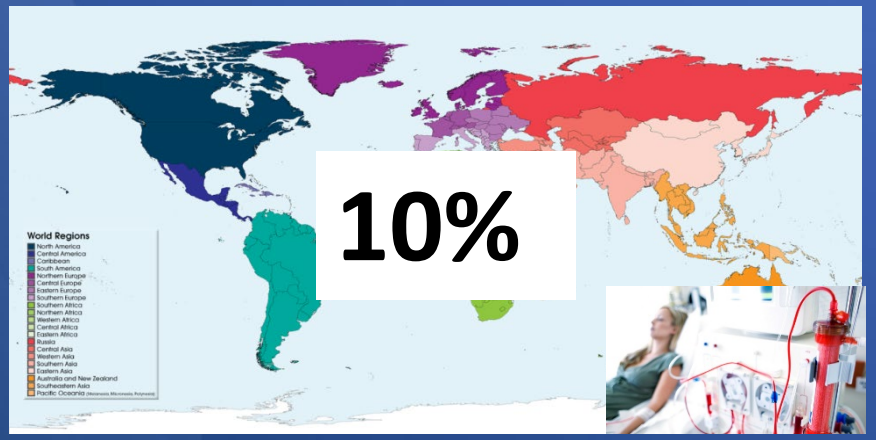
Professor Jonathan Barratt
University of Leicester
&
John Walls Renal Unit, Leicester

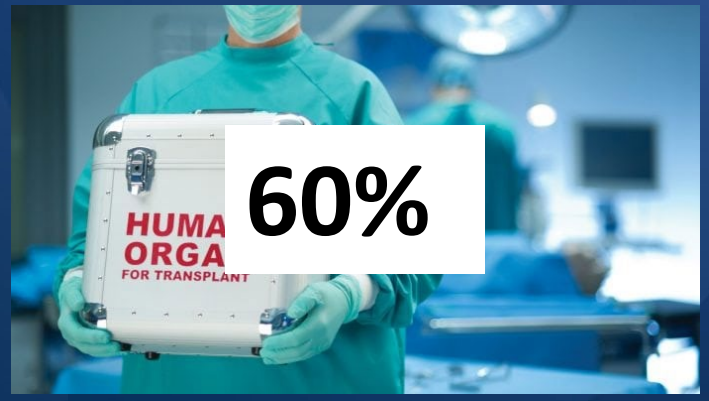
UNIVERSITY OF LEICESTER

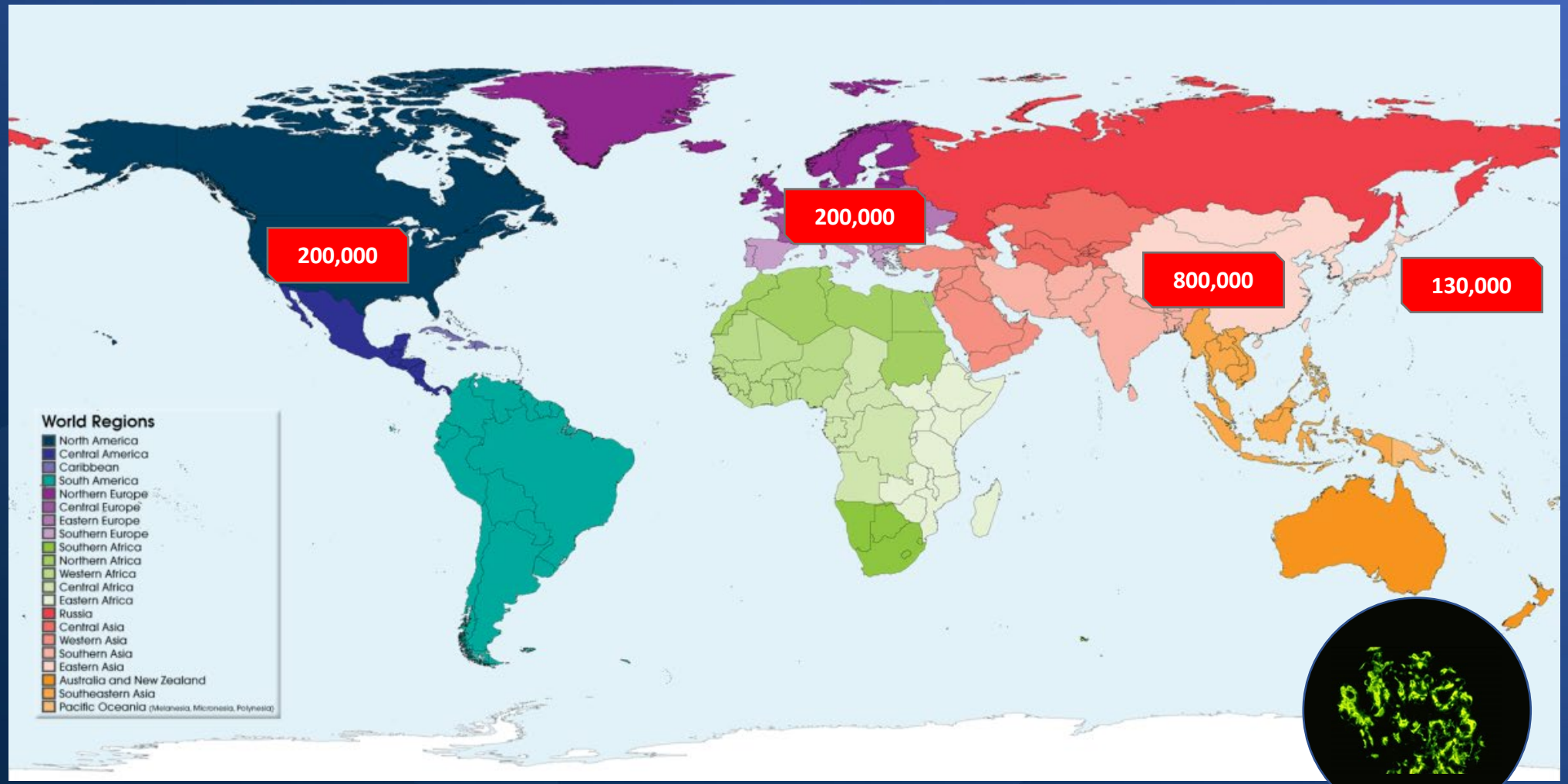
Leicester IgA Nephropathy Research Group










200,000
200,000
800,000
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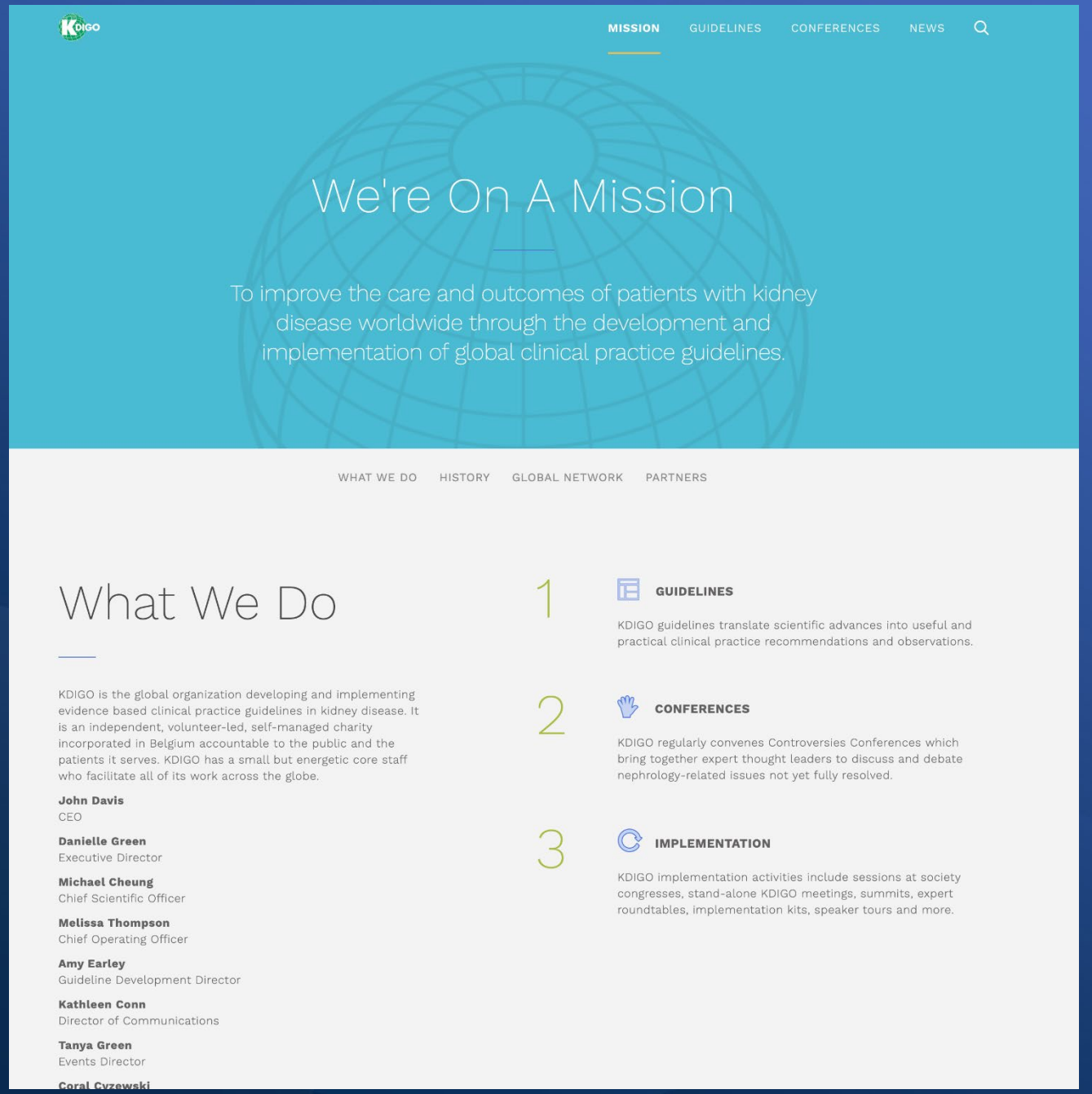
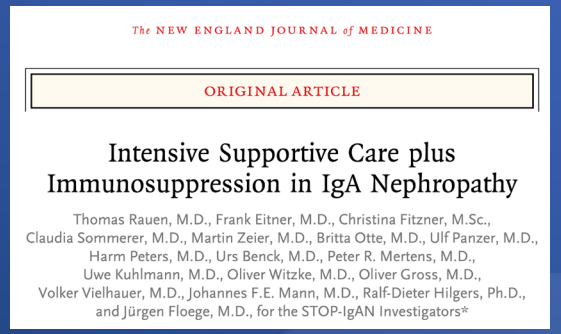
World Regions
North America
Central America
Caribbean
South America
Northern Europe
Central Europe
Eastern Europe
Southern Europe
Southern Africa
Northern Africa
Western Africa
Central Africa
Eastern Africa
Russia
Central Asia
Western Asia
Southern Asia
Eastern Asia
Australia and New Zealand
Southeastern Asia
Pacific Oceania (Melanesia, Micronesia, Polynesia)

In 2020 there are NO therapies approved for the treatment of IgAN


MISSION
GUIDELINES
CONFERENCES
NEWS
We're On A Mission
To improve the care and outcomes of patients with kidney disease worldwide through the development and implementation of global clinical practice guidelines.
WHAT WE DO
HISTORY
GLOBAL NETWORK
PARTNERS
What We Do
KDIGO is the global organization developing and implementing evidence based clinical practice guidelines in kidney disease. It is an independent, volunteer-led, self-managed charity incorporated in Belgium accountable to the public and the patients it serves. KDIGO has a small but energetic core staff who facilitate all of its work across the globe.
John Davis
CEO
Danielle Green
Executive Director
Michael Cheung
Chief Scientific Officer
Melissa Thompson
Chief Operating Officer
Amy Earley
Guideline Development Director
Kathleen Conn
Director of Communications
Tanya Green
Events Director
Coral Cyzewski
1
GUIDELINES
KDIGO guidelines translate scientific advances into useful and practical clinical practice recommendations and observations.
2
CONFERENCES
KDIGO regularly convenes Controversies Conferences which bring together expert thought leaders to discuss and debate nephrology-related issues not yet fully resolved.
3
IMPLEMENTATION
KDIGO implementation activities include sessions at society congresses, stand-alone KDIGO meetings, summits, expert roundtables, implementation kits, speaker tours and more.



2.3. Treatment

Practice Point 2.3.1. Considerations for treatment of all patients with IgAN who do not have a variant form of primary IgAN:

- **The primary focus of management should be optimised supportive care.**
- **Assess cardiovascular risk and commence appropriate interventions as necessary.**
- **Give lifestyle advice, including information on dietary sodium restriction, smoking cessation, weight control, and exercise as appropriate.**
- **Other than dietary sodium restriction, no specific dietary intervention has been shown to alter outcomes in IgAN.**
- **Variant forms of IgAN: IgA deposition with minimal change disease (MCD); IgAN with acute kidney injury (AKI) and IgAN with rapidly progressive glomerulonephritis may require specific immediate treatment.**

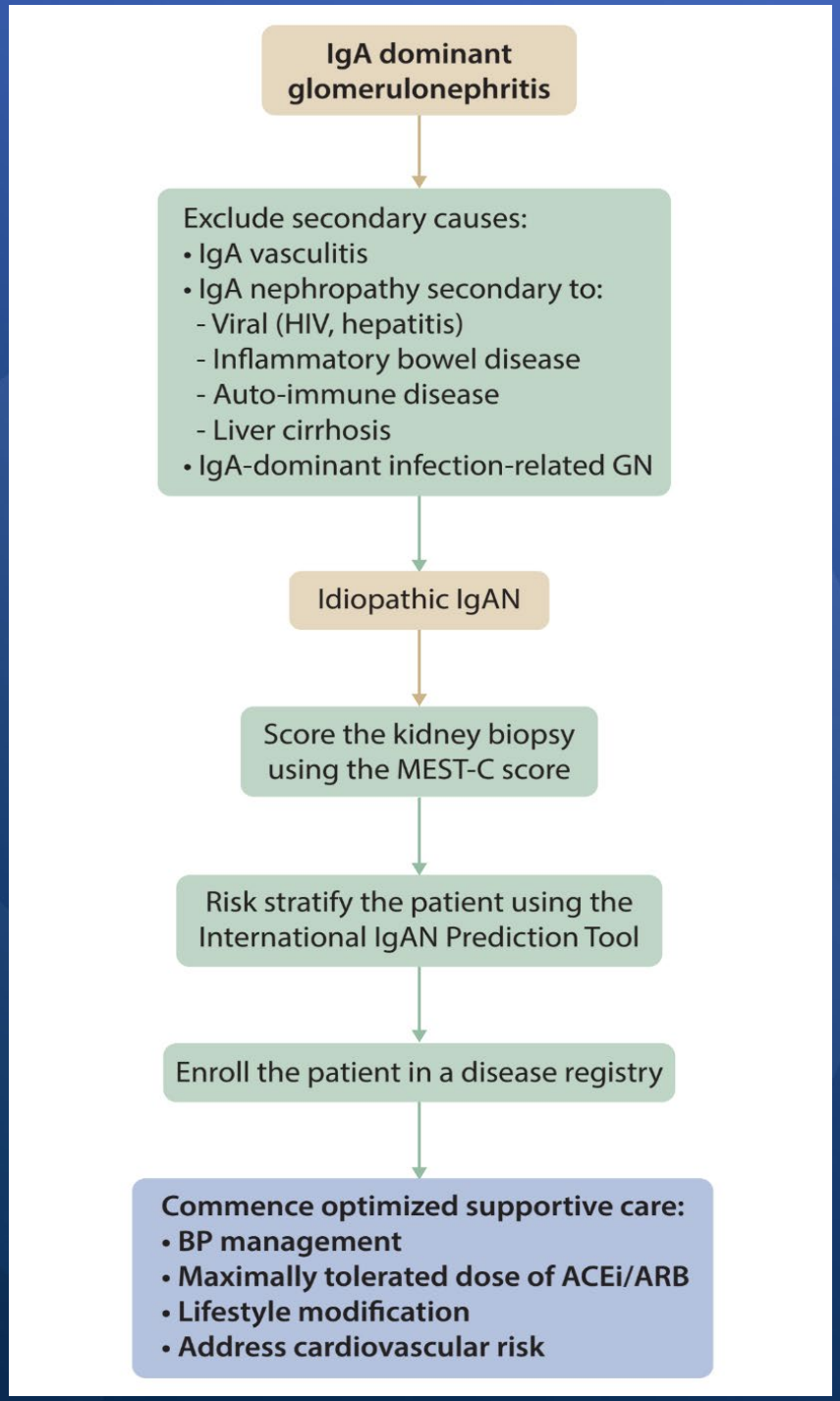
2.3. Treatment

Recommendation 2.3.1.

