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A Randomized Controlled Clinical Trial Testing Effects of Lademirsen on Kidney Function Decline in Adults with Alport Syndrome

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Key Points

- Lademirsen, an anti–microRNA-21 therapy, was generally well-tolerated in adults with Alport syndrome at risk of rapid disease progression.
- There were no significant differences between lademirsen-treated and placebo-treated participants in eGFR at any timepoint.
- The proportions of participants with prespecified reductions in eGFR at weeks 24 and 48 were not significantly different for lademirsen versus placebo.

Abstract

Background Preclinical models of disease have suggested that targeting microRNA-21 (miRNA-21) may slow the decline in kidney function in individuals with Alport syndrome (AS). The objective of this study was to investigate the effects of the anti–miRNA-21 oligonucleotide, lademirsen, on rate of eGFR decline in adults with AS at risk of rapid disease progression.

Methods This study was a phase 2 trial of lademirsen, with a randomized, double-blind, placebo-controlled period followed by an open-label period. Adults with AS, eGFR >35 to <90 ml/min per 1.73 m^2, and evidence of rapidly progressive kidney dysfunction were randomized 2:1 to lademirsen 110 mg subcutaneously once weekly or placebo for 48 weeks. After a planned interim analysis (after 24 of 43 randomized participants completed the week 48 study visit or discontinued before week 48), the trial was terminated for futility.

Results Forty-three adults with AS (26 men, 17 women) participated (mean age 34 years), and 28 (lademirsen: n=19; placebo: n=9) completed 48 weeks of double-blind treatment. All participants in both groups developed treatment-emergent adverse events, mainly respiratory tract infections, headache, dizziness, metabolic/electrolyte disturbances, and anemia. Treatment was discontinued in three lademirsen-treated participants in the double-blind period and one participant in the open-label period, owing to treatment-emergent adverse events. The least squares mean eGFR slope (95% confidence interval) over 48 weeks in the lademirsen and placebo groups was −5 (−8.7 to −1.1) and −5 (−10.2 to 0.8) ml/min per 1.73 m^2 per year, respectively. No significant differences between groups were identified in eGFR at any timepoint or in proportion of participants with prespecified reductions in eGFR at week 24 or 48.

Conclusions While anti–miRNA-21 therapy with lademirsen was generally well-tolerated with an acceptable safety profile, no meaningful improvement in rate of kidney function decline in adults with AS at risk of rapidly progressive disease was observed.

Clinical Trial registration number: NCT02855268.

CJASN 19: 995–1004, 2024. doi: https://doi.org/10.2215/CJN.0000000000000458

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Received: October 9, 2023 **Accepted:** April 29, 2024
Published Online Ahead of Print: June 3, 2024

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*The members of the HERA Clinical Trial Group are included in Supplemental Text 1.

See related editorial, "Lessons Learned from HERA: the First Alport Syndrome Therapeutic Clinical Trial," on pages 946–948.

Introduction

Alport syndrome (AS) describes a heterogeneous group of genetic disorders affecting the kidney, cochlea, and eye[1] and is one of the most common forms of inherited kidney disease.[2,3] AS is caused by pathogenic variants in the *COL4A3*, *COL4A4* (both autosomal dominant and recessive inheritance), and *COL4A5* (X-linked inheritance) genes that affect the α3, α4, and α5 chains, respectively, which form trimers of type IV collagen.[4] Failure to form an α3, α4, α5 (IV) network in the glomerular basement membrane (GBM) results in replacement with an α1, α1, α2 (IV) network, which is insufficient to maintain normal glomerular permeability.[4–6] Alterations in the biomechanical properties of the GBM initiate a cascade of intercellular signaling events that leads to podocyte and glomerular endothelial cell injury, fibrosis, and progressive kidney failure.[6] Affected individuals may also develop sensorineural hearing loss and ocular changes, including corneal lesions and retinal flecks.[5] Global prevalence data for AS are lacking,[5] but estimates suggest AS affects between one in 2000 and one in 53,000 people, depending on the disease definition.[7–9]

Angiotensin-converting enzyme inhibitors, and to a lesser extent angiotensin receptor blockers, are considered as first-line disease-modifying therapy for AS.[10,11] Other potential nephroprotective therapies, such as sodium–glucose cotransporter 2 inhibitors, have been investigated to a much lesser extent.[10,12] However, many people with AS will progress to kidney failure, requiring dialysis or kidney transplantation.[13] Thus, there is an unmet need for treatments that slow, halt, or reverse the progression of kidney dysfunction in AS.

Lademirsen (RG-012, SAR339375; Regulus Therapeutics, Sanofi) is an investigational oligonucleotide targeting microRNA-21 (miRNA-21).[14] MiRNA-21 is a post-transcriptional regulator of the tissue repair response, and its expression is upregulated in many disease states, including kidney disease.[15] In the kidney, miRNA-21 activation represses multiple miRNA-21 target messenger RNAs, including peroxisome proliferator-activated receptor α, causing fibrosis.[16] Levels of miRNA-21 in the kidney are elevated in both animal models of AS and kidney biopsy samples from people with AS, and kidney miRNA-21 expression is negatively correlated with kidney function.[17] Anti–miRNA-21 oligonucleotides, including lademirsen, showed nephroprotective effects in animal models of AS, slowing the progression of kidney fibrosis and improving survival.[14,18] This led to the clinical development of lademirsen as a potential treatment for AS.

