

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215842Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	215842
Priority or standard	STANDARD
Submit date(s)	9/30/2022
Received date(s)	9/30/2022
PDUFA goal date	9/30/2023
Division/office	Division of Cardiology and Nephrology (DCN)
Review completion date	9/29/2023
Established/proper name	Nedosiran
(Proposed) proprietary name	Rivfloza
Pharmacologic class	Small interfering RNA
Other product name(s)	DCR-PHXC
Applicant	NOVO NORDISK INC
Dosage form(s)/formulation(s)	INJECTION
Dosing regimen	Once a month subcutaneous injection: (dose expressed as free acid equivalent) (b) (4) ≥12 years (<50 kg): 128 mg ≥12 years (≥50 kg): 160 mg
Applicant-proposed indication(s)/ population(s)	The treatment of primary hyperoxaluria type 1 (PH1) in pediatric (b) (4) years of age and older) and adult patients.
SNOMED CT code for proposed indication disease term(s)¹	17901006 Primary hyperoxaluria (disorder)
Regulatory action	Approval
Approved dosage (if applicable)	Once a month subcutaneous injection: (dose expressed as free acid equivalent) 9 to <12 years (<50 kg): 3.3 mg/kg (not to exceed 128 mg) 9 to <12 years (≥50 kg): 160 mg ≥12 years (< 50 kg) : 128 mg ≥12 years (≥ 50 kg) : 160 mg
Approved indication(s)/ population(s) (if applicable)	To lower urinary oxalate levels in children 9 years of age and older and adults with primary hyperoxaluria type 1 (PH1) and relatively preserved kidney function, e.g., eGFR ≥30 mL/min/1.73 m ²
SNOMED CT code for approved indication disease term(s)¹	65520001 Primary hyperoxaluria, type 1 (disorder)

¹ For internal tracking purposes only.

Abbreviations: PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

ADA	antidrug antibodies
AE	adverse event
AGT	alanine glyoxalate aminotransferase
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ASGPR	asialoglycoprotein receptor
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
bpm	beats per minute
BSA	body surface area
CK	creatine kinase
CKD	chronic kidney disease
C _{max}	maximum plasma concentration
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
CYP	cytochrome P450
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
FAE	free acid equivalent
FDA/the Agency	Food and Drug Administration
FMQ	Food and Drug Administration Medical Dictionary for Regulatory Activities query
GalNAc	N-acetyl-D-glucosamine
GD	gestational day
GLP	good laboratory practices
HAO1	hydroxyacid oxidase 1
HI	hepatic impairment
IC ₅₀	half-maximal inhibitory concentration
ITT	intent-to-treat
LDH	lactate dehydrogenase
LDHA	lactate dehydrogenase A gene
MATE	multidrug and toxin extrusion
mITT	modified intent-to-treat
MRHD	maximum recommended human dose
mRNA	messenger ribonucleic acid
MRP	multidrug resistance-associated protein
NDA	new drug application
NOAEL	no observed adverse effect level
OAT	ornithine aminotransferase
PD	pharmacodynamic
PH1/2/3	primary hyperoxaluria type 1/2/3
PI	Prescribing Information

NDA 215842
Rivfloza (nedosiran)

PK	pharmacokinetic
Pox	plasma oxalate
Q1M	once monthly
RI	renal impairment
RNAi	ribonucleic acid interference
SAE	serious adverse event
SC	subcutaneous
siRNA	small interfering ribonucleic acid
TB	total bilirubin
TEAE	treatment-emergent adverse event
T _{max}	time to maximum concentration
ULN	upper limit of normal
UO ₂₄	24 h urinary oxalate
Uox	urinary oxalate

I. Executive Summary

1. Summary of Regulatory Action

On September 30, 2022, Novo Nordisk, Inc. submitted an original New Drug Application for Rivfloza® (nedosiran) for the treatment of primary hyperoxaluria type 1 (PH1) in adult and pediatric patients ^(b)₍₄₎ years of age and older. Nedosiran is a subcutaneously administered, synthetic, double-stranded small interfering ribonucleic acid that inhibits the messenger RNA of the lactate dehydrogenase A gene, thus reducing urinary oxalate levels.

In support of the proposed indication, the Applicant submitted the results of an adequate and well-controlled trial that enrolled 35 patients with PH1 or primary hyperoxaluria type 2 (PH2) and an estimated glomerular filtration rate ≥ 30 mL/min/1.73 m² (Study DCR-PHXC-201). The Applicant also submitted data from an ongoing single-arm extension study of Study DCR-PHXC-201 in which all patients were treated with nedosiran (Study DCR-PHXC-301), as confirmatory evidence of effectiveness.

Although the development program, as originally designed, was intended to support an indication for the treatment of both PH1 and PH2, ^(b)₍₄₎

 the Applicant proposed marketing approval only for patients with PH1.

The review team has concluded that the application provides substantial evidence of nedosiran's effectiveness in reducing urinary oxalate levels, a surrogate for important clinical manifestations of PH1, including nephrolithiasis, its related complications, and loss of kidney function in patients with relatively preserved kidney function (generally an estimated glomerular filtration rate >30 mL/min/1.73 m²). The safety database is limited because of the size of the affected population but does not raise significant concerns and is acceptable in the context of this rare disease. As such, the review team believes the data provide compelling evidence of a benefit that outweighs the risks and recommends approval, and the signatory authority agrees. Given that the study did not enroll participants less than 9 years of age, the indication will be limited to patients 9 years of age and older with PH1.

Although the Agency did not object to the Applicant's proposal to assess the efficacy of nedosiran using a primary efficacy endpoint of area under the concentration-time curve for percentage change from Baseline in 24 h urinary oxalate from study Days 90 to 180, such an endpoint may not be easily understood by prescribers of nedosiran. Therefore, information will also be included in labeling on the least-squares mean percentage change from Baseline in 24 h urinary oxalate excretion (corrected for body surface area in patients <18 years of age) averaged over Days 90, 120, 150, and 180.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	- Primary hyperoxaluria type 1 (PH1) is a rare, serious disease that often manifests in childhood or adolescence. - PH1 is caused by an inherited deficiency of the liver enzyme alanine-glyoxylate aminotransferase (AGT), which leads to overproduction of oxalate by the liver. - Patients with PH1 have recurrent kidney stones and can have deposition of calcium in the kidneys (nephrocalcinosis), leading to a loss of kidney function. As kidney function declines, oxalate accumulates in the body and deposits in other tissues, leading to systemic manifestations, including arrhythmias and cardiac arrest, gangrene, bone/joint pain and fractures, blindness, peripheral neuropathy, dental abnormalities, skin and subcutaneous nodules, plaques, ulceration, pancytopenia, and hypothyroidism.	PH1 is a rare, serious genetic disease that usually presents in childhood with recurrent kidney stones and complications thereof including infection, pain, and urinary tract obstruction. Manifestations of more advanced disease include kidney failure, bone and joint abnormalities, cardiac arrhythmias and arrest, blindness, peripheral neuropathy, dental abnormalities, skin and subcutaneous nodules, plaques, ulceration, pancytopenia, and hypothyroidism.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	• Lumasiran is approved to lower urinary and plasma oxalate levels in pediatric and adult patients with PH1. Urinary oxalate is a surrogate for kidney stones and loss of kidney function in patients with PH1 with relatively preserved kidney function (estimated glomerular filtration rate [eGFR] >30 mL/min/1.73 m² or serum creatinine within normal for patients <12 months of age) and plasma oxalate is a surrogate for the systemic manifestations of PH1 in patients with an eGFR <30 mL/min/1.73 m² including patients on hemodialysis. • Pyridoxine may reduce hepatic oxalate production in patients with certain genetic mutations. • Patients are treated with high fluid intake and medications such as citrate and magnesium to reduce calcium oxalate crystallization, though many progress despite these interventions. • Liver transplant replaces the missing AGT enzyme and is essentially curative but is associated with substantial morbidity.	There is an unmet need for additional therapies to treat PH1. Nedosiran targets a different enzyme than the currently approved lumasiran.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	- To establish benefit, the Applicant primarily relied upon the results of an adequate and well-controlled trial (Study DCR-PHXC-201) that enrolled 35 patients with PH1 or PH2 and an eGFR ≥ 30 mL/min/1.73 m². (b) (4) - the Applicant proposed marketing approval only for patients with PH1. - Study DCR-PHXC-201 met its primary endpoint (the area under the concentration-time curve for percentage change from Baseline in 24 h urinary oxalate from study Days 90 to 180) in the overall trial population, with a statistically persuasive p-value ($p < 0.0001$). - Among the patients with PH1, the mean change from baseline in 24 h urinary oxalate levels averaged over Days 90, 120, 150, and 180 was -50% with nedosiran compared to 6% with placebo (treatment difference -56%; 95% confidence interval [CI] -80%, -33%), reflecting a substantial reduction in urinary oxalate levels with nedosiran. - In an exploratory analysis in the overall population, eGFR decreased at a rate of 1.1 mL/min/1.73 m²/month in the placebo group and 0.35 mL/min/1.73 m²/month in the nedosiran group for a between-group difference of -0.75 mL/min/1.73 m²/month (95% CI -2.1, 0.6). The percentage change in the number of measurable kidney stones on ultrasound in the overall population from baseline to Day 180 was assessed as an exploratory endpoint and showed no difference between the two arms.	Nedosiran substantially reduces 24 h urinary oxalate levels in participants with PH1. Given the pathophysiology of PH1 and the available epidemiologic data, the effects on urinary oxalate are expected to translate to benefits on kidney stone events and kidney function. Given that calcium oxalate stones are slow to form and pass, and the rate of loss of kidney function in the population, such effects were not established nor were they expected over the relatively short duration of followup. Nedosiran will add another treatment option for patients ≥ 9 years of age with PH1 and relatively preserved kidney function.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	After 6 months of treatment in Study DCR-PHXC-201, patients could enroll in an ongoing single-arm extension study, DCR-PHXC-301, in which all patients were treated with nedosiran. Among the eight patients randomized to placebo in DCR-PHXC-201 who received nedosiran for 6 months in DCR-PHXC-301, 24 h urinary oxalate decreased from a mean of 1872 $\mu\text{mol/day}$ (95% CI: 851, 2894) at the end of DCR-PHXC-201 to 816 $\mu\text{mol/day}$ (95% CI: 591, 1042), reflecting a mean percent decrease of 46% (95% CI: 24%, 67%). The reduction in urinary oxalate was maintained in the 13 patients with PH1 who received nedosiran in DCR-PHXC-201 and received an additional 6 months of treatment in Study DCR-PHXC-301.	
Risk and risk management	- Nedosiran was generally well-tolerated; however, the safety database was small and of limited duration. - The most common adverse events were injection site reactions, which occurred throughout the study period, were generally mild, and did not lead to treatment discontinuation.	The safety database is acceptable in the context of this rare disease. Nedosiran was well-tolerated. Risks were generally mild and included injection site reactions. There were no apparent significant or irreversible toxicities.

2.2. Conclusions Regarding Benefit-Risk

Data from DCR-PHXC-201 demonstrate that nedosiran leads to a meaningful decrease in 24 h urinary oxalate levels in participants with PH1 and relatively preserved kidney function. Given this size of the treatment effect and knowledge of the pathophysiology of the disease, these findings are expected to translate to a benefit on important clinical manifestations of the disease, including nephrolithiasis, related complications, and loss of kidney function. Approval is supported for patients down to 9 years of age based on the population enrolled in the study. The most common risk was injection site reactions, which were generally mild, and did not lead to treatment discontinuation. There were no other apparent significant or irreversible toxicities. As such, the benefits outweigh the risks.

II. Interdisciplinary Assessment

3. Introduction

Disease Background

Primary hyperoxaluria type 1 (PH1) is the most common and severe type of primary hyperoxaluria, a group of rare genetic inborn errors of hepatic glyoxylate metabolism characterized by overproduction of oxalate by the liver. To date, three types of PH have been described, defined by the affected gene. PH1 accounts for 70 to 80% of PH cases and is caused by recessively inherited mutations in the alanine-glyoxylate aminotransferase gene, which lead to a deficiency of the hepatic peroxisomal enzyme alanine glyoxylate aminotransferase (AGT). Under normal circumstances, AGT catalyzes the conversion of glyoxylate to glycine. AGT deficiency results in accumulation of glyoxylate, which is rapidly metabolized to oxalate, a poorly soluble organic acid that is excreted by the kidneys.

