

Clinical trial recommendations for potential Alport syndrome therapies

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Alport syndrome is experiencing a remarkable increase in preclinical investigations. To proactively address the needs of the Alport syndrome community, as well as offer clarity for future clinical research sponsors, the Alport Syndrome Foundation hosted a workshop to generate consensus recommendations for prospective trials for conventional drugs. Opinions of key stakeholders were carefully considered, including those of the biopharmaceutical industry representatives, academic researchers, clinicians, regulatory agency representatives, and—most critically—patients with Alport syndrome. Recommendations were established for preclinical researchers, the use and selection of biomarkers, standards of care, clinical trial designs, trial eligibility criteria and outcomes, pediatric trial considerations, and considerations for patient engagement, recruitment, and treatment. This paper outlines their recommendations.

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KEYWORDS: Alport syndrome; chronic kidney disease; CKD; clinical trial design; end-stage kidney disease; ESKD; end-stage renal disease; ESRD; genetic disease; rare disease

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Alport syndrome (AS) is a progressive, hereditary, type IV collagen disorder defined and caused by mutations in the autosomal *COL4A3* and *COL4A4* genes and the X-linked *COL4A5* gene. Its primary kidney manifestations that result in end-stage kidney disease (ESKD) are glomerulosclerosis, tubular atrophy, and interstitial fibrosis.¹ To date, effective therapy for AS is limited to the off-label use of renin-angiotensin-aldosterone system blockade drugs such as angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. However, retrospective studies suggest that this standard of care merely delays the onset of ESKD.^{2,3} Thus, preventative or curative therapies for AS currently do not exist.

The prevalence of AS and genetically related disorders

Because AS is estimated to affect fewer than 200,000 people in the United States,⁴ it meets US Food and Drug Administration (FDA) and US Orphan Drug Act orphan disease criteria.⁵ The true incidence of AS is unknown and is highly dependent upon disease definition. Historically, an AS diagnosis was equated primarily with males with X-linked disease, and secondarily, either males or females with autosomal-recessive disease, or with females with *COL4A5* ± mutations who were characterized as carriers of X-linked AS but were not directly affected by AS.⁶ The currently accepted AS diagnosis uses a more inclusive genetic-based approach that recognizes that women with X-linked disease are, indeed, patients, and that the autosomal-recessive and -dominant forms of AS are more prevalent than previously understood.¹ Of note, the AS community no longer accepts the term *carrier* in reference to women with X-linked AS, as they themselves are affected. Furthermore, an increasing body of genetic research involving whole-exome sequencing shows that a nontrivial proportion of cases of idiopathic glomerulosclerosis and other types of chronic kidney disease are in fact associated with mutations in *COL4A3*, *COL4A4*, or *COL4A5*, consistent with AS.^{7–12} Thus, although AS is still a rare disorder, it is more heterogeneous and prevalent than previously believed.

Table 1 | Current Phase 2 and 3 trials enrolling patients with AS

Drug/sponsor	Target and theorized mechanism	Trial phase and design	Main eligibility criteria
SAR339375/Sanofi ¹³	Anti-microRNA-21 Theorized mechanism: antifibrotic	Phase 2: randomized, double-blind, placebo-controlled Enrollment target: 45 48 weeks randomized + 48-week open-label extension	Age 18–55 yr Male or female Confirmed AS diagnosis eGFR >35 ml/min per 1.73 m ² EITHER: 1. eGFR decline of ≥4 ml/min per 1.73 m ² per yr 2. Proteinuria >2000 mg/g 3. Male age 18–23 yr with eGFR <90 ml/min per 1.73 m ²
Bardoxolone methyl/ Reata Pharmaceuticals ¹⁴	Activates Nrf2 pathway and inhibits nuclear factor-κB pathway Theorized mechanism: antioxidant, mitochondria- protective, anti- inflammatory	Phase 2/3/ Phase 2: open-label Enrollment: 30 12 weeks + open-label extension Phase 3: randomized, double-blind, placebo-controlled Enrollment: 187 48 weeks randomized + 4-week washout + 48-week open-label extension	Age 12–60 yr Male or female Confirmed AS diagnosis; eGFR ≥30 and ≤90 ml/min per 1.73 m ² ; albumin-to-creatinine ratio ≤3500 mg/g

AS, Alport syndrome; eGFR, estimated glomerular filtration rate.