The current phase 2 HERA study was designed to investigate the safety and tolerability of lademirsen and the effects on kidney function in people with AS at risk of rapid progression, as well as the pharmacokinetics and pharmacodynamics of this anti–miRNA-21 therapy. The study was terminated after interim analysis showed no evidence of benefit, and this article reports the final outcomes of the study following the last participant last visit and subsequent database lock.

Methods

Study Design

The phase 2 HERA clinical trial had a parallel-group design and was conducted in an outpatient setting at 20 sites across seven countries (Australia, China, France, Germany, Spain, the United Kingdom, and the United States; NCT02855268). The trial had a 48-week double-blind, placebo-controlled period followed by a 48-week open-label lademirsen treatment period.

Randomization

Participants were randomized 2:1 to lademirsen (110 mg subcutaneously, once weekly) or placebo (subcutaneously, once weekly) using a centralized treatment allocation system (interactive response technology [IRT]) (Figure 1). The IRT generated the participant randomization list and allocated a treatment number and corresponding treatment. Two randomization listings for participants with stratification factors of screening eGFR <60 or ≥ 60 ml/min per 1.73 m^2 were generated (block size 6), with a randomization ratio of lademirsen to placebo of 2:1. Based on sequence of enrollment and eGFR stratum at screening, participants were allocated treatment. To maintain blindness of treatment assignment, the process of randomization was handled by an independent IRT vendor. The participants, investigator, and study team members remained blinded until database lock.

Study Population

Recruitment took place between November 2, 2019, and December 15, 2021. Participants were enrolled and randomized between November 18, 2019, and December 30, 2021. The 48-week double-blind period lasted from November 25, 2019, to July 30, 2022, followed by a 48-week open-label period (November 5, 2020, to July 16, 2022).

Eligible participants were aged 18–55 years, had a diagnosis of AS confirmed by genetic study and/or kidney biopsy, an eGFR of >35 to <90 ml/min per 1.73 m^2, normal hematological and hepatic function, on stable treatment with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for ≥ 30 days, and met the criteria for rapidly progressive AS. The CKD Epidemiology Collaboration Creatinine Equation 2021 was used for calculating eGFR.[19] Rapidly progressive AS was defined as meeting at least one of the following: (*1*) a decline in eGFR of ≥ 4 ml/min per 1.73 m^2 per year (eGFR slope ≤ -4 ml/min per 1.73 m^2 per year), based on a linear regression slope analysis of ≥ 4 eGFR measurements within 3 years before the study and with a minimum 2-year time span; (*2*) a urine protein-to-creatinine ratio of >2000 mg/g or urine albumin-to-creatinine ratio of >1000 mg/g; or (*3*) eGFR <90 ml/min per 1.73 m^2 in males aged 18–23 years.

Participants were excluded if they had any of the following: a kidney disease other than AS, kidney failure requiring dialysis or kidney transplantation, another clinically significant illness within 30 days of screening, weight >110 kg, history of active malignancy in last year, or any history of alcohol or recreational drug abuse.

Female participants were required to have a negative pregnancy test before treatment, and both male and female participants were required to use adequate contraception throughout the study.

Participant-reported ethnicity and race data were collected, where permitted by local regulations, as a requirement for some regulatory agencies.

