Sponsor: Sanofi **Drug substance:** Lademirsen	**Study Identifiers:** NCT02855268, EudraCT Number: 2019-004394-10 **Study code:** ACT16248

Title of the study:

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, 2-Stage Seamless Study to Evaluate the Efficacy, Safety, Pharmacodynamics, and Pharmacokinetics of Lademirsen (SAR339375) for Once Weekly Subcutaneous Injection in Patients Aged 12 Years and Older with Alport Syndrome

Study centers:

This study was conducted in 7 countries at 20 centers that screened 67 participants. Among them, 17 centers enrolled/randomized 43 participants.

Study period:

Date first participant enrolled: 02/Nov/2019

Date last participant completed: 22/Sep/2022

Study Status: Terminated (The results of the futility analysis led to the study termination. No unexpected safety findings were identified.)

The study period was planned into 2 stages in the study protocol #13. However, due to the termination of the study, the participants in Stage 1/Cohort 1 were screened, randomized, and treated according to the amended protocol #11 and #12. There was a screening period of up to 4 weeks followed by a double-blind, placebo-controlled treatment period of 48 weeks, an open-label extension period of 48 weeks, and a post-treatment follow-up period of 10 weeks. Stage 2/Cohort 2 was never enrolled at all.

For transparency, in study protocol #13, Stage 1/Cohort 1 and Stage 2/Cohort 2 were described as below.

For Stage 1/Cohort 1, there were a screening period of up to 4 weeks followed by double-blind, placebo-controlled treatment period of 48 weeks, open-label extension treatment period of 96 weeks, and a post-treatment follow-up period of 10 weeks.

For Stage 2/Cohort 2, it was planned to have a screening period of up to 4 weeks followed by a double-blind, placebo-controlled treatment period of 96 weeks, open-label extension treatment period of 48 weeks, and a post-treatment follow-up period of 10 weeks.

Phase of development: Phase 2

Objectives:

Primary:

To assess the efficacy of lademirsen in reducing the rate of decline in kidney function as compared to placebo in participants at risk for rapidly progressive Alport syndrome in the primary population.

Secondary:

- To assess the efficacy of lademirsen in reducing the absolute decline in kidney function at Week 48 (using both Stage 1 and Stage 2 data) and Week 96 (using Stage 2 data only) in the primary population.
- To assess the efficacy of lademirsen in delaying time to reach the composite endpoint, that includes ≥40% reduction in eGFR, kidney failure (defined by an eGFR <15 mL/min/1.73 m^2 at two consecutive visits, or initiation of hemodialysis or kidney transplant), in the primary population.
- To assess the efficacy of lademirsen in fatigue at Week 48 in Stage 2 primary population.
- Assess the safety and tolerability of lademirsen in patients with Alport syndrome in the safety population.
- To assess plasma pharmacokinetic (PK) parameters in the PK population. Concentration at 4 hours post dosing (approximate Cmax for the parent compound) for lademirsen, its active major metabolite (RG0005), and the sum of lademirsen and RG0005 (SUM) following administration of lademirsen. Ctrough will be assessed in terms of SUM only.
- To assess potential formation of anti-drug antibodies (ADAs) following administration of lademirsen in the ADA population.
- To assess the pharmacodynamic effect of lademirsen on miR-21 and on changes in kidney injury and function biomarkers in the primary population.

Methodology:

The purpose of this study was to evaluate the efficacy, safety, pharmacodynamics, and pharmacokinetics of lademirsen for subcutaneous injection administered once weekly in male and female participants aged 12 years and older with Alport Syndrome.

The key study features included:

- The study duration: 158 weeks in both Stage 1 and in Stage 2 (from screening through completion of follow-up).
- The treatment duration: 144 weeks in Stage 1 (48 weeks in double-blind period followed by 96 weeks in open-label treatment period) and 144 weeks in Stage 2 (96 weeks in double-blind period followed by 48 weeks in open-label treatment period).
- The visit frequency: once weekly with the options of performing certain visits at home or at an alternate location or by phone call. However, the quarterly visits were to be performed at study site.

The methodology described above was the methodology included in last version of the protocol (amended protocol 13) but due to the early termination of the study, the methodology of amended study protocol #11 or #12 (for sites in France only) was used in this study report, where Stage 1/Cohort 1 was 48 weeks DB + 48 weeks OL period in ADULT only.

Number of participants:

A total of 130 participants (including 43 participants in Stage 1/Cohort 1 [participants in the Phase 2 study of the amended study protocol #11 or #12] and 87 participants in Stage 2/Cohort 2) with Alport Syndrome at multiple investigative centers was planned in amended study protocol #13.

Forty-three participants in Stage 1/Cohort 1 and 0 participants in Stage 2/Cohort 2 were enrolled and analyzed.

Diagnosis and criteria for inclusion:

Adult or adolescent participants with confirmed Alport syndrome (free of kidney failure or any chronic kidney diseases other than Alport syndrome) were chosen to include in this study.

Study products

- SC administration of lademirsen QW for adults (18 years and above) 110 mg or for adolescents (12 to <18 years) 1.5 mg/kg (maximum dose not to exceed 110 mg/week) for 96 weeks,

or

- SC administration of placebo QW for adults (18 years and older) 110 mg or for adolescents (12 to <18 years) 1.5 mg/kg (maximum dose not to exceed 110 mg) for 96 weeks.

Duration of study intervention:

This study was planned to have 2 Stages/Cohorts based on the amended study protocol #13:

- Stage 1/Cohort 1 (participants in the Phase 2 study in the amended study protocol #11 or #12 for France, randomization completed by the end of December 2021) included 48-week double-blind, placebo-controlled period followed by 96-week open-label treatment period.
- Stage 2/Cohort 2 included 96-week double-blind, placebo-controlled period followed by 48-week open-label treatment period.