We recommend that all patients have their blood pressure managed, as described in Chapter 1. If the patient has proteinuria >0.5 g/24h, we recommend that initial therapy be with either an ACEi or ARB, but not both *(1B)*.

Recommendation 2.3.2.

We recommend that all patients with proteinuria >0.5 g/24h, irrespective of whether they have hypertension, are treated with either an ACEi or ARB but not both *(1B)*.


IgA dominant glomerulonephritis
Exclude secondary causes:
• IgA vasculitis
• IgA nephropathy secondary to:
- Viral (HIV, hepatitis)
- Inflammatory bowel disease
- Auto-immune disease
- Liver cirrhosis
• IgA-dominant infection-related GN
Idiopathic IgAN
Score the kidney biopsy using the MEST-C score
Risk stratify the patient using the International IgAN Prediction Tool
Enroll the patient in a disease registry
Commence optimized supportive care:
• BP management
• Maximally tolerated dose of ACEi/ARB
• Lifestyle modification
• Address cardiovascular risk

UNIVERSITY OF LEICESTER

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Intensive Supportive Care plus Immunosuppression in IgA Nephropathy

Thomas Rauen, M.D., Frank Eitner, M.D., Christina Fitzner, M.Sc., Claudia Sommerer, M.D., Martin Zeier, M.D., Britta Otte, M.D., Ulf Panzer, M.D., Harm Peters, M.D., Urs Benck, M.D., Peter R. Mertens, M.D., Uwe Kuhlmann, M.D., Oliver Witzke, M.D., Oliver Gross, M.D., Volker Vielhauer, M.D., Johannes F.E. Mann, M.D., Ralf-Dieter Hilgers, Ph.D., and Jürgen Floege, M.D., for the STOP-IgAN Investigators*

clinical trial

After ten years of follow-up, no difference between supportive care plus immunosuppression and supportive care alone in IgA nephropathy

JAMA | Original Investigation

Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA Nephropathy
The TESTING Randomized Clinical Trial

Leicester IgA Nephropathy Research Group

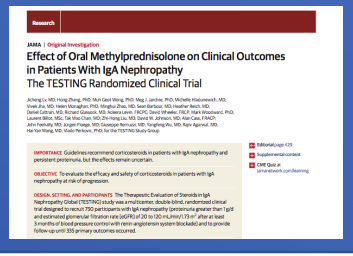
2.3. Treatment

Practice Point 2.3.3. Considerations for treatment of patients with IgAN who are at high risk of progressive CKD despite maximal supportive care.

- **High risk of progression in IgAN is currently defined as proteinuria >1g/24h despite at least 90 days of optimized supportive care.**

- **Immunosuppressive drugs should only be considered in patients with IgAN who remain at high risk of progressive CKD despite maximal supportive care** (the patients enrolled in the only large RCT suggesting benefit of immunosuppression had an average of 2.4 g/day of proteinuria)**.**

KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES KDIGO

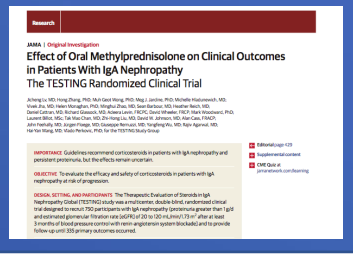


2.3. Treatment

Practice Point 2.3.3. Considerations for treatment of patients with IgAN who are at high risk of progressive CKD despite maximal supportive care.

- **In view of the current uncertainty over the safety and efficacy of current immunosuppressive treatment choices all patients who remain at high risk of progressive CKD despite maximal supportive care should be offered the opportunity to take part in a clinical trial.**

- **In all patients in whom immunosuppression is being considered, a detailed discussion of the risks and benefits of each drug should be undertaken with the patient with a recognition that adverse treatment effects are more likely in patients with an eGFR below 50 ml/min/1.73 m^2.**



2.3. Treatment

Recommendation 2.3.3.

We suggest that patients who remain at high risk of progressive CKD despite maximal supportive care are considered for a six-month course of corticosteroid therapy. The important risk of treatment-emergent toxicity must be discussed with patients, particularly those who have an eGFR below 50 ml/min/1.73 m^2 *(2B)*.


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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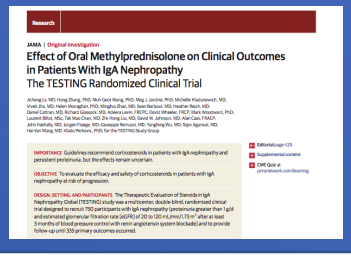
clinical trial www.kidney-international.org

After ten years of follow-up, no difference between supportive care plus immunosuppression and supportive care alone in IgA nephropathy

see commentary on page 836

Thomas Rauen[1], Stephanie Wied[2], Christina Fitzner[2], Frank Eitner[1,3], Claudia Sommerer[4], Martin Zeier[4], Britta Otte[1], Ulf Panzer[5], Klemens Budde[1], Urs Benck[6], Peter R. Mertens[7], Uwe Kuhlmann[1,8], Oliver Witzke[1], Oliver Gross[1,2], Volker Vielhauer[1,3], Johannes F.E. Mann[1,9], Ralf-Dieter Hilgers[2] and Jürgen Floege[1]; for the STOP-IgAN Investigators[1,2]


Research

JAMA | Original Investigation

Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA Nephropathy

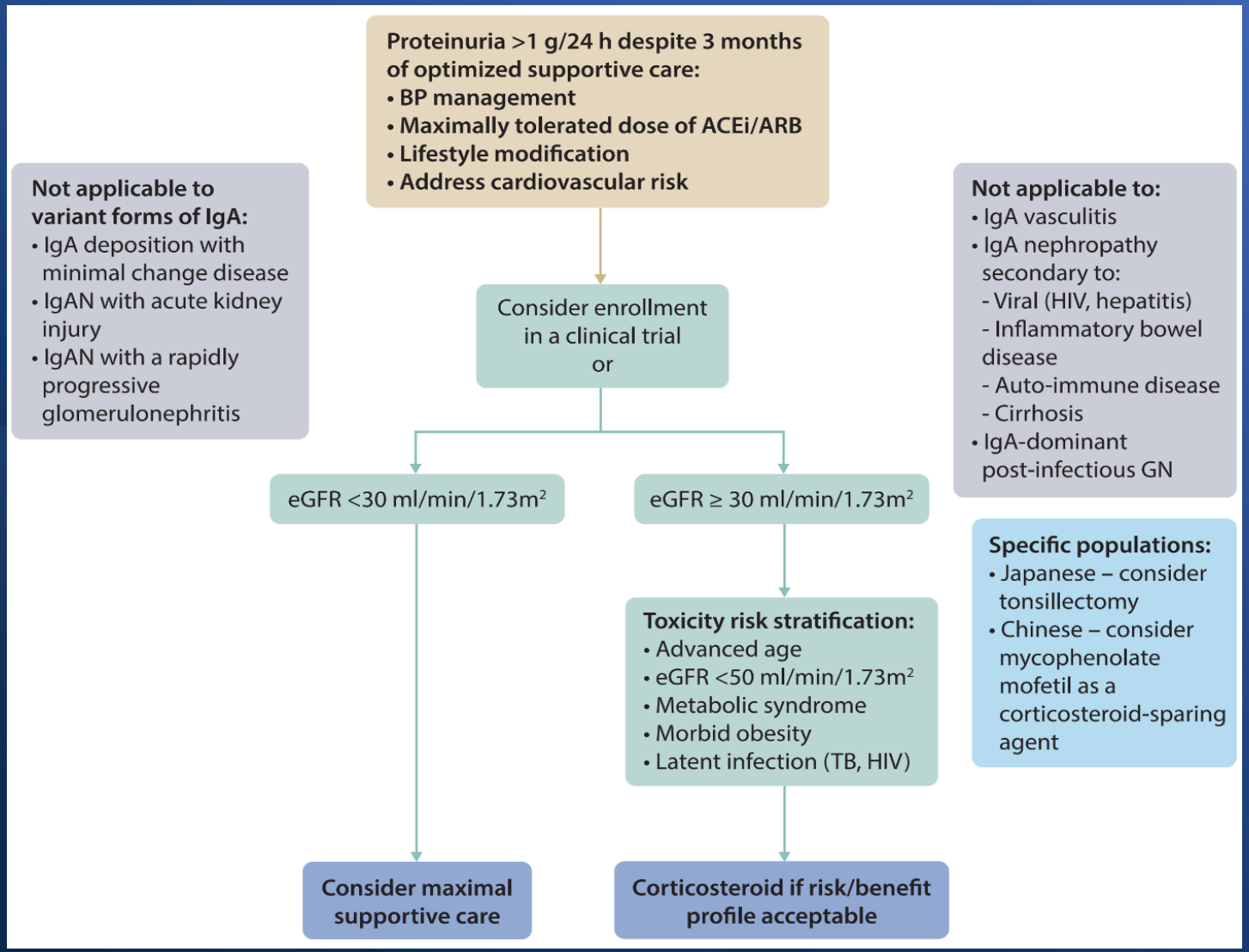
The TESTING Randomized Clinical Trial

2.3. Treatment

Practice Point 2.3.5. Use of corticosteroids in IgAN:

- **Clinical benefit of corticosteroids in IgAN is not established and should be given with extreme caution or avoided entirely in the following situations:**

eGFR <30 mL/min/1.73m^2 *
Diabetes
Obesity (BMI >30 kg/m^2) **
Latent infections (e.g. viral hepatitis, TB)
Secondary disease (e.g. cirrhosis)
Active peptic ulceration
Uncontrolled psychiatric illness


Proteinuria >1 g/24 h despite 3 months of optimized supportive care:
• BP management
• Maximally tolerated dose of ACEi/ARB
• Lifestyle modification
• Address cardiovascular risk
Not applicable to variant forms of IgA:
• IgA deposition with minimal change disease
• IgAN with acute kidney injury
• IgAN with a rapidly progressive glomerulonephritis
Consider enrollment in a clinical trial or
eGFR <30 ml/min/1.73m²
eGFR ≥ 30 ml/min/1.73m²
Not applicable to:
• IgA vasculitis
• IgA nephropathy secondary to:
- Viral (HIV, hepatitis)
- Inflammatory bowel disease
- Auto-immune disease
- Cirrhosis
• IgA-dominant post-infectious GN
Specific populations:
• Japanese – consider tonsillectomy
• Chinese – consider mycophenolate mofetil as a corticosteroid-sparing agent
Toxicity risk stratification:
• Advanced age
• eGFR <50 ml/min/1.73m²
• Metabolic syndrome
• Morbid obesity
• Latent infection (TB, HIV)
Consider maximal supportive care
Corticosteroid if risk/benefit profile acceptable


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intensive Supportive Care plus Immunosuppression in IgA Nephropathy

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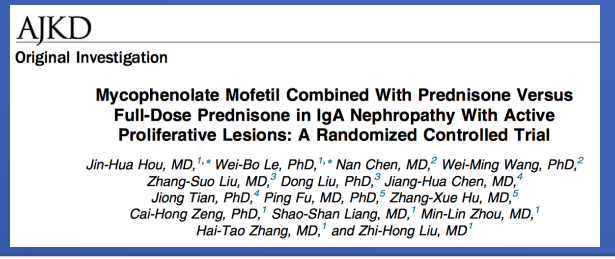
see commentary on page 836

Thomas Rauen[1], Stephanie Wied[2], Christina Fitzner[2], Frank Eitner[1,3], Claudia Sommerer[4], Martin Zeier[4], Britta Otte[5], Ulf Panzer[6], Klemens Budde[7], Urs Benck[8], Peter R. Mertens[9], Uwe Kuhlmann[10], Oliver Witzke[11], Oliver Gross[12], Volker Vielhauer[13], Johannes F.E. Mann[14], Ralf-Dieter Hilgers[2] and Jürgen Floege[1] for the STOP-IgAN Investigators[15]


AJKD

Original Investigation

Mycophenolate Mofetil Combined With Prednisone Versus Full-Dose Prednisone in IgA Nephropathy With Active Proliferative Lesions: A Randomized Controlled Trial

Jin-Hua Hou, MD,[1,*] Wei-Bo Le, PhD,[1,*] Nan Chen, MD,[2] Wei-Ming Wang, PhD,[2] Zhang-Suo Liu, MD,[3] Dong Liu, PhD,[3] Jiang-Hua Chen, MD,[4] Jiong Tian, PhD,[4] Ping Fu, MD, PhD,[5] Zhang-Xue Hu, MD,[5] Cai-Hong Zeng, PhD,[1] Shao-Shan Liang, MD,[1] Min-Lin Zhou, MD,[1] Hai-Tao Zhang, MD,[1] and Zhi-Hong Liu, MD[1]