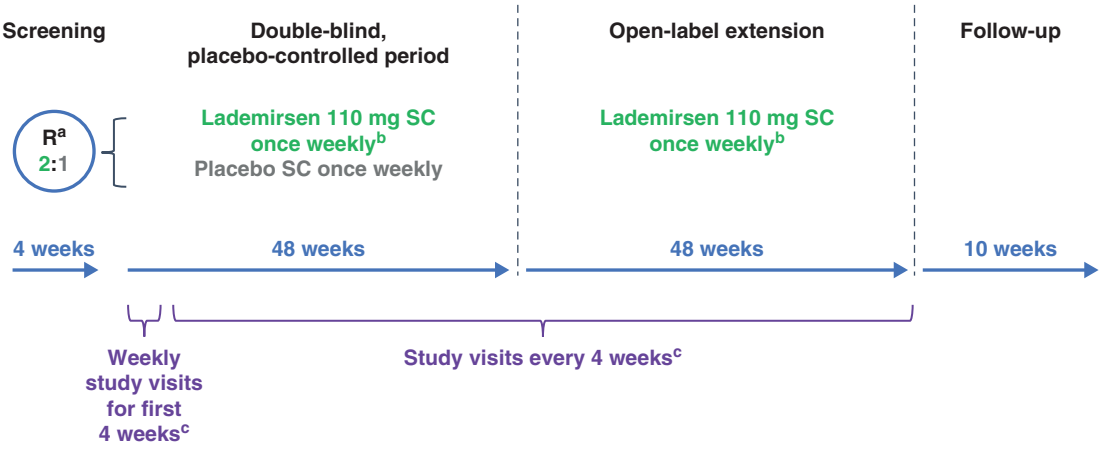

Figure 1. Study design. [a]Randomization (R) was performed using a centralized treatment allocation system (IRT) and stratified by baseline eGFR (>35 to <60 and ≥60 ml/min per 1.73 m^2). [b]Administered by trained personnel at (or between) study visits, by a qualified health care professional or by participant or caregiver after appropriate training. [c]Blood and urine samples were collected at each visit (standard hematology and chemistry panels plus assessment for blood urea nitrogen, UACR, urine cystatin C, urine neutrophil gelatinase-associated lipocalin, UPCR, blood and urine transforming growth factor-β, and epidermal growth factor. Participants were also assessed for TEAEs and adherence to treatment (by returning used/unused medication). Pharmacokinetic samples were taken up to 4 hours predose on day 1 and weeks 4, 12, 24, 36, and 48 and 4 hours postdose on day 1 and weeks 24 and 48. ADAs were assessed at baseline and weeks 4, 12, 24, 36, and 48. ADA, anti-drug antibody; IRT, interactive response technology; SC, subcutaneous; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.

The study was conducted according to the International Council for Harmonization Good Clinical Practice Guidelines and ethical principles of the Declaration of Helsinki, with institutional review board approval. All participants provided written informed consent before enrollment.

Study Endpoints

Primary Endpoints

The study had two primary endpoints: one was the number of participants with treatment-emergent adverse events (TEAEs) and serious TEAEs. The other was kidney function measured by the annualized rate of change (slope) in eGFR during the placebo-controlled treatment period.[19]

Secondary Endpoints

The key secondary endpoints were absolute change in eGFR from baseline at week 48 and proportion of participants with a decrease from baseline in eGFR of <10%, <20%, <30%, or <40% at weeks 24 and 48.

TEAEs of special interest (TEAESI) were also evaluated, namely an eGFR decrease from baseline of grade ≥3 severity (≥30%), grade ≥2 thrombocytopenia (platelet counts ≤100,000 cells/μl), and grade ≥2 elevations in aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase to ≥2.5×upper limit of normal (ULN), direct bilirubin (above ULN), or total bilirubin (≥1.6×ULN).

Additional secondary endpoints included plasma concentrations of lademirsen, the active metabolite RG0005, and their sum. The incidence and titer of anti-drug antibodies (ADAs) were also assessed, as was the relationship between TEAEs and ADAs.

Post Hoc *Analyses*

Subgroup analyses were conducted to assess whether eGFR slope was affected by genetic category (hemizygous [male *COL4A5*] or heterozygous [*COL4A3*, *COL4A4*, female *COL4A5*]) and in those with biallelic *COL4A3/4* or hemizygous *COL4A5* genetic variants.

An additional *post hoc* analysis was conducted to identify predictors of eGFR slope (Supplemental Text 2).

Statistical Analysis

Sample Size

A sample size of 45 was estimated to have 75% power to detect a reduction of approximately 50% in rate of decline in eGFR (5 ml/min per 1.73 m^2 per year) through a Bayesian mixed-effect model with random effect, assuming a dropout rate of 10% per year. In this model, prior distribution of the placebo arm assumes a normal distribution for the slope of eGFR, with a mean (SD) of −10 (2.2) ml/min per 1.73 m^2 per year, based on data from a natural history study (unpublished data; NCT02136862). Noninformative prior distribution was used for all other parameters. An overall two-sided alpha level of 0.10 was used for sample size calculation. However, at the time of final analysis, the Bayesian model was not implemented because, based on data actually collected, the prior distribution assumption of the placebo arm was inconsistent with the observed mean slope for the 48-week treatment period. Instead, a frequentist mixed-effect model was used for the estimation.

A prespecified, nonbinding, interim futility analysis was planned to review safety and efficacy once 43 participants had enrolled and 24 had completed the week 48 study visit or discontinued before week 48 (data cutoff March 25, 2022). The criterion for futility was a between-group difference

of <1 ml/min per 1.73 m^2 per year in the slope of the least squares (LS) mean change in eGFR, calculated per CKD Epidemiology Collaboration equation[19] by an independent statistician.

Numbers Analyzed

The safety primary endpoint was assessed in the safety population, which comprised all randomized participants who received ≥1 dose of study treatment (lademirsen or placebo), and participants were analyzed according to the study treatment they received. The primary endpoint of annualized change in eGFR was assessed in the primary population, comprising all randomized participants who completed the 48-week double-blind treatment period or discontinued before week 48. Participants in the primary population were analyzed according to the treatment allocated by randomization. Supportive analysis for the primary efficacy endpoint and other efficacy analyses were performed in the intention-to-treat (ITT) population, which included all randomized participants. The pharmacokinetic population included all randomized participants who received ≥1 dose of lademirsen and had ≥1 postdose pharmacokinetic measurement of lademirsen serum concentration. Randomized participants who received ≥1 dose of study treatment and had ≥1 postbaseline ADA sample comprised the ADA population.

Endpoint Analysis

The safety primary endpoint was analyzed by incidence and severity of TEAEs and serious TEAEs. The annualized change in eGFR primary endpoint was compared between lademirsen and placebo using a random coefficient linear mixed-effect model. The dependent variable (eGFR) was collected over 48 weeks during the double-blind treatment period, with time as a continuous variable, and fixed effects of treatment (lademirsen or placebo), screening eGFR stratification factor (>35 to <60 versus ≥60 ml/min per 1.73 m^2), time, and treatment-by-time interaction. Random intercept and random slope following bivariate normal distribution were used with a mean of zero and variance covariance were estimated from the model. The LS mean slope difference was calculated, along with SEM and 95% confidence intervals (CIs). No imputation of eGFR data was conducted. The primary estimand was the difference in mean slope of eGFR estimated from baseline to up to 48 weeks during the double-blind treatment period and included data from participants who did not complete 48 weeks of treatment. Data collected after study drug discontinuation during the 10-week follow-up period were included for analysis. The same method was used for *post hoc* subgroup analysis of eGFR slope in primary population participants categorized as hemizygous or heterozygous.