  Since amended study protocol #13 was not implemented, the actual duration of study intervention for participants in Stage 1/Cohort 1 was 48-week double-blind, placebo-controlled period followed by 48-week open-label treatment period based on the amended study protocol #11 or #12, and no participants were randomized for Stage 2/Cohort 2.

Criteria for evaluation:

Primary:

Annualized rate of change in estimated glomerular filtration rate (eGFR) during the placebo-controlled treatment period in the primary population.

Secondary:

- Absolute change in eGFR values from baseline at Week 48 (using both Stage 1 and Stage 2 data), and Week 96 (using Stage 2 data only) during the placebo-controlled treatment period in the primary population.
- Time to reach the composite endpoint that includes ≥40% reduction in eGFR, kidney failure (defined by an eGFR <15 mL/min/1.73 m^2 at two consecutive visits or initiation of hemodialysis, or kidney transplant) during the placebo-controlled treatment period in the primary population.
- Percent change from baseline in fatigue, as measured by the FACIT-F scales, at Week 48 during the Stage 2 placebo-controlled treatment period, in the primary population.
- Incidence and severity of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs).
- Plasma concentrations of lademirsen, RG0005, and SUM (lademirsen+RG0005) in 4 hours post-dose (approximate C_{max}) samples and SUM only in C_{trough} samples, in the PK population.
- Incidence and titer of ADAs in ADA population.
- Changes in circulating miR-21 at Week 24, Week 48 (using both Stage 1 and Stage 2 data), and Week 96 (using Stage 2 data only) during the placebo-controlled treatment period in the primary population.

  Change in kidney injury and function biomarkers from baseline at Weeks 24 and 48 (using both Stage 1 and Stage 2 data) and Week 96 (using Stage 2 data only) during the placebo-controlled treatment period in the primary population:

  -In blood: blood urea nitrogen (BUN);

  -In urine: protein/creatinine ratio, albumin/creatinine ratio, and epidermal growth factor (EGF);

  -In both blood and urine: creatinine, cystatin C, transforming growth factor-β (TGFβ), and neutrophil gelatinase-associated lipocalin (NGAL).

Statistical methods:

The SAP was developed based on final amended protocol 13 of this study. As the study was terminated early prior to all Stage 1 participants completed the double blind (DB) period of the study, and no Stage 2 participants were enrolled, only key endpoints were planned to be analyzed and the time frame of analysis was reduced to Week 48 for efficacy and most of the safety analyses.

The modified objectives and endpoints are specified in Table 1, which is aligned with the endpoints defined in amended Study protocol #13. There was no major change of the analysis plan regarding the statistical method. For efficacy analyses, as no Stage 2 participants were enrolled, the population of all statistical analysis is Stage 1 participants and the covariates in the statistical models only include those pertinent to Stage 1 participants.

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Table 1 - Objectives and endpoints for final analysis (modified after the decision of study termination)

a) Population[a]	b) Objectives	c) Endpoints
Primary		
Primary population	To assess the efficacy of lademirsen in reducing the rate of decline in kidney function as compared to placebo in participants at risk for rapidly progressive Alport syndrome	Annualized rate of change in estimated glomerular filtration rate (eGFR) during the placebo-controlled treatment period
Secondary		
ITT population	To assess the efficacy of lademirsen in reducing the absolute decline in kidney function at Week 48	Absolute and percentage change in eGFR values from baseline at Week 24 and 48 Proportion of participants with a reduction from baseline in eGFR of <10%, <20%, <30%, or <40% at Week 24 and 48
ITT population	To assess the efficacy of lademirsen in delaying time to reach the ESRD	Number and proportion of participants who reach ESRD as defined by an eGFR≤15 mL/min/1.73 m^2 or initiation of hemodialysis or renal transplantation (composite endpoint) during the placebo-controlled treatment period
Safety population for analysis during the placebo-controlled period. Lademirsen population for analysis during the lademirsen treatment period	To assess the safety and tolerability of lademirsen in participants with Alport syndrome.[c]	Incidence and severity of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) during the placebo-controlled treatment period and lademirsen treatment period, respectively Number of participants with PCSA in clinical laboratory parameters during the placebo-controlled treatment period Number of participants with PCSA in vital signs during the placebo-controlled treatment period Number of participants with PCSA in 12-lead electrocardiogram (ECG) during the placebo-controlled treatment period
Lademirsen population for analysis during the lademirsen treatment period		Number of participants with PCSA in clinical laboratory parameters during the placebo-controlled treatment period Number of participants with PCSA in vital signs during the placebo-controlled treatment period Number of participants with PCSA in 12-lead electrocardiogram (ECG) during the placebo-controlled treatment period
PK population	To assess plasma pharmacokinetic (PK) parameters. Concentration at	Plasma concentrations of lademirsen, RG0005, and SUM (lademirsen + RG0005) in Cmax samples and

	4 hours post dosing (approximate C_{max} for the parent compound) for lademirsen, its active major metabolite (RG0005), and the sum of lademirsen and RG0005 (SUM) following administration of lademirsen. C_{trough} will be assessed in terms of SUM only.	SUM only in C_{trough} samples during the placebo-controlled treatment period
ADA population	To assess potential formation of anti-drug antibodies (ADAs) following administration of lademirsen.	Incidence and titer of ADAs during the placebo-controlled treatment period Association of AEs with ADAs during the placebo-controlled treatment period
ITT population	To assess the pharmacodynamic effect of lademirsen on changes in kidney injury and function biomarkers.	Change in kidney injury and function biomarkers from baseline at Weeks 24 and 48 during the placebo-controlled treatment period: • In blood: blood urea nitrogen (BUN); • In urine[b]: protein/creatinine ratio, albumin/creatinine ratio, and epidermal growth factor (EGF)/creatinine ratio; • In both blood and urine[b]: creatinine, Cystatin C, transforming growth factor-β (TGFβ), and neutrophil gelatinase-associated lipocalin (NGAL).

a The definition of population is available in SAP.

b Urine biomarkers will be standardized by creatinine before analysis. If the urine parameter is collected through 24-hour urine, then the standardized value will be calculated by the original value divided by 24-hour urine creatinine; else if the urine parameter is collected through instant urine, then the standardized value will be calculated by divided by instant urine creatinine.

c This is one of the primary objectives for Amended Protocol 11 and 12, and secondary objective for Amended Protocol 13.