2.3. Treatment

Practice Point 2.3.7. Other pharmacologic therapies evaluated in IgAN

Agent	Suggested usage	Remarks
Anti-platelet agents	Not recommended	No documented evidence of efficacy
Anticoagulants	Not recommended	No documented evidence of efficacy
Azathioprine	Not recommended	No evidence for efficacy as monotherapy or when combined with corticosteroids
Cyclophosphamide	Not recommended	Unless in the setting of rapidly progressive IgAN
Calcineurin inhibitors	Not recommended	No documented evidence of efficacy
Rituximab	Not recommended	No documented evidence of efficacy
Fish oil	Not recommended	Patients who wish to take fish oil should be advised of the dose and formulation used in the published clinical trials that reported efficacy
Mycophenolate mofetil (MMF)	**Chinese patients** In those patients in whom corticosteroids are being considered MMF may be used as a steroid-sparing agent	In a single RCT conducted in China, MMF with low dose corticosteroids was non-inferior to standard dose corticosteroids for the treatment of incident IgAN presenting with proliferative histologic lesions (E or C lesions with or without necrosis) on kidney biopsy and proteinuria >1.0 g/day. There were significantly fewer corticosteroid related side effects in the combination therapy arm. (PICO 18.16)[1, 6]
	Non-Chinese patients There is insufficient evidence to support the use of mycophenolate mofetil	In the RCTs of MMF in non-Chinese patients there was no evidence for efficacy of MMF monotherapy. (PICO 18.15)[2, 3, 4, 5, 6]

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Original Investigation AJKD

Effects of Hydroxychloroquine on Proteinuria in IgA Nephropathy: A Randomized Controlled Trial

Li-Jun Liu, Ya-zi Yang, Su-Fang Shi, Yun-Fei Bao, Chao Yang, Sai-Nan Zhu, Gui-Li Sui, Yu-Qing Chen, Ji-Cheng Lv, and Hong Zhang

Leicester IgA Nephropathy Research Group

2.3. Treatment

Practice Point 2.3.7. Other pharmacologic therapies evaluated in IgAN

Hydroxychloroquine	**Chinese patients** In those patients who remain at high risk of progression in spite of optimized supportive care	In a small, short-term RCT conducted in China, hydroxychloroquine introduced to patients with proteinuria of 0.75-3.5 g/d despite optimized ACEi/ARB reduced proteinuria by 48% versus 10% in the placebo group at 6 months (PICO 11.5)[7]
	Non-Chinese patients There is insufficient evidence to support the use of hydroxychloroquine	Hydroxychloroquine has not been evaluated in non-Chinese patients.

Yang *et al. BMC Nephrology* (2019) 20:297
https://doi.org/10.1186/s12882-019-1488-6

BMC Nephrology

RESEARCH ARTICLE Open Access

Comparison of the effects of hydroxychloroquine and corticosteroid treatment on proteinuria in IgA nephropathy: a case-control study

Ya-zi Yang†, Pei Chen†, Li-Jun Liu*, Qing-Qing Cai, Su-Fang Shi, Yu-Qing Chen, Ji-Cheng Lv and Hong Zhang

American Journal of Nephrology

Original Report: Patient-Oriented, Translational Research

Am J Nephrol 2018;47:145–152
DOI: 10.1159/000487330

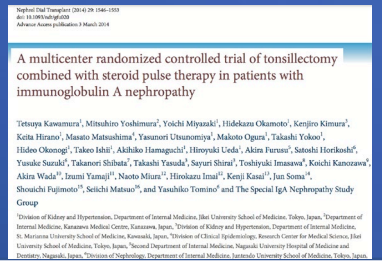
Received: December 8, 2017
Accepted: February 1, 2018
Published online: March 2, 2018

Effects of Hydroxychloroquine on Proteinuria in Immunoglobulin A Nephropathy

Ya-Zi Yang Li-Jun Liu Su-Fang Shi Jin-Wei Wang Yu-Qing Chen Ji-Cheng Lv Hong Zhang

Renal Division, Peking University First Hospital, Institute of Nephrology, Peking University, Key Laboratory of Renal Disease, Ministry of Health of China, Beijing, PR China

KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES KDIGO


A multicenter randomized controlled trial of tonsillectomy combined with steroid pulse therapy in patients with immunoglobulin A nephropathy

2.3. Treatment

Practice Point 2.3.8. Tonsillectomy in IgAN:

- **Tonsillectomy should not be performed as a treatment for IgAN in Caucasian patients.**
- **Tonsillectomy may be indicated in some national guidelines for the treatment of recurrent tonsillitis in patients with IgAN.**
- **Multiple studies from Japan have reported improved kidney survival and partial or complete remission of hematuria and proteinuria following tonsillectomy alone or with pulsed corticosteroids.**

	Japanese IgAN	Chinese IgAN	Caucasian IgAN
Clinical practice	Performed routinely (often with pulsed corticosteroids)	Not routinely performed	Not performed
Remarks	Multiple cohort studies including a large retrospective study with propensity matching report improved kidney survival following tonsillectomy. A single RCT failed to show a difference in eGFR at 1 year comparing tonsillectomy vs tonsillectomy and pulsed corticosteroids, no longer-term data is available from this study	Inconsistent data from small retrospective cohort studies and a small single center RCT	Very few data available in this population. Available data does not support the efficacy of tonsillectomy as a treatment for IgAN in Caucasian patients

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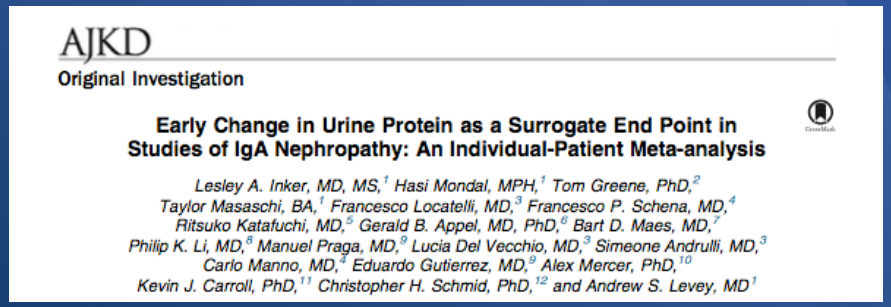
2.3. Treatment

Practice Point 2.3.4. Proteinuria reduction to under 1 g/d is a surrogate marker of improved kidney outcome in IgAN and reduction to under 1g/d is a reasonable treatment target.

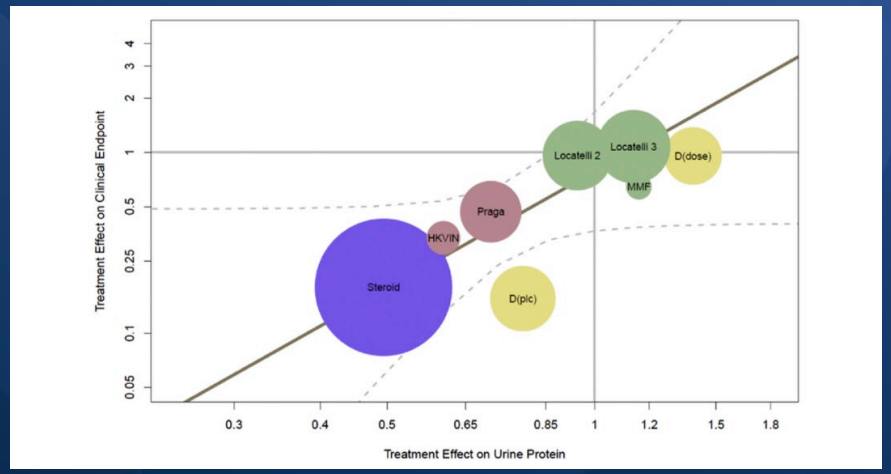


AJKD

Original Investigation

Early Change in Urine Protein as a Surrogate End Point in Studies of IgA Nephropathy: An Individual-Patient Meta-analysis

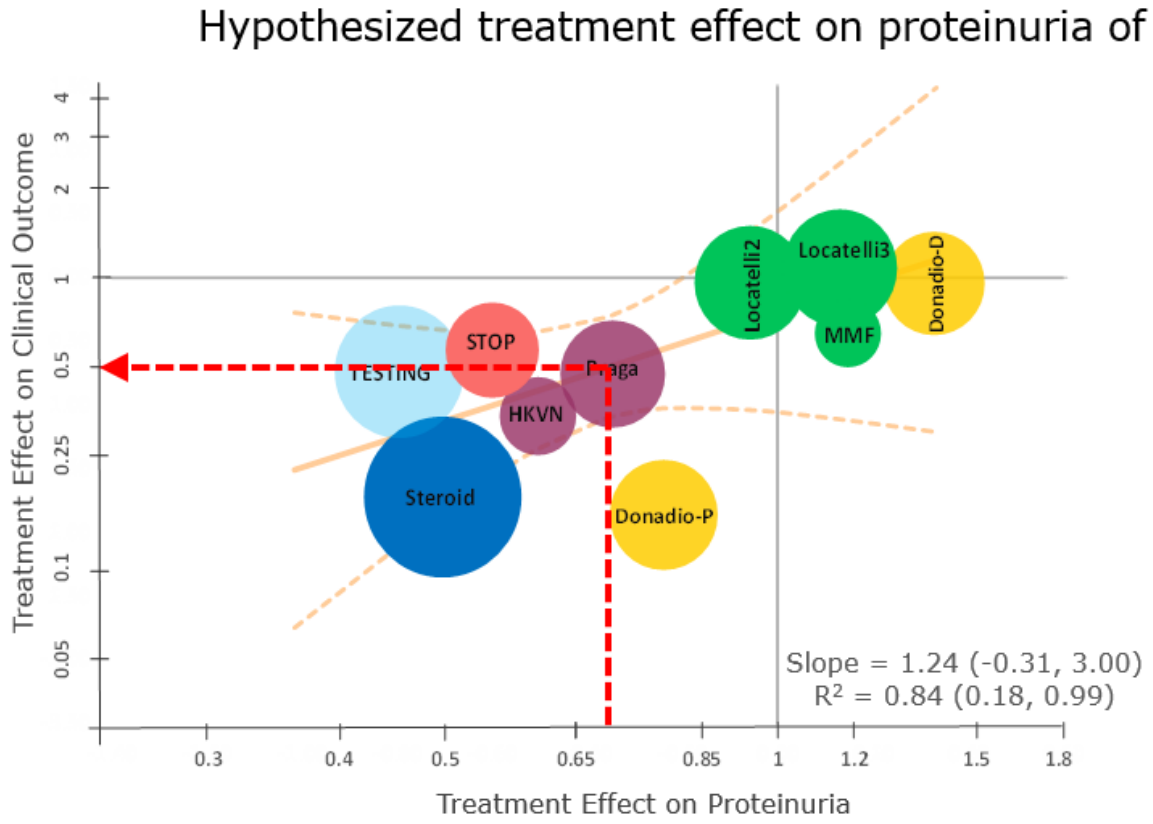
Lesley A. Inker, MD, MS,[1] Hasi Mondal, MPH,[1] Tom Greene, PhD,[2] Taylor Masaschi, BA,[1] Francesco Locatelli, MD,[3] Francesco P. Schena, MD,[4] Ritsuko Katafuchi, MD,[5] Gerald B. Appel, MD, PhD,[6] Bart D. Maes, MD,[7] Philip K. Li, MD,[8] Manuel Praga, MD,[9] Lucia Del Vecchio, MD,[3] Simeone Andrulli, MD,[3] Carlo Manno, MD,[4] Eduardo Gutierrez, MD,[9] Alex Mercer, PhD,[10] Kevin J. Carroll, PhD,[11] Christopher H. Schmid, PhD,[12] and Andrew S. Levey, MD[1]



KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES KDIGO

KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES KDIGO

Kidney Health Initiative (2019): Predicted Treatment Effect on ESKD given change in Proteinuria



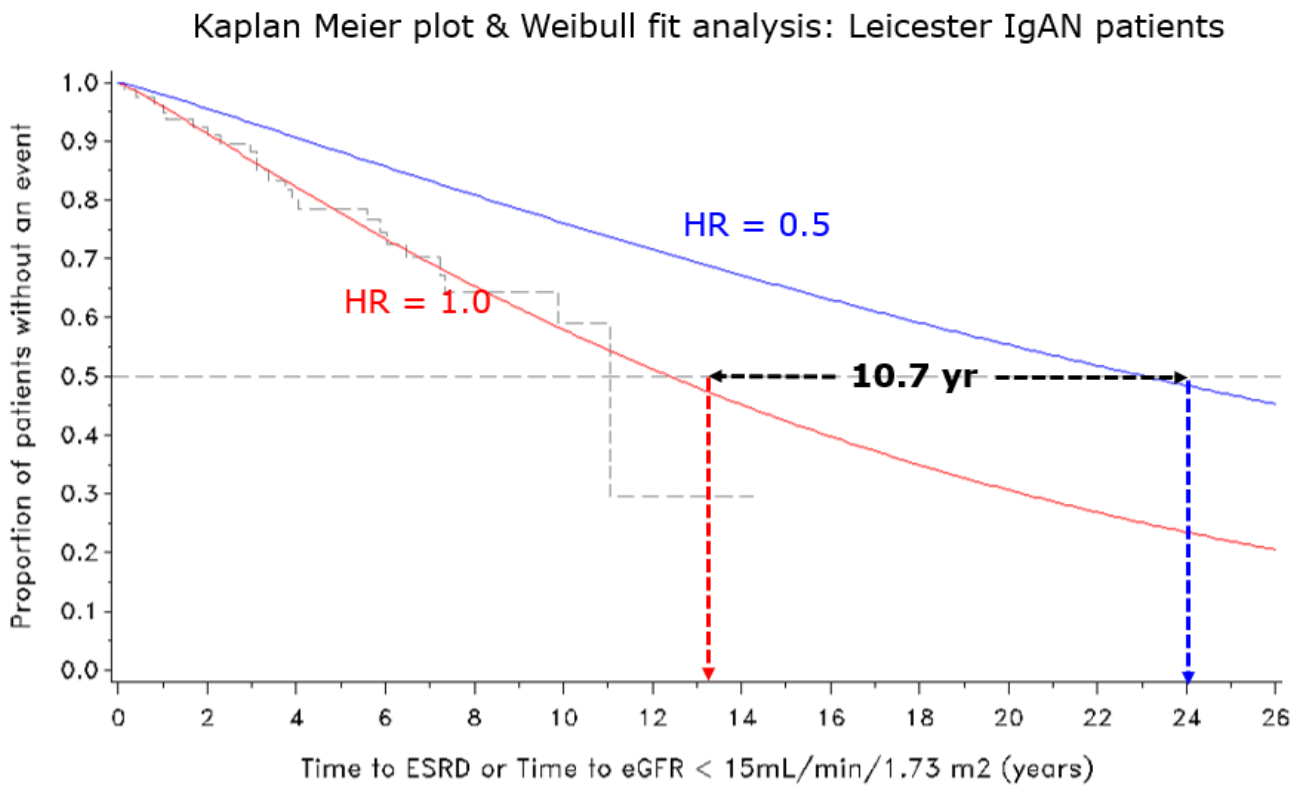
Drug vs Control Treatment Effect* on PU at 9 months	Corresponding % Treatment effect for Drug if Control ineffective	Predicted HR for ESRD	95% CI
0.90	10%	0.6750	(0.363, 1.252)
0.85	15%	0.6290	(0.366, 1.080)
0.80	20%	0.5840	(0.365, 0.934)
0.75	25%	0.5390	(0.356, 0.816)
0.70	30%	0.4950	(0.336, 0.730)
0.65	35%	0.4520	(0.302, 0.677)

*Treatment Effect = $\{[9\ mo\ PU/Base\ PU]_{DRUG}\}/\{[9\ mo\ PU/Base\ PU]_{CONT}\}$

*RASB: renin-angiotensin system blockade

Thompson et al., Clin J Am Soc Nephrol (2018)

Proteinuria reduction important treatment target to delay progression of disease and time towards ESKD



Analysis on patients with
- proteinuria ≥1g/day
- eGFR ≥30 mL/min/1.73m²

HR = 1.0 represents RASB:
Median time to event 12.4 yr, 90% CI (15.9, 33.5)

HR = 0.5 represents hypothesized treatment effect of 30% for sparsentan:
Median time to event 23.1 yr, 90% CI (13.5, 28.5)

*Source: data on file

RESEARCH RECOMMENDATIONS

The following areas are of high priority for future research to improve the treatment and outcomes of patients with IgAN:

❖ **Evaluation of therapeutic strategies that minimize or avoid systemic corticosteroid exposure:**

Emerging data are required to clarify the role of novel therapies in **non-immunosuppressive comprehensive supportive care**.