In patients with PH1, oxalate binds to calcium, saturates the urine with calcium oxalate, and deposits in various parts of the kidneys, leading to the primary clinical manifestations of the disease. Patients present, usually in childhood, with symptoms and sequelae of calcium oxalate crystalluria, recurrent urolithiasis, urinary tract infections, nephrocalcinosis, kidney scarring, and eventual kidney failure. As kidney function declines, urinary excretion of oxalate decreases and oxalate accumulates in the body, leading to systemic oxalosis, a debilitating condition that can cause arrhythmias, cardiac arrest, gangrene, bone and joint pain, reduced mobility, fractures, blindness, peripheral neuropathy, dental abnormalities, skin and subcutaneous nodules, plaques, ulceration, pancytopenia, and hypothyroidism. When moderate to severe kidney failure develops, patients require combined or sequential liver and kidney transplant, often preceded by a period on intensive dialysis.

To date, one therapy has been approved for the treatment of PH1. On November 23, 2020, FDA approved lumasiran to lower urinary oxalate levels, a surrogate for kidney stones and loss of kidney function, in pediatric and adult patients with PH1 who have relatively preserved kidney function. Lumasiran is a small interfering ribonucleic acid (siRNA) that reduces levels of the glycolate oxidase enzyme by targeting the hydroxyacid oxidase 1 (HAO1) messenger ribonucleic acid (mRNA) in hepatocytes. On October 6, 2022, lumasiran was also approved to lower plasma oxalate, a surrogate for systemic manifestations of PH1, in patients with more advanced kidney disease.

Other general measures that are used in patients with PH1 include increased fluid intake to maintain a brisk flow of dilute urine as well as the administration of agents such as citrate and magnesium supplements to increase urinary oxalate solubility. Pyridoxine, a coenzyme of AGT, is variably effective in some genotypes that result in mislocalization of AGT within the hepatocyte. Liver transplant is curative but is associated with significant morbidity.

Nedosiran

Nedosiran is a subcutaneously administered, synthetic, double-stranded siRNA conjugated to an N-acetyl-D-galactosamine (GalNAc) ligand. The ligand is designed to target delivery to hepatocytes via asialoglycoprotein receptors (ASGPRs). The siRNA inhibits the mRNA of the LDHA gene, which encodes LDH, the enzyme that metabolizes glyoxylate to oxalate. Suppression of LDH should, therefore, reduce hepatic oxalate production, in turn reducing oxaluria and its sequelae.

Urinary Oxalate as a Surrogate for Clinical Outcomes in PH1

Although the manifestations of PH1 can be serious, calcium oxalate stones are slow to form and pass, and loss of kidney function is generally gradual. Given the rarity of the disease, it would be challenging to detect effects on clinical events over the course of a feasible development program. As such, the nedosiran development program was designed to assess effects on urinary oxalate excretion. Support for the use of urinary oxalate as a surrogate for clinical outcomes in PH1 was based primarily on:

1. Knowledge of the pathophysiology of the disease and the causal role of urinary oxalate in kidney stone formation, nephrocalcinosis, and loss of kidney function;
2. Epidemiologic data showing an association between urinary oxalate and loss of kidney function, particularly in patients with high levels of urinary oxalate; and
3. Observational data from patients treated with pyridoxine or liver transplant showing associations between reductions in urinary oxalate and preservation of kidney function.

During discussions of the design of the trial, the Agency expressed a willingness to accept a substantial change in urinary oxalate in patients with high baseline levels as a basis for full approval. As previously noted, another siRNA, lumasiran, was approved in 2020 to lower urinary oxalate levels in pediatric and adult patients with PH1 with relatively preserved kidney function based on such an effect.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Interpretability of AUC (Area Under Curve) as a Descriptor of Efficacy

3.1.2. Key Safety Review Issues

No finding rose to the level of a key safety review issue.

3.2. Approach to the Clinical Review

The clinical review focused on Study DCR-PHXC-201, which provides the primary support for efficacy for the proposed indication in patients (b)(4) years of age and older, and Study DCR-PHXC-301, which provides confirmatory evidence of effectiveness. Safety analyses also focused on these trials. [Table 3](#) provides an overview of these trials.

Table 3. Clinical Studies/Trials Submitted in Support of Efficacy and/or Safety Determinations¹ for Nedosiran

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	No. of Patients Planned; Actual Randomized	No. of Centers and Countries
201	Patients with PH1 or PH2	Control type: Placebo concurrent Randomization: Adaptive randomization Blinding: Double-blind Biomarkers: No biomarkers Innovative design features: None	Drug (established name): Nedosiran Dose: 170 mg (adults/adolescents weighing ≥50 kg) 136 mg (adults/adolescents weighing <50 kg) Number treated: 23 Duration (quantity and units): 6 months, 1 dose/month	Primary: AUC from Day 90 to Day 180, based on percent change from Baseline in 24 h Uox Secondary: The proportion of participants with a 24 h Uox level <0.46 mmol/24 h or 0.46 to <0.60 mmol/24 h (adjusted per 1.73 m ² BSA in participants aged <18 years) on at least 2 consecutive visits, beginning with Day 90	Planned: 36 Actual: 35	Centers: 19 Countries: 11
301	Patients with PH1, PH2, or PH3	Control type: No treatment concurrent (single-arm) Randomization: No randomization Blinding: Open-label Biomarkers: No biomarkers Innovative design features: None	Drug (established name): Nedosiran Dose: 170 mg (adults/adolescents weighing ≥50 kg) 136 mg (adults/adolescents weighing <50 kg) Number treated: 51 Duration (quantity and units): up to 36 months, 1 dose/month	Primary: not reported Secondary: not reported	Planned: NA Actual: None	Centers: 18 Countries: 11

Source: Clinical Study Report and adsl.xpt.

¹ Includes all submitted clinical trials, even if not reviewed in-depth, except for Phase 1 and pharmacokinetic studies.

Abbreviations: AUC, area under curve; BSA, body surface area; PH1, primary hyperoxaluria 1; PH2, primary hyperoxaluria 2; PH3, primary hyperoxaluria 3; Uox, urinary oxalate

4. Patient Experience Data

The Applicant collected information about patient quality of life and impact on caregivers ([Table 4](#)). The experiences and perspectives shared by patients and caregivers during an Externally-led Patient Focused Drug Development meeting hosted by the Oxalosis and Hyperoxaluria Foundation on October 5, 2020, and the publications listed in [Table 4](#) also informed the benefit-risk assessment.

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical Outcome Assessment Data Submitted in the Application		
☒	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☒	Perspectives shared at patient stakeholder meeting	
☒	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☒	Other: Publications	
	1. Lawrence and Wattenberg (2020)	
	2. Milliner et al. (2020)	

Source: Data provided in Application, Externally-led Patient Focused Drug Development meeting hosted by the Oxalosis and Hyperoxaluria Foundation on October 5, 2020, and published literature.

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

5.1.1. Primary Pharmacology

Nedosiran is a dicer-substrate siRNA oligonucleotide conjugated with GalNAc amino sugar residues for preferential uptake by hepatocytes via the asialoglycoprotein receptor (ASGPR). The antisense strand for nedosiran is designed to target LDHA mRNA via the RNA interference (RNAi) pathway, thereby reducing the levels of LDHA mRNA and LDH protein, leading to decreased production of oxalate by the liver.

The pharmacological characteristics of nedosiran were studied in cynomolgus monkeys and mice to assess on-target and off-target hybridization effects, respectively. The target sequence of nedosiran in LDHA mRNA is conserved in humans and nonhuman primates, but not in mice; thus, nedosiran is fully active in cynomolgus monkeys but inactive in mice. The effects of knockdown of LDHA mRNA were also assessed in genetically or chemically induced mouse models of PH using the pharmacologically active mouse-specific analog DCR-m355.

5.1.2. Proof of Concept for Efficacy in Animal Models

The nonclinical pharmacology data support proof of concept, as well as the dosing regimen of nedosiran that was evaluated in the clinical studies based on the following data:

- Administration of nedosiran to mice expressing human LDHA mRNA by an adeno-associated virus system resulted in a significant reduction of LDHA mRNA. A single subcutaneous (SC) dose of 1 to 6 mg/kg resulted in reduction of LDHA mRNA by approximately 90% for a 4-week duration, with recovery towards baseline by Week 6 postdose. The long duration of action of nedosiran indicates sustained silencing of LDHA mRNA and provides a rationale for the clinical dosing frequency of once every 4 weeks.
- A single SC dose of nedosiran 1 or 3 mg/kg to cynomolgus monkeys reduced LDHA mRNA expression by 29% and 72%, respectively, indicating that a single low dose of 1 mg/kg is a potentially effective dose.
- No age-related differences in the level of expression of ASGPR mRNA were observed in human liver from 0 to 2-year-olds versus adults, indicating that the relative uptake of the GalNAc-conjugated siRNA in the liver is unlikely to be affected by age.

- In a mouse model of PH1 with knockout of the alanine-glyoxylate aminotransferase gene involved in limiting glyoxylate oxidation to oxalate, administration of the mouse active analog of nedosiran (DCR-m355) at doses of 0.5, 1, and 5 mg/kg caused dose-dependent suppression of hepatic LDH protein, which correlated with a reduction in the urinary oxalate-to-creatinine ratio, indicating that inhibition of hepatic LDHA mRNA expression reduced oxalate production.
- Administration of DCR-m355 (5 mg/kg) to mice subjected to running on a treadmill resulted in reduced expression of LDHA mRNA in the liver, with no effect on skeletal muscle LDHA mRNA expression or changes in measures of skeletal muscle LDHA isozyme activity as assessed using circulating lactate, pyruvate and creatine kinase levels, thus demonstrating selective knockdown of liver LDHA mRNA.

5.2. Clinical Pharmacology / Pharmacokinetics

Table 5. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information						
	Pharmacologic Activity						
Established pharmacologic class (EPC)	Nedosiran is a lactate dehydrogenase A (LDHA)-directed small interfering ribonucleic acid (siRNA) indicated for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary oxalate levels in pediatric and adult patients.						
Mechanism of action	Nedosiran is a double-stranded siRNA that reduces production of oxalate by the liver by targeting LDHA messenger ribonucleic acid (mRNA) via the RNA interference pathway.						
Active moieties	Nedosiran						
QT prolongation	Safety pharmacology studies in monkeys did not demonstrate QT or QTc (Bazett's; QTcB) prolongation after three subcutaneous repeat doses of 30 and 300 mg/kg administered on Days 1, 4, and 10, respectively. The IC ₅₀ for the inhibitory effect of nedosiran on human ether-a-go-go (hERG) potassium current is estimated to provide a safety margin of >390-fold compared to the unbound maximum plasma concentration (C _{max}) values in patients receiving the maximum recommended dose (160 mg once monthly) of nedosiran. Exposures achieved after clinical doses of nedosiran are not expected to produce meaningful hERG-related QT prolongation.						
General Information							
Bioanalysis	Nedosiran concentrations in the plasma and urine were measured using a validated anion-exchange high performance liquid chromatography (AEX-HPLC) method with a quantification range of 1 to 2000 ng/mL. Urinary oxalate was measured using an enzymatic oxidation-based colorimetric method with a quantification range of 50-2000 µmol/L. The performance of bioanalytical methods and the results of quantification were acceptable.						
Healthy participants versus patients	The exposures (area under the concentration-time curve from time 0 to the last observed concentration [AUC _{0-last}] and C _{max}) in participants with PH1 were 1.3 to 1.6-fold higher compared to healthy participants after single doses of 1.5, 3, and 6 mg/kg						
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	<table> <tr> <th>Parameter</th><th>Mean (percentage coefficient of variation [CV])^a</th></tr> <tr> <td>AUC_(0-T) (h·ng/mL)</td><td>14,700 (36.0)</td></tr> <tr> <td>C_{max} (ng/mL)</td><td>607 (52.5)</td></tr> </table> ^a Population pharmacokinetic (PK) prediction for monthly dosing of 170 mg in adolescents/adults	Parameter	Mean (percentage coefficient of variation [CV]) ^a	AUC _(0-T) (h·ng/mL)	14,700 (36.0)	C _{max} (ng/mL)	607 (52.5)
Parameter	Mean (percentage coefficient of variation [CV]) ^a						
AUC _(0-T) (h·ng/mL)	14,700 (36.0)						
C _{max} (ng/mL)	607 (52.5)						

NDA 215842
Rivfloza (nedosiran)