Summary Results:

As the study was terminated early (Sponsor decision applicable on 8 July 2022), no Stage 2/Cohort 2 participants were enrolled in the study. Only key endpoints were analyzed in Stage 1/Cohort 1 participants, and the time frame of analysis was reduced to Week 48 for efficacy and most of the safety analyses.

Disposition of participants

A total of 43 participants (lademirsen: 29; placebo: 14) were randomized and treated during this study.

Of the 43 participants, 28 participants (lademirsen:19; placebo: 9) completed the 48 weeks double-blind, placebo-controlled treatment period. Reasons for discontinuation among the 15 participants who did not complete double-blind treatment period are as follows: 11 participants (lademirsen: 7; placebo: 4) discontinued due to other reasons (eg, sponsor's decision, early study termination), 2 participants in lademirsen group discontinued treatment due to adverse events and 1 participant in each treatment group discontinued voluntarily.

Among the 28 participants who were rolled over to 48 weeks open-label treatment extension period, only 1 participant from placebo group completed the 48 weeks open-label treatment extension period and 27 participants (lademirsen: 19; placebo: 8) did not complete.

Demographic and other baseline characteristics:

Of the 43 participants who were randomized in the study, 26 participants were male and 17 participants were female, with a median age of 33 years (Min; Max: 18 ; 55) and median body weight of 74 kg.

The median eGFR of participants at baseline was 53.006 mL/min/1.73 m^2 (Min ; Max: 31.21 ; 96.47) and the median age at diagnosis of Alport syndrome was 20.9 years (Min ; Max: at birth ; 53).

Exposure:

Median treatment compliance in double-blind treatment period was reported to be 93.8% (Min ; Max: 47.92% ; 100%) for lademirsen and 94.3% (Min ; Max: 60.42% ; 100%) for placebo.

Cumulative exposure (in patient-years) to study treatment in 48 weeks double-blind period was 24.559 for lademirsen (n = 29) and was 11.42 for placebo (n = 14) with median duration of treatment of 335 days for both groups.

Efficacy/pharmacodynamic results:

Primary Endpoint

Estimated glomerular filtration rate (eGFR)

During this study, the annualized rate of change (slope) for eGFR from baseline to Week 48 was derived using linear mixed effect model using all eGFR measurements of primary population and compliant primary population.

All randomized participants from Stage 1 excluding participants with low baseline eGFR (ie, baseline eGFR of 20 to 35 mL/min/1.73 m^2) were considered primary population. LS mean (SE) values of eGFR slope (derived from the 30 participants [lademirsen: 20; placebo: 10] who have completed 48-week treatment or discontinued early) for primary population was -4.91 (1.86) mL/min/1.73 m^2 for lademirsen and -4.70 (2.69) mL/min/1.73 m^2 for placebo. The difference of LS mean value was -0.22 (3.27) with a two-sided P-value of 0.9472 Table 2.

All randomized participants who completed the double-blinded period (first 48 weeks) or discontinued early but received >=80% planned treatment during the double-blinded treatment period were considered compliant primary population. LS mean (SE) values of eGFR slope (derived from the 24 participants [lademirsen: 16; placebo: 8]) for compliant primary population was -3.18 (1.88) mL/min/1.73 m^2 for lademirsen and -5.00 (2.79) mL/min/1.73 m^2 for placebo. The difference of LS mean value was 1.82 (3.37) with a two-sided P-value of 0.5944 Table 3.

Secondary Endpoints

Changes in eGFR values

Summaries of changes and percentage changes from baseline to 48 weeks in eGFR values using a mixed model for repeated measures in ITT population are presented in Table 4 and in Table 5, respectively. The absolute and percentage changes in eGFR values (LS mean [SE]) from baseline at Week 48 were -7.08 (3.00) mL/min/1.73 m^2 and -10.05 (5.64%), respectively, in placebo, and -6.89 (2.02) mL/min/1.73m^2 and -12.77 (3.79) %, respectively, in lademirsen treatment group.

Kidney injury and function biomarkers

To assess the pharmacodynamic effect of lademirsen, the changes in kidney injury and function biomarkers from baseline at Weeks 24 and 48 during the placebo-controlled treatment period were analyzed. A summary of mean (+/-SE) observed values in urine protein/creatinine ratio (g/g) over time in double-blind period in ITT population is presented in Figure 1 and a summary of mean (+/-SE) observed values in urine albumin/creatinine ratio over time in double-blind period in ITT population is presented in Figure 2.

Safety results:

Adverse events

A summary of the treatment-emergent adverse events reported in the lademirsen treated population in both double-blind and open-label extension period is presented in Table 6. There were 37 (97.4%) participants who experienced any types of TEAEs, 5 (13.2%) participants experienced any types of treatment-emergent SAEs, 4 (10.5%) participants experienced TEAEs leading to permanent treatment discontinuation and 11 (28.9%) participants experienced treatment-emergent AESIs. There were no AE-related deaths or AE related dose reductions.