- Endothelin Receptor Antagonism: **sparsentan (PROTECT) & atrasentan (ALIGN)**
- SGLT2 inhibition: (kidney and cardiovascular outcomes in non-diabetic kidney disease)

RESEARCH RECOMMENDATIONS

The following areas are of high priority for future research to improve the treatment and outcomes of patients with IgAN:

- **Evaluation of therapeutic strategies that minimize or avoid systemic corticosteroid exposure:**

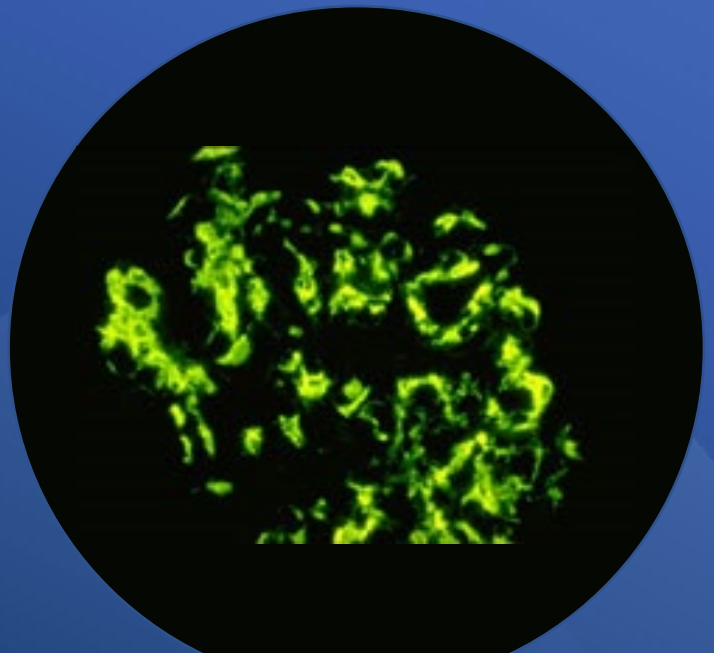
  We need to better understand the value of mycophenolate mofetil and hydroxychloroquine in the management of IgAN in different racial groups, and clinical disease severity.

RESEARCH RECOMMENDATIONS

The following areas are of high priority for future research to improve the treatment and outcomes of patients with IgAN:

❖ **Evaluation of therapeutic strategies that minimize or avoid systemic corticosteroid exposure:**

- Targeted-release formulation (TRF) of budesonide
- Inhibition of the complement system (lectin (MASP-2), alternative (Factor B) and final common (C5) pathways)
- Inhibition of B cell activation and survival (by blocking BAFF and APRIL signalling to B cells).



THE NEXT 10 YEARS

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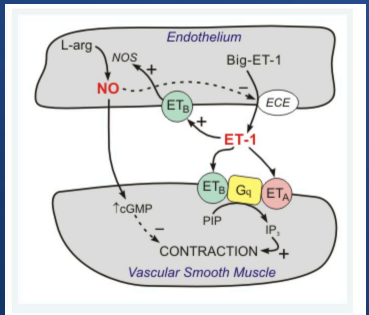
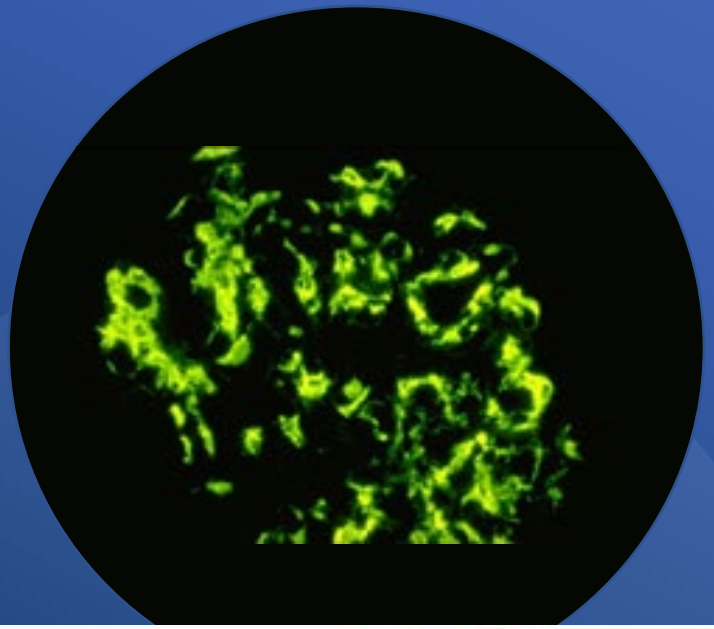
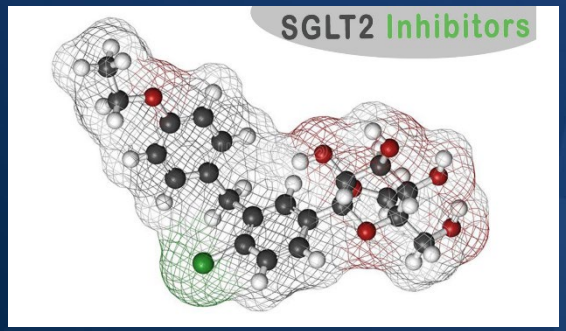
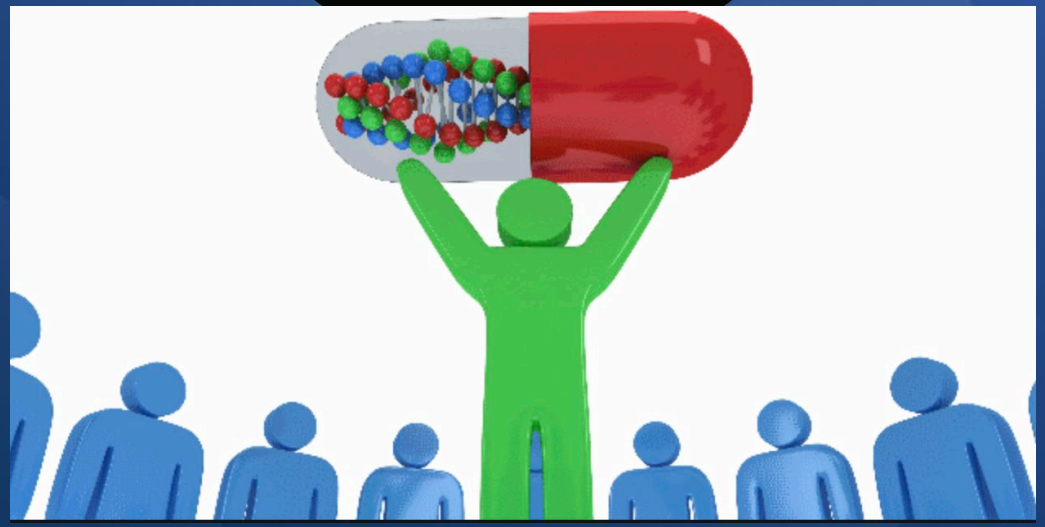
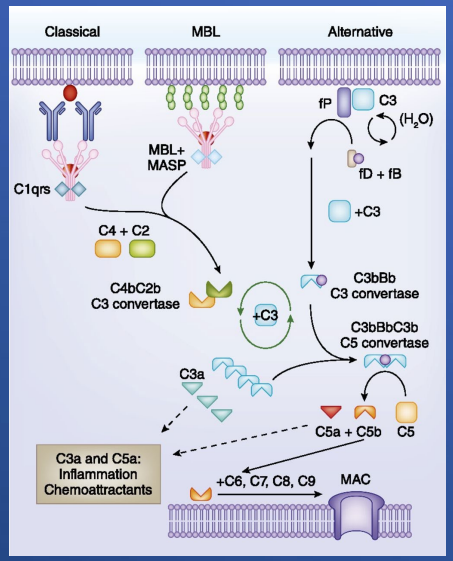
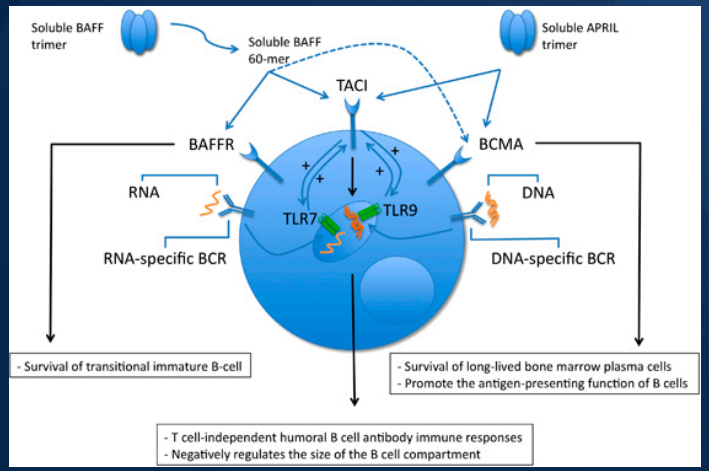




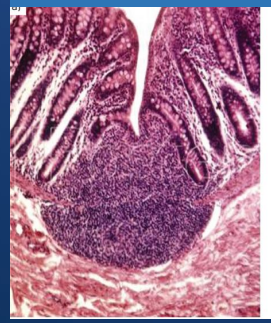


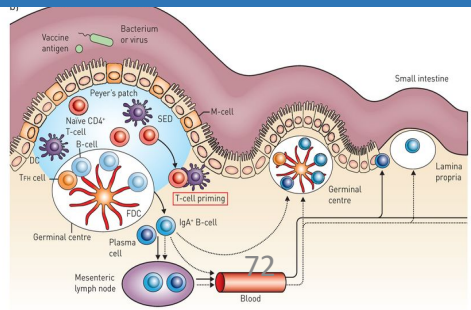






Mucosa Associated Lymphoid Tissue





The Clinical Path to Shaping the Treatment Paradigm for IgAN

Noah Rosenberg, MD – Chief Medical Officer

TRAVERE™ THERAPEUTICS

FSGS and IgAN Share Common Renal Injury Pathways

Kidney injury in FSGS

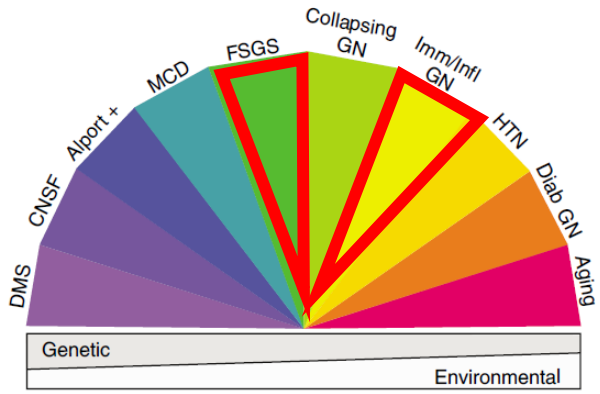
Factors affecting podocyte structural integrity

Podocyte Pathology

Proteinuria

Glomerulosclerosis

Tubulointerstitial Fibrosis



Kidney Failure = Transplant/ Dialysis

Kidney injury in IgAN

Formation of glomerular deposition of immune complexes with hypogalactosylated IgA

Mesangial Cell Activation

Glomerular Inflammation

Proteinuria

Hematuria

Glomerulosclerosis

Tubulointerstitial Fibrosis

Source: Wiggins, Kidney International (2007)

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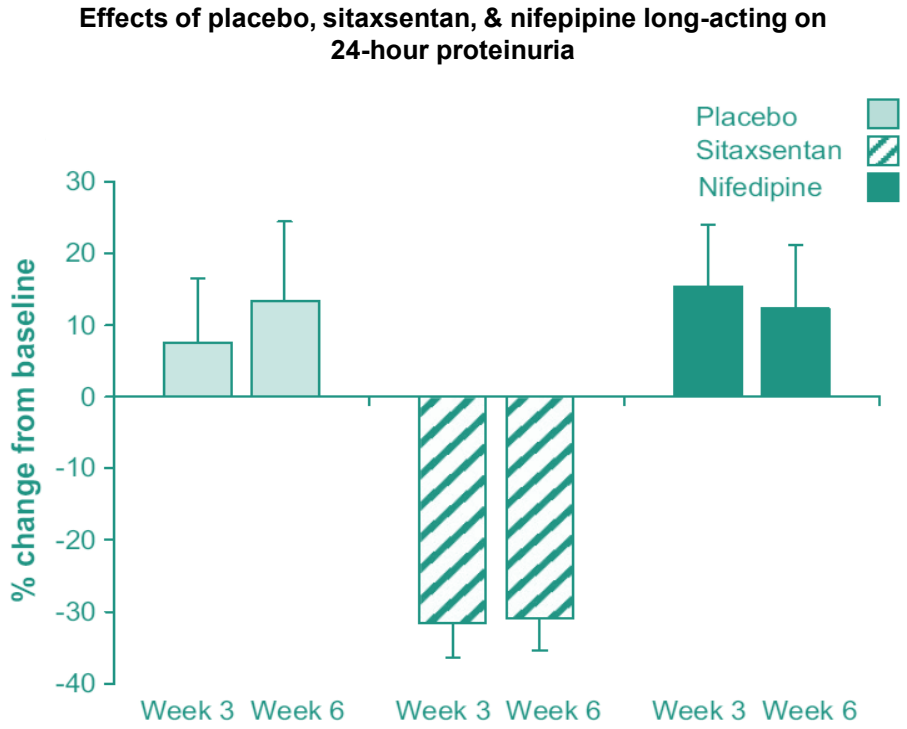
Combined RAAS and Selective ET_A Inhibition Has Demonstrated a Substantial Antiproteinuric Effect

