MarketVue®

Alport syndrome

June 2022

REACH
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1. DISEASE OVERVIEW

A progressive, inherited nephropathy

Alport syndrome is a hereditary progressive disease that affects the function of the kidneys causing irreversible kidney damage and inevitable renal failure. Patients not only face the prospect of declining kidney function, dialysis, and the eventual need for a life-saving kidney transplant, many also live with hearing loss and eye abnormalities. The underlying cause of Alport syndrome is a mutation in one of three genes (*COL4A3, COL4A4, or COL4A5*) of the type IV collagen protein, a structural protein that is essential for the proper functioning of the basement membrane. While awareness of Alport syndrome is increasing, it remains astoundingly low among both general practitioners and nephrologists. Moreover, misconceptions about the disease abound including the idea that Alport syndrome predominantly affects males, it does not. In fact, females are affected at twice the rate as males albeit with a less severe presentation of the disease in most cases.

ALPORT SYNDROME PROGRESSES IN FOUR PHASES

While the timeline of disease progression in Alport syndrome varies by sex and genotype (Figure 1.2), there are four distinct phases of the disease regardless of the progression rate (Figure 1.1). The first hint that the kidneys have some impairment is the presence of microscopic levels of blood in the urine (hematuria). In fact, this laboratory result is an important trigger for patient referral to a nephrologist. The progression of Alport syndrome is marked by inflammation in and scarring of the kidney that impairs its function and leads to chronic kidney disease (CKD). The detection of protein in the urine (proteinuria) signaling kidney damage is an important sign of disease progression and delineates the second phase of the disease. Moreover, proteinuria is a key risk factor for progression to end stage renal disease (ESRD)[1]. After the onset of proteinuria, kidney function continues to decline in the third phase of the disease. The last and most severe phase of the disease is when a patient's kidneys no longer function requiring them to go on dialysis or get a kidney transplant to live.

Figure 1.1. Phases of Alport syndrome disease progression

Blood in the urine (hematuria)	Protein in the urine (proteinuria)	Declining kidney function	Kidney failure (ESRD)
Hematuria is a hallmark of Alport syndrome; it is present in most patients; microscopic levels often seen at birth.	Kidney damage causes protein to spill into the urine signaling declining kidney function.	Once kidney function drops below 30%, patients will not benefit from drug treatment.	Loss of kidney function means patients cannot survive without dialysis or a kidney transplant.
"The main and initial presentation is blood in the urine, and mostly it's microscopic hematuria, which means the patient may not even see it, but it is present." ***– U.S. nephrologist***	*"As nephrologists, we want to suppress the amount of protein in the urine as much as we can. The most important marker of inflammation and disease in the kidney is the protein in the urine."* ***– U.S. nephrologist***	*"Patients below 30% [kidney function] have been deemed to reach kidney failure soon regardless of what you do because they already have significant scarring, and at that point, they reach a point of no return."* ***– U.S. nephrologist***	*"At this point patients need renal replacement therapy otherwise they will die. A kidney from a living donor is ideal and sometimes we can even do a pre-emptive kidney transplant and skip Dialysis."* ***– U.S. nephrologist***

1. Pochet JM, *Nephrol Dial Transpl.* 1989;4:1016–1021

2. EPIDEMIOLOGY & PATIENT POPULATIONS

United States, EU5, and Japan

DISEASE DEFINITION

For this analysis, we defined the Alport syndrome population as patients of any age with a confirmed diagnosis of one of the three modes of inheritance — XLAS, ARAS, or ADAS, including patients with a positive genetic test for a mutation in the *COL4A3*, *COL4A4*, or *COL4A5* genes. While there is very limited and consistent data on the point prevalence of Alport syndrome, the prevalence of the disease does not appear to vary among different ethnic groups or across geographies.