A summary of the TEAEs reported during the double-blind treatment-emergent period among enrolled participants in both the lademirsen and placebo treatment groups showed that all participants in both groups experienced any types of TEAEs (100%). Two participants (6.9%) experienced treatment-emergent SAEs and 3 participants (10.3%) experienced TEAEs leading to permanent treatment discontinuations in the lademirsen group compared to none in the placebo treatment group. Six participants (20.7%) in lademirsen group and 1 participant (7.1%) in placebo group experienced treatment-emergent AESIs Table 7.

eGFR decrease from baseline was monitored as AESI in this study. Six participants (20.7%) in Lademirsen treatment group and 1 participant (7.1%) in placebo group experienced eGFR decreased during the double-blind treatment-emergent period of this study.

Anti-drug antibodies (ADA)

Table 2 - eGFR slope calculated using linear mixed effect model in double blind treatment period (Treatment policy estimand) - Primary population

Period	Statistics	Placebo (N=10)	Lademirsen (N=20)	Difference
DB Treatment	Number of participants*	10	20	
	LSmean (SE)**	-4.70 (2.69)	-4.91 (1.86)	-0.22 (3.27)
	95 % CI**	(-10.21, 0.81)	(-8.73, -1.10)	(-6.92, 6.48)
	Two-sided P-value**			0.9472

Cut-off date: 22-Sep-2022.

* Number of participants with value at both baseline and at least one value at DB Treatment period.

**Estimated by linear mixed effect model. eGFR measurements collected from baseline to WK 48 is the response variable, and the model includes fix effects of treatment (lademirsen or placebo), screening eGFR stratification factor (<60 versus ≥60 mL/min/1.73 m^2), time, and treatment-by-time interaction. In addition, it includes random intercept and random slope for time to account for the between subject variability.

Treatment policy estimand: All eGFR data collected within 48 weeks (the max duration of exposure is around 339 days) since the first infusion of IMP (but prior to the introduction of rescue medication) are included.

Primary population: All randomized participants who completed the double-blinded period (the first 48 weeks) or discontinued double-blinded period early.

CKD-EPI Creatinine equation (2021) is used.

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Table 3 - eGFR slope calculated using linear mixed effect model in DB (Treatment policy estimand) - Compliant primary population

Period	Statistics	Placebo (N=8)	Lademirsen (N=16)	Difference
DB Treatment	Number of participants*	8	16	
	LSmean (SE)**	-5.00 (2.79)	-3.18 (1.88)	1.82 (3.37)
	95 % CI**	(-10.77, 0.78)	(-7.11, 0.76)	(-5.17, 8.81)
	Two-sided P-value**			0.5944

Cut-off date: 22-Sep-2022.

* Number of participants with value at both baseline and at least one value at DB Treatment period.

**Estimated by linear mixed effect model. eGFR measurements collected from baseline to WK 48 is the response variable, and the model includes fix effects of treatment (lademirsen or placebo), screening eGFR stratification factor (<60 versus ≥60 mL/min/1.73 m^2), time, and treatment-by-time interaction. In addition, it includes random intercept and random slope for time to account for the between subject variability.

Treatment policy estimand: All eGFR data collected within 48 weeks (the max duration of exposure is around 339 days) since the first infusion of IMP (but prior to the introduction of rescue medication) are included.

Compliant primary population: All randomized participants who completed the double-blinded period (the first 48 weeks) or discontinued double-blinded period early, and received ≥80% planned study intervention during the double-blinded treatment period.

CKD-EPI Creatinine equation (2021) is used.

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Table 4 - Analysis of change in eGFR (mL/min/1.73m^{super 2}) from baseline to 48 weeks using a mixed model for repeated measures - ITT population

Visit		Statistics	Placebo (N=14)	Lademirsen (N=29)	Difference
Baseline	Observed value	Number of participants with value	14	29	
		Mean (SD)	57.40 (16.51)	54.80 (15.73)	
		Median	53.40	53.01	
		Min ; Max	37.7 ; 96.5	31.2 ; 90.9	
Week 12	Observed value	Number of participants with value	12	28	
		Mean (SD)	53.89 (17.26)	52.90 (16.33)	
		Median	47.03	50.14	
		Min ; Max	40.3 ; 98.7	31.2 ; 92.3	
	Change from baseline	Number of participants with value	12	28	
		Mean (SD)	-2.53 (10.79)	-1.15 (6.94)	
		Median	-3.47	-0.11	
		Min ; Max	-22.8 ; 20.4	-17.5 ; 11.9	
		LSmean (SE)*	-2.77 (2.56)	-0.84 (1.71)	1.93 (2.99)
		95 % CI*	(-7.98, 2.45)	(-4.32, 2.64)	(-4.17, 8.03)
		P-value for the within treatment comparison*	0.2880	0.6266	
		P-value for the difference between groups*			0.5242
Week 24	Observed value	Number of participants with value	12	28	
		Mean (SD)	54.73 (18.21)	49.48 (16.91)	
		Median	48.11	45.16	
		Min ; Max	35.7 ; 93.9	18.3 ; 95.1	
	Change from baseline	Number of participants with value	12	28	
		Mean (SD)	-3.33 (9.15)	-5.11 (9.55)	
		Median	-1.08	-4.88	
		Min ; Max	-17.6 ; 15.6	-27.1 ; 19.1	
		LSmean (SE)*	-3.43 (2.74)	-5.15 (1.84)	-1.72 (3.22)
		95 % CI*	(-8.96, 2.10)	(-8.86, -1.44)	(-8.24, 4.80)
		P-value for the within treatment comparison*	0.2176	0.0077	