Characteristic	Drug Information
Range of effective dose(s) or exposure	Doses that were evaluated were either body weight based (3.3 mg/kg in 9 to 11-year-olds) or weight band-based in adolescents and adults (160 mg for ≥50 kg and 128 mg for <50 kg) and targeted near-complete inhibition of oxalate production in the liver. With the above dosing, 24 h urinary oxalate was reduced by a placebo-adjusted least-squares mean average (standard error [SE]) of 59% (11%) from Baseline in PH1 participants in Study DCR-PHXC-201
Maximally tolerated dose or exposure	A maximum tolerated dose (MTD) was not determined. The highest tested clinical dose was 12 mg/kg (single ascending dose in healthy participants, Study DCR-PHXC-101)
Dose proportionality	Nedosiran exhibited a dose-proportional increase in plasma exposure following single subcutaneous doses from 1.5 to 6.0 mg/kg (Study DCR-PHXC-103)
Accumulation	No accumulation in plasma is observed with once-monthly dosing
Time to achieve steady state	Maximal reduction in mean urinary oxalate from baseline was achieved between 3 to 4 months with once monthly dosing
Bridge between to-be-marketed and clinical trial/study formulations	The to-be-marketed formulations – a vial (0.5 mL) and a prefilled syringe (0.8 mL or 1 mL) – were used for subcutaneous administration in the clinical trials
Absorption	
T _{max}	6 h (range 2 to 12 h)
Distribution	
Volume of distribution	126 L (Apparent Vz/F)
Plasma protein binding	Plasma protein binding is expected to be greater than 86% at clinically relevant concentrations. Binding was determined as 86% at 5 µg/mL, while binding decreased at 10 and 20 µg/mL to 74% and 51%, respectively. Binding was not assessed at clinically relevant concentrations of nedosiran below 1.5 µg/mL due to technical issues related to detection of very low unbound concentrations.
Drug as substrate of transporters	Nedosiran was not a substrate for uptake or efflux transporters
Elimination	
Mass balance results	A human radiolabeled absorption, distribution, metabolism, excretion study was not conducted due to the risk of prolonged residence time in liver. Following administration of 5 mg/kg [3H]-nedosiran to mice, the distribution of radioactivity was predominately to the liver and the urinary bladder (liver uptake and renal elimination).
Clearance	5.7 L/h (CL/F)
Half-life	The terminal plasma half-life of nedosiran was 15 h
Metabolic pathway(s)	Nedosiran was not identified to be a substrate for cytochrome P450 (CYP) enzymes
Primary excretion pathways (% dose)	22-35% of nedosiran was excreted unchanged in urine over the nedosiran dose range of 1.5 to 6 mg/kg in participants with PH1

Characteristic	Drug Information
<i>Intrinsic Factors and Specific Populations</i>	
Body weight	The dosing is once-monthly (Q1M) based on weight bands and body weight. For adults and adolescents (≥12 years) weighing ≥50 kg and <50 kg, the Q1M dose is 160 mg and 128 mg, respectively. (b) (4)
Age	The youngest patient enrolled in the trials was ~9 years old. Based on population PK/pharmacodynamics (PD) modeling, age was not a significant covariate that influenced the PK or the PD response to nedosiran in the age range of 9 years and older. Dose adjustment is not needed based on age in this age range.
Renal impairment	No dosage adjustment is needed for patients with mild or moderate impairment of renal function. The efficacy of nedosiran is not established in patients with severe renal impairment.
Hepatic impairment	No dosage adjustment is needed for patients with mild impairment of hepatic function. Nedosiran was not studied in patients with moderate or severe impairment of hepatic function.
<i>Drug Interaction Liability (Drug as Perpetrator)</i>	
Inhibition/induction of metabolism	Nedosiran did not show any direct or time-dependent inhibition of any of the major CYP enzymes in vitro at clinically relevant concentrations. Nedosiran did not induce CYP1A2, 2B6 or 3A4 at clinically relevant concentrations.
Inhibition/induction of transporter systems	Nedosiran was not an inhibitor of uptake or efflux drug transporters.
<i>Immunogenicity</i>	
Bioanalysis	Antidrug antibodies (ADA) to nedosiran were detected using a validated enzyme-linked immunosorbent assay. This method used an aliquot of 30 µL of human serum with an assay minimum required dilution of 1:10.
Incidence	There was no treatment-emergent ADA among the 59 patients tested with the ADA assay. Three patients tested positive for ADA at screening and one of them continued to have ADA titers, which continually decreased during the 12-month treatment period.
Clinical impact	There were no differences observed in the PK, PD response, and safety of nedosiran in patients that tested-positive for ADA at screening.

Source: Module 2.7.2 Summary of Clinical Pharmacology Studies; Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods.

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

The Applicant proposed the dosing regimen for adults and pediatric patients ^(b)₍₄₎ years of age and older shown in [Table 6](#).

Table 6. Applicant-Proposed Dosing Regimen for Patients ^(b)₍₄₎ Years of Age and Older

Age	Body Weight	Dosing Regimen
Adults and adolescents 12 years and older	Greater than or equal to 50 kg	160 mg once monthly (Pre-filled Syringe, 1.0 mL)
	Less than 50 kg	128 mg once monthly (Pre-filled Syringe, 0.8 mL)
^(b) ₍₄₎		

Source: Proposed-uspi, Table 1.
The dose level in mg refers to nedosiran free base weight.

In the randomized, placebo-controlled, double-blind PHYOX2 study in pediatric and adult patients with PH1 and PH2 9 to 46 years of age, 23 participants received the proposed dosing regimen, which, as discussed elsewhere in this review, demonstrated an acceptable efficacy and safety profile.

A population pharmacokinetics (PK) model was developed based on a dataset containing plasma nedosiran concentrations from Studies DCR-PHXC-101, DCR-PHXC-102, DCR-PHXC-103, DCR-PHXC-201, and DCR-PHXC-301, representing a total of 143 participants 9 to 73 years of age, weighing 31.8 kg to 132 kg. Given that maturation of kidney and hepatic function is close to completion at 6 years of age, and that a maturation function for estimated glomerular filtration rate (eGFR) was included in the population PK model simulation, the nedosiran PK profile estimated by the model down to 6 years of age is considered acceptable.

The population PK model simulation showed the three groups (patients ≥ 12 years of age with body weight ≥ 50 kg, patients ≥ 12 years of age with body weight < 50 kg, and pediatric patients aged 6 to < 12 years of age) achieved a similar nedosiran area under the concentration-time curve (AUC) at steady state with the proposed dosing regimen. The steady-state maximum plasma concentration ($C_{\max}$) appeared to be 76% higher in pediatric patients 6 to < 12 years of age (estimated median $C_{\max}$ of 896 ng/mL) compared with that in patients ≥ 12 years of age with body weight ≥ 50 kg (estimated median $C_{\max}$ of 510 ng/mL). Of note, in the Phase 1 Study DCR-PHXC-101, no concerning findings were seen in three healthy volunteers who received a single nedosiran dose of 12 mg/kg, which resulted in an arithmetic mean $C_{\max}$ over 4010 ng/mL (over two-fold higher than the maximum estimated steady state $C_{\max}$ [approximately 1500 ng/mL] in pediatric patients 6 to < 12 years of age with the proposed dosing regimen). As discussed elsewhere in this review, data from clinical studies conducted in patients with PH have also not identified any major safety concerns for nedosiran. The higher pediatric $C_{\max}$ is within a safe range identified in nonclinical studies. In addition, a new dose cap of 128 mg proposed by the review team for pediatric patients 6 to < 12 years of age could attenuate the increased $C_{\max}$ for pediatric patients. Hence, the higher estimated $C_{\max}$ at steady state for pediatric patients 6 to 12 years of age is not considered a major safety concern.

To further support dose selection, a population PK/PD model was developed based on data from 46 participants with PH1 in Studies DCR-PHXC-101, DCR-PHXC-201, and DCR-PHXC-301. The 46 participants were between 9 to 46 years of age (only 1 pediatric participant [a 9-year-old] was < 12 years of age), with body weight ranging from 35 kg to 116 kg. The covariate analysis did not reveal any statistically significant covariate effects. Because no patient < 9 years of age was included in the PK/PD model development, the effect of age on the PK/PD relationship in pediatric patients below 9 years of age remains uncertain. PK/PD model simulations indicate that the proposed dosing regimen results in a similar 24 h U_{ox} response in participants ≥ 12 years of age with body weight ≥ 50 kg, participants ≥ 12 years of age with body weight < 50 kg, and pediatric participants aged 9 to < 12 years of age. See [Section 14.5](#) for details.

Conclusions on the Proposed Dosing Regimen

Because the PK/pharmacodynamics (PD) model development did not include data from pediatric patients below 9 years of age, the effect of age on the PK/PD relationship is unknown for the age group 6 to < 9 years of age. (b) (4)

[REDACTED]

The review team also recommends including an additional dose cap at 128 mg for pediatric patients 9 to < 12 years of age and body weight < 50 kg to prevent a potential decrease in dose when 11-year-old patients who weigh < 50 kg turn 12 years of age. The PKPD simulations also confirmed that the dose cap of 128 mg would not compromise efficacy in patients 9 to < 12 years of age weighing < 50 kg (see [Section 14.6](#)).

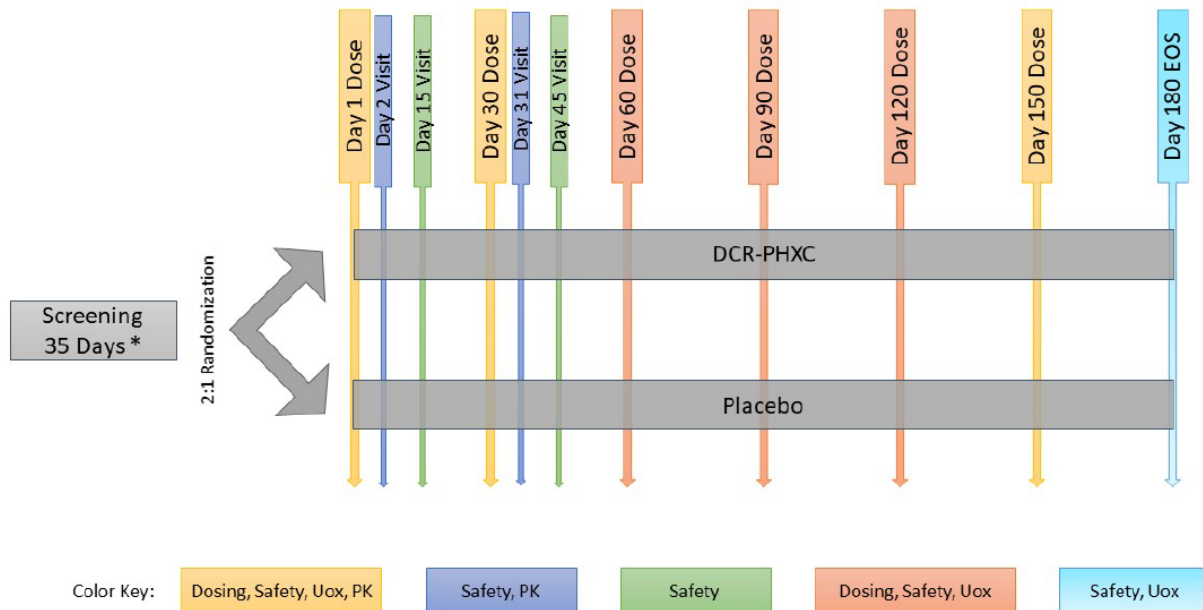
6.2. Clinical Studies/Trials Intended to Demonstrate Efficacy

6.2.1. Study DCR-PHXC-201

6.2.1.1. Design, DCR-PHXC-201

Trial DCR-PHXC-201 (Study 201), summarized in [Table 3](#) was a 6-month, parallel-group, double-blind, placebo-controlled, multicenter trial that randomized 35 participants with primary hyperoxaluria 1 (PH1) or 2 (PH2) in a 2:1 ratio to nedosiran or placebo. Randomization was adaptive, with randomization ratios determined during enrollment stratified by age (6 to 11, 12 to 17, or ≥ 18 years of age) and baseline eGFR (<45 or ≥ 45 mL/min/1.73 m²). The primary endpoint was the area under the curve for the percentage change from Baseline in 24 h urinary oxalate (Uox) from Days 90 to 180 (Days 90 to 180), normalized by body surface area (BSA) if patients were less than 18 years of age. The overall schema for the study is provided in [Figure 1](#).

Figure 1. Schema for Study 201



* An additional 7 days of screening may be added for participants who require repeated 24-hour urine collections or for repeat of initially unanalyzable screening laboratory test samples.

Abbreviations: EOS = end of study; PK = pharmacokinetics; Uox = urinary oxalate

Source: Figure 1 of the Clinical Study Report.