Clinical trials

As recently as 2016, not a single clinical trial had investigated any potential AS therapy beyond renin-angiotensin-aldosterone system -blockade. However, because of several unrelated factors, there is now a dramatic increase in AS-relevant biopharmaceutical research. Such factors include, but are not limited to, a growing body of natural history data, regulatory and financial incentives to create therapies for rare disorders,⁵ recent discoveries in anti-fibrotic therapies, availability of preclinical models that mimic AS disease in patients, a clearer genotype–phenotype relationship versus other causes of chronic kidney disease, and pathophysiologic similarities between AS and a wider spectrum of glomerular disease, including diabetic nephropathy.

At the time of this writing, Sanofi Genzyme was continuing its Regulus Therapeutics' HERA AS study¹³ and Reata Pharmaceuticals had successfully completed enrollment for Phase 3 of its CARDINAL AS study¹⁴ (see Table 1). In addition, several other compounds, compound families, and mechanisms of action have been researched preclinically as potential AS therapies.^{15,16}

Patient advocacy activities

The Alport Syndrome Foundation (ASF) is the primary advocacy organization for the US AS community. In addition to serving as an interactive educational advocate, the ASF coordinates and funds research into potential AS therapies and cures. Considering the recent surge in the AS investigational pipeline, the ASF has created AS clinical trial recommendations resulting from 2 coordinated activities:

- (i) An externally led patient-focused drug development meeting with the US FDA, held jointly by the ASF and the National Kidney Foundation in August 2018.¹⁷

- (ii) An ASF-hosted workshop with key stakeholders at the American Society of Nephrology Kidney Week in October 2018.

This paper summarizes recommendations resulting from the latter (“the Workshop”). The Workshop was hosted with support from Retrophin, Reata Pharmaceuticals, and Regulus Therapeutics. The 60 attendees included representatives from the biopharmaceutical industry, academic research laboratories, clinicians, and regulatory agencies, along with patients with AS, and caregivers and family members of patients with AS. The Workshop first summarized the current understanding of AS from the clinical and patient perspectives, as well as concerns and expectations from the FDA and industrial sponsors. Participants then divided into working groups, with each focusing on 1 of the following: preclinical research, clinical trial design, clinical trial outcomes, pediatric concerns, and patient concerns pertaining to conventional medications. Although nonconventional therapies such as clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9- and adeno-associated virus–mediated gene therapy, stem cell therapy, organoid or regenerative medicine therapies, and others are certainly concerns of the AS community, these were not discussed and are thus not mentioned further here.

What follows are the Workshop's consensus recommendations for conventional drug preclinical research and clinical trial design and outcomes in AS. This document does not establish legally enforceable responsibilities unless specific regulatory or statutory requirements are cited. The use of the word *should* in this document implies a suggestion or recommendation but not a requirement. This document is not intended to function as a recommendation for general, rare-disease, or genetic, preclinical, or clinical trial design; existing guidelines should be consulted,^{18–20} and it is assumed that the reader is familiar with these general guidelines. Thus,

this document is intended for supplemental recommendations specific and unique to AS, only.

Finally—and critically—the intent of the recommendations presented in this paper is to foster and expedite interest in what the authors perceive as an underserved condition: AS. The collective authors do not explicitly support or endorse any single pharmaceutical company or research laboratory beyond indicating appreciation for their attention to AS and their participation in and support of the Workshop.

Preclinical research

As there exist excellent, well-characterized AS animal models, particularly in mice, sponsors of new or repurposed investigational agents are strongly encouraged to test their agent in an AS animal model before initiating a clinical trial in patients with AS. Despite the emergence of new technologies such as human organoids and kidney-on-a-chip assays, AS animal models remain far better characterized as models of human AS. It is acknowledged, however, that although AS mouse models show robust kidney phenotypes that mimic the human disease in many respects, they nevertheless do not reflect the wide variation of human phenotypes.