Visit		Statistics	Placebo (N=14)	Lademirsen (N=29)	Difference
		P-value for the difference between groups*			0.5962
Week 36	Observed value	Number of participants with value	9	24	
		Mean (SD)	55.47 (17.93)	48.36 (13.65)	
		Median	57.81	46.09	
		Min ; Max	33.6 ; 83.8	27.5 ; 82.8	
	Change from baseline	Number of participants with value	9	24	
		Mean (SD)	-6.22 (7.53)	-7.46 (8.54)	
		Median	-5.73	-7.37	
		Min ; Max	-16.9 ; 5.5	-25.6 ; 10.8	
		LSmean (SE)*	-6.16 (2.62)	-8.21 (1.72)	-2.04 (3.07)
		95 % CI*	(-11.50, -0.82)	(-11.71, -4.70)	(-8.30, 4.22)
		P-value for the within treatment comparison*	0.0251	<.0001	
		P-value for the difference between groups*			0.5107
Week 40	Observed value	Number of participants with value	9	20	
		Mean (SD)	50.62 (14.92)	51.65 (15.03)	
		Median	45.16	49.03	
		Min ; Max	33.3 ; 79.5	19.3 ; 77.7	
	Change from baseline	Number of participants with value	9	20	
		Mean (SD)	-3.71 (8.01)	-5.85 (9.48)	
		Median	-0.19	-4.34	
		Min ; Max	-19.8 ; 4.0	-22.4 ; 13.1	
		LSmean (SE)*	-5.92 (3.07)	-6.99 (2.04)	-1.07 (3.63)
		95 % CI*	(-12.18, 0.34)	(-11.15, -2.82)	(-8.48, 6.34)
		P-value for the within treatment comparison*	0.0630	0.0018	
		P-value for the difference between groups*			0.7704
Week 44	Observed value	Number of participants with value	7	20	
		Mean (SD)	52.60 (14.09)	50.23 (16.30)	
		Median	46.62	46.56	
		Min ; Max	37.3 ; 75.6	18.5 ; 81.0	

Visit		Statistics	Placebo (N=14)	Lademirsen (N=29)	Difference
	Change from baseline	Number of participants with value	7	20	
		Mean (SD)	-3.17 (6.43)	-6.27 (8.54)	
		Median	-2.70	-5.17	
		Min ; Max	-12.8 ; 7.3	-25.5 ; 7.0	
		LSmean (SE)*	-3.58 (2.81)	-7.09 (1.81)	-3.51 (3.29)
		95 % CI*	(-9.30, 2.14)	(-10.79, -3.39)	(-10.22, 3.20)
		P-value for the within treatment comparison*	0.2119	0.0005	
		P-value for the difference between groups*			0.2942
Week 48	Observed value	Number of participants with value	9	17	
		Mean (SD)	49.52 (13.91)	48.93 (18.09)	
		Median	49.16	44.96	
		Min ; Max	32.2 ; 73.4	17.7 ; 87.6	
	Change from baseline	Number of participants with value	9	17	
		Mean (SD)	-4.82 (5.96)	-4.36 (8.84)	
		Median	-4.91	-4.53	
		Min ; Max	-14.4 ; 3.4	-17.3 ; 9.1	
		LSmean (SE)*	-7.08 (3.00)	-6.89 (2.02)	0.20 (3.57)
		95 % CI*	(-13.26, -0.90)	(-11.04, -2.73)	(-7.16, 7.55)
		P-value for the within treatment comparison*	0.0264	0.0021	
		P-value for the difference between groups*			0.9568
Overall	Change from baseline	Number of participants with value at any visit	14	29	
		LSmean (SE)*	-4.82 (2.20)	-5.86 (1.48)	-1.04 (2.58)
		95 % CI*	(-9.30, -0.35)	(-8.88, -2.84)	(-6.28, 4.20)
		P-value for the within treatment comparison*	0.0356	0.0004	
		P-value for the difference between groups*			0.6898

The * estimates are from MMRM model. Change from baseline = treatment + eGFR stratum + visit + visit x treatment. Week 12, 24, 36, 40, 44 and 48 are considered as repeated measurements.

CKD-EPI Creatinine equation (2021) is used.

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Table 5 - Analysis of % change in eGFR (mL/min/1.73m^{super 2}) from baseline to 48 weeks using a mixed model for repeated measures - ITT population

Visit		Statistics	Placebo (N=14)	Lademirsen (N=29)	Difference
Baseline	Observed value	Number of participants with value	14	29	
		Mean (SD)	57.40 (16.51)	54.80 (15.73)	
		Median	53.40	53.01	
		Min ; Max	37.7 ; 96.5	31.2 ; 90.9	
Week 12	Observed value	Number of participants with value	12	28	
		Mean (SD)	53.89 (17.26)	52.90 (16.33)	
		Median	47.03	50.14	
		Min ; Max	40.3 ; 98.7	31.2 ; 92.3	
	%Change from baseline	Number of participants with value	12	28	
		Mean (SD)	-3.32 (15.91)	-1.96 (12.26)	
		Median	-6.53	-0.22	
		Min ; Max	-23.6 ; 26.1	-27.3 ; 19.8	
		LSmean (SE)*	-2.84 (4.06)	-1.10 (2.70)	1.75 (4.72)
		95 % CI*	(-11.05, 5.37)	(-6.56, 4.36)	(-7.81, 11.30)
		P-value for the within treatment comparison*	0.4880	0.6866	
		P-value for the difference between groups*			0.7134
Week 24	Observed value	Number of participants with value	12	28	
		Mean (SD)	54.73 (18.21)	49.48 (16.91)	
		Median	48.11	45.16	
		Min ; Max	35.7 ; 93.9	18.3 ; 95.1	
	%Change from baseline	Number of participants with value	12	28	
		Mean (SD)	-5.38 (13.24)	-9.12 (16.37)	
		Median	-2.47	-8.53	
		Min ; Max	-27.1 ; 20.0	-50.6 ; 25.2	
		LSmean (SE)*	-4.78 (4.51)	-8.44 (3.03)	-3.66 (5.32)
		95 % CI*	(-13.91, 4.34)	(-14.56, -2.33)	(-14.42, 7.09)
		P-value for the within treatment comparison*	0.2960	0.0080	
		P-value for the difference between groups*			0.4949
Week 36	Observed value	Number of participants with value	9	24	
		Mean (SD)	55.47 (17.93)	48.36 (13.65)	
		Median	57.81	46.09	
		Min ; Max	33.6 ; 83.8	27.5 ; 82.8	
	%Change from baseline	Number of participants with value	9	24	