6.2.1.2. Eligibility Criteria, DCR-PHXC-201

Inclusion Criteria

For inclusion in Study 201, patients were required to fulfill all of the following criteria:

1. At least 6 years of age, at the time of signing the informed consent/assent.
2. Documented diagnosis of PH1 or PH2, confirmed by genotyping (historically available genotype information was acceptable for study eligibility).
3. Twenty-four-hour Uox excretion ≥ 0.7 mmol (adjusted per 1.73 m^2 BSA in participants < 18 years of age) in both collections performed in the screening period. At least 12 participants must have had at least one 24 h Uox excretion ≥ 1.6 mmol (adjusted per 1.73 m^2 BSA in participants aged < 18 years).
4. Less than 20% variation between the two 24 h urinary creatinine excretion values obtained during screening. Individuals who did not achieve $< 20\%$ variation between the two screening values may have undergone a second round of urine collection. An extra seven calendar days could have been added to the screening window for participants to complete a second urine collection. If potential participants again failed to achieve the within-20% variation, they were excluded from participation.
5. eGFR at Screening $\geq 30 \text{ mL/min/1.73 m}^2$.
6. Male participants:
 - a. A male participant with a female partner of childbearing potential must have agreed to use contraception during the treatment period and for at least 12 weeks after the last dose of study intervention and refrain from donating sperm during this period.
7. Female participants:
 - a. Not pregnant, not breastfeeding, and at least one of the following conditions applied:
 - b. Not of childbearing potentialOR
 - c. Of childbearing potential who agreed to follow the contraceptive guidance of the protocol during the treatment period and for at least 12 weeks after the last dose of study intervention

Exclusion Criteria

Patients were excluded if they met any of the following criteria:

1. Had a prior renal or hepatic transplantation, or planned transplantation within the study period.
2. Was receiving dialysis, or anticipated requirement for dialysis during the study period.
3. Plasma oxalate (Pox) $> 30 \text{ } \mu\text{mol/L}$.
4. Documented evidence of clinical manifestations of systemic oxalosis (including preexisting retinal, heart, or skin calcifications, or history of severe bone pain, pathological fractures, or bone deformations).

5. Presence of any condition or comorbidities that would have interfered with study compliance or data interpretation or potentially impacted patient safety including, but not restricted to:
 - a. Severe intercurrent illness
 - b. Known causes of active liver disease/injury or transaminase elevation (e.g., alcoholic liver disease, nonalcoholic fatty liver disease/steatohepatitis)
 - c. Physician concerns about intake of drugs of abuse or excessive alcohol intake, or history of excessive alcohol intake in the 2 years prior to enrollment
 - d. History of serious mental illness that included, but was not limited to, schizophrenia, bipolar disorder, or severe depression requiring hospitalization or pharmacological intervention
 - e. Clinically relevant history or presence of cardiovascular, respiratory, gastrointestinal, hematological, lymphatic, neurological, musculoskeletal, genitourinary, immunological diseases, including dermatological (e.g., rash, severe eczema or dermatitis), or connective tissue diseases or disorders.
6. Use of an RNAi drug within the last 6 months.
7. History of one or more of the following reactions to an oligonucleotide-based therapy:
 - a. Severe thrombocytopenia (platelet count $\leq 100,000/\mu\text{L}$)
 - b. Hepatotoxicity, defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $> 3\text{x}$ the upper limit of normal (ULN) and total bilirubin $> 2\text{x}$ ULN or international normalized ratio > 1.5
 - c. Severe flu-like symptoms leading to discontinuation of therapy
 - d. Localized skin reaction from the injection (graded severe) leading to discontinuation of therapy
 - e. Coagulopathy/clinically significant prolongation of clotting time.
8. Participants receiving pyridoxine, an unapproved standard of care for patients with PH1, must have been at a stable dose for at least 4 weeks prior to Day 1 and must have been willing to remain on the same stable dose throughout the study.
9. Participation in any clinical study in which they received an investigational medical product within 4 months before Screening. For investigational medical products with the potential to reduce urine and/or Pox concentrations, these concentrations must have returned to historical baseline levels prior to Screening and Diagnostic assessments.
10. Liver test abnormalities: ALT and/or AST $> 1.5\text{x}$ ULN for age and gender.
11. Positive screening for hepatitis B surface antigen, hepatitis C virus antibodies, or human immunodeficiency virus-1 or -2 antibodies. If a participant had been tested in the past 3 months, medical record documentation of this testing could have been used for screening. Viral serology testing was not required in participants < 18 years of age.
12. Positive urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, and benzodiazepines). Investigator discretion was allowed. Urine drug screening was not required in participants ≤ 12 years of age.
13. Known hypersensitivity to nedosiran, or any of its ingredients.
14. Inability or unwillingness to comply with the specified study procedures, including collection of 24 h urine samples.

6.2.1.3. Statistical Analysis Plan, DCR-PHXC-201

The primary endpoint and associated analyses in the final statistical analysis plan, dated July 16, 2021, were consistent with those proposed earlier in the protocol, finalized on August 13, 2020. (b) (4)

See “Interpretability of Results for PH2” for further discussion.

Primary Endpoint

The primary endpoint, 24 h Uox AUC of percentage change from Baseline calculated from Uox data collected on Days 90, 120, 150, and 180, was analyzed using analysis of covariance with fixed effects for age category, eGFR category, and baseline 24 h urinary oxalate.

Secondary Endpoints

The key secondary endpoint was the percentage of patients with normal or near-normal Uox.¹ Other secondary endpoints included the percentage change in the summed surface area and number of kidney stones on kidney ultrasound from Baseline to Day 180, percentage change from baseline Pox on Day 180, and the rate of change in estimated glomerular filtration rate. Percentage normal or near-normal Uox was analyzed using Fisher’s exact test, change from baseline oxalate was analyzed using the exact Wilcoxon two-sample test, and rate of change in eGFR was analyzed using mixed model repeated measures with a different intercept and slope for each patient. To control type 1 error, analyses were conducted in a hierarchy ordered in the following sequence:

1. AUC from Day 90 to Day 180, based on percentage change from Baseline in 24 h Uox,
2. proportion of participants with a normalization ($<0.46\text{mmol}/24\text{ h}$) or near-normalization (≥ 0.46 to $<0.60\text{mmol}/24\text{ h}$) of 24 h Uox on at least two consecutive visits, beginning with Day 90,
3. percentage change in Pox from Baseline to Day 180 (for adults only),
4. percentage change in the number of kidney stones identified via kidney ultrasound from Baseline to Day 180,
5. percentage change in the summed surface area identified via kidney ultrasound from Baseline to Day 180
6. rate of change in eGFR from Baseline to Day 180.

Analysis Population

Despite the Agency’s recommendation to conduct key efficacy analyses on the intent-to-treat (ITT) rather than the modified ITT (mITT) population, all of the Applicant’s analyses were conducted on the mITT population, defined as all randomized participants who had at least one efficacy assessment after the Day 90 dosing visit. Consistent with the Agency’s recommendation, analyses which conform to the ITT principle are provided in this review.

¹ Normal or near normal Uox were respectively defined as 24 h Uox <0.46 or ≥ 0.46 to $<0.60\text{ mmol}/24\text{ h}$, adjusted per 1.73 m^2 body surface area in participants aged <18 years on at least two consecutive visits beginning with Day 90.

Missing Data

Missing data was imputed using the missing-at-random assumption using a fully conditional regression-based multiple imputation model, which included treatment, age category, eGFR category, baseline, and outcomes at Days 90, 120, 150, and 180. For each analysis, 50 imputations were conducted, with the results summarized using Rubin's method.

Sample Size Calculation

Sample size calculations were based on the primary endpoint AUC 24 h Uox from Day 90 to Day 180 for percentage change from baseline. Calculations accounted for a pre-planned, but not implemented, group sequential design, with control of alpha-spending. The randomization ratio was 2-to-1 (active-to-placebo), with a primary hypothesis test for one-sided superiority at the significance level of 2.5%. The AUC 24 h Uox in the placebo arm was assumed to be 0 and, in the active arm, was assumed to be -3600 based on a 40% decrease over the 90 days. Under these assumptions, a sample size of 36 participants (24 in the active arm and 12 in the placebo arm) would yield a power of approximately 94%.

Calculation of p-Values

In all of the statistical tests by the Applicant, p-values were calculated using classical statistical tests. These are not necessarily correct given the adaptive randomization conducted in the trial. Details of the adaptive randomization and the associated 'rerandomization tests' for statistical significance are provided in [Section 16.2](#).

Interpretability of Results for PH2

(b) (4)
[REDACTED]

the Applicant proposed marketing approval only for patients with PH1, with results reported from a post hoc study analysis, which excluded PH2 patients.

Completeness Criteria and Data Collection

During data collection and analysis, to help ensure that measurement of 24 h Uox was measured over the required 24 h period, the Applicant eliminated outliers from the analysis using a 'completeness criterion.' In particular, at screening, before randomization, baseline urinary creatinine was calculated as the average concentration from two 24 h collections of urine. If the percentage change from the common average in urinary creatinine concentration was more than 20%, then the data collection for the two screening measurements was repeated a second time. After randomization, if the 24 h urine creatinine excretion changed more than 20% compared with the baseline 24 h excretion, participants were required to complete another 24 h urine collection within 10 calendar days from the time of the visit for which the collection was intended. In the event the urinary creatinine in that repeated 24 h urine collection again changed more than 20% compared with the baseline 24 h excretion, the 24 h urine collection for that visit

² The sole modification from the original analysis is a change in the analyzed population, from PH1 and PH2 to PH1 only.

was not repeated. For the analyses of AUC-related endpoints, only 24 h Uox measurements that met this completeness criterion were used. If more than one measurement was collected that did not violate the completion criterion, the average was calculated for use in the analysis.

Similarly, any urine collection with a duration of less than 22 h or greater than 26 h was considered invalid and was therefore repeated.

6.2.1.4. Results of Analyses, DCR-PHXC-201

Baseline Demographics and Disease Characteristics

Baseline demographics for the ITT population showed an imbalance according to race, with all Asian participants assigned to nedosiran ([Table 7](#), [Table 8](#)). Analyses that were conducted to understand the potential impact of this imbalance on the efficacy findings did not raise concern. In addition, the point estimate for mean baseline urinary oxalate was higher in the placebo arm; however the analysis of the primary endpoint accounted for this issue by inclusion of the Baseline value as a factor in the statistical model.

Table 7. Baseline Demographics and Disease Characteristics. Safety and ITT Populations, PH1 and PH2 Participants

Group	Subgroup	Number (%)		
		Nedosiran	Placebo	Total
All	All	23 (100)	12 (100)	35 (100)
Sex	Female	12 (52.2)	6 (50)	18 (51.4)
	Male	11 (47.8)	6 (50)	17 (48.6)
Age category	12 to 17 years	6 (26.1)	4 (33.3)	10 (28.6)
	6 to 11 years	3 (13)	2 (16.7)	5 (14.3)
	≥18 years	14 (60.9)	6 (50)	20 (57.1)
Age	Mean (SD)	24 (12)	24 (12)	24 (12)
	Median (min, max)	20 (9, 46)	21 (10, 41)	20 (9, 46)
Race	Asian	6 (26.1)	0 (0)	6 (17.1)
	Multiple	0 (0)	1 (8.3)	1 (2.9)
	White	15 (65.2)	10 (83.3)	25 (71.4)
Ethnicity	Hispanic or Latino	2 (8.7)	0 (0)	2 (5.7)
	Not Hispanic or Latino	19 (82.6)	11 (91.7)	30 (85.7)
PH Type	PH1	18 (78.3)	11 (91.7)	29 (82.9)
	PH2	5 (21.7)	1 (8.3)	6 (17.1)
eGFR	≥90 mL/min/1.73 m ²	10 (43.5)	5 (41.7)	15 (42.9)
	≥60 to <90 mL/min/1.73 m ²	9 (39.1)	3 (25)	12 (34.3)
	≥30 to <60 mL/min/1.73 m ²	4 (17.4)	4 (33.3)	8 (22.9)
Pyridoxine	Yes	12 (52.2)	9 (75)	21 (60.0)
	No	13 (47.8)	3 (25)	14 (40.0)
Plasma oxalate (μmol/L)	Mean (SD)	8 (5.1)	9 (5.1)	8.2 (5.0)
	Median (min, max)	6 (2, 21)	9 (2, 18)	7 (2, 21)
Urinary oxalate ^a (μmol/day)	Mean (SD)	1329 (465)	1964 (706)	1547 (628)
	Median (min, max)	1275 (715, 2597)	1789 (1152, 3684)	1401 (715, 3684)

Source: Reviewer program demographics itt.sas, pyridoxine.sas.

^a Normalized by body surface area for patients <18 years of age.