Figure 2.1. G7 diagnosed prevalent cases of Alport syndrome by region

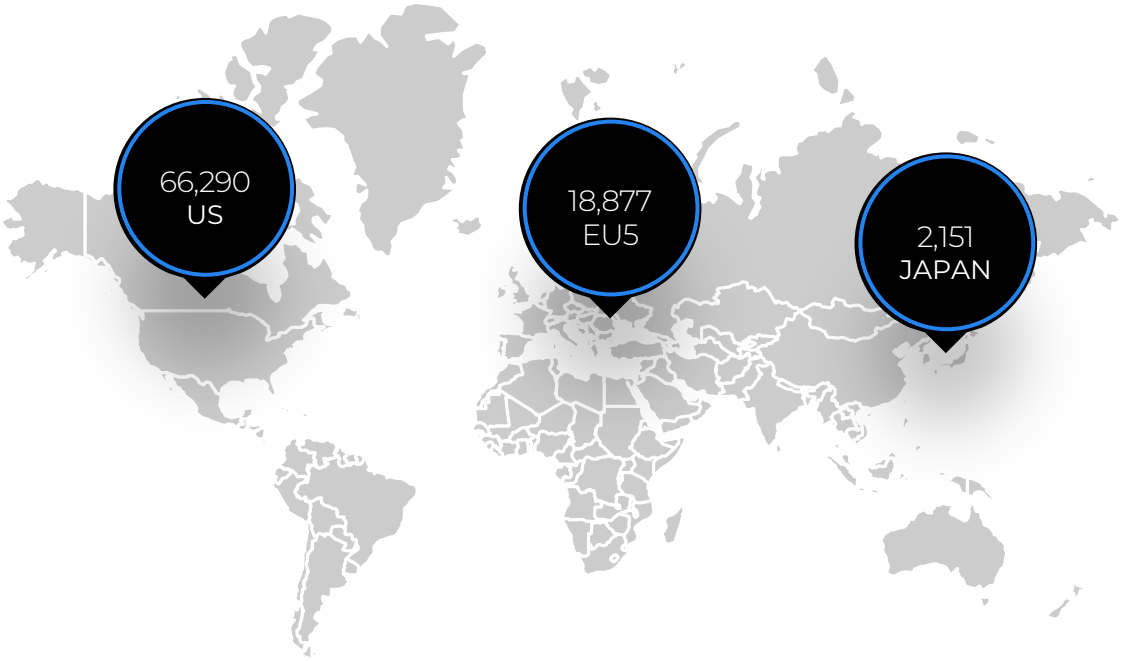


Table 2.1 Diagnosed prevalent and drug-treated patients in the G7[1]

	US	France	Germany	Italy	Spain	UK	Japan	Total
Diagnosed prevalence (per 100k)	20	5.8	5.8	5.8	5.8	5.8	5.8	-
Diagnosed prevalent cases	66,290	3,890	4,823	3,498	2,712	3,954	3,154	88,321
Drug-treated rate	83%	83%	83%	83%	83%	83%	83%	83%
Drug-treated patients	55,021	3,229	4,003	2,903	2,251	3,282	2,618	73,306

A note on U.S. prevalence estimates

The most widely cited study of Alport syndrome prevalence is the 1983 Hasstedt study that estimated disease prevalence of 1/5,000 (20/100,000) based on cases in Utah and southern Idaho populationa. However, it is possible that these numbers are an over estimation of prevalence given that they were likely enriched due to the nature of the study focused on large families with Alport syndrome. Moreover, a second U.S. study in Rhode Island estimates Alport syndrome disease prevalence at 1/13,000 (7.7/100,000)[2]; at this rate diagnosed prevalence cases of Alport syndrome in the U.S. would be 25,611.

1. See section for epidemiology references and methodology
2. Chazan JA, Am J Med 1971; 50(6):764-771.

3. CURRENT TREATMENT

The main treatment goal of Alport syndrome is to protect the kidneys from further damage.

Nephrologists want to preserve kidney function and delay the onset of renal failure for as long as possible.

There are no approved therapies for Alport syndrome.

Physicians rely on nutritional changes and off label anti-hypertensive medicines to slow the rate of kidney function decline.

Off-label use of blood pressure-lowering meds slows disease progression.

Although early use slows kidney damage, delays renal failure, and improves life expectancy, unmet need remains very high.