Visit		Statistics	Placebo (N=14)	Lademirsen (N=29)	Difference
		Mean (SD)	-9.72 (10.39)	-12.11 (13.70)	
		Median	-12.38	-10.17	
		Min ; Max	-24.0 ; 7.1	-33.5 ; 20.0	
		LSmean (SE)*	-10.11 (4.54)	-13.04 (2.94)	-2.93 (5.31)
		95 % CI*	(-19.38, -0.83)	(-19.06, -7.02)	(-13.80, 7.93)
		P-value for the within treatment comparison*	0.0337	0.0001	
		P-value for the difference between groups*			0.5849
Week 40	Observed value	Number of participants with value	9	20	
		Mean (SD)	50.62 (14.92)	51.65 (15.03)	
		Median	45.16	49.03	
		Min ; Max	33.3 ; 79.5	19.3 ; 77.7	
	%Change from baseline	Number of participants with value	9	20	
		Mean (SD)	-6.41 (12.50)	-9.02 (17.17)	
		Median	-0.48	-9.01	
		Min ; Max	-27.4 ; 6.1	-38.0 ; 24.2	
		LSmean (SE)*	-7.62 (5.68)	-11.48 (3.74)	-3.85 (6.73)
		95 % CI*	(-19.26, 4.01)	(-19.15, -3.81)	(-17.64, 9.94)
		P-value for the within treatment comparison*	0.1904	0.0048	
		P-value for the difference between groups*			0.5712
Week 44	Observed value	Number of participants with value	7	20	
		Mean (SD)	52.60 (14.09)	50.23 (16.30)	
		Median	46.62	46.56	
		Min ; Max	37.3 ; 75.6	18.5 ; 81.0	
	%Change from baseline	Number of participants with value	7	20	
		Mean (SD)	-4.17 (12.77)	-10.91 (15.51)	
		Median	-3.45	-10.02	
		Min ; Max	-23.4 ; 18.6	-40.8 ; 18.5	
		LSmean (SE)*	-3.02 (5.34)	-11.98 (3.39)	-8.96 (6.25)
		95 % CI*	(-13.92, 7.89)	(-18.92, -5.03)	(-21.75, 3.82)
		P-value for the within treatment comparison*	0.5763	0.0014	
		P-value for the difference between groups*			0.1623
Week 48	Observed value	Number of participants with value	9	17	
		Mean (SD)	49.52 (13.91)	48.93 (18.09)	

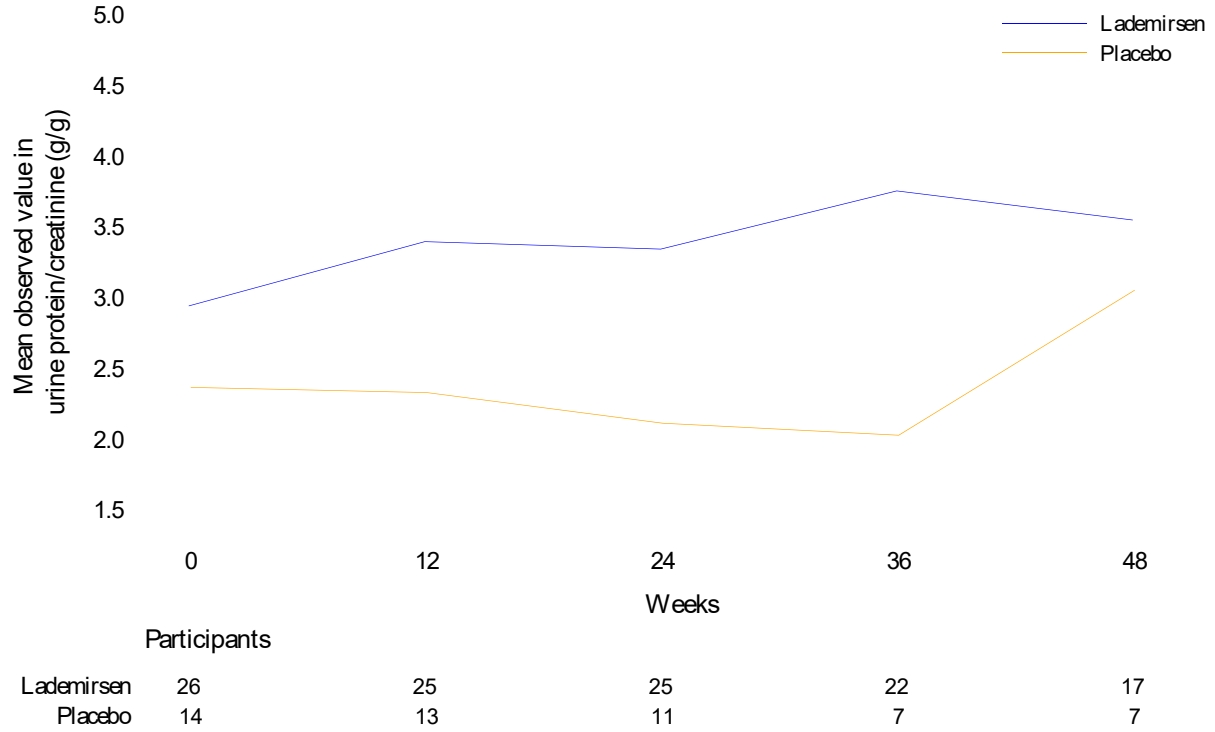
Visit		Statistics	Placebo (N=14)	Lademirsen (N=29)	Difference
		Median	49.16	44.96	
		Min ; Max	32.2 ; 73.4	17.7 ; 87.6	
	%Change from baseline	Number of participants with value	9	17	
		Mean (SD)	-8.48 (11.91)	-9.02 (17.93)	
		Median	-8.40	-11.98	
		Min ; Max	-26.4 ; 7.4	-43.2 ; 20.1	
		LSmean (SE)*	-10.05 (5.64)	-12.77 (3.79)	-2.72 (6.73)
		95 % CI*	(-21.66, 1.56)	(-20.53, -5.00)	(-16.56, 11.13)
		P-value for the within treatment comparison*	0.0869	0.0023	
		P-value for the difference between groups*			0.6899
Overall	%Change from baseline	Number of participants with value at any visit	14	29	
		LSmean (SE)*	-6.40 (3.81)	-9.80 (2.55)	-3.40 (4.46)
		95 % CI*	(-14.20, 1.40)	(-15.02, -4.58)	(-12.54, 5.74)
		P-value for the within treatment comparison*	0.1040	0.0006	
		P-value for the difference between groups*			0.4528