In a randomized, double-blind, 3-way crossover study, patients (N=27; n=14 IgAN diagnoses) on recommended ACEi/ARB treatment received sitaxsentan, nifedipine long acting or placebo for 6 weeks



- Sitaxsentan is a selective ET_A antagonist
- Nifedipine is a Ca^{2+} channel blocker (active comparator)

- Compared with placebo, sitaxsentan reduced 24-hour proteinuria (*p*=0.0069), protein:creatinine ratio (p=0.0102), blood pressure (p=0.0069) and pulse wave velocity (measure of arterial stiffness; p=0.0052)

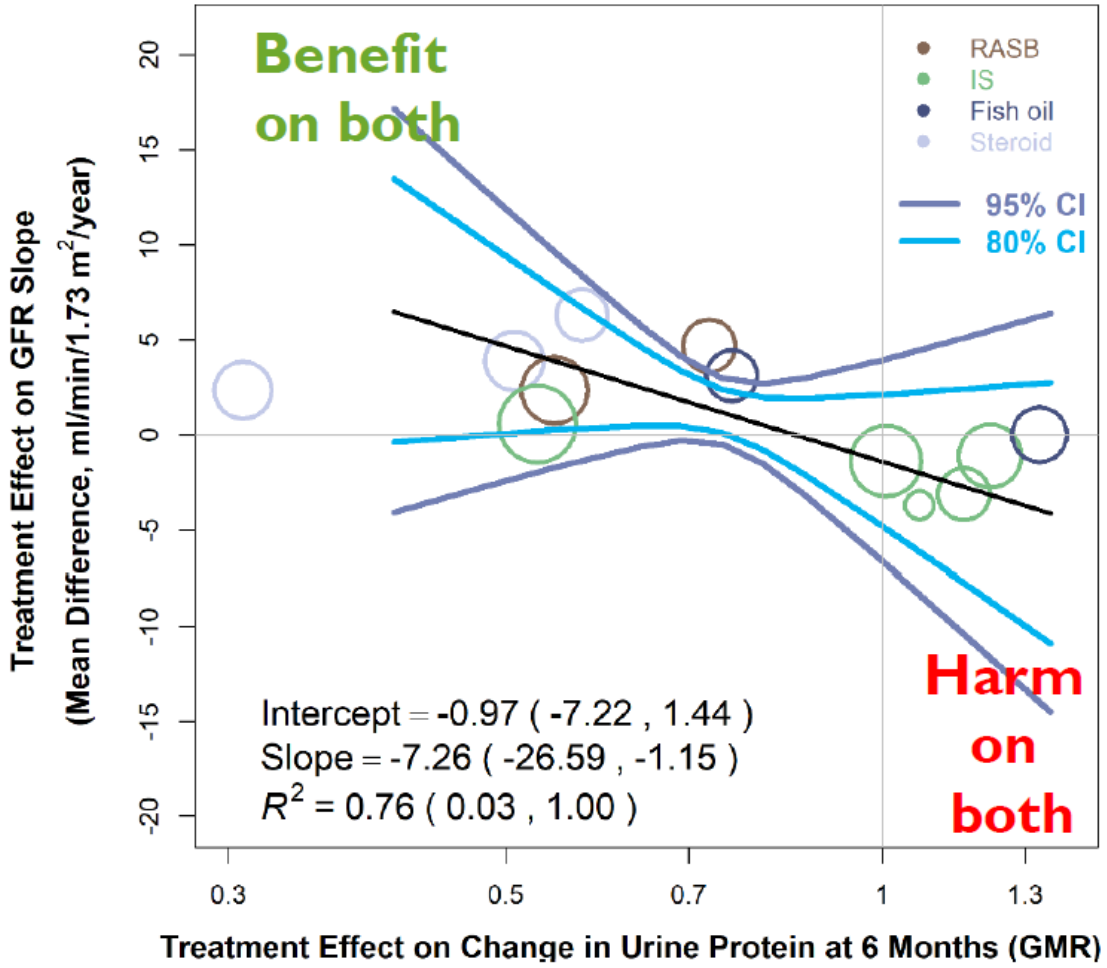
- Nifedipine matched the BP and pulse wave velocity reductions seen with sitaxsentan but did not reduce proteinuria

- Selective ET_A receptor antagonism may provide additional cardiovascular and renal protection by reducing proteinuria, blood pressure and arterial stiffness

Dhaun N, *et al. Hypertension* 2011; **4**:772–779

TRAVERE™ THERAPEUTICS

Studies Suggested Greater Reduction in Proteinuria Also Resulted in Slower Progression of IgAN

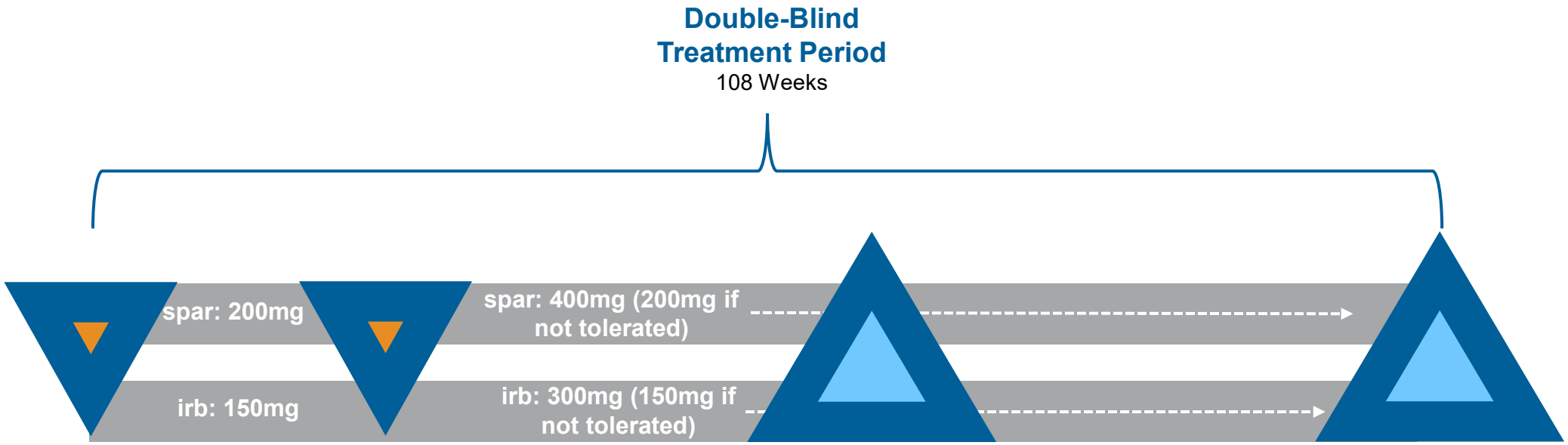


- **Recent analyses of trial-level data from ~1,000 patients with IgAN show associations between treatment effect on change in proteinuria and rate of change in GFR[1]**
  - Predicted treatment effects on GFR slope were strongest for larger treatment effects on change in UP/C

1. Inker on behalf of CKD-EPI et al. ASN Kidney Week 2019;

TRAVERE™ THERAPEUTICS

Leveraging Learnings from DUET, Historical ET_A Inhibition and Trial-Level Data to Design PROTECT in IgAN



DAY 1
- Discontinue prior ACE and/or ARB
- Randomize 1:1
- Baseline UP/C
- Initial dose

WEEK 2
Achieve target dose of 400mg sparsentan or 300mg irbesartan

WEEK 36
Primary endpoint of change from baseline UP/C
~280 patients

WEEK 58
Secondary endpoints rate of change in eGFR
~380 subjects

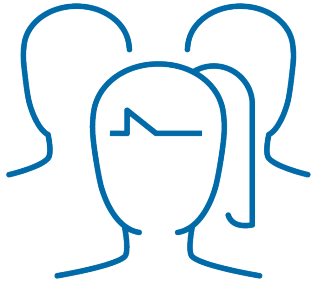
WEEK 110
End of treatment, confirmatory analysis of rate of change in eGFR
~380 subjects

- **90% powered to detect a 30% difference in proteinuria between sparsentan and irbesartan arms**

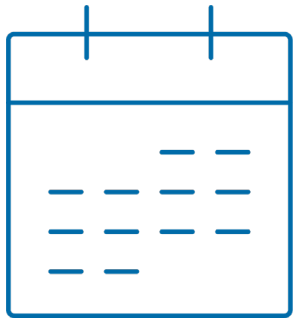
TRAVERE™ THERAPEUTICS

PROTECT On Course for Topline Proteinuria Data in 3Q21

PROTECT achieved enrollment of the first 280 patients to support the interim assessment of UP/C reduction after 36 weeks



PROTECT continues to enroll towards a total sample size of ~380 patients with IgAN – completion of enrollment is expected in 2021



Topline data from the 36-week interim proteinuria analyses are expected in 3Q21; if successful, expected to support accelerated approval submissions in the US and EU

TRAVERE™ THERAPEUTICS

The Need for Treatments in FSGS and IgAN

Peter Heerma, Chief Commercial Officer

The Devasting Impact of Progressive Kidney Disease for Patients, its Caretakers and Healthcare Costs for Society

The devastating impact of progressive kidney disease:

- Kidney disease is one of the leading causes of death
- About 1-in-4 patients die within first year of dialysis
- High mortality rate prior to ESKD due to kidney related vascular events

Progressive kidney disease has a dramatic impact on healthcare cost:

- CKD accounts for ~20% in traditional Medicare spending upwards of $114B/year
- Total Medicare expenditures $49.2B for beneficiaries with ESKD in the US
- >125,000 patients start dialysis each year in the US; this number is growing

Results in disproportional number of patients with FSGS and IgAN in ESKD due to progressive nature of disease

ESKD = End Stage Kidney Disease
Xu et. al, NCHS Data Brief No. 355, January 2020; USRDS 2020 Annual Report; HHS Press Office, 2019;

TRAVERE™ THERAPEUTICS

The Burden of FSGS and IgA Nephropathy

FSGS

- Primary FSGS generally affects patients in their mid-forties to fifties
- High proteinuria levels in (sub)nephrotic range is hallmark of disease
- Majority of patients relapse, many within 20-36 months
- 30-60% progress to ESKD with 5-10 years; Recurrent disease develops in 40% of transplant patients

- Growing incidence and prevalence

IgAN

- Most commonly reported primary glomerulonephritis
- Affects young adults, often leading to dialysis or transplant in their 40s or early 50s
- ~30-40% of patients have a progressive course to ESKD
- The prognosis is worse for those with persistent proteinuria >1gr/day

Sources: Gipson et al. *Kidney Int.* (2011); Healthagen 2007 – 2019; Korbet et al., *J Am Soc Nephrol.* (2012); Market Dynamix 2020; USRDS (2019); Rauen et al. *Kidney Int.* (2020); Moranne et al., *Q J Med* (2008) Jarrick et al., *JASN* (2019); Le et al., *Nephrol Dial Transplant* (2011); Selvaskandan et al., *Clin and Exp Nephrol* (2019); proprietary market research

TRAVERE™ THERAPEUTICS

Patient Journey: Referral, Diagnosis and Treatment Path

Referral

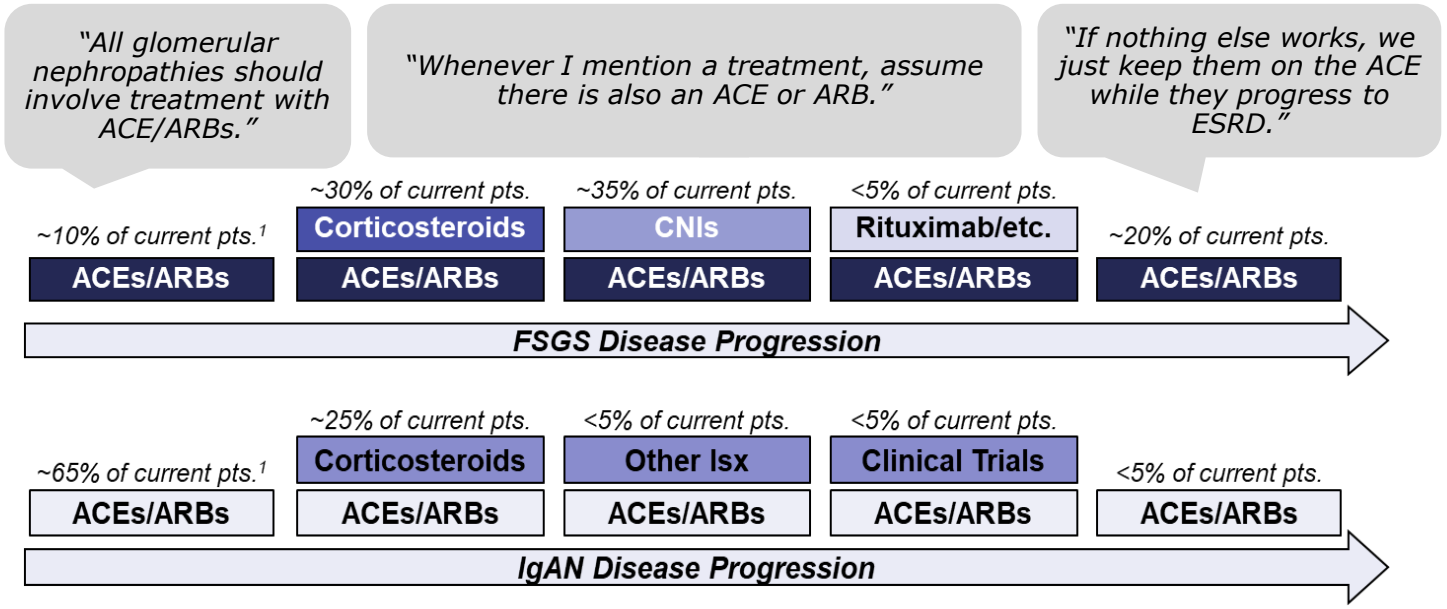
- ~50% of patients have progressed to CKD3 by the time they are referred to a nephrologist