Abbreviations: eGFR, estimated glomerular filtration rate; ITT, intent-to-treat; max, maximum; min, minimum; PH1/2, primary hyperoxaluria type1/2

Table 8. Baseline Demographics and Disease Characteristics, Safety and ITT Populations, PH1 Participants

Group	Subgroup	Number (%)		
		Nedosiran	Placebo	Total
All	All	18 (100)	11 (100)	29 (100)
Sex	Female	10 (55.6)	6 (54.5)	16 (55.2)
	Male	8 (44.4)	5 (45.5)	13 (44.8)
Age category	12 to 17 years	4 (22.2)	4 (36.4)	8 (27.6)
	6 to 11 years	1 (5.6)	2 (18.2)	3 (10.3)
	≥18 years	13 (72.2)	5 (45.5)	18 (62.1)
Age	Mean (SD)	25 (11)	22 (11)	24 (11)
	Median (min, max)	22 (9, 46)	15 (10, 37)	22 (9, 46)
Race	Asian	5 (27.8)	0 (0)	5 (17.2)
	Multiple	0 (0)	1 (9.1)	1 (3.4)
	White	11 (61.1)	9 (81.8)	20 (69)
Ethnicity	Hispanic or Latino	2 (11.1)	0 (0)	2 (6.9)
	Not Hispanic or Latino	14 (77.8)	10 (90.9)	24 (82.8)
eGFR	≥90 mL/min/1.73 m ²	7 (38.9)	4 (36.4)	11 (37.9)
	≥60 to <90 mL/min/1.73 m ²	7 (38.9)	3 (27.3)	10 (34.5)
	≥30 to <60 mL/min/1.73 m ²	4 (22.2)	4 (36.4)	8 (27.6)
Pyridoxine	Yes	12 (66.7)	8 (72.7)	20 (69.0)
	No	6 (33.3)	3 (27.2)	9 (31.0)
Plasma oxalate (μmol/L)	Mean (SD)	8.6 (5.4)	8.7 (5.3)	8.6 (5.3)
	Median (min, max)	7.5 (2, 21)	8 (2, 18)	8 (2, 21)
Urinary oxalate ^a (μmol/day)	Mean (SD)	1396 (480)	1981 (738)	1618 (646)
	Median (min, max)	1351 (801, 2597)	1798 (1152, 3684)	1426 (801, 3684)

Source: Reviewer program demographics itt.sas, pyridoxine.sas.

^a Normalized by body surface area for patients <18 years of age.

Abbreviations: eGFR, estimated glomerular filtration rate; ITT, intent-to-treat; max, maximum; min, minimum; PH1, primary hyperoxaluria type1

Disposition and Missing Data

Of 57 patients screened, 35 were enrolled in the trial ([Table 9](#)). All were retained in the ITT population ([Table 10](#)). The majority of screen failures did not meet the inclusion criteria related to 24 h Uox or creatinine values.

Table 9. Patient Screening and Enrollment, DCR-PHXC-201, Overall Population

Disposition	Study 201
Patients screened	57
Screening failures	22
Patients enrolled	35
Patients randomized	35

Source: ds.xpt and Clinical Study Report; software: R.

Among the 35 participants randomized, one from each trial arm discontinued the trial prior to collection of data on Day 90 ([Table 10](#)). Participant (b) (6) from the nedosiran arm discontinued due to tachycardia, and Participant (b) (6) from the placebo arm discontinued due to initiation of dialysis.

Table 10. Disposition

Disease Type	Baseline	N (%)		Total
		Nedosiran	Placebo	
PH1 and PH2	Randomized	23 (100)	12 (100)	35 (100)
	mITT	22 (95.7)	12 (100)	34 (97.1)
	Treatment to end of study	22 (95.7)	11 (91.7)	33 (94.3)
	Received all six doses	17 (73.9)	11 (91.7)	28 (20)
	Discontinued study	1 (4.3)	1 (8.3)	2 (5.7)
PH1	Randomized	18 (100)	11 (100)	29 (100)
	mITT	17 (94.4)	11 (100)	28 (96.6)
	Treatment to end of study	17 (94.4)	10 (90.9)	27 (93.1)
	Received all six doses	14 (77.8)	10 (90.9)	5 (17.2)
	Discontinued study	1 (5.6)	1 (9.1)	2 (6.9)

Source: Reviewer program disposition.sas.

Abbreviations: mITT, modified intent-to-treat; PH1/2, primary hyperoxaluria type 1/2

Observations were imputed at timepoints for which all urinary creatinine values indicated over or under collection, or if data were missing. After randomization, the percentage of imputed 24 h urinary oxalate data ranged from 8.3% to 26.1% ([Table 11](#)).

Table 11. Percentage of 24 h Urinary Oxalate Observations Imputed

Timepoint	% Nedosiran (n)	% Placebo (n)	Total (n)
	N=23	N=12	N=35
Baseline	0 (0)	0 (0)	0 (0)
Day 30	8.7 (2)	16.7 (2)	11.4 (4)
Day 60	17.4 (4)	25.0 (3)	20.0 (7)
Day 90	8.7 (2)	16.7 (2)	11.4 (4)
Day 120	26.1 (6)	16.7 (2)	22.9 (8)
Day 150	13.0 (3)	25.0 (3)	17.1 (6)
Day 180 / EOS	8.7 (2)	8.3 (1)	8.6 (3)

Source: Reviewer program disposition.sas.

Abbreviation: EOS, end of study

Efficacy Results

Primary Efficacy Endpoint

The Applicant's analysis of the primary efficacy endpoint, 24 h Uox AUC of percentage change from Baseline calculated from Days 90 to 180, indicated efficacy, both in the prespecified analysis, which included patients with PH1 and PH2, as well as in the post hoc study analysis, which included only patients with PH1 ([Table 12](#)).

Table 12. Primary Endpoint, 24 h Uox AUC Δ% Days 90 to 180, mITT Population

Population	Placebo	Nedosiran	Difference (95% CI) p-Value
PH1 and PH2	1664 (N=12)	-3507 (N=22)	-5172 (-7414, -2929) <0.0001
PH1	1317 (N=11)	-4575 (N=17)	-5892 (-8101, -3683) <0.0001

Source: Reviewer program primary efficacy AUC urinary oxalate mi itt.sas, adapted from analysis for CSR Tables A1 and A10.
Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; CSR, clinical study report; mITT, modified intent-to-treat; PH1/2, primary hyperoxaluria type1/2; Uox, urinary oxalate

As previously discussed, the Applicant's use of the mITT rather than the ITT population may fail to preserve the original randomization. Therefore, estimates using the ITT population are preferable and, henceforth, unless otherwise stated, all results provided subsequently in this review are based on the ITT population. The results from the ITT population ([Table 13](#)) are consistent with the Applicant's analysis conducted on the mITT population ([Table 12](#)).

Table 13. Primary Endpoint, 24 h Uox AUC Δ% Days 90 to 180, ITT Population

Population	Placebo	Nedosiran	Difference (95% CI) p-Value
PH1 and PH2	1490 (N=12)	-3486 (N=23)	-4976 (-7149, -2803) <0.0001
PH1	980 (N=11)	-4557 (N=18)	-5537 (-7692, -3382) <0.0001

Source: Reviewer program primary efficacy AUC urinary oxalate mi itt.sas.
Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; CSR, clinical study report; ITT, intent-to-treat; PH1/2, primary hyperoxaluria type1/2; Uox, urinary oxalate

Additional analyses were conducted to explore the impact of the baseline imbalance in treatment assignments among Asian participants and a reduced dosing regimen during the trial among adults weighing <50 kg. Rerandomization tests (to compensate for the adaptive randomization) and tipping point analyses (to assess for the impact of missing data) were also conducted. These analyses confirmed the robustness of the primary endpoint analysis findings. See [Section 16](#) for further discussion.

Secondary Efficacy Endpoints

Urinary Oxalate

The percentage of participants with normalized or near-normalized 24 h Uox at two consecutive visits during Days 90 to 180 was statistically significantly higher in the nedosiran arm (48%) than in the placebo arm (0%) ([Table 15](#)). However, the mean Baseline value of Uox was lower in the nedosiran arm than in the placebo arm (mean baseline value of 1330 μmol/day and 1965 μmol/day, respectively). This imbalance is further illustrated in [Figure 2](#), which shows that the lowest 10 Baseline values occurred in patients randomized to nedosiran. Given this imbalance, the results of this secondary endpoint analysis are challenging to interpret. An

analysis similar to that prespecified for normalized or near-normalized urinary oxalate, did not indicate statistical significance for normalization of 24 h Uox ([Table 14](#)). Further, among the four PH1 patients randomized to nedosiran who achieved normalized urinary oxalate, two had Baseline values <1000µmol/24 h.

Table 14. Percentage Normalized Urinary Oxalate, PH1 and PH2 Participants, ITT Population

Endpoint	Placebo % (n/N)	Nedosiran % (n/N)	Difference (p-Value)
Normalized or near normalized 24 h Uox	0% (0/12)	48% (11/23)	48% (0.003)
Normalized 24 h Uox ^a	0% (0/12)	17.4% (4/23)	17.4% (0.17) ^b

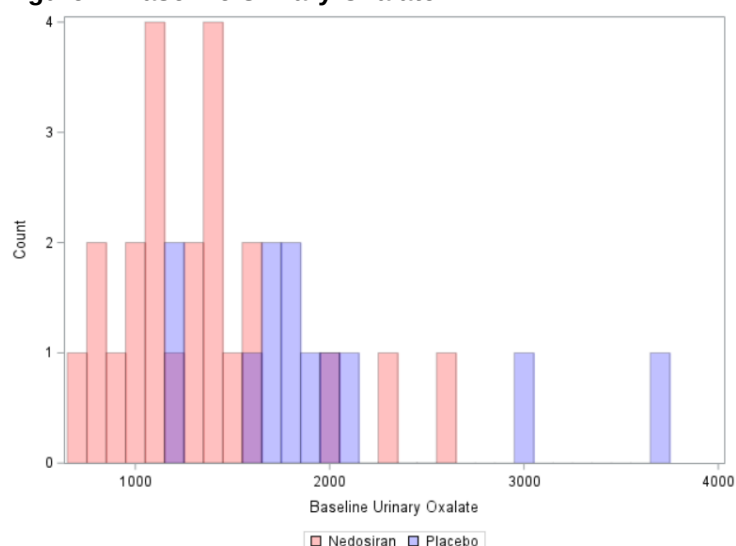
Source: Reviewer program respuox itt.sas adapted from analysis for CSR Table 14.2.2.1.

^a 24 h Uox values were considered normalized if, on at least two consecutive visits, beginning with Day 90, the value was <460µmol/24 h. BSA-adjusted 24 h Uox values were used for all subjects <18 years of age, and were considered near-normalized if the value on at least two consecutive visits was ≥460 but <600µmol/24 h

^b Nominal confidence limits and p-value – endpoint selected post hoc without multiplicity adjustment.

Abbreviations: CSR, clinical study report; ITT, intent-to-treat; PH1/2, primary hyperoxaluria type1/2; Uox, urinary oxalate

Figure 2. Baseline Urinary Oxalate



Source: Reviewer program respuox itt.sas.

Plasma Oxalate

The difference between treatments for percentage change from baseline Pox just missed the one-sided $p < 0.025$ criterion for statistical significance ([Table 15](#)). Even if the results had been statistically significant, the clinical significance of the finding would have been unclear since Pox levels are not substantially increased in patients with PH with relatively preserved kidney function, and what constitutes a clinically relevant reduction in this population is unclear. Of note, the mean treatment effect was also skewed in favor of nedosiran by data from a single subject in the placebo arm ^{(b) (6)}, in whom Pox was 2 mg/L at Baseline and 9 mg/L at Day 180, resulting in a 350% increase in Pox in that patient.

Table 15. Percentage Change From Baseline Pox. PH1 and PH2 Participants, ITT Population

Endpoint	Placebo % (n/N)	Nedosiran % (n/N)	Difference (p-Value)
Percentage change from Baseline Pox	73% N=5 ^b	-26% N=14	99% (0.026)

Source: Reviewer program respuox itt.sas adapted from analysis for CSR Table 14.2.2.1, reviewer program Pox.sas adapted from analysis for CSR Table 18.

^a The 24 h Uox values were considered normalized if the value was <460 µmol/24 h and near normalized if the value was ≥460 to <600 µmol/24 h. BSA-adjusted 24 h Uox values were used for all participants <18 years of age.

^b Day 180 data were neither collected nor imputed for a single patient, randomized N=6.

Abbreviations: CSR, clinical study report; ITT, intent-to-treat; PH1/2, primary hyperoxaluria type1/2; Pox, plasma oxalate; Uox, urinary oxalate

Exploratory Efficacy Endpoints

Although number of kidney stones, kidney stone burden, and rate of change in eGFR were prespecified as secondary endpoints, their predecessor in the analysis hierarchy, percentage change from Baseline Pox failed to achieve statistical significance, and the results discussed below are therefore considered exploratory.

Number of Kidney Stones and Kidney Stone Burden

In Study DCR-PHX-201, the summed two-dimensional surface area of kidney stones at least 5 mm in diameter was measured using ultrasound. The nedosiran group had a median percentage decrease from Baseline in summed surface area of kidney stones of 2%, while the placebo group had a median increase of 22%; however the difference was not statistically significant (p=0.083). Per the Applicant, there was a high degree of measurement variability using two-dimensional ultrasound to quantify the surface area of kidney stones because of their “very complex and irregular” shapes. No difference was observed between the nedosiran group and the placebo group in the percent change from Baseline to Day 180 in the number of measurable kidney stones (−2.22% and −2.99%, p=0.46).