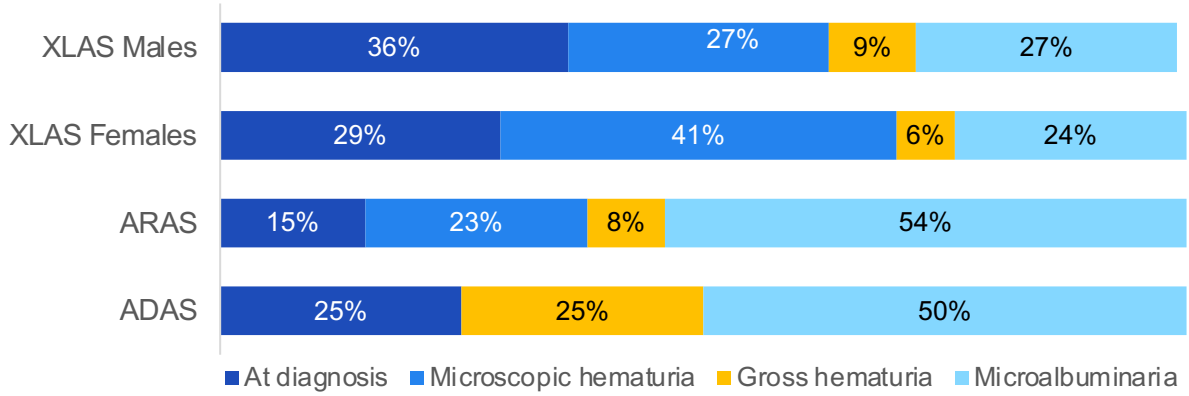
DRUG-TREATED PATIENTS AND TREATMENT RATES

Given the heterogeneity in disease presentation, there are notable differences in when nephrologists initiate treatment for patients with Alport syndrome, particularly in those at risk of rapid disease progression (XLAS males and ARAS patients) versus those whose disease progresses slowly (XLAS females and ADAS). However, interviewed and surveyed nephrologists agree that rapidly progressing patients are treated as soon as patients are diagnosed, while a wait-and-watch approach is chosen for the ”slow progressors” until there is evidence of proteinuria. In case of XLAS female patients, more than a quarter of the surveyed nephrologists initiate treatment at diagnosis while a quarter of them wait for proteinuria to develop before they initiate treatment[1]. Overall, nephrologists report that early treatment is key to slow disease progression, preserve kidney function, and delay end-stage renal failure. At present there is no FDA-approved therapy for Alport syndrome; renin-angiotension-system (RAS) blockade with angiotensin converting enzyme inhibitors (ACEis) and/or angiotensin receptor blockers (ARBs) is the current standard of care.

Table 3.1. Treatment initiation and rates by risk of disease progression

Type of disease progression	Rapid (XLAS males and ARAS patients)	Slow (XLAS females and ADAS patients)
Drug treatment rate[1]	87%	81%
Guideline-recommended time to start ACEi/ARB[2]	At time of diagnosis	Protein in the urine (microalbuminuria)

Figure 3.1. Percentage of nephrologists initiating treatment with ACEis/ARBs in Alport patients[1]



1. REACH primary market research; see Section 7 for methodology
2. Kashtan CE, Gross O. Pediatr Nephrol. 2021 Mar;36(3):711-719

4. UNMET NEED

TREATMENT-RELATED UNMET NEEDS

Surveyed and interviewed nephrologists rank slowing down kidney damage at the top of the list of unmet needs in Alport syndrome. In patients with severe forms of Alport syndrome, the rapid progression of the disease robs them of a normal childhood and leaves them living a life of fatigue, stress, and renal failure during adulthood. While ACEi/ARBs have been a godsend for Alport syndrome patients by delaying the need for renal replacement therapy by up to 20 years in those who start treatment early, patients still live with chronic disease progression with many eventually requiring dialysis and/or kidney transplantation. In the absence of a cure, having therapies that modify the course of the disease by either slowing down kidney damage and ensuing renal failure, reducing fibrosis, and halting disease progression will address the leading unmet needs in Alport syndrome (Figure 4.1).