Absolute changes in eGFR from baseline to week 48 as a dependent variable were analyzed using a mixed-effect model with repeated measures by treating time as a categorical variable, and fixed effects of treatment (lademirsen or placebo), screening eGFR stratification factor, time, and treatment-by-time interaction. Other endpoints, including the *post hoc* subgroup analysis of eGFR slope in participants with biallelic *COL4A3/4* or hemizygous *COL4A5* variants, were summarized using descriptive statistics.

For the *post hoc* statistical analyses of predictors of eGFR slope, see Supplemental Text 2.

Results

The decision to terminate the study was made on July 8, 2022. Subsequently, the last visit of the last participant took place on September 22, 2022, which is the data cutoff date for the results reported in this manuscript.

Forty-three participants were enrolled and randomized to lademirsen (n=29) or placebo (n=14). Participants enrolled based on eGFR <90 ml/min per 1.73 m^2 (n=7) also met the other criteria for rapidly progressive disease. Participant characteristics including genetic categories are shown in Table 1. Participants were aged 18–55 years (mean [SD], 33 [11.6] years). Baseline eGFR ranged from 31 to 96 (mean [SD], 56 [15.8]) ml/min per 1.73 m^2 and was <60 ml/min per 1.73 m^2 in 28 participants (65%) and ≥60 ml/min per 1.73 m^2 in 15 (35%) participants, with a similar distribution between treatment groups. Mean (SD) eGFR slope at baseline was −8 (7.8) and −8 (6.6) ml/min per 1.73 m^2 per year for the lademirsen and placebo groups, respectively.

At data cutoff, 28 participants had completed the double-blind, placebo-controlled phase (19 in the lademirsen group and nine in the placebo group), and one participant in the placebo group during the double-blind phase also completed the open-label lademirsen treatment phase (Figure 2). In the double-blind period, there were 30 participants in the primary population, and 43 in the safety population, which was identical to the ITT population. Thirty-eight individuals participated in both the double-blind and open-label periods. Owing to TEAEs, treatment was discontinued in three lademirsen-treated participants in the double-blind period (eGFR decrease in one participant, complement factor decrease in one participant, and chills, fatigue, migraine, and nausea in one participant) and in one participant in the open-label period (eGFR decrease). In the aforementioned participant with complement factor decrease, the TEAE occurred on the day of switching from the double-blind to the open-label period, before the participant receiving a first open-label lademirsen dose.

Cumulative exposure to study treatment during the 48-week double-blind period was 25 patient-years for lademirsen (n=29) and 11 patient-years for placebo (n=14), with a median treatment duration of 335 days in both groups. Overall, 24 participants in the lademirsen group (83%) and 12 in the placebo group (86%) were ≥80% adherent to treatment.

Primary Outcomes

Adverse Events: Double-Blind Period

TEAEs were reported in all participants in both groups (Table 2). The most common were injection-site reactions, respiratory tract infections, metabolic or nutrition disorders, anemia, headache, and dizziness (Table 2). Most TEAEs were mild or moderate in severity. Severe TEAEs occurred in nine (31%) lademirsen-treated participants (respiratory tract infection [n=1], migraine [n=1], decreased eGFR [n=7]) and one (7%) placebo-treated participant (decreased eGFR).

Two serious TEAEs were seen, both in lademirsen-treated participants: respiratory tract infection (n=1) and decrease in eGFR (n=1). The respiratory tract

Table 1. Demographic and clinical characteristics at baseline (randomized population, *N*=43)

Characteristic	Lademirsen (*n*=29)	Placebo (*n*=14)
Age, yr, mean (SD)	35 (12)	31 (12)
Sex, *n* (%)		
Male	19 (66)	7 (50)
Female	10 (35)	7 (50)
BMI		
Mean (SD)	26 (4.5)	24 (4.1)
Range: min–max	17.0–37.8	16.0–33.2
Race, *n* (%)		
Asian	8 (28)	5 (36)
Black	0	1 (7)
White	19 (66)	7 (50)
Not reported	2 (7)	1 (7)
Ethnicity, *n* (%)		
Hispanic or Latino	4 (14)	2 (14)
Non-Hispanic or Latino	25 (86)	12 (86)
Genetic category, *n* (%)		
Autosomal heterozygous	10 (35)[a]	5 (36)[a]
Biallelic *COL4A3* or *COL4A4*	3 (10)	1 (7)
Digenic (female *COL4A5* plus *COL4A3/4*)	2 (7)[b]	1 (7)
Female *COL4A5*	1 (3)	1 (7)
Male *COL4A5*	12 (41)[c]	6 (43)
Not reported	1 (3)	0
Time since AS diagnosis, yr, mean (SD)	11 (10.6)	7 (7.3)
Prior use of ACE inhibitors or ARBs, *n* (%)	27 (93)	14 (100)
Prior use of SGLT2 inhibitors, *n* (%)	1 (3)	0
eGFR, ml/min per 1.73 m^2, mean (SD)	55 (15.7)	57 (16.5)
eGFR slope, ml/min per 1.73 m^2 per year, mean (SD)	–8 (7.8)	–8 (6.6)
eGFR category, ml/min per 1.73 m^2, *n* (%)		
<60	19 (66)	9 (64)
≥60	10 (35)	5 (36)
UPCR, mg/g, mean (SD)	2944 (1812.5)	2369 (1346.2)
UPCR, mg/g, median (min–max)	2681 (195.7–7403.8)	1914 (478.0–4414.4)
UACR, mg/g, mean (SD)	2265 (1500.5)	1856 (1052.8)
UACR, mg/g, median (min–max)	2137 (175.5–5716.3)	1626 (447.4–3549.2)