AS has been modelled in mice with *Col4a3*, *Col4a4*, and *Col4a5* mutations.^{21–23} These models vary with regard to the type of mutation, genetic background, and phenotype, with some strains exhibiting faster progression to kidney failure than others. It is therefore important to select a model—or, ideally—multiple models that allow for more precise discovery of an investigational agent's efficacy. At a minimum, AS mouse studies should include kidney function measurements (blood urea nitrogen and creatinine), urinary protein excretion,²⁴ and histopathologic analysis at specific time points. Survival to a humane endpoint (e.g., 15% loss of peak body weight) as an ESKD surrogate should also be tracked.²⁵

For comparison, investigational agents should be tested both in parallel to and in combination with the clinical standard of care, currently defined as the maximum tolerated dose of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker. However, sponsors should be aware that due to the impressive efficacy of renin-angiotensin-aldosterone system blockade alone in mice,²⁶ the results of the investigational arms that include the investigational agent may be underwhelming by comparison. Nonetheless, even modest improvements in kidney outcomes with an investigational agent in mice, either alone or in combination with renin-angiotensin-aldosterone system blockade, could translate to and be beneficial for patients by prolonging kidney function.

Sponsors are encouraged to perform dose–response studies and to investigate the impact of their investigational agents on the extra-renal complications of AS, especially hearing loss. However, such investigations should not detract from or interfere with the primary goal of developing effective kidney therapies.

Clinical trial design

The clinical course of patients with AS is heterogeneous and depends on the location of the mutation, the type and severity of the mutation, and the patients' age and sex. It is thus critical that the eligibility criteria capture patients who exhibit the parameters of interest and who would likely experience meaningful disease progression over the time course of the trial so that a treatment effect might be detected, if one exists.²⁷ Likewise, clinically meaningful endpoints that would be accepted by regulators for marketing authorization approval should be specified. As with any clinical trial, practical, patient-centered consideration of the trial design is essential for ensuring patient recruitment and continued engagement.

Diagnosis and eligibility criteria. Table 2 summarizes the diagnosis of AS. The optimal patient population for inclusion in an AS clinical trial depends upon the study objectives and the mechanism of action of the investigational agent. For kidney function–based trials, enrollment of patients considered to be at high risk for decrease of glomerular filtration rate (GFR) or for ESKD should be prioritized (Rheault MN, Gross O, Knebelmann B, et al. Urine and blood biomarkers correlate with rate of eGFR decline in Alport syndrome, Abstract FR-PO626, American Society of Nephrology Annual Meeting, 26 October 2018, San Diego, CA). Table 3 suggests potential criteria.

To investigate agents that potentially block early disease stages in which GFR is normal or very slowly decreasing, patients with milder disease manifestations may be included if they are monitored for surrogate outcome markers such as proteinuria.

Although trials should be powered based on a high-risk population, patients at lower risk of short-term loss of kidney function should be included in Phase $\geq 2b$ trials, either as a subset or in a separate study, for the results to be applicable to the wider range of patients with AS. With this model, although initial marketing approval may be limited to higher-risk patients, it may enable supplemental approval in a broader population by providing essential safety data in the lower-risk population.

Because X-linked AS can lead to kidney failure in a significant proportion of women, it is important that studies include adequate representation of both sexes. Children and adolescents should also be included if feasible from a safety and tolerability standpoint (see Special Considerations for Pediatric and Adolescent Clinical Trials, below).

Design. Pivotal trials should be double-blind, randomized, and placebo controlled. Trials should be of sufficient duration for enough patients to develop the stated outcome/endpoint (see OUTCOMES, below). For trials utilizing surrogate endpoints (i.e., proteinuria, estimated GFR [eGFR], slope, etc.), longer-term extension studies and/or post-term studies are recommended to assess the benefit of the investigational agent on traditional kidney outcomes (e.g., ESKD, doubling of serum creatinine).

The off-label use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers has been

Table 2 | Diagnosis of AS

Alport syndrome	X-linked (male and female)	Autosomal recessive	Autosomal dominant	Digenic inheritance ²⁸
Primary diagnostic criteria: Confirmed pathologic mutation ^a	<i>COL4A5</i> in patient or family	Both alleles of <i>COL4A3</i> and/ or <i>COL4A4</i> in patient	Heterozygous <i>COL4A3</i> and/or <i>COL4A4</i> mutation(s) in patient ^b	
Secondary diagnostic criteria	AND 1 or more of the following:			
	<ul style="list-style-type: none"> • Hematuria • Persistent proteinuria (e.g., ACR >30 mg/g) • Decreased eGFR • Kidney biopsy findings typical of AS in the patient^a 			
Supplemental diagnostic criteria	IN ADDITION, any of the following can be considered supplemental support for diagnosis:			
	<ul style="list-style-type: none"> • High-frequency sensorineural hearing loss • Anterior lenticonus of the lenses of the eyes • Central fleck retinopathy of the eyes 			

ACR, albumin–creatinine ratio; AS, Alport syndrome; eGFR, estimated glomerular filtration rate.