Diagnosis

- Glomerular disease diagnosis is based on confirmatory biopsy in ~ 60-90%

Treatment

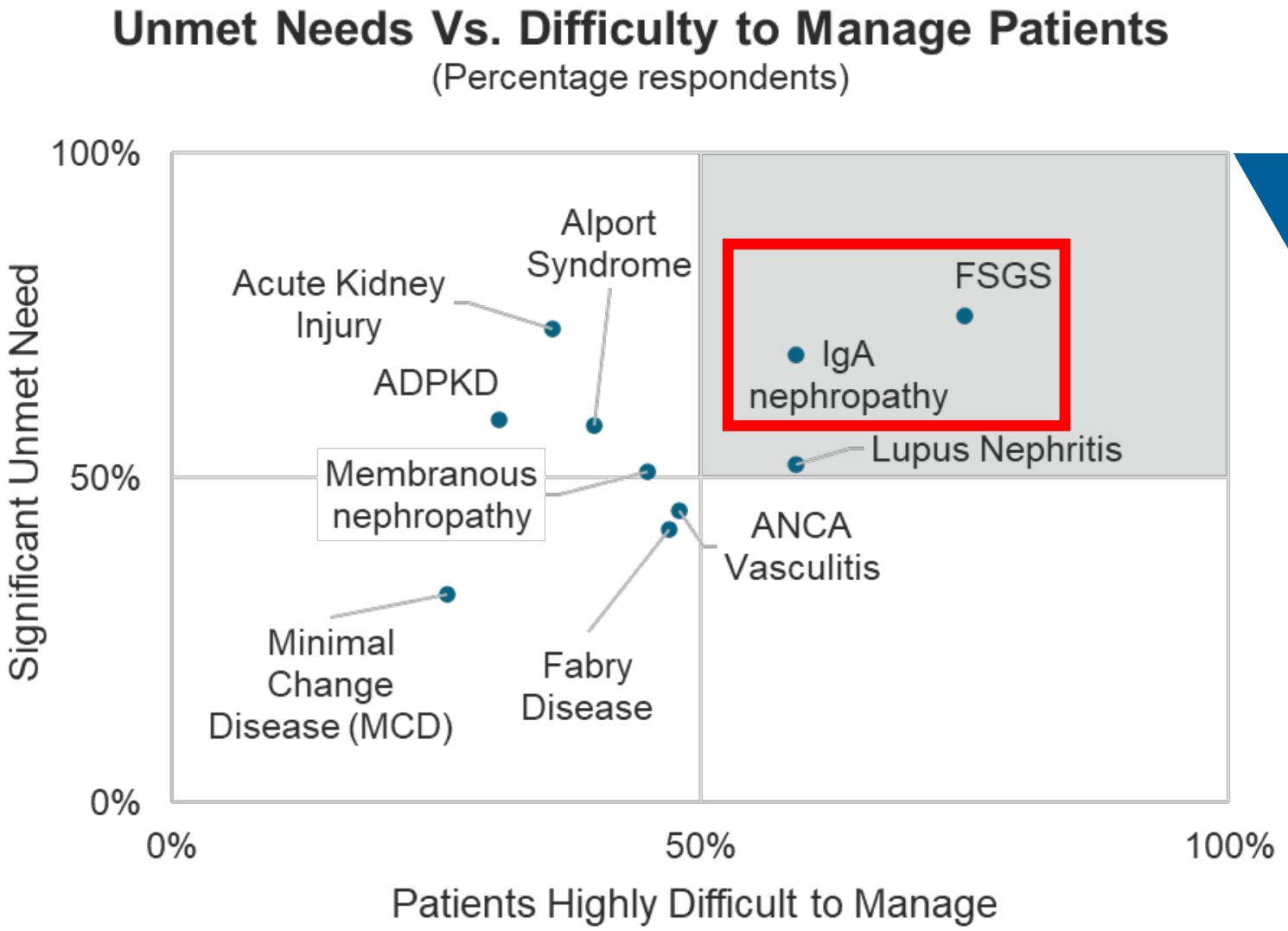
- **ACE/ARBs are the backbone** therapy for glomerular nephropathies
- Nephrologists are more likely to use **add-on immune suppressant therapies (ISTs)** like steroids and calcineurin inhibitors in FSGS vs IgAN



Source: Independent market research, data on file

TRAVERE™ THERAPEUTICS

Nephrologists Rate FSGS & IgAN as Most Challenging to Manage



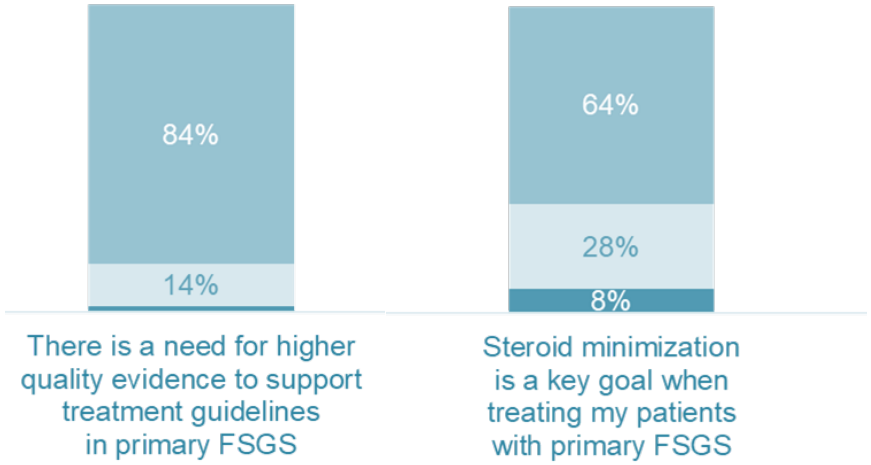
Surveyed nephrologists believe *only 8%* of their FSGS patients are "optimally managed"

Surveyed nephrologists: *only 19%* of IgAN patients are "optimally managed"

Source: Independent market research, data on file

TRAVERE™ THERAPEUTICS

Need for Evidence-Based Medicine, Addressing Limited Efficacy and Tolerability/Safety Concerns with Current SOC



We put a patient on steroids for six months, and suddenly, a 120 pound woman is now 165 pounds, she has acne, thin hair, and is a borderline diabetic. ***These are not benign medicines. The problem with all of this is that the initial treatment is steroids…***

These steroids are, at the very minimum, three months, but usually, you are looking at six months to a year. That is the tradeoff. We sit there and say: "Gee, we are sorry to have to do this to you… but ***if you want to save your kidneys and stay off dialysis, other parts of your body are going to suffer."*** *– Nephrologist*

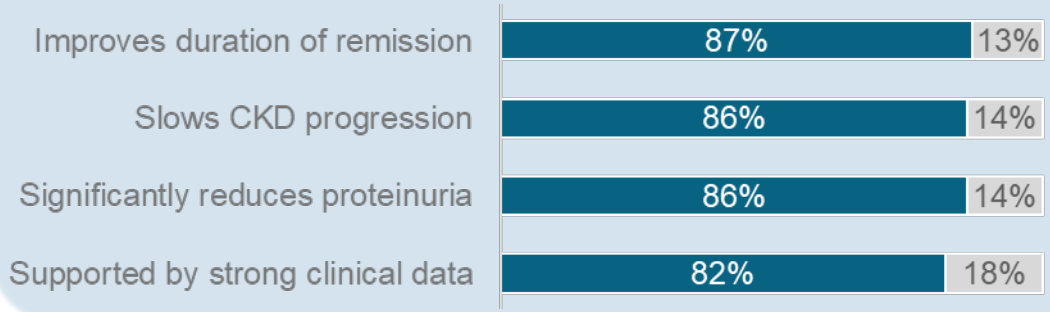
- No medicines currently indicated for glomerular diseases FSGS and IgAN
- Current options associated with:
  - limited efficacy
  - safety and tolerability issues
  - limited duration of response
- Nephrologists express a high need for evidence-based medicine that is *efficacious, safe & tolerable and durable*

TRAVERE™ THERAPEUTICS

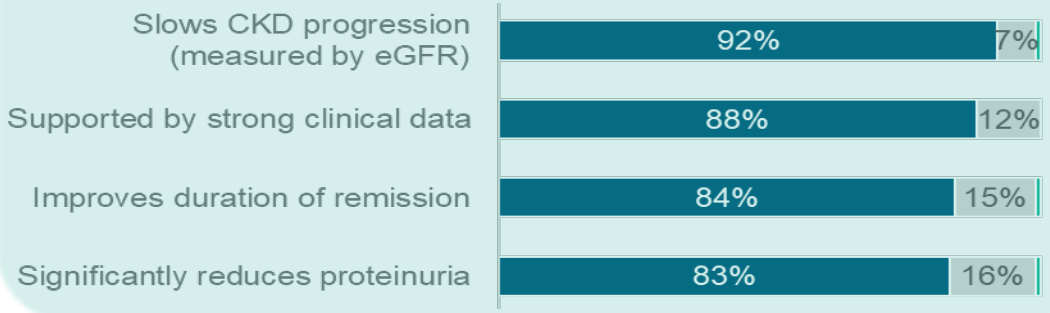
Source: Independent market research, data on file

Desired Product Attributes and Perception of Potential Future Sparsentan Product Profile*

Top 4 Most Desired Attributes in a New Pharmacologic Treatment for FSGS (Percent of respondents)



Top 4 Most Desired Attributes in a New Pharmacologic Treatment for IgAN (Percent of respondents)



According to an independent survey with >100 participating nephrologists, **sparsentan's potential future product profile* rose to the top of the most desirable pipeline programs** for FSGS and IgAN

*Pending Phase 3 data and if approved
Source: Independent and syndicated market research, data on file

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Value Demonstration for Any New FSGS & IgAN product

Innovative MoA	▪ **Lack of recent innovation** in treatment of progressive renal diseases highlights need for therapies that can address the injury pathway, and potentially protect the kidney from damage beyond currently available mechanistic approaches
Delay to ESKD	▪ **Slowing progression of disease** and delaying ESKD with severe morbidity and mortality impact to patients will be most important clinical outcome ▪ **Reducing time towards renal replacement therapy** and its associated high costs as dialysis and transplantation will be important value drivers
Quality of life	▪ Improve/maintain **quality of life** with patient relevant impact, including **lower work productivity losses** and decrease use of disability benefits
Safety	▪ New therapies to be tolerable and safe ▪ Potential for **"steroid sparing"** proposition

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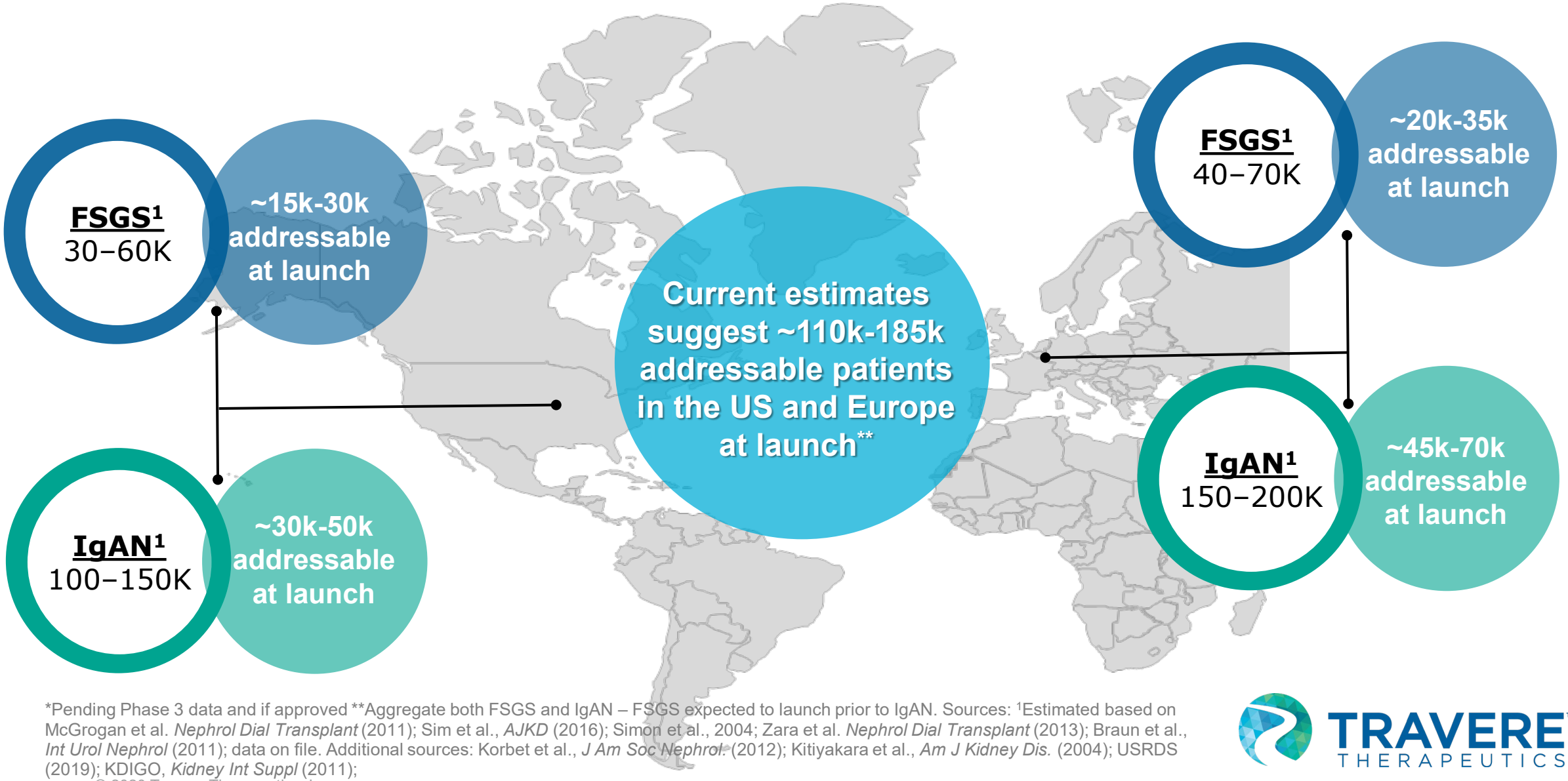
Epidemiology and Projected Addressable Patient Population at Launch*



*Pending Phase 3 data and if approved **Aggregate both FSGS and IgAN – FSGS expected to launch prior to IgAN. Sources: [1]Estimated based on McGrogan et al. *Nephrol Dial Transplant* (2011); Sim et al., *AJKD* (2016); Simon et al., 2004; Zara et al. *Nephrol Dial Transplant* (2013); Braun et al., *Int Urol Nephrol* (2011); data on file. Additional sources: Korbet et al., *J Am Soc Nephrol.* (2012); Kitiyakara et al., *Am J Kidney Dis.* (2004); USRDS (2019); KDIGO, *Kidney Int Suppl* (2011);