eGFR was calculated using the CKD Epidemiology Collaboration (2021) equation: $eGFR = 142 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.012$ (if female), where Scr is serum creatinine in mg/dl, κ is 0.7 for female participants and 0.9 for male participants, α is −0.241 for female participants and −0.302 for male participants, and age (in years) is calculated as (laboratory sampling date−informed consent date)/365.25+age at informed consent. ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; AS, Alport syndrome; CKD-EPI, CKD Epidemiology Collaboration; SGLT2, sodium–glucose cotransporter 2; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.

[a]Two participants in the placebo arm and three in the lademirsen arm had an additional variant of undetermined significance in a relevant *COL4A3/4/5* gene.

[b]One of these participants had two different variants of undetermined significance.

[c]Two of the ten male participants with X-linked Alport syndrome had suspicious variants of undetermined significance in *COL4A5* and no explaining variant in any other *COL4A3/4* gene.

infection was not considered treatment-related and resolved with appropriate treatment, but the decrease in eGFR was considered treatment-related and was persistent. No serious TEAEs were seen in placebo-treated participants. No deaths occurred.

TEAESIs developed in six lademirsen recipients (21%) and one placebo recipient (7%); in all individuals, the TEAESI was a decrease in eGFR. The event was considered serious in one lademirsen-treated participant, who discontinued treatment.

Adverse Events: Open-Label Period

Three serious TEAEs were reported in one participant: hand fracture and increased blood creatinine (both were resolved and not considered related to treatment) and complex regional pain syndrome (not resolved, not considered related to treatment).

Annualized Rate of Change in eGFR

In the primary population, the LS mean (95% CI) slope in the eGFR curve over 48 weeks was −5 (−8.7 to −1.1) in the lademirsen group and −5 (−10.2 to 0.8) ml/min per 1.73 m^2 per year in the placebo group, with no significant difference between groups (Table 3).

With regard to change from baseline in eGFR, while a numerically greater eGFR slope decrease (*i.e.*, worsening) was observed in the lademirsen group, there was no significant difference between the lademirsen and placebo groups at any timepoint (Figure 3).

Secondary Outcomes

Change from Baseline in eGFR

Overall LS mean (95% CI) change from baseline in eGFR averaged across 48 weeks in the ITT population was −6