^aAll AS clinical trials should include confirmation of a pathologic diagnosis by gene sequencing.

^bBecause some patients with heterozygous *COL4A3* or *COL4A4* mutations have nonprogressive disease (isolated microhematuria), evidence of progression (proteinuria, decreased eGFR) or likelihood of progression (typical AS kidney biopsy findings) is recommended to determine trial eligibility.

associated with significant delay in the development of ESKD in the AS population,^{2,3} and their use is considered standard of care. Thus, all trial patients should receive the maximum tolerated dose of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, unless clinically contraindicated.

If the investigational agent's proposed therapeutic mechanism of action is alteration of renal pathology, examination of histologic effects is encouraged in at least a subpopulation of a Phase 2 trial and, if possible, during Phase 3.

The impact of a therapy on the key burdens and experiences of patients with AS should be assessed. The FDA encourages incorporation of patient-reported outcome measures as endpoints.³² Therefore, the National Kidney Foundation and ASF plan to identify patient-reported outcome measures that can be used in clinical trials as well as in the clinical management of AS patients. Until these are available, when a standardized patient-focused survey is used in a clinical trial, the sponsor is encouraged to focus primarily on the questions relating to the concerns of AS patients as described in the Voice of the Patient Report (see Special Considerations for the Patient Perspective: Engagement, below).

Genetic testing should be considered mandatory for any trial, even for patients who already carry a diagnosis of AS.

This will enable investigation into the correlation between different genetic variants and the varying clinical presentations of AS. It may also enable more precise targeting and dosing of a potential therapy to specific AS genotypes.

Outcomes

Given the practical constraints on the duration of clinical trials, outcomes that reflect the likelihood of having an impact on definitive endpoints are reasonable. A primary endpoint should be a slowing of kidney function loss, as measured by stabilization of—or improvement in—eGFR or the slope of eGFR over a meaningful duration of the treatment period.³³ Specifically, the following criteria apply:

- (i) phase 2: minimum of 1 year, and
- (ii) phase ≥3: minimum of 2 years.

It is crucial that such an endpoint is designed to detect treatment effects on disease progression and/or irreversible loss of kidney function, but not be confounded by other effects of the investigational agent. For example, acute changes in eGFR are likely to reflect hemodynamic rather than structural changes, and the persistence of any change in eGFR must be confirmed after a washout period appropriate to the agent's pharmacokinetic and pharmacodynamic profiles. The trial should also prespecify a mechanism for

Table 3 | Recommended eligibility criteria for a conventional drug clinical trial in Alport Syndrome (AS)

Eligibility criteria	
Diagnosis of AS (see Table 2)	
AND	
Between the ages of 12 ^a and 60 yr, inclusive	
AND	
eGFR <60 ml/min per 1.73 m ²	eGFR >60 ml/min per 1.73 m ²
AND ≥1 of the following:	
<ul style="list-style-type: none"> • Recent history of progressively worsening eGFR • Proteinuria >300 mg/24 h on 24-h urine collection^{29–31} • Protein:creatinine ratio >300 mg/g on random urine collection^{29–31} 	

eGFR, estimated glomerular filtration rate.

^aSee SPECIAL CONSIDERATIONS FOR PEDIATRIC AND ADOLESCENT CLINICAL TRIALS. Note that the age of 12 yr is a general suggestion. Factors such as the mechanism of action of the investigational agent, its safety profile, and the endpoints of the clinical trial should be carefully considered when determining the eligible lower age limit.

patients' post-trial follow-up to monitor for kidney function stability.

Unless non-kidney outcomes such as hearing loss, eye abnormalities, and patient-reported outcomes are included as primary endpoints, trials should investigate such assessments as secondary endpoints.

Special considerations for pediatric and adolescent clinical trials

Clinical manifestations of AS often appear in childhood, as do the initial pathologic processes that ultimately lead to irreversible kidney injury. Because the ultimate goal should be the prevention of renal fibrosis, sponsors should always consider including children and adolescents as soon as possible in the clinical development of an agent, as safety and tolerability profiles allow.