Figure 4.1. Top Unmet Needs in Alport syndrome[1]

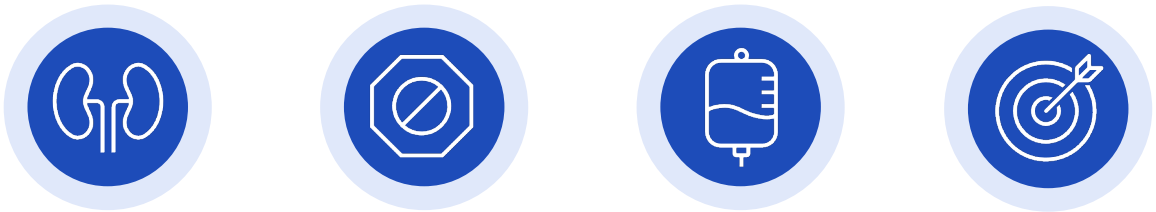
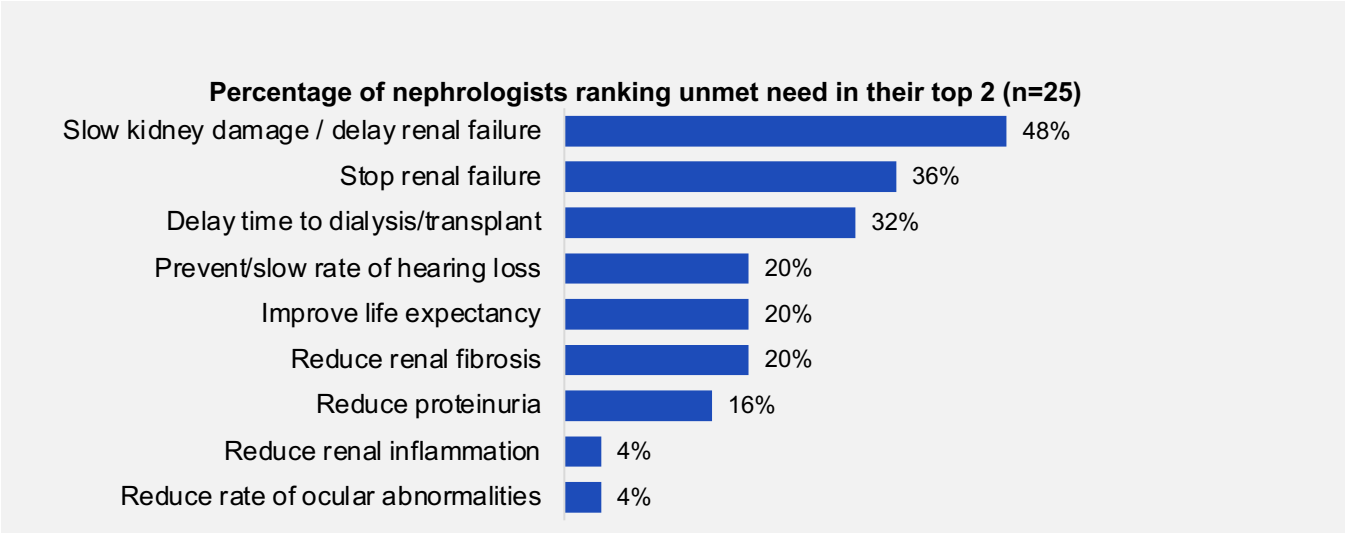


Figure 4.2. Nephrologist ranking of unmet needs in Alport syndrome[1]



> *"There is absolutely no specific effective therapy now so it's a big area where there has to be a lot of research and development in finding [treatments] that can prevent or if not prevent then slow down the development of chronic kidney disease in Alport syndrome."* **– Nephrologist, U.S.**
>
> *"I think the problem for Alport patients is there is no disease-targeted therapy. This is an ultrastructural problem where there's a defect in the collagen that's in the basement membranes in their ears, their kidneys, and in their eyes, so a drug delivery system that could address that would be marvelous. I think that would be very disease specific."* – **Nephrologist, U.S.**