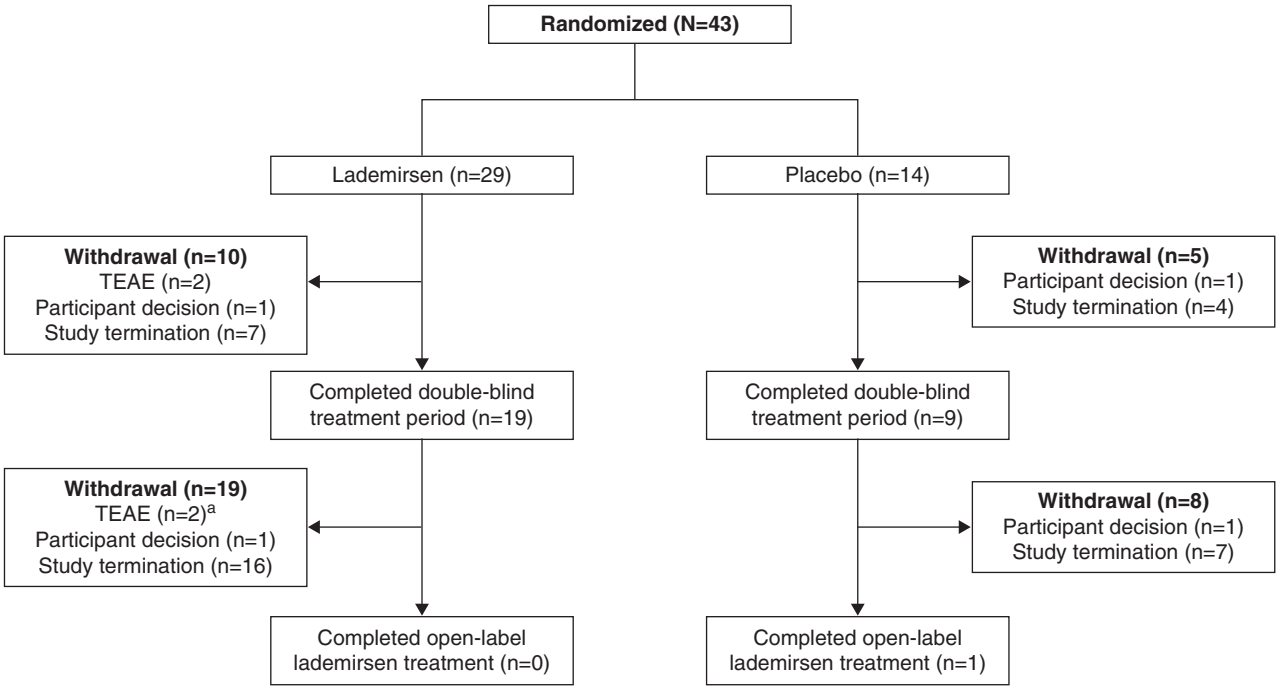

Figure 2. Participant disposition (randomized population, *N*=43). One participant experienced a TEAE that led to treatment discontinuation on the day of switching from the double-blind to the open-label period, before the participant receiving the first dose of the open-label period. However, because this participant completed the electronic case report form to enter the open-label treatment period, the participant was considered to have discontinued treatment during the open-label period. TEAE, treatment-emergent adverse event.

(−8.9 to −2.8) in the lademirsen group and −5 (−9.3 to −0.4) ml/min per 1.73 m^2 in the placebo group, and the LS mean (95% CI) percent change from baseline was −10 (−15.0 to −4.6)% and −6 (−14.2 to 1.4)%, respectively.

There was no significant difference between the lademirsen and placebo groups in the proportion of participants who had a <10%, <20%, <30%, or <40% reduction in eGFR at week 24 or 48. One person in the lademirsen group developed kidney failure (eGFR <15 ml/min per 1.73 m^2).

No clinically significant changes in electrocardiogram findings, BP, weight, or laboratory parameters were identified between treatment groups.

Pharmacokinetics and Pharmacodynamics

Lademirsen pharmacokinetic findings were consistent with concentrations observed for this dose in the multiple-ascending-dose healthy volunteer study.[20] No meaningful improvement in proteinuria was observed in those treated with lademirsen; see Supplemental Text 3 and Supplemental Table 1 for detailed pharmacokinetic/pharmacodynamic results.

ADAs

ADA data were available for 22 participants in the lademirsen group and 11 in the placebo group. One participant in the placebo group was ADA-positive at baseline, but no placebo recipients developed ADAs during the double-blind phase. In lademirsen recipients, none were ADA-positive at baseline, but 6/22 (27%) developed ADAs during double-blind treatment. The peak ADA titers ranged from 25 to 12,800 (median 250). There was no obvious relationship between ADA status, change from baseline in eGFR slope, and TEAE development.

Post Hoc *Analyses*

Subgroup analysis of eGFR slope difference in participants categorized as hemizygous or heterozygous in the primary population showed no marked difference between groups (Supplemental Figure 1).

In addition, the subgroup analysis of the 14 participants with biallelic *COL4A3*/*COL4A4* or hemizygous *COL4A5* variants who completed the 48-week treatment period showed no notable difference in rate of eGFR loss between those receiving lademirsen and those receiving placebo (Supplemental Table 2).

For results on *post hoc* analysis of predictors of eGFR slope, see Supplemental Text 2.

Discussion

In this phase 2 clinical trial conducted in individuals with AS at risk of rapid disease progression, lademirsen was generally well-tolerated, and trial termination was not driven by safety concerns. Most TEAEs were mild or moderate injection-site reactions, and many of the other TEAEs were those that may be expected in people with kidney dysfunction, including fatigue, anemia, metabolic/electrolyte abnormalities, and worsening kidney function. A decrease in eGFR of ≥30% was a TEAESI and developed in six lademirsen-treated participants (21%) versus one placebo-treated participant (7%). Because miRNA-21 is

Table 2. Treatment-emergent adverse events (safety population, *N*=43)