Kidney stones can be asymptomatic and it is not clear whether and to what extent effects on stone burden predict clinically meaningful stone events. Further, quantifying urinary tract stones by ultrasound is prone to variability because the measurements are dependent on the equipment used and the skill of the ultrasonographer ([Milliner et al. 2020](#)).

Rate of Change in eGFR

Differences between treatment and placebo in rate of eGFR change were not statistically significant ([Table 16](#)). Although the point estimates of monthly rate of eGFR decline favor the nedosiran arm, these results should be interpreted with caution given the baseline imbalances in eGFR (median 86 mL/min/1.73 m² [range 35 to 197 mL/min/1.73 m²] in the nedosiran group and 77 mL/min/1.73 m² [range 44 to 131 mL/min/1.73 m²] in the placebo group) and differences in 24 h Uox ([Table 8](#)) between the treatment arms, suggesting that patients in the placebo group had more severe/advanced disease at baseline.

Table 16. Rate of Decline in eGFR, Study 201, PH1 and PH2

Endpoint	Placebo (N=12)	Nedosiran (N=23)	Difference ^a (95% CI) p-Value
Rate of decline in eGFR (mL/min/1.73 m ² /month) ^b	1.10	0.35	-0.75 (-2.1, 0.6) 0.14

Source: Reviewer program fda egfrchange itt.sas, adapted from analysis for CSR Table 21

^a Nominal confidence limits and p-value – endpoint selected post hoc without multiplicity adjustment.

^b For adults (≥18 years), calculations of eGFR used the CKD-EPI (creatinine-based) equation, except for the 2 Japanese participants, in which whom eGFR was calculated using a Japanese-specific creatinine-based equation (Matsuo et al. 2009). For pediatric participants (6 to 17 years), eGFR was calculated using the creatinine-based 2009 bedside Schwartz equation since cystatin data was not collected at screening.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; PH1/2, primary hyperoxaluria type 1/2

Percentage Reduction in 24 h Urinary Oxalate

The Applicant proposed to include information in Section 14 of the label on the percentage reduction from Baseline in Uox; however, as described in [Section 16.6](#), the Applicant used various methods of calculation which produced conflicting results. To resolve this issue, the review team conducted an ITT analysis for percentage change in Uox directly, imputing 50 datasets for 24 h urinary oxalate measurements at Days 0, 30, 60, 90, 120, 150, and 180 and then evaluating mean change from baseline of 24 h Uox over Days 90, 120, 150, and 180 for each imputed dataset using mixed model repeated measures with independent factors treatment, eGFR group, age group, baseline 24 h Uox concentration, and visit by treatment interaction, with a compound symmetric covariance matrix, with the results subsequently combined using Rubin's rule. The effect of treatment on the percentage change from Baseline in 24 h Uox was nominally significant regardless of whether the analysis was performed for all enrolled participants or only for PH1 participants ([Table 17](#)).

Table 17. Percentage Change in 24 h Urinary Oxalate, Days 90 to 180

Population	Placebo Change (95% CI)	Nedosiran Change (95% CI)	Difference* (95% CI) p-Value
PH1 and PH2	12% (-12%, 36%)	-37% (-53%, -21%)	-49% (-72%, -26%) <0.0001
PH1	6% (-20%, 32%)	-50% (-69%, -31%)	-56% (-80%, -33%) <0.0001

Source: Reviewer program pchg urinary oxalate itt all visits lt 2023 06 02.sas, admioxfdaalldays.sas

* Statistical significance nominal only endpoint selected post hoc without multiplicity adjustment.

Abbreviations: CI, confidence interval; PH1/2, primary hyperoxaluria type 1/2

Absolute Change in 24 h Urinary Oxalate

Compared to placebo, there was a nominally significant reduction in mean Uox from Baseline to mean Uox from Days 90 to 180 ([Table 18](#)). The analysis used is similar to that for [Table 17](#).

Table 18. Change in 24 h Urinary Oxalate Excretion, Days 90 to 180

Population	Placebo μmol/day (95% CI)	Nedosiran μmol/day (95% CI)	Difference* (95% CI) p-Value
PH1 and PH2	152 (-181, 485) N=12	-514 (-731, -298) N=23	-667 (-1000, -333) <0.0001
PH1	83 (-324, 490) N=11	-689 (-971, -407) N=18	-777 (-1125, -418) <0.0001

Source: Reviewer program primary efficacy urinary oxalate itt all visits It 2023 04 24.sas.

* Statistical significance nominal only – endpoint selected post hoc without multiplicity adjustment. Calculated using mixed model repeated measures combined using Rubin's rule.

Abbreviations: CI, confidence interval; PH1/2, primary hyperoxaluria type 1/2

Confirmatory Evidence of Effectiveness

After 6 months of treatment in PHYOX2, participants could enroll in an ongoing single-arm extension study, PHYOX3, in which all participants were treated with nedosiran. Eight patients randomized to placebo in DCR-PHXC-201 received nedosiran for 6 months in DCR-PHXC-301; 24 h urinary oxalate decreased from a mean (SD) of 1872 μmol/day (95% CI: 851, 2894) at the end of DCR-PHXC-201 to 816 μmol/day (95% CI: 591, 1042). The mean percentage decrease was 46% (95% CI: 24%, 67%), in contrast to the lack of a decrease in 24 h urinary oxalate with placebo during the double-blind portion of the trial.

Additional confirmatory evidence of effectiveness is also provided from 13 participants who were enrolled in a single-dose study, DCR-PHXC-101, who also subsequently participated in Study DCR-PHXC-301. In these participants, 24 h Uox decreased from a mean (SD) baseline of 1411 μmol/day (570) to 420 μmol/day (272), a 69% (SD 19%) reduction after a single dose on nedosiran. Twenty-four-hour Uox then increased off treatment to a mean (SD) of 927 μmol/day (279) at the time of enrollment in Study DCR-PHXC-301, and decreased to a mean of 229 μmol/day (169) after restarting nedosiran in Study DCR-PHXC-301.

Maintenance of Treatment Effect on Urinary Oxalate

The reduction in Uox was maintained in 13 participants with PH1 who received 6 months of treatment with nedosiran in PHYOX2 and an additional 6 months of treatment in PHYOX3 ([Table 19](#)). Data beyond Month 6 of PHYOX3 are limited.

Table 19. Percentage Change in 24 h Urinary Oxalate, Study 301, PH1 Participants Randomized to Nedosiran in Study 201

Study Time	No. of Patients Measured (% Missing)	Percentage Change from Baseline Uox (95% CI)
Randomized to Nedosiran in Study 201	18 (0)	0 (0)
Day 90 of Study 301	14 (22)	-57 (-50, -64)
Day 180 of Study 301	13 (28)	-62 (-54, -70)
Month 9 of Study 301	7 (61)	-63 (-53, -73)
Month 12 of Study 301	3 (83)	-47 (-33, -60)
Month 15 of Study 301	1 (94)	-60 (-37, -82)

Source: Reviewer program admiuoxfdaalldays301.sas.

Abbreviations: CI, confidence interval; PH1, primary hyperoxaluria; Uox, urinary oxalate

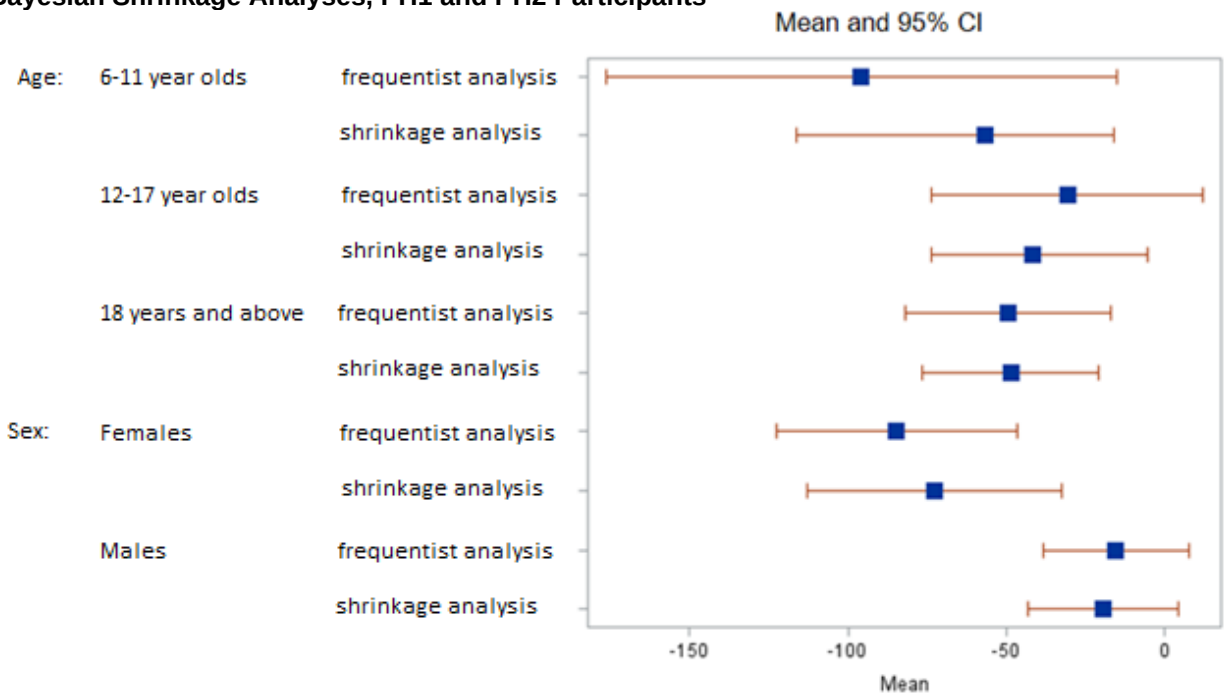
Subgroup Efficacy Analyses

Subgroup analyses did not indicate any differences in the treatment effect on the change in 24 h Uox between demographic subgroups, in PH1 and PH2 participants combined ([Figure 3](#) and [Table 20](#)) and in PH1 participants alone ([Figure 4](#) and [Table 21](#)). Subgroup analyses were not conducted according to race (only white participants in both trial arms) or ethnicity (Hispanic / Latino participants missing from placebo arm).

A Bayesian hierarchical model was used to conduct the shrinkage analyses shown in these tables and figures. Specifically, for $i = 1, \dots, k$ subgroups:

- Y_i = estimated treatment effect in subgroup level i ,
- σ_i^2 = the estimated variance for subgroup level i ,
- $\mu_i \sim N(\mu, \tau^2)$,
- $\mu \sim N(0, \text{std_dev}=\omega)$, ω chosen to be 100, and
- $\tau^2 \sim \text{Half-Cauchy}(0, \text{scale}=25)$.

Figure 3. Percentage Change From Baseline Urinary Oxalate by Subgroup. Frequentist and Bayesian Shrinkage Analyses, PH1 and PH2 Participants



Source: Reviewer programs subgroups Bayes itt all visits It 12 2023 06 09.sas and Subgroups pchg Urinary Oxalate itt all visits It 12 2023 06 02.sas.

Abbreviation: PH1/2, primary hyperoxaluria type 1/2

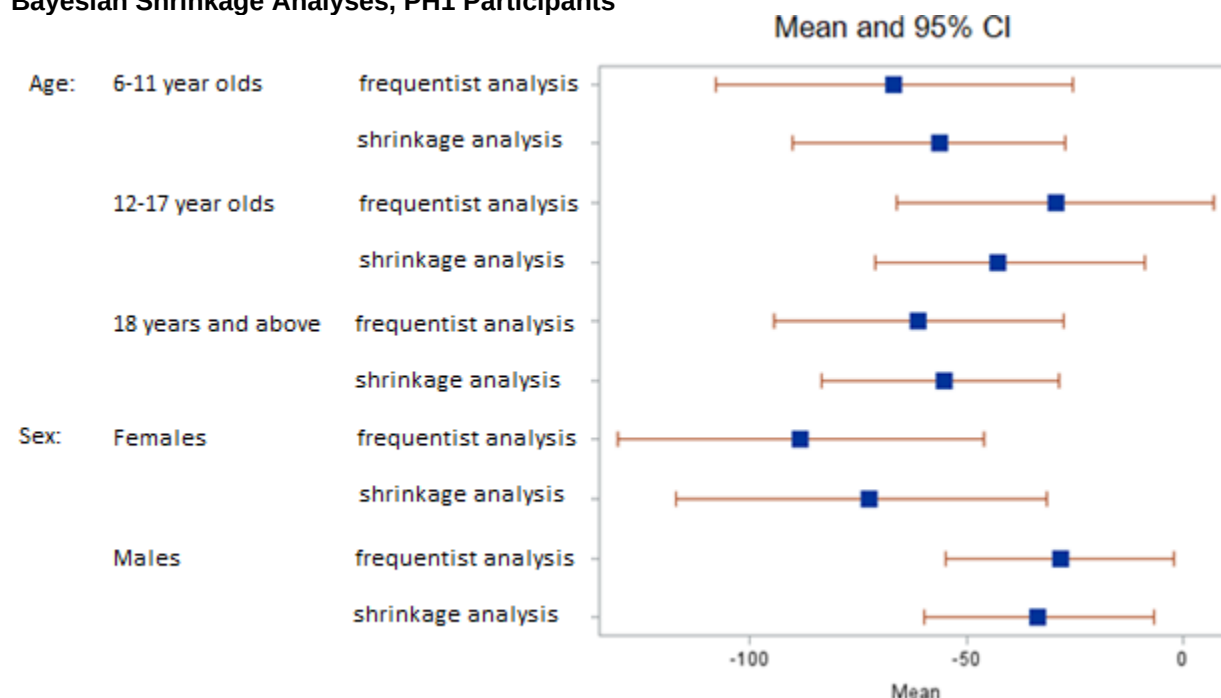
Table 20. Percentage Change From Baseline Urinary Oxalate by Subgroup. Bayesian Shrinkage Analyses. PH1 and PH2 Participants

Group	Subgroup	Treatment Effect		
		Mean	95% Lower CI	95% Upper CI
Sex	Female	-73%	-113%	-32%
Sex	Male	-19%	-43%	4%
Age	6 to 11 Years	-56%	-116%	-16%
Age	12 to 17 Years	-42%	-73%	-6%
Age	≥18 Years	-48%	-77%	-21%

Source: Reviewer programs subgroups Bayes itt all visits It 12 2023 06 09.sas and subgroups pchg Urinary Oxalate itt all visits It 12 2023 06 02.sas.