The * estimates are from MMRM model. % change from baseline = treatment + eGFR stratum + visit + visit x treatment. Week 12, 24, 36, 40, 44 and 48 are considered as repeated measurements.

CKD-EPI Creatinine equation (2021) is used.

PGM=PRODOPS/SAR339375/ACT16248/CSR_2022/REPORT/PGM/eff_mmrm_chg_egfr_i_t.sas
OUT=REPORT/OUTPUT/eff_mmrm_pchg_egfr_i_t_i.rtf (12DEC2022 3:28)

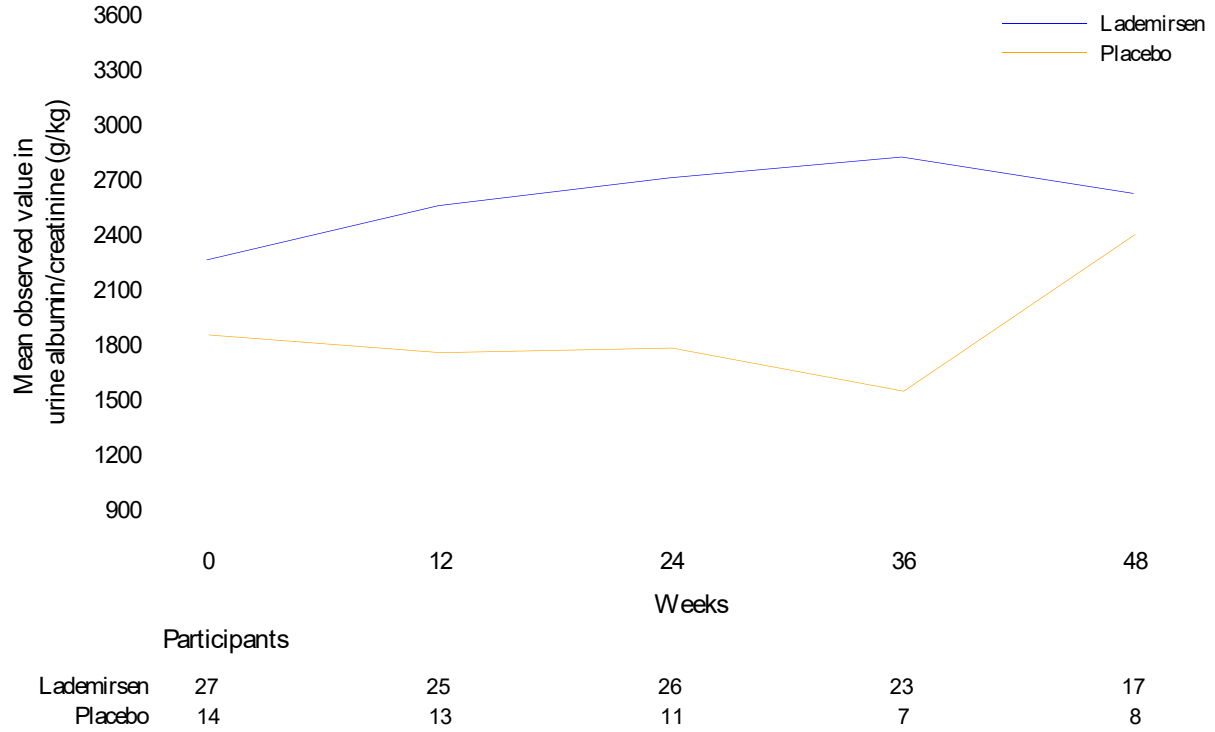
Figure 1 - Mean (+/-SE) observed value in urine protein/creatinine (g/g) over time in double-blind period - ITT population



Participants					
Lademirsen	26	25	25	22	17
Placebo	14	13	11	7	7

Cut-off date: 22-Sep-2022.
The upper and lower bounds for each time visits are mean +/- SE.
PGM=PRODOPS/SAR339375/ACT16248/CSR_2022/REPORT/PGM/pd_mean_i_f.sas
OUT=REPORT/OUTPUT/pd_mean_aval_pcr_i_f_i.rtf (12DEC2022 3:29)