Proteinuria (or microalbuminuria) precedes the development of overt renal fibrosis and eGFR decline in both animals and humans with AS, and it is currently the earliest event in the progression of AS that can be clinically measured. Thus, reduction in proteinuria levels, with appropriate adjustments for age, orthostasis, etc., should be considered a primary outcome for pediatric and adolescent AS trials.^{34–38}

The identification and use of novel biomarkers that may demonstrate the initiation of profibrotic processes indicative of kidney injury, even before proteinuria develops, is encouraged.

As with trials in adults, eGFR in younger populations should be tracked to ensure that the agent does not cause kidney injury or accelerate kidney function loss. Demonstration of efficacy in preserving eGFR in adult participants may be sufficient to support use in adolescents and/or children if results in adults can be rationally extrapolated, or if biomarker analyses provide evidence that a target pathway relevant to eGFR preservation is modulated in these younger participants.

Consultation with regulatory health authorities and pediatric nephrologists with expertise in AS is encouraged before designing any trial featuring children. Providing additional communication, education, and support—particularly regarding safety data—to parents who are considering enrolling their child in a pediatric trial is encouraged. The creation of materials to help pediatric patients understand the trial and their role is also encouraged.

Special considerations for the patient perspective

In this paper, the term *patients* is inclusive of patients, patient caregivers, and patient advocates.

The patient perspective in trial design was developed to address each trial phase, including:

- (i) engagement;
- (ii) recruitment;
- (iii) participation; and
- (iv) post-trial.

Each of these phases is discussed below.

Engagement. The early engagement of the patient community in the drug development process is critical to an investigational agent's success. Sponsors should seek input from the ASF and other AS patient groups at the earliest planning stages, and well before development of the clinical trial protocol.

Conducting workshops early in the process with ASF representatives, key AS opinion leaders, and patients will provide critical input regarding the disease state, patient priorities, natural history data and registries, demographics, and recommended expert clinicians and clinical sites to facilitate an effective trial design. Workshops can also be instrumental in generating awareness in the community about AS and emerging therapeutics.

Sponsors are also strongly encouraged to review the Voice of the Patient Report¹⁷ that was developed during an AS externally led patient-focused drug development meeting held in conjunction with the National Kidney Foundation and the US FDA in August 2018. At this workshop, patients offered insights into the daily burden of living with AS, along with how to increase participation and alleviate the family burden associated with AS trial participation. AS externally led patient-focused drug development considerations should be incorporated into all trials. For example:

- (i) Anxiety, stress, chronic fatigue, and hearing loss were indicated as having significant impacts on the routine well-being of AS patients and their caregivers. However, these issues are often overlooked in routine care for AS, which tends to focus exclusively on kidney health measures.
- (ii) Although anxiety, stress, chronic fatigue, and hearing loss significantly impact the lives of AS patients, a therapy that can delay or prevent the development of ESKD in pre-ESKD AS patients is the primary hope and goal of the AS community.

Review of the proceedings of the International Workshops on Alport Syndrome^{39–41} is also recommended for understanding the latest concerns and activities of the global AS community.

Recruitment. Sponsors are encouraged to engage with the nephrology community as well as ASF and other AS patient groups to improve awareness of trial opportunities. Communication with patient groups is vital for efficient recruitment: ASF and other global AS advocacy groups can engage the AS community in easily understood language using a variety of platforms, including social media. Such outreach is especially important for engaging adolescents and younger adults who account for a large proportion of the AS patient community and who tend to be more severely affected. Additionally, AS patient groups are effective at engaging family members because of the genetic nature of the disease; their engagement is essential in facilitating trial recruitment and retention.

It is the ASF's policy to facilitate awareness about AS trials listed on clinicaltrials.gov. However, the ASF does not accept

funds or gifts for any recruitment efforts. The ASF's policy for pharma engagement is provided on its website.⁴²

Participation. Open, responsive communication between the sponsor, study site coordinators, and trial participants is imperative. Patients must understand not only the expectations of the trial protocol but also the importance of completing their trial participation. Patients benefit from having a specific contact who can address their concerns and questions and assist with the logistics of travel and/or time off from work necessary to fulfill trial requirements. Sponsors are encouraged to think creatively when possible and appropriate, to ease the trial and travel burdens. Establishing clear communication channels will increase participant engagement and protocol compliance. The ASF and other AS groups can assist with these efforts by educating the community on the importance of the community's role in developing potential AS therapies and cures.