TEAE	During Double-Blind Treatment		During Double-Blind or Open-Label Treatment
	Lademirsen (*n*=29)	Placebo (*n*=14)	Lademirsen (*n*=38)
TEAEs, *n* (%), occurring in any participant			
Any TEAE	29 (100)	14 (100)	37 (97)
Any serious TEAE	2 (7)	0	5 (13)
Any severe TEAE	9 (31)	1 (7)	8 (21)
TEAE leading to discontinuation	3 (10)	0	4 (11)
TEAESI	6 (21)	1 (7)	11 (29)
TEAEs, *n* (%), occurring in ≥10% of participants[a]			
General disorders and admin-site conditions	24 (83)	9 (64)	32 (84)
ISRs	21 (72)	6 (43)	26 (68)
Injection-site pain	5 (17)	0	7 (18)
Pyrexia	5 (17)	0	5 (13)
Asthenia	3 (10)	0	3 (8)
Fatigue	2 (7)	2 (14)	4 (11)
Chills	3 (10)	0	4 (11)
Injection-site erythema	2 (7)	1 (7)	4 (11)
Infections and infestations	18 (62)	7 (50)	23 (61)
Upper respiratory tract infection	6 (21)	1 (7)	9 (24)
COVID-19	5 (17)	5 (36)	8 (21)
Nasopharyngitis	4 (14)	1 (7)	4 (11)
Blood and lymphatic system disorders	8 (28)	4 (29)	10 (26)
Anemia	3 (10)	2 (14)	5 (13)
Iron deficiency anemia	0	2 (14)	1 (3)
Thrombocytopenia	3 (10)	0	3 (78)
Metabolism and nutrition disorders	16 (55)	5 (36)	19 (50)
Hyperkalemia	5 (17)	1 (7)	7 (18)
Metabolic acidosis	5 (17)	1 (7)	8 (21)
Hypertriglyceridemia	2 (7)	1 (7)	4 (11)
Gout	2 (7)	2 (14)	2 (5)
Vitamin D deficiency	1 (3)	2 (14)	1 (3)
Nervous system disorders	11 (38)	4 (29)	13 (34)
Headache	6 (21)	3 (21)	6 (16)
Dizziness	4 (14)	1 (7)	5 (13)
Migraine	3 (10)	0	3 (8)
GI disorders	14 (48)	4 (29)	20 (53)
Nausea	5 (17)	0	6 (16)
Diarrhea	4 (14)	2 (14)	6 (16)
Vomiting	3 (10)	1 (7)	6 (16)
Skin and subcutaneous tissue disorders	9 (31)	4 (29)	9 (24)
Skin discoloration	3 (10)	0	3 (8)
Pruritus	0	2 (14)	1 (3)
Musculoskeletal disorders	6 (21)	4 (29)	9 (24)
Back pain	1 (3)	2 (14)	4 (11)
Investigations	22 (76)	13 (93)	28 (74)
eGFR decreased	20 (69)	10 (71)	26 (68)
Blood bicarbonate decreased	0	2 (14)	0
BP increased	0	2 (14)	0

COVID-19, coronavirus disease 2019; GI, gastrointestinal; ISR, injection-site reaction; SC, subcutaneous; TEAE, treatment-emergent adverse event; TEAESI, treatment-emergent adverse event of special interest.
[a]Of the treatment groups shown.

widely expressed throughout the body, there is potential for off-target effects with anti-miRNA-21 therapy[20]; however, we found little evidence of this and no signs of hepatotoxicity.

Both treatment groups exhibited a slower rate of eGFR decline compared with eGFR slope before randomization. However, the slopes of eGFR decline were similar in both treatment groups of the primary population (LS mean of −5 and −5 for the lademirsen and placebo groups, respectively), with a between-group difference of LS mean change of eGFR slope of −0.2 ml/min per 1.73 m^2 per year. These results are consistent with the results observed at the time of the futility analysis (*i.e.*, between-group eGFR slope difference <1 ml/min per 1.73 m^2 per year).

For the secondary endpoints (ITT population) of absolute and percent change in eGFR from baseline, although not statistically significantly different, a numerically greater decrease (*i.e.*, worsening) was seen in those receiving lademirsen (LS mean change, −6 ml/min per 1.73 m^2; LS mean percent change, −10%) versus those receiving placebo (LS mean change, −5 ml/min per 1.73 m^2; LS mean percent change, −6%).

Table 3. eGFR slope during double-blind treatment using a random coefficient linear mixed-effect model (primary, *N*=30, and intention-to-treat, *N*=43, populations)

Primary Population (*N*=30)			
	Lademirsen (*n*=20)	Placebo (*n*=10)	Difference
LS mean (SEM) eGFR slope ml/min per 1.73 m^2 per year 95% CI	−5 (1.9) −8.7 to −1.1	−5 (2.7) −10.2 to 0.8	−0 (3.3) −6.9 to 6.5
ITT Population (*N*=43)			
	Lademirsen (*n*=29)	Placebo (*n*=14)	Difference
LS mean (SEM) eGFR slope ml/min per 1.73 m^2 per year 95% CI	−9 (2.1) −13.7 to −5.1	−7 (3.1) −13.2 to −0.7	−2 (3.8) −10.1 to 5.2

CI, confidence interval; ITT, intention to treat; LS, least squares.