Figure 2 - Mean (+/-SE) observed value in urine albumin/creatinine (g/kg) over time in double-blind period - ITT population



Cut-off date: 22-Sep-2022.
The upper and lower bounds for each time visits are mean +/- SE.
PGM=PRODOPS/SAR339375/ACT16248/CSR_2022/REPORT/PGM/pd_mean_i_f.sas
OUT=REPORT/OUTPUT/pd_mean_aval_acr_i_f_i.rtf (12DEC2022 3:29)

Table 5 - Overview of adverse event profile: Treatment-emergent adverse events in lademirsen treatment-emergent period - Lademirsen treated population

n (%)	All (N=38)
Patients with any TEAE	37 (97.4%)
Patients with any treatment emergent SAE	5 (13.2%)
Patients with any TEAE leading to death	0
Patients with any TEAE leading to dose reduction	0
Patients with any TEAE leading to permanent treatment discontinuation	4 (10.5%)
Patients with any TEAE of special interest (AESI)	11 (28.9%)

TEAE: Treatment emergent adverse event, SAE: Serious adverse event

n (%) = number and percentage of participants with at least one event

Cut-off date: 22-Sep-2022.

Only data collected since the first administration of lademirsen are included in this analysis.

n (%)	All (N=38)

PGM=PRODOPS/SAR339375/ACT16248/CSR_2022/REPORT/PGM/ae_overview_s_t.sas OUT=REPORT/OUTPUT/ae_overview_s_t3_i.rtf (12DEC2022 3:27)

Table 6 - Overview of adverse event profile: Treatment-emergent adverse events in double-blind treatment-emergent period - Safety population

n (%)	Placebo (N=14)	Lademirsen (N=29)
Patients with any TEAE	14 (100%)	29 (100%)
Patients with any treatment emergent SAE	0	2 (6.9%)
Patients with any TEAE leading to death	0	0
Patients with any TEAE leading to dose reduction	0	0
Patients with any TEAE leading to permanent treatment discontinuation	0	3 (10.3%)
Patients with any TEAE of special interest (AESI)	1 (7.1%)	6 (20.7%)

TEAE: Treatment emergent adverse event, SAE: Serious adverse event

n (%) = number and percentage of participants with at least one event

Cut-off date: 22-Sep-2022.

PGM=PRODOPS/SAR339375/ACT16248/CSR_2022/REPORT/PGM/ae_overview_s_t.sas OUT=REPORT/OUTPUT/ae_overview_s_t1_i.rtf (12DEC2022 3:27)

Pharmacokinetic results:

Summary results of lademirsen, RG0005, and SUM (lademirsen+RG0005) plasma concentrations are presented in Table 8

Table 8 – Summary of lademirsen, RG0005, and SUM (lademirsen+RG0005) plasma concentrations at 4 hours post-dose following lademirsen administration at 110 mg QW

Analyte	Statistic	4 hours post-dose[a] concentrations (ng/mL)		
		Day 1	Day 169 (Week 24)	Day 337 (Week 48)
	N	21	14	9
Lademirsen	Mean ± SD (Geometric Mean) [CV%]	2070 ± 1150 (1690) [55.4]	2180 ± 976 (1580) [44.7]	3080 ± 2170 (2590) [70.5]
RG0005	Mean ± SD (Geometric Mean) [CV%]	765 ± 524 (480) [68.4]	835 ± 441 (625) [52.8]	876 ± 460 (783) [52.5]
	Mean ± SD	2840 ± 1660	3020 ± 1410	3960 ± 2350

SUM[b] (lademirsen + RG0005)	(Geometric Mean) [CV%]	(2230) [58.6]	(2230) [46.7]	(3430) [59.2]
Additional Information: All concentrations are presented to 3 significant figures				

Abbreviations: C_{max}, maximum concentration; CV%, coefficient of variation; N, number of observations; SD, standard deviation; t_{max}, time to reach maximum concentration

a: 4 hours post-dose concentrations correspond to approximate C_{max} (based on median t_{max} in Phase 1 studies)

b: SUM concentrations (4 hours post-dose) are calculated values (sum of measured lademirsen+RG0005)

Summary results of SUM (lademirsen+RG0005) minimum plasma concentrations (Ctrough) are presented in Table-9

Table 9 – Summary of SUM (lademirsen+RG0005) minimum plasma concentrations (C_{trough}) following lademirsen administration at 110 mg QW

Time	SUM (lademirsen+RG0005)[a] concentrations (ng/mL)	
	N	Mean ± SD (Geometric mean) [CV%]
Pre-dose – Day 1[b]	16	<LLOQ ± 0.00 (NA) [NC]
C_{trough} – Day 29 (Week 4)	13	7.65 ± 3.36 (6.87) [44.0]
C_{trough} – Day 85 (Week 12)	12	12.6 ± 7.05 (11.1) [55.8]
C_{trough} – Day 169 (Week 24)	11	15.1 ± 8.65 (12.8) [57.4]
C_{trough} – Day 253 (Week 36)	7	18.6 ± 8.18 (17.2) [44.0]
C_{trough} – Day 337 (Week 48)	5	19.5 ± 10.2 (17.2) [52.3]
Additional Information: All concentrations are presented to 3 significant figures		

Abbreviations: C_{trough}, minimum concentration (concentration just before administration of next dose); CV%, coefficient of variation; LLOQ, lower limit of quantitation (LLOQ for assay used to measure SUM concentrations in pre-dose/C_{trough} samples was 0.623 ng/mL); N, number of observations; NA, not applicable; NC, not calculable

a: SUM concentrations (trough) are measured values (assay measures lademirsen+ RG0005)

b: Before first lademirsen dose

Issue date	06/Jul/2023