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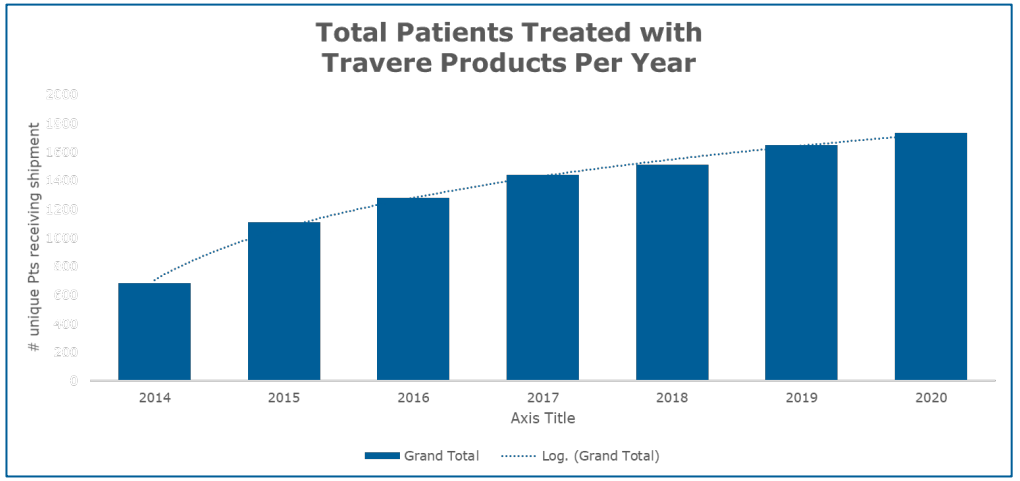
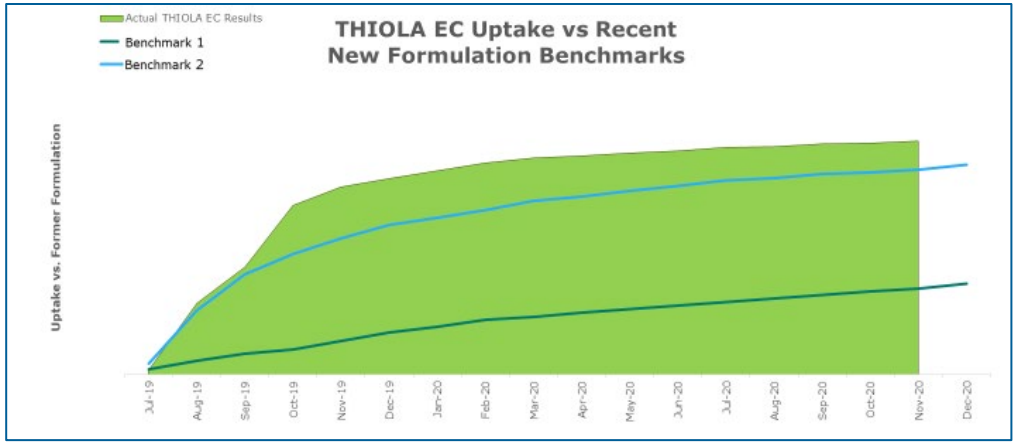
Building on Strength in Preparing for Sparsentan Launch by Utilizing Established Commercial Rare Disease Capabilities and Nephrology Footprint*

- **Proven commercial capabilities and infrastructure**
  - Organic year-over-year growth for last five years
- **Experience planning and executing new product launches in rare disease**
  - Recent Thiola EC launch outperformed benchmarks
- **Established nephrology network, Patient Hub and expertise**
  - Field-force currently calling on ~2,000 nephrologists in US
  - Ability to build upon established customer support services
  - Experienced central distribution capabilities to meet the needs of rare patients





*Pending Phase 3 data and if approved

ThiolaEC (tiopronin) 300 Enteric-Coated, Delayed-Release Tablets

Thiola (tiopronin)

Cholbam (cholic acid) capsules

CHENODAL (Chenodiol Tablets 250 mg)

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In Summary

- Nephrologists consider FSGS and IgAN as the most challenging diseases to manage
- There are no medicines indicated for FSGS and IgAN; current options associated with:
  - limited efficacy
  - safety and tolerability issues
  - limited duration of response
- Market research suggests that sparsentan is considered by surveyed nephrologists to have the most desired product profile of product candidates currently in the clinic for FSGS and IgAN
- The high burden-of-disease along with recognized personal and economic impact should allow for strong product value proposition
- Potential to reach a significant number of people living with FSGS and IgAN
  - Current estimates suggest ~110k-185k addressable patients living with FSGS and IgAN in the US and Europe at launch in 2022
- Travere Therapeutics is positioned to be able to successfully bring sparsentan to market* with its proven commercialization capabilities and established network in rare nephrology

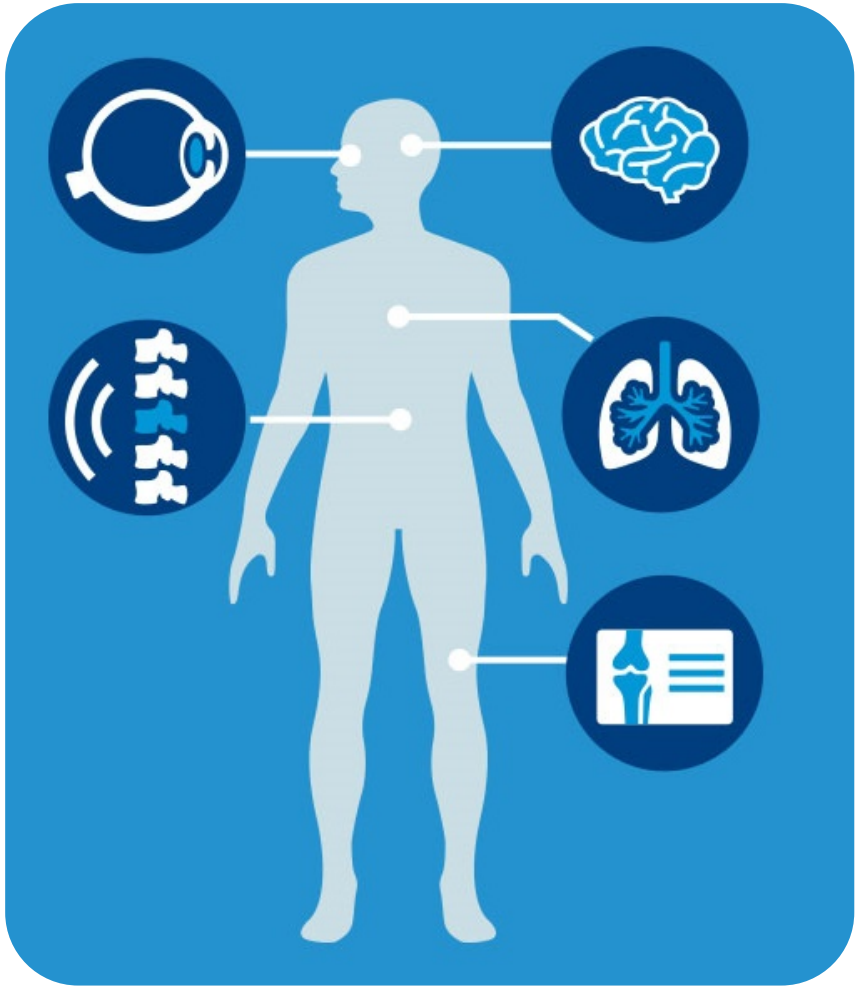
*Pending Phase 3 data and if approved

TRAVERE™ THERAPEUTICS

TVT-058 – The First Potential Disease Modifying Therapy for Classical Homocystinuria (HCU)

Bill Rote, PhD – Head of Research and Development

Classical Homocystinuria (HCU) is a Rare Disorder that can Lead to Life-Threatening Complications



- **Rare autosomal recessive disorder caused by mutations in cystathionine beta-synthase (CBS) gene, leading to deficient activity of CBS**
  - Metabolic deficiency of CBS leads to bodily buildup of toxic homocysteine (Hcy)
- **Toxic levels of Hcy can lead to serious complications for people living with classical HCU**
  - Continuous risk of developing life-threatening thrombotic events including heart attack and stroke
  - Other symptoms of classical HCU include dislocation of the eye lens and extreme nearsightedness, skeletal complications including osteoporosis, and developmental delay
- **There are no approved treatments that address the underlying genetic cause of HCU**
  - Current standard of care includes vitamin B6, low-protein diet + supplements, betaine
- **Estimates suggest at least 3,500 patients in US, similar number in Europe**

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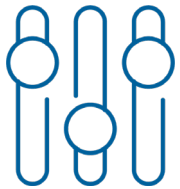
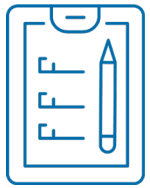
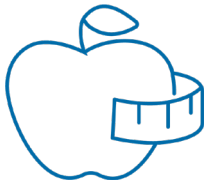
With Largely Ineffective Treatment Options, a Significant Unmet Need Remains for People Living with HCU



Generally accepted therapeutic goal is to reduce total homocysteine (tHcy) levels but current treatment options rarely sustain reductions in tHcy



Significant challenges for patients to maintain compliance; periods of poor metabolic control have a cumulative deleterious effect



Patients struggle with severe dietary protein restrictions as they age; liberalized diet is amongst top needs

Inability to sustain reductions in Hcy results in life-long risk of thrombotic and cardiac events + cognitive impairment

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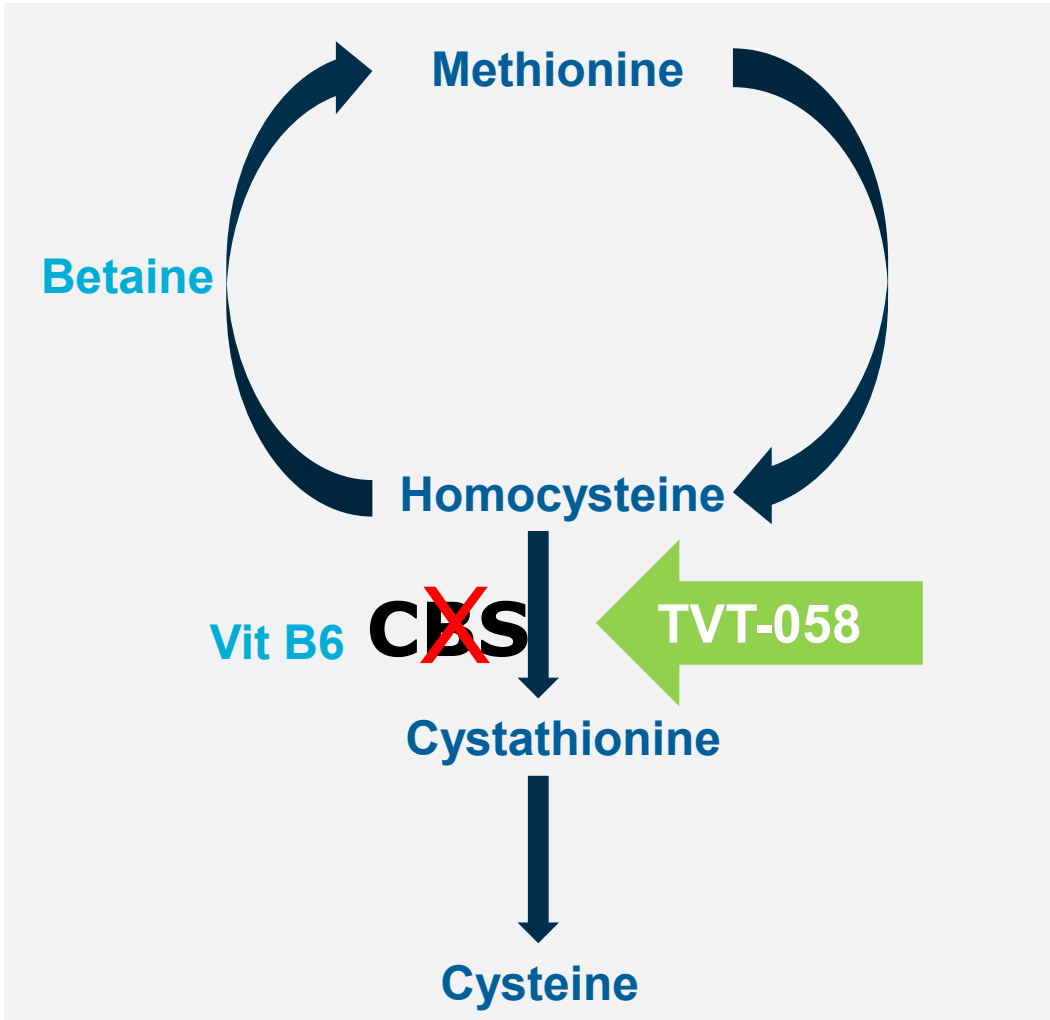
TVT-058 is a Novel, Investigational, Modified Recombinant CBS Enzyme Therapy

- **TVT-058 is a pegylated, modified recombinant truncated human enzyme, designed to address the underlying genetic cause of HCU**
  - Mechanism of action is pathology agnostic
- **TVT-058 is administered subcutaneously and designed to be active and stable in plasma unlike native CBS**
- **Designed to introduce the CBS enzyme into circulation and reduce intracellular and plasma Hcy levels**
- **TVT-058 has been granted multiple regulatory designations:**
  - FDA Rare Pediatric Disease designation
  - FDA Fast Track designation
  - Orphan Drug designation in the US and Europe.