Because dynamic communication is even more important for trials that include children, adolescents, and young adults, sponsors are encouraged to develop innovative ways to keep them engaged, such as mobile apps and appropriate social media platforms.

Post-trial. Upon trial completion, participants should be given an outlet to provide feedback to the sponsor and to applicable health authorities regarding their trial experience.

Sponsors are strongly encouraged to publish trial results in the peer-reviewed literature, regardless of the trial's outcome. In addition, sponsors should permit investigators to perform secondary data analyses to answer ancillary questions that may be leveraged to increase interest, enrollment, and participation in future trials. These steps will facilitate increased knowledge on the pathogenesis and natural history across the general AS community and will also increase the medical and patient communities' trust in the sponsor.

As per good clinical practices, trial participants should be considered for an open-label extension after trial completion, if desired and consistent with the safety profile, while awaiting commercial availability. Also, diagnosed, consenting AS patients who did not meet eligibility criteria or were unable to enroll should be considered for expanded access, if desired and consistent with the investigational agent's safety profile, while awaiting commercial availability.

Conclusions

This paper is intended to convey the consensus recommendations for the design and implementation of AS clinical trials for conventional drugs, as discussed by the broader AS community of patients, caregivers, researchers, clinicians, biopharmaceutical industry representatives, and regulatory body representatives at a US-based workshop held in October 2018.

It is highly recommended that pharmaceutical and biopharmaceutical companies that are considering developing therapeutic agents for AS engage the authors, the ASF, and other international AS patient organizations prior to starting

clinical research, in order to understand the dynamic challenges of performing an optimized AS clinical trial, as well as the current needs of the AS community.

APPENDIX

Other workshop participants

NOTE: Workshop participants who are not listed as authors or as acknowledged FDA reviewers did not contribute to the drafting of this paper subsequent to their workshop input.

Workshop participants are listed below according to their affiliation as of October 2018.

The Alport Syndrome Foundation (Scottsdale, AZ): Lisa Bonebrake, Marty Dunleavy, Phil Kumnick, Sharon Lagas (author, speaker, workgroup lead), Gina Parziale (speaker), Janine Reed, André Weinstock (author, speaker); Alport UK (Cirencester, UK): Susie Gear; Boehringer Ingelheim (Ingelheim am Rhein, Germany): Kristen Binaso, Raymond Manuel; Cleveland Clinic (Cleveland, OH): James Simon (author, speaker, workgroup lead); Columbia University (New York, NY): Gerald Appel; FDA (Silver Spring, MD): Melanie Blank (FDA reviewer), Winson Tang, Aliza Thompson (FDA reviewer, speaker); Puigvert Foundation (Barcelona, Spain): Roser Torra; Hackensack Meridian (Hackensack, NJ): Kenneth Lieberman; Hospital for Sick Children (Toronto, ON, Canada): Christoph Licht; Institut de Pathologie et de Genetique (Charleroi, Belgium): Karin Dahan; Kobe University (Kobe, Japan): Kandai Nozu; Kumamoto University (Kumamoto, Japan): Hirofumi Kai; Monash University (Clayton, VIC, Australia): Sharon Ricardo; National Institutes of Health (Bethesda, MD): Anne Pariser; National Kidney Foundation (New York NY): David Feldman (author); PHARMALOGIC (San Rafael, CA): Heather Cook; Reata (Plano, TX): Melanie Chin, Angela Goldsberry, Colin Meyer; Regulus (Plano, TX): Lisa Anne Melia; Retrophin (San Diego, CA): Radko Komers, Michael Markels, Alex Mercer; Roche (Basel, Switzerland): Marco Prunotto; Roseman University (Henderson, NV): Bruce Morgenstern; Sanofi-Genzyme (Cambridge, MA): Ali Hariri, Vijay Modur; University of Edinburgh (Edinburgh, Scotland, UK): Neil Turner (workgroup lead); Göttingen University of Medicine (Göttingen, Germany): Oliver Gross (author, speaker); University of Manchester (Manchester, UK): Rachel Lennon (author, workgroup lead); University of Miami (Coral Gables, FL): Alessia Fornoni (author); University of Minnesota (Minneapolis, MN): Clifford Kashtan (author, speaker, workgroup lead), Michelle Rheault (author, speaker); University of Oxford (Oxford, UK): Colin Baigent; University of Southern California (Los Angeles, CA): Stephano DeSacco, Laura Perin; University of Toronto (Toronto, ON, Canada): Mounita Barua; Wakayama Medical University (Wakayama, Japan): Koichi Nakanishi; Washington University (St. Louis, MO): George Jarad, Jeffrey Miner (author).