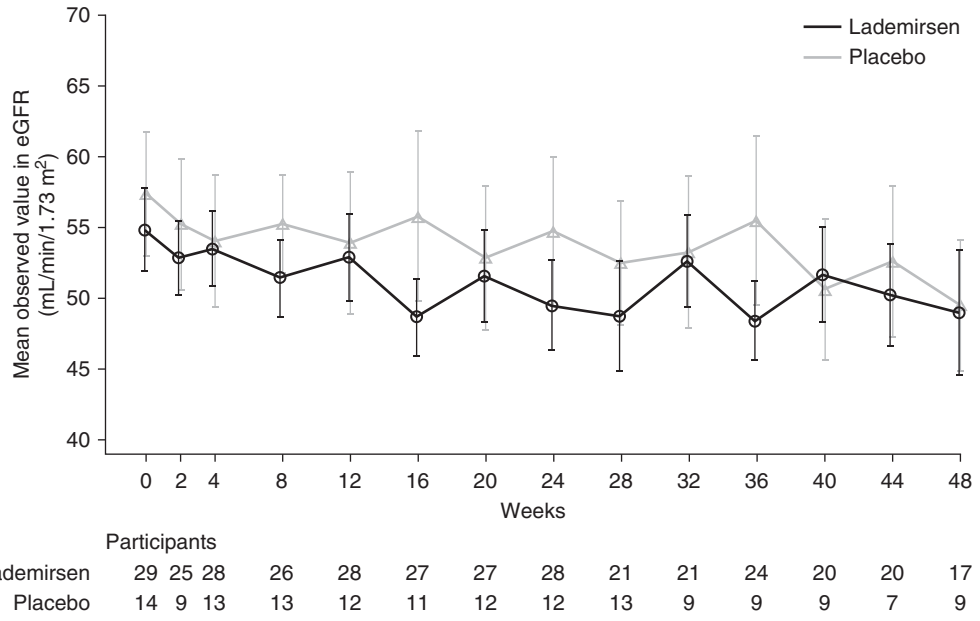

Figure 3. Mean (SEM) eGFR over time in participants receiving lademirsen or placebo (ITT population, *N*=43). ITT, intention to treat.

Although lademirsen has previously been demonstrated to slow progression of kidney fibrosis in animal models with a similar severity of CKD to participants of this study, no such effect of lademirsen was observed for the (human) participants in this study.[14,18]

It is possible that disease modifiers in humans are different to those in animal models and that heterogeneous disease in humans responds differently to that seen in mouse models, where the genetic background is less varied (*e.g.*, 129/Sv or F1 hybrid). The most commonly reported animal model of AS is the homozygous *Col4a3* knockout model (*Col4a3*$^{-/-}$),[21] and this was the model used in the preclinical studies with miRNA-21 inhibitors.[14,17] Collagen containing the 5α chain is present in the GBM of *Col43a*$^{-/-}$ mice, whereas it is not in *Col45a*$^{-/-}$ models.[21] However, the *Col4A5*$^{-/-}$ model is used less often because survival of these mice is more variable. Most participants in this study had hemizygous or heterozygous *COL4A5* as the predominant genetic abnormality, rather than biallelic *COL4A3* deficiency, so it is not impossible that the effects of lademirsen on kidney function could differ according to genotype. However, *post hoc* subgroup analysis of the 14 individuals with biallelic *COL4A3*/*COL4A4* or hemizygous *COL4A5* variants who completed the study showed no notable difference in rate of eGFR loss between those receiving lademirsen (−3 ml/min per 1.73 m^2 per year, n=9) and those receiving placebo (−3 ml/min per 1.73 m^2 per year, n=5). Similarly, *post hoc* analysis of eGFR slope difference in participants categorized as hemizygous or heterozygous also showed no marked difference between subgroups, although it should be noted that the study was not powered to detect small treatment effects in these two *post hoc* subgroup analyses.

With limited treatment options for people with AS, gene editing approaches, such as clustered regularly interspaced short palindromic repeats (CRISPR), are under investigation,[22] but as the genetic variants causing AS may include rearrangements, deletions, splicing, and missense variants,[23] no single gene editing technique would be effective in all individuals with the syndrome.

Our study had a number of strengths, including a double-blind, randomized, placebo-controlled design, which can be difficult to achieve in rare diseases because of the small and often geographically dispersed participant population.[24] In addition, we identified a group of participants with AS with rapidly progressive disease by evaluating historical eGFR data, which made it possible to assess lademirsen efficacy on kidney disease progression in a relatively short period and with a small sample size; this was made possible by close collaboration with AS patient organizations and the UK National Registry of Rare Kidney Diseases (RaDaR). Furthermore, the study results demonstrated the importance of including a placebo arm for this kidney disease because of the potential for variation in rate of eGFR decline[25] (*i.e.*, the improvement seen among participants in the placebo arm).

While lademirsen was generally well tolerated, it did not slow the rate of decline in kidney function compared with placebo in participants with AS and rapidly progressive kidney dysfunction. As a result, this randomized, double-blind, placebo-controlled clinical trial was stopped for futility. There were no safety concerns that led to the discontinuation of the study.

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at http://links.lww.com/CJN/B894.

Funding

Sponsorship for this study was funded by Sanofi, Paris, France. Editorial assistance was provided by Fishawack Communications Ltd., part of Avalere Health, and was funded by Sanofi.

Acknowledgments

The authors thank the study participants, trial staff, and HERA Clinical Trial Group investigators (Supplemental Text 1). We thank Kristin Leonberg, MS, RD (Sanofi) for coordinating the development, facilitating author discussions, and review of this manuscript. Editorial assistance was provided by Heather St Michael, BSc, and Emiliana Jelezarova, PhD, CMPP, of Fishawack Communications Ltd., part of Avalere Health.

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Data Sharing Statement

Qualified researchers may request access to participant-level data and related documents. Participant-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at https://www.vivli.org/.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/CJN/B895.

Supplemental Text 1. HERA Clinical Trial Group.

Supplemental Text 2. Predictors of eGFR Slope: Methods and Results.

Supplemental Text 3. Pharmacokinetics and Pharmacodynamics: Results.

Supplemental Table 1. UPCR and UACR change from baseline at week 48 during double-blind treatment (ITT population, $N=43$).

Supplemental Table 2. eGFR slope during double-blind treatment in a subgroup analysis of participants with biallelic COL4A3/4 or hemizygous COL4A5 variants.

Supplemental Figure 1. LS mean (95% CI) difference in eGFR slope by genotype during double-blind treatment (per linear mixed-effect model) in the primary population ($N=30$).

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