Abbreviations: CI, confidence interval; PH1/2, primary hyperoxaluria type 1/2

Figure 4. Percentage Change From Baseline in Urinary Oxalate by Subgroup. Frequentist and Bayesian Shrinkage Analyses, PH1 Participants



Source: Reviewer programs subgroups Bayes itt all visits It 12 2023 06 09.sas and subgroups pchg Urinary Oxalate itt all visits It 12 2023 06 02.sas.

Abbreviations: CI, confidence interval; PH1, primary hyperoxaluria type 1

Table 21. Percentage Change From Baseline in Urinary Oxalate by Subgroup. Bayesian Shrinkage Analyses, PH1 Participants

Group	Subgroup	Treatment Effect		
		Mean	95% Lower CI	95% Upper CI
Sex	Female	-72%	-117%	-32%
Sex	Male	-34%	-60%	-7%
Age	6 to 11 Years	-56%	-90%	-27%
Age	12 to 17 Years	-43%	-71%	-9%
Age	≥18 Years	-55%	-83%	-29%

Source: Reviewer programs subgroups Bayes itt all visits It 12 2023 06 09.sas and Subgroups pchg Urinary Oxalate itt all visits It 12 2023 06 02.sas.

Abbreviations: CI, confidence interval; PH1, primary hyperoxaluria type 1

6.3. Key Efficacy Review Issues

6.3.1. The Interpretability of AUC as Descriptor of Efficacy

Interpretability and statistical properties of the Applicant's primary endpoint, AUC for percentage change from Baseline in 24 h Uox from study Days 90 to 180, and the relationship between AUC and mean percentage change in 24 h Uox.

Background

Regulations and guidance state that the principal objective for Section 14 of the label is "to provide the information that is most useful to prescribers in treating their patients," and that the label should include "endpoints the Agency has accepted as evidence of effectiveness, or closely related endpoints that may be more easily understood." Although the Agency did not object to the Applicant's proposal to assess the efficacy of nedosiran using the AUC for percentage change from Baseline in 24 h Uox from study Days 90 to 180, such an endpoint may not be an ideal descriptor of nedosiran's effect on Uox or easily understood by prescribers.

Assessment

Section [16.1](#) of the review discuss the statistical properties of the Applicant's primary endpoint and associated challenges with its interpretation as a descriptor of efficacy. Unlike mean percentage change, the value of AUC may vary according to the temporal sequence in which the underlying values of percentage change are recorded and, as a consequence, in small trials, such as the present one, AUC is more likely to generate random highs and lows in mean outcome that are not clinically meaningful. Further complicating interpretation of AUC as a measure of mean percentage change, a single value of AUC may represent several different values of mean percentage change in Uox. These two issues would be expected to add "noise" in the calculation of AUC that could bias towards the null hypothesis of no treatment effect of nedosiran. The fact that the treatment effect of nedosiran on AUC was large and highly statistically significant despite this "noise" supports the conclusion that there is a true treatment effect.

One other issue with the Applicant's calculation of AUC is that it uses single imputation of missing values, in direct violation of recommendations by the National Academy of Sciences based on the fact that single imputation methods underestimate uncertainty in estimates of treatment effect. Also, the single imputation method used, linear interpolation, produces results that do not match observed data. Although these latter two issues raise uncertainty about the Uox values imputed for 87 of the 90 days used to calculate AUC, it is noteworthy that nedosiran shows consistently large reductions in Uox on Days 90, 120, 150, and 180 compared to Baseline.

Conclusion

Although the Agency did not object to the Applicant's proposal to assess the efficacy of nedosiran using this primary endpoint, it may not be easily understood by prescribers and also has undesirable statistical properties. The Applicant wishes to still include this endpoint in the labeling because it was the primary efficacy endpoint of the trial. This is acceptable but, consistent with the regulations discussed in the [Background](#) section, the review team has also

requested inclusion in labeling of the least-squares mean percentage change from Baseline in 24 h urinary oxalate excretion (corrected for body surface area in patients <18 years of age) averaged over Days 90, 120, 150, and 180 as this will be more easily understood by prescribers and this analysis does not have the same statistical issues as the AUC endpoint.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Nonclinical studies, including safety pharmacology, general toxicology, genetic toxicology, and reproductive and developmental toxicology, were conducted to assess the safety of nedosiran in the mouse, monkey and rabbit. The key safety findings from these studies and their clinical relevance are discussed below (see detailed nonclinical study summaries in Section [13.1](#)).

Embryo-Fetal Development Toxicity

In an embryo-fetal development study in mice, no maternal or developmental toxicities were observed with nedosiran at doses up to 2000 mg/kg/dose (58x the maximum recommended human dose (MRHD) or with the mouse active analog DCR-m355.

However, in rabbits, subcutaneous administration of nedosiran resulted in maternal toxicity as shown by body weight loss of 6.5% and 6%, and lower food consumption following the first dose of 6 and 20 mg/kg, respectively. Thereafter, body weights and body weight gain were comparable to the controls up to the end of the dosing period. Higher postimplantation loss and lower numbers of live fetuses were observed at doses of ≥ 6 mg/kg/dose (0.7x the MRHD, based on body surface area), and fetal cardiovascular and skeletal malformations were observed at a dose of 20 mg/kg/dose (2x the MRHD). A dose level of 2 mg/kg/dose (0.2x the MRHD) had no effect on maternal toxicity and embryo-fetal development in rabbits. In the rabbit, fetal exposure was minimal, and nedosiran had no effect on RNAi-mediated changes in LDHA mRNA expression, indicating that maternal toxicity, postimplantation loss, and fetal malformations are unrelated to on-target hybridization effects, and thus, other factors could be contributing, such as extrahepatic silencing of the mRNA and/or the bulk chemical and physical properties of the molecule (e.g., high molecular weight, polyanionic macromolecules). Nedosiran did not reduce LDHA mRNA expression in the liver of the rabbit, but it reduced citrate synthase mRNA expression, which is the last step in the Krebs cycle ATP generation. Post-implantation loss may be related to the maternal toxicity in the rabbit, but the cause for fetal malformations is unclear, and could be related to citrate synthase inhibition. The relevance of the rabbit findings to humans is unknown.

General Toxicology Studies

General toxicity studies were conducted for durations up to 26 weeks in juvenile mice and 39 weeks in juvenile and adult monkeys. The ages of the animals in the nonclinical program were appropriate to support the safety evaluation for the indicated clinical population. Key findings in the pivotal toxicology studies are discussed below.

Liver

Histological changes in the liver (Kupffer cells), which included minimal to moderate macrophage basophilic hypertrophy, were observed following administration of nedosiran at a dose level of 300 mg/kg administered every 4 weeks for up to 9 months in juvenile monkey. Additional findings included minimal to mild hepatocyte basophilia at doses ≥ 100 mg/kg, and minimal hypertrophy and mixed inflammatory cell infiltrates in the liver at 300 mg/kg. Electron-microscopic evaluations of the liver revealed an increase in the number and size of clear vacuoles and lysosomes within the hepatocytes, but there was no degeneration or necrosis. During the 8-week recovery period, the findings in the liver were still evident at a dose of 300 mg/kg. The hypertrophic changes in the Kupffer cell/macrophage in the liver may be due to accumulation of the test article and are considered a class effect of oligonucleotides.

Lymph Nodes and Testes

Microscopic findings of minimal to moderate macrophage basophilic hypertrophy were observed in the mesenteric lymph nodes at doses ≥ 30 mg/kg, as well as in the mandibular lymph nodes and testes at a dose level of 300 mg/kg in the juvenile monkeys, indicating hybridization-independent proinflammatory effects. During the 8-week recovery period, the findings in the lymph nodes and testes were still evident at the high dose of 300 mg/kg, which could be due to accumulation of oligonucleotides in cells with macrophagic lineage. Given nedosiran's long tissue half-life, several weeks to months may be needed for full recovery.

Injection Site Reactions

At the injection sites, minimal to mild macrophage basophilic hypertrophy was observed in the subcutaneous tissues in the juvenile mice and monkeys, which resolved following an 8-week recovery period, indicating hybridization-independent effects.

Findings in Young Adult Monkeys

In the young adult cynomolgus monkey study, nedosiran was tested at one dose level of 300 mg/kg once every 4 weeks for 9 months. Key findings, including Kupffer cell basophilic hypertrophy and hepatocyte basophilia in the liver, and macrophage basophilic hypertrophy in the lymph nodes (mesenteric, mandibular), testes, and injection sites, were similar to those observed in the juvenile monkeys. There were no apparent differences in the incidence and/or severity of the findings between the juvenile and young adult monkeys.

Conclusion for General Toxicity Studies

Overall, the findings discussed above reflect cellular uptake and accumulation of oligonucleotide and were evident at high dose levels. Given the safety margin of at least 11-fold of the MRHD (see safety margins in [Table 21](#) and [Table 22](#) below) based on the no observed adverse effect level (NOAEL) determined in the monkey toxicology study, these changes are considered of minimal safety concern for the proposed clinical use.

Safety Margins to the Maximum Recommended Human Dose

The NOAEL for nedosiran in the most sensitive and relevant species, the juvenile monkey, is 100 mg/kg, with a corresponding AUC_{0-48h} 400 $\mu\text{g}\cdot\text{h/mL}$, which is approximately 29-fold higher

than the exposure achieved in humans dosed at 2.8 mg/kg, which resulted in an AUC_{last} of 13.6 µg·h/mL (Table 22). Nedosiran is quickly cleared from the plasma and taken up by the tissues, and the tissue residence time is very long (elimination half-life in the liver ranged from 12 to 23 days), which is much longer than the plasma distribution phase; therefore, the plasma exposure levels (AUC) may not reflect the full spectrum of the drug concentration-time curve in the tissues. For this reason, the safety margin is also estimated using body surface area-based dose scaling, which represents a more conservative (compared to AUC) estimate of 8.6-fold higher than the MRHD of 2.8 mg/kg (Table 23).

Table 22. Safety Margins by Plasma Exposure

Study	NOAEL (mg/kg)	Nonclinical Exposure (AUC _{0-48h} µg·h/mL)	Human Exposure* Safety Multiples
6-month mouse (juvenile)	300	526	38
9-month monkey (juvenile)	100	400	29

Source: Nonclinical Review analysis.

* Maximum recommended human dose (MRHD) 2.8 mg/kg systemic exposures of AUC_{last} 13.6 µg·h/mL.

Abbreviations: AUC, area under the concentration-time curve; NOAEL, no observed adverse effect level

Table 23. Safety Margins by Dose (Body Surface Area-Based Scaling)

Study	NOAEL (mg/kg)	HED (mg/kg)	MRHD 2.8 mg/kg Safety Multiples
6-month mouse (juvenile)	300	24	8.6
9-month monkey (juvenile)	100	32	11.4

Source: Nonclinical Review analysis.

MRHD, 170 mg/dose (2.8 mg/kg).

Abbreviations: HED, human equivalent dose; MRHD, maximum recommended human dose; NOAEL, no observed adverse effect level

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Potential Risks With GalNAC-Conjugated siRNAs

Toxicities associated with GalNAC-conjugated siRNA products include injection site reactions, serum ALT and AST elevations, increases in serum creatinine and decreases in eGFR, positive antidrug antibodies (ADA), and hypersensitivity (including anaphylactic reactions).