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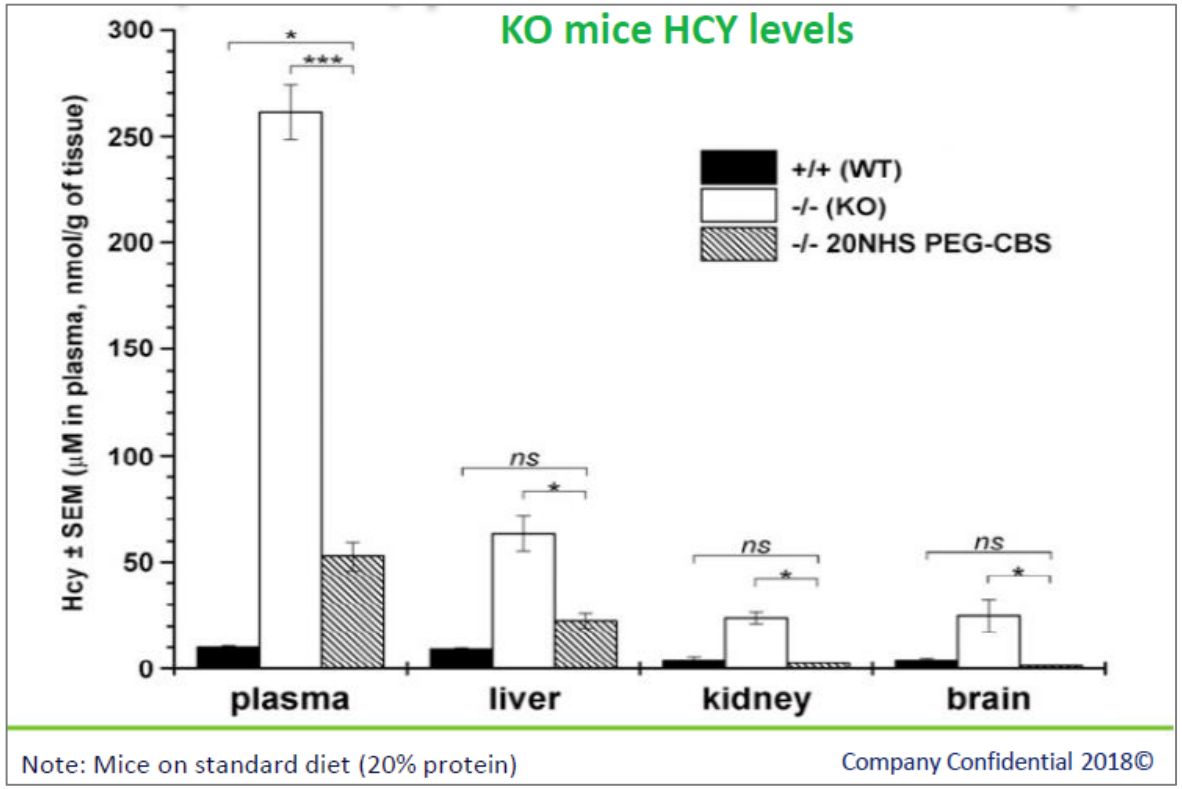
Administration of TVT-058 Resulted in Up To 70-90% Reduction of Plasma and Tissue Hcy Levels in Mouse Models

Dosing with TVT-058 resulted in a decrease of extracellular Hcy

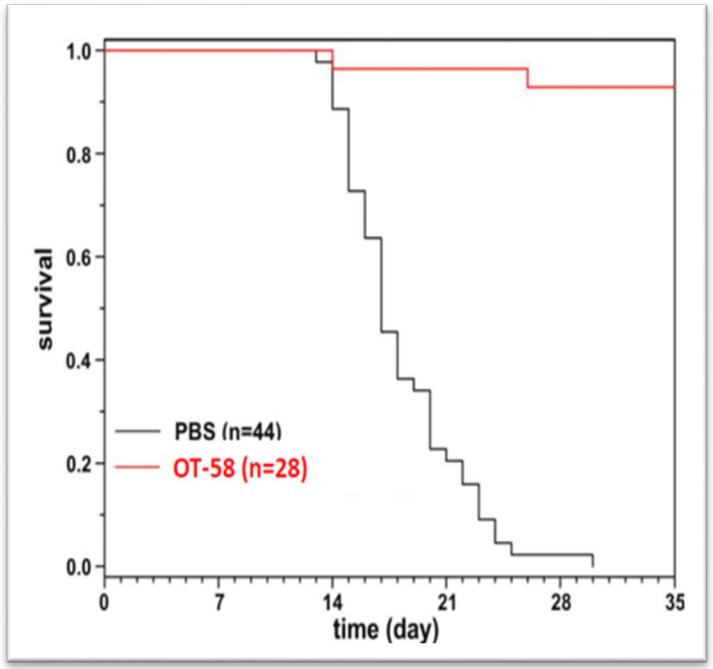


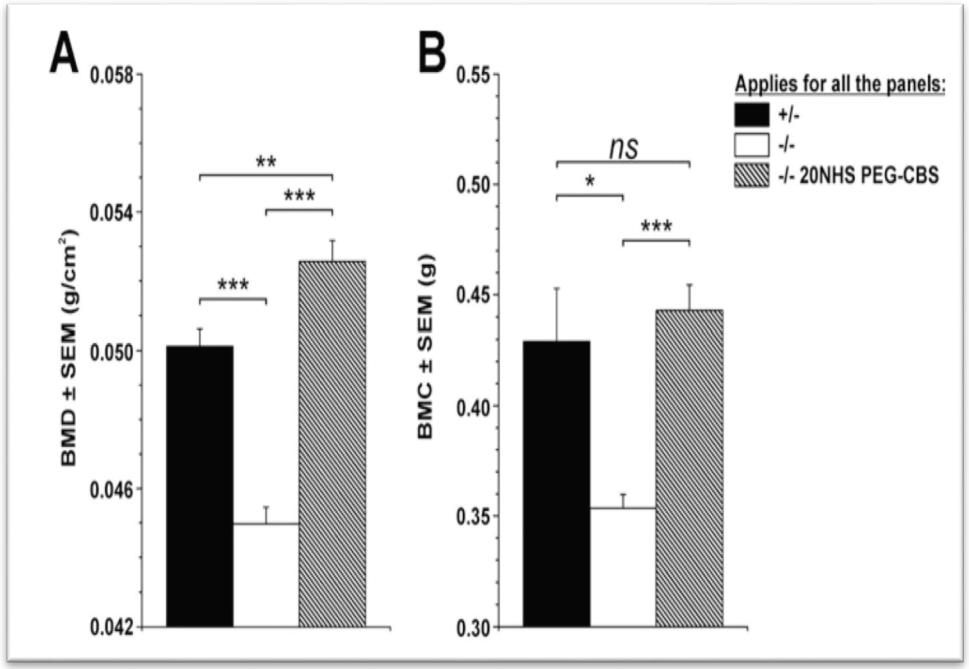
"Metabolic Sink"

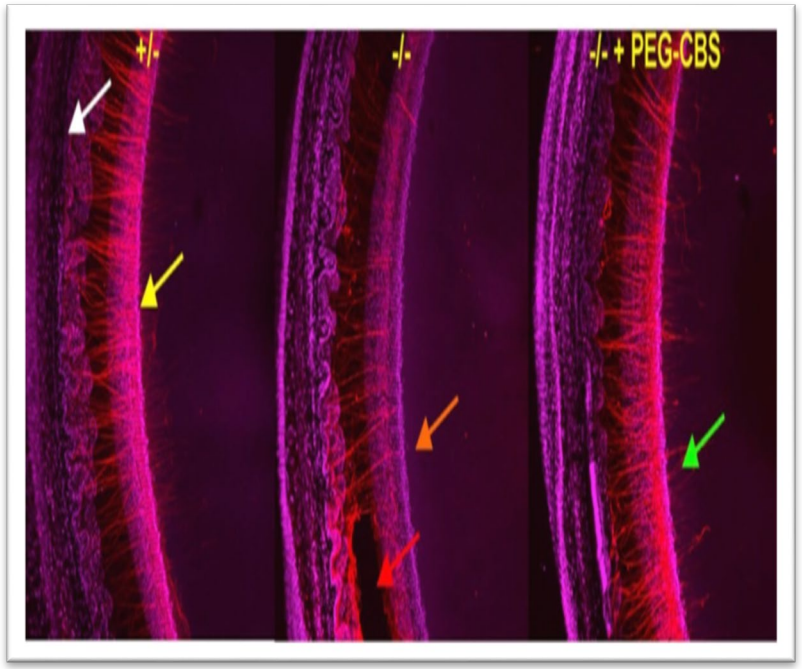
By lowering the Hcy levels in the blood, TVT-058 has been shown to create a concentration gradient that causes excess Hcy in tissues to move to plasma, where it is metabolized

Source: Majtan T. et al., *FASEB J.* 2017; 31(12):5495-5506

Treatment with TVT-058 Appeared to Prolong Survival, Prevent Osteoporosis and Rescue Ocular Structure in Mouse Models







Negative Control | Untreated | TVT-058 treated

Treatment with TVT-058 appeared to prolong survival in KO mouse models[1]

Untreated KO mouse models resulted in significant liver damage and death within 20-30 days

Early treatment with TVT-058 appeared to prevent loss of bone mineralization and fat content in KO mice[1]

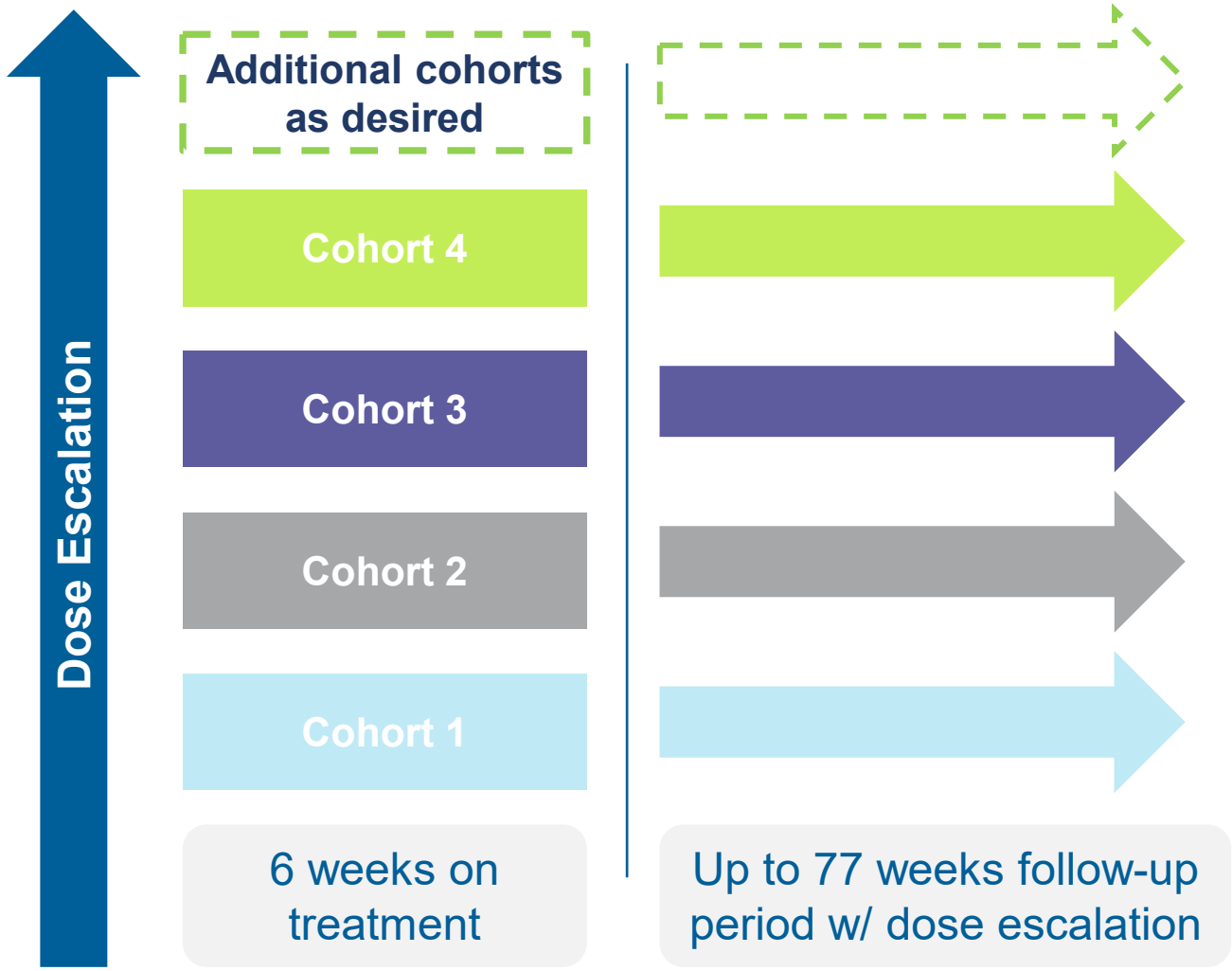
Treatment with TVT-058 appeared to preserve fiber integrity and prevent the degradation of the structure that secures the lens in the eye[2]

Source: 1. Majtan T. et al., *FASEB J.* 2017;31(12):5495-5506; 2. Majtan,T et al., *Mol Ther*. 2018;26(3):834-844

TRAVERE™ THERAPEUTICS

TVT-058 is Advancing in Ongoing Phase 1/2 Clinical Proof-of-Concept Study in HCU

- TVT-058 is advancing in a Phase 1/2 double blind, randomized, placebo-controlled study
- Cohorts are enrolled in a dose escalating fashion; following completion of each cohort, unblinded safety data are reviewed by DMC prior to activating next cohort
- Primary endpoint
  - Incidence of treatment-emergent adverse events
- Secondary endpoints
  - Total plasma homocysteine (tHcy)
  - Cognitive function changes
  - Ocular assessment
  - Bone mineral density
  - Patient QoL scales: Neuro-QoL, EQ-5D & SF-36



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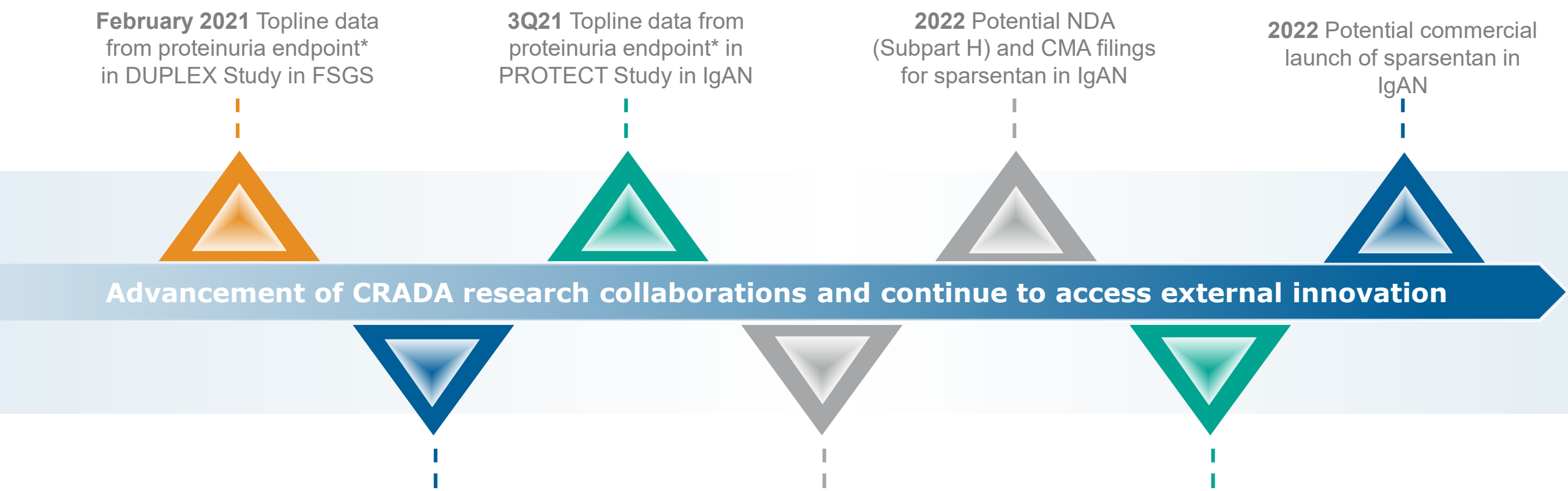
Path to Potential Breakthrough Growth for Travere Therapeutics



*Interim endpoint; confirmatory endpoint is slope of eGFR

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Q&A