DISCLOSURE

BAW is a volunteer and unpaid board member of the Alport Syndrome Foundation (ASF, Scottsdale, AZ) and an employee of Teleflex Medical (Wayne, PA). DLF has served as a consultant for Ironwood Pharmaceuticals (Cambridge, MA), but the consultancy fees were donated to the National Kidney Foundation (New York, NY). AF is an inventor on pending or issued patents intended to diagnose or treat proteinuric kidney diseases, including Alport syndrome. She stands to gain royalties from their future commercialization. Relevant to this topic, AF is Chief Scientific Officer of L&F Health LLC (Miami, FL) and founder of Liponext LLC (Miami, FL). In the past 2 years, she has served as consultant for several pharmaceutical companies working in this space, including Variant Pharmaceuticals (now ZyVera Therapeutics; Weston, FL), ONO Pharmaceuticals (Osaka, Japan), Reata Pharmaceuticals (Plano, TX), and Novartis (Basel, Switzerland). OG is the initiator and principal investigator of the EARLY PROTECT Alport trial, which was sponsored by the German Ministry of Education and Research (01KG1104; Bonn, Germany). He is national principal investigator for Germany for the CARDINAL trial (Reata; Plano, TX) and is the initiator and principal investigator of the European Alport registry (Göttingen, Germany). His employer, The University of Göttingen (Göttingen, Germany), has had or still has consulting relationships with Regulus Therapeutics (San Diego, CA), Reata Pharmaceuticals (Plano, TX), Retrophin (San Diego, CA), Roche (Basel, Switzerland), Novartis (Basel, Switzerland), Boehringer-Ingelheim (Ingelheim am Rhein, Germany), and Ono Pharmaceuticals (Osaka, Japan). CEK has had consulting relationships with Regulus Therapeutics (San Diego, CA), Reata Pharmaceuticals (Plano, TX), Retrophin (San Diego, CA), Boehringer-Ingelheim (Ingelheim am Rhein, Germany), Ono Pharmaceuticals (Osaka, Japan), and Daiichi Sankyo (Tokyo, Japan). He is a site investigator for the CARDINAL trial (Reata; Plano, TX) and the HERA trial (Sanofi-Genzyme; Cambridge, MA), has had research support from the Novartis Institute for Biomedical Research (Cambridge, MA) and National Institutes of Health (1R21DC017019-01A1, P. Santi,

principal investigator; Bethesda, MD), and is the Executive Director of the Alport Syndrome Treatments and Outcomes Registry (ASTOR; Minneapolis, MN), which is supported by the ASF (Scottsdale, AZ) and private philanthropy. SL is cofounder, volunteer, and unpaid board member (past president) of the ASF (Phoenix, AZ). RL is supported by a Wellcome Trust Senior Fellowship award (202860/Z/16/Z; London, UK) and has consulted for Retrophin (San Diego, CA) and ONO Pharmaceuticals (Osaka, Japan) regarding AS therapies in the past 12 months. JHM has received grant support from Reneo Pharmaceuticals (San Diego, CA) and Reata Pharmaceuticals (Plano, TX) and has served as a consultant to Regulus Therapeutics (San Diego, CA) and Retrophin (San Diego, CA). MNR is a site primary investigator for clinical trials for Retrophin (San Diego, CA), Reata Pharmaceuticals (Plano, TX), and Genentech (South San Francisco, CA), and has received research funding from Goldfinch Bio (Cambridge, MA), Novartis (Basel, Switzerland), Advicenne (Nimes, France), the National Institute of Diabetes and Digestive and Kidney Diseases (Bethesda, MD), and the US Department of Defense (Alexandria, VA). JFS is a member of the speakers' bureau for Alexion Pharmaceuticals (Boston, MA).

The intent of the recommendations presented in this paper is to foster and expedite interest in what the authors perceive as an underserved condition: AS. The collective authors do not explicitly support or endorse any single pharmaceutical company or research laboratory beyond appreciation for their attention to AS and their participation and support of the Workshop.

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