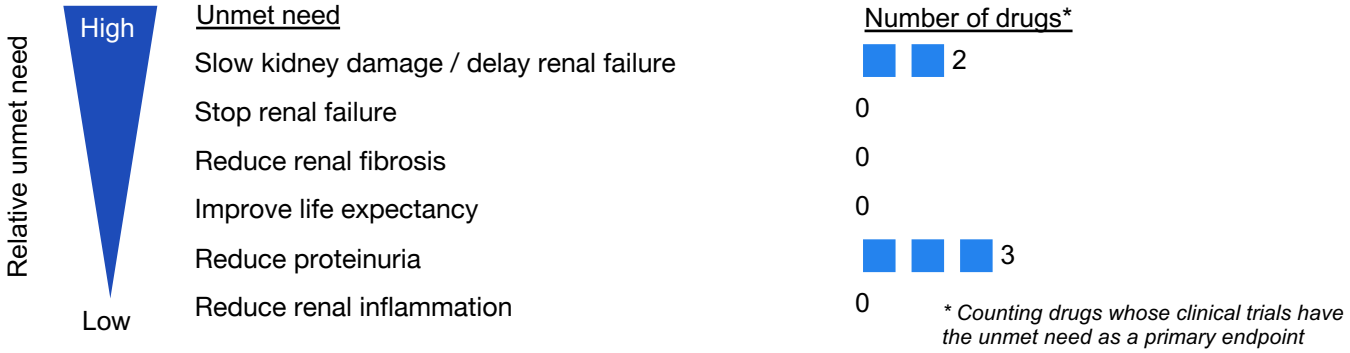
1. REACH primary market research; see Section 7 on methodology

5. PIPELINE ANALYSIS

OVERVIEW

Drug development for Alport is limited to a handful of clinical-stage therapies focused on either reducing renal inflammation or fibrosis, two contributors to progressive renal decline. The efficacy of emerging therapies is being evaluated by either measuring a therapy's effect on estimated glomerular filtration rate (eGFR), the best test to measure kidney function and the stage of kidney disease, or its effect on proteinuria (assessed by change in urinary protein:creatinine ratio) over time.

Figure 5.1. Number of emerging therapies addressing unmet needs in Alport syndrome[1]



New therapies for Alport syndrome are on the horizon, but not as soon as initially hoped. In February 2022, following a negative Advisory Committee vote, the FDA issued a CRL to Reata, rejecting bardoxolone's NDA and requesting additional efficacy and safety data. While Reata has stated they will continue to work with the FDA to find a path towards approval, it is currently unclear what this will entail or how long it will take. With this setback, the availability of first new therapy for Alport syndrome is now likely delayed by several years. Beyond bardoxolone, two therapies (Sanofi's lademirsen and Chinook's atrasentan) are in Phase 2 development with results expected in mid and late 2023, respectively. When asked which emerging Alport syndrome therapies they are aware of (aided awareness), nephrologists most often selected bardoxolone, followed by sparsentan and atrasentan. Of note, <10% of surveyed nephrologists were not aware of any emerging therapies shared with them.

Table 5.1. Emerging clinical-stage therapies for Alport syndrome and nephrologist awareness[2]

Company Drug	Phase	Renal Target	Dosing Form	Dosing Frequency	Percentage of nephrologists aware of therapy[1]
Reata's bardoxolone	PR†	Inflammation	Oral capsule	QD	68%
Travere's sparsentan*	Ph2	Inflammation	Oral suspension	QD	52%
Chinook's atrasentan	Ph 2	Inflammation	Film-coated tablet	QD	48%
Sanofi's lademirsen	Ph 2	Fibrosis	SC injection	QW	20%
River 3 Renal Corp's R3R01	Ph2	Lipids	Oral tablet	BID	Not assessed

† FDA rejected bardoxolone's NDA and issued a CRL requesting additional clinical data. Reata has stated they are discussing with the FDA a potential path to approval
*A basket trial of proteinuric glomerular diseases including Alport syndrome is ongoing, however Travere's pipeline does not list Alport syndrome as a target indication

1. REACH primary market research; see Section 7 on methodology
2. www.clinicaltrials.gov

6. VALUE AND ACCESS

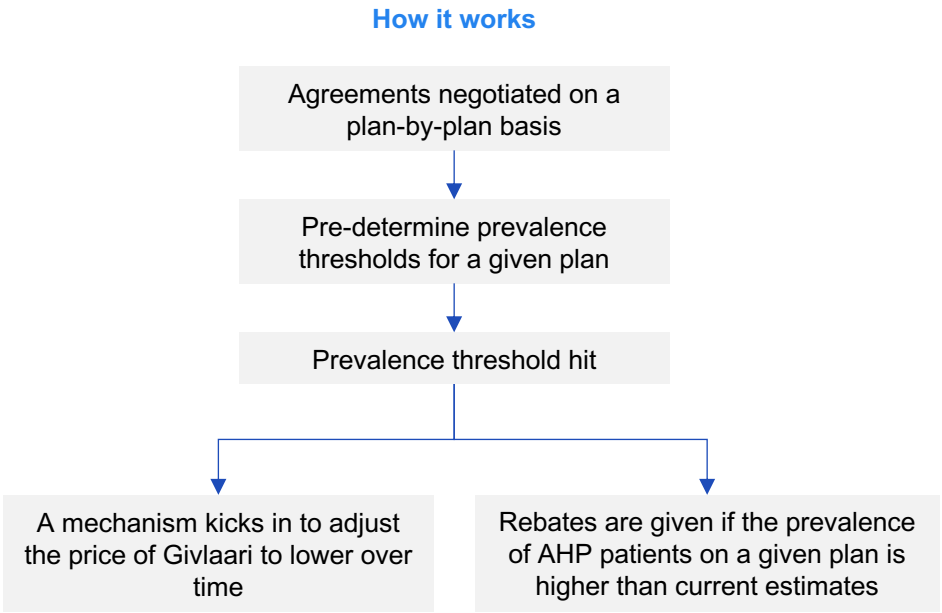
OVERVIEW

The value and access landscape for Alport syndrome has yet to unfold given that there are no regulatory-approved therapies for the disease in the United States or Europe. Hence, insights gleaned from other rare disease markets can offer some direction on various market access strategies, particularly diseases where the standard of care was off-label use of safe and effective generic options prior to the launch of drugs approved for the disease. Herein, insights on two rare disease markets offer different approaches in somewhat analogous rare disease markets - chronic progressive diseases with a generic SOC and high unmet need for disease modifying therapy. In one market, sickle cell disease, new brands took a traditional approach to market access while in the other market, acute hepatic porphyria, the manufacturer took a highly innovative approach to its negotiations with payers.

VALUE & ACCESS ANALOGUE: AN INNOVATIVE APPROACH IN ACUTE HEPATIC PORPHYRIA

Alnylam introduces a prevalence-based adjustment (PBA) value-based agreement (VBA) strategy for its therapy to treat an ultra rare disease. In November 2019, Alnylam won FDA approval for its RNAi therapy Givlaari, the first-ever approved treatment for acute hepatic porphyria (AHP)[1]. AHP is an ultra-rare disease that affects an estimated 3,000 patients in the United States and Europe; however, uncertainties exist around AHP prevalence and diagnosis rates such that the population could be larger than current epidemiologic estimates. In a plan to address the possibility of a higher AHP patient population than current estimates, Alnylam launched a first-of-its-kind reimbursement strategy called prevalence-based adjustments. The premise of this approach is that it will reduce the financial risk to payers if it turns out that that there are many more AHP patients than current estimates. This model is particularly noteworthy because of its potential utility in rare diseases that are underdiagnosed like Alport syndrome.

Figure 6.1. Prevalence-based adjustments



Givlaari Costs

- Average annual cost of $575,000 per patient based on a list price of $39,000 per vial.
- After mandatory discounts, the annual patient price will approximately $442,000 according to Alnylam.

Progress on VBAs

By December 2020, Alnylam had finalized over 10 VBAs finalized for Givlaari in the United States – including its first state-level VBA with MassHealth.

1. https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-inherited-rare-disease