Potential Risks Due to Drug-Specific Factors

Nedosiran inhibits LDHA, which metabolizes glyoxylate to oxalate. In patients with PH1 treated with nedosiran, the precursor glyoxylate is expected to be converted to glycolate by glyoxylate reductase/hydroxypyruvate reductase. Effects of chronic elevations in plasma or urine glycolate are unknown; however, the available clinical and nonclinical data suggest such elevations are likely to be benign. In humans, the gene HAO1 encodes glycolate oxidase, an enzyme that converts glycolate to glyoxylate in the peroxisomes of liver cells. As such, suppression of HAO1 is expected to lead to the accumulation of glycolate. Glycolate is highly water-soluble and readily excreted in urine. In a case report published in 2014, an 8-year-old male with a homozygous splice site mutation in HAO1 was noted to have marked elevations of urinary glycolate. He had normal kidney and liver function, and no kidney stones (Frishberg et al. 2014). Similarly, glyoxalate-deficient mice (Hao1^{-/-}) have asymptomatic marked urinary glycolate

elevation without phenotypic differences in urinary sediment, kidney crystal deposition, kidney histology, growth, or development compared with Hao1^{+/+} mice ([Martin-Higueras et al. 2016](#)).

PH2 is caused by absent or decreased activity of glyoxylate reductase/hydroxypyruvate reductase; hence, glyoxylate cannot be converted to glycolate. The excess glyoxylate is converted to oxalate by LDHA. In patients with PH2 treated with nedosiran, it is not clear whether the precursor glyoxylate accumulates in cells or if it is further metabolized; hence, the upstream effects of inhibiting LDHA in patients with PH2 are not fully understood.

Nedosiran is conjugated to GalNAc aminosugar residues, which bind to ASGPR to deliver nedosiran to hepatocytes; hence, nedosiran activity is expected to be targeted to the liver. Additional potential risks of nedosiran could occur if nedosiran were to inhibit extra-hepatic LDHA. In human, LDHA deficiency can occur because of recessively inherited genetic mutations in the LDHA gene, causing a deficiency of the skeletal muscle isoform of LDH, leading to glycogen storage disease XI. This condition usually presents in childhood with myopathy resulting in symptoms of fatigue, muscle pain, muscle stiffness, cramps during exercise (exercise intolerance), and rhabdomyolysis during strenuous exercise or activity.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Nedosiran is not approved in the United States or any foreign market.

7.4. FDA Approach to the Safety Review

Data from the double-blind, placebo-controlled period of Study DCR-PHXC-201 were used to support the safety of nedosiran. In addition, safety data from the ongoing single-arm Study DCR-PHXC-301, submitted on September 30, 2022 with data cutoff of January 10, 2022, were reviewed for additional safety concerns. The Safety Update Report submitted on January 27, 2023, contained additional safety data from Study DCR-PHXC-301 (data cutoff of August 11, 2022) and was reviewed for any new findings.

Safety data from Studies DCR-PHXC-201 and -301 were not pooled given differences in study design. Safety analyses used the Safety Population, defined as all patients who received any amount of study drug.

The safety review focused on known and potential toxicities of nedosiran based on its mechanism of action, nonclinical findings, and the experience with other GalNAc-conjugated siRNA products. These known and potential toxicities included injection site reactions, hepatic and kidney toxicity, immunogenicity, and hypersensitivity reactions.

Adverse events (AEs) were analyzed by Medical Dictionary for Regulatory Activities (MedDRA) v. 23.1 preferred term and by pooling similar AEs (referred to as the FDA Medical Dictionary for Regulatory Activities Query [FMQ]). The FMQ analysis is similar to a customized Medical Dictionary for Regulatory Activities query. Adverse events of interest specified by the Applicant included injection site reactions (defined as signs or symptoms at the injection site with a time to onset of four or more hours from the time of study drug administration), kidney stone events, and muscle pain or weakness. A treatment-emergent

adverse event (TEAE) was defined as an AE that started, changed in intensity, or changed relationship to the study treatment at the time of or after the first dose date and before the study completion date.

7.5. Adequacy of the Clinical Safety Database

The clinical safety database is limited given the size of the affected population. In the placebo-controlled Study, DCR-PHXC-201, 23 patients ≥ 9 years of age received nedosiran for a mean duration of 4.7 months ([Table 24](#)).

Table 24. Duration of Exposure, Safety Population, DCR-PHXC-201

Parameter	Nedosiran N=23 n (%)	Placebo N=12 n (%)
Duration of treatment, months		
Mean (SD)	4.7 (0.9)	4.8 (0.3)
Median (Q1, Q3)	4.9 (4.9, 5)	4.9 (4.8, 4.9)
Minimum, maximum	0.9, 5.4	4, 5.1
Patients treated, by duration		
<3 months	1 (4.3)	0
3 to 6 months	22 (95.7)	12 (100)

Source: adex.xpt and adsl.xpt; software: R.

Duration is the 6-month treatment period.

Abbreviations: N, number of patients in treatment arm; n, number of patients with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

As previously noted, the Applicant has also submitted uncontrolled safety data from their ongoing single-arm Study (DCR-PHXC-301), which enrolled participants with PH who (1) had previously completed a study of nedosiran, or (2) are pediatric siblings with PH of participants who successfully completed a study of DCR-PHXC and who met eligibility criteria. Following completion of DCR-PHXC-201, 22 of 23 participants randomized to nedosiran and 11 of 12 participants randomized to placebo enrolled in Study DCR-PHXC-301 and received open-label nedosiran. As of data cutoff of August 11, 2022, Study DCR-PHXC-301 had enrolled a total of 54 participants with PH and relatively intact kidney function, including 40 participants with PH1, 10 with PH2, and four with PH3. All but one participant (a sibling 12 years of age with PH2) had rolled over from a previous study of nedosiran. As of data cutoff, the mean (SD) and median (min, max) durations of exposure were 21 (9) months and 21 (0.9, 36) months, respectively. For participants that were enrolled in Study DCR-PHXC-201, this duration of exposure reflects the sum of the exposure in Studies DCR-PHXC-201 and -301; for participants that rolled over from single dose studies (DCR-PHXC-101 and DCR-PHXC-104), the duration of exposure does not include the single-dose period. Thirty-five participants (64%) have been on nedosiran for 18 months or longer.

7.6. Safety Results

7.6.1. Safety Results, Pooled Analyses, DCR-PHXC-201 and DCR-PHXC-301

The review team did not conduct integrated analyses of safety because of differences in the design of Studies DCR-PHXC-201 and DCR-PHXC-301. See [Sections 7.6.2](#) and [7.6.3](#) for analyses of individual trial results.

7.6.2. Safety Results, DCR-PHXC-201

7.6.2.1. Overview of Treatment-Emergent Adverse Events Summary, DCR-PHXC-201

The proportion of participants with TEAEs was similar between the treatment groups ([Table 25](#)). Most TEAEs were mild or moderate in severity. There were two serious adverse events (SAEs) in the placebo arm compared with one SAE with nedosiran. There were no deaths. One participant in each treatment arm discontinued study drug because of an AE (see [Section 7.6.2.4](#) for details).

Table 25. Overview of Treatment-Emergent Adverse Events, Safety Population, DCR-PHXC-201

Event Category	Nedosiran N=23 n (%)	Placebo N=12 n (%)	Nedosiran vs. Placebo Risk Difference (%) (95% CI)
SAE	1 (4)	2 (17)	-12 (-35, 10)
SAEs with fatal outcome	0	0	0 (0, 0)
Life-threatening SAEs	0	0	0 (0, 0)
AE leading to permanent discontinuation of study drug	1 (4)	1 (8)	-4 (-22, 14)
AE leading to dose modification of study drug	0	0	0 (0, 0)
AE leading to interruption of study drug	0	0	0 (0, 0)
AE leading to reduction of study drug	0	0	0 (0, 0)
AE leading to dose delay of study drug	0	0	0 (0, 0)
Other	0	0	0 (0, 0)
Any AE	19 (83)	10 (83)	0 (-27, 25)
Severe	1 (4)	4 (33)	-29 (-57, -1)
Moderate	5 (22)	2 (17)	5 (-22, 32)
Mild	13 (57)	4 (33)	23 (-10, 57)

Source: adae.xpt; software: R.

Treatment-emergent adverse events defined as any AE with an onset date/time on or after administration (including any partial administration) of the first dose of study intervention and through the study completion date from the end of study case report form. Duration is the 6-month treatment period.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Severity as assessed by the investigator.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with at least one event; PH, primary hyperoxaluria subtypes combined; SAE, serious adverse event

7.6.2.2. Deaths, DCR-PHXC-201

There were no deaths in DCR-PHXC-201.

7.6.2.3. Serious Treatment-Emergent Adverse Events, DCR-PHXC-201

One participant (4%) in the nedosiran arm and two participants (17%) in the placebo arm experienced an SAE (Table 26).

Table 26. Patients With Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, Safety Population, DCR-PHXC-201

System Organ Class Preferred Term	Nedosiran N=23 n (%)	Placebo N=12 n (%)	Nedosiran vs. Placebo Risk Difference (%) (95% CI)
Any SAE	1 (4)	2 (17)	-12 (-35, 10)
Cardiac disorders (SOC)	1 (4)	0	4 (-4, 13)
Tachycardia	1 (4)	0	4 (-4, 13)
Investigations (SOC)	0	1 (8)	-8 (-24, 7)
Blood creatinine increased	0	1 (8)	-8 (-24, 7)
Renal and urinary disorders (SOC)	0	1 (8)	-8 (-24, 7)
Nephrolithiasis	0	1 (8)	-8 (-24, 7)
Renal colic	0	1 (8)	-8 (-24, 7)

Source: adae.xpt; software: R.

Treatment-emergent adverse events defined as any adverse event with an onset date/time on/after administration (including any partial administration) of the first dose of study intervention and until the study completion date from the end of study case report form.

Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Duration was the 6-month treatment period.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; PH, primary hyperoxaluria subtypes combined; SAE, serious adverse event; SOC, system organ class

The participant (b) (6) who experienced an SAE (tachycardia) in the nedosiran arm discontinued treatment and withdrew consent because of the SAE. The narrative for this patient is provided below; based on the narrative, it seems unlikely that the SAE was related to nedosiran.

- **Participant (b) (6):** A 14-year-old male with a history of PH1, hematuria, myopia, malnutrition, and iron deficiency. His baseline weight was 43.7 kg. The patient was on concomitant potassium citrate, mouthwash for gingivitis (aspegic [a nonsteroidal anti-inflammatory agent], lidocaine, and sodium bicarbonate), paracetamol, phloroglucinol (used for spasmodic gastrointestinal pain), and Fortimel (a nutritional high protein supplement). The patient had no reported previous cardiac history.
 - Baseline heart rate was 83 beats per minute (bpm), blood pressure 105/71 mm Hg, hemoglobin 13.4 g/dL, blood urea nitrogen 17 mg/dL, serum creatinine 1.06 mg/dL, and serum albumin 4.4 g/dL. The patient was randomized to nedosiran and received the first dose of 136 mg by subcutaneous injection on Day 1 (b) (6) and the second dose on Day 28 (b) (6). On Day 34 (b) (6), 6 days after the second dose of nedosiran, the patient complained of palpitations, tachycardia, and chest pain. On Day 35 (b) (6) the patient was seen in the emergency department for these symptoms. Blood pressure was 108/61 mmHg, chest X-ray was reportedly normal, electrocardiogram (ECG) revealed a heart rate of 72 bpm, hemoglobin was 13.4 g/dL, serum troponin was normal, serum electrolytes were unremarkable, blood

urea nitrogen was 24 mg/dL, and serum creatinine was 1.15 mg/dL. He was discharged home on paracetamol, but returned the next day ((b) (6) ; Day 36) and was admitted to the hospital for persistent chest pain, tachycardia, and palpitations. His heart rate in the hospital, captured on telemetry, was noted to intermittently increase from approximately 70 bpm to 140 to 150 bpm for about 1 to 3 min. Holter ECG from (b) (6), was read as “sinus accelerations” without specific arrhythmia (e.g., supraventricular tachycardia, atrial tachycardia, or ventricular extrasystoles). The chest pain and tachycardia were resolved by Day 39 (b) (6). On Day 49 (b) (6) transthoracic echocardiogram was normal.

- Based on a recommendation from the Data Safety and Monitoring Committee, nedosiran was discontinued (no additional doses were administered after the second dose). The participant withdrew from the study on Day 111 (b) (6). No additional AEs were reported for this participant after Day 39.
- The clinical data and Holter ECG were reviewed by independent pediatric and adult electrophysiology cardiologists. The pediatric cardiologist noted that the Holter ECG was normal for the participant’s age and gender, the tachycardia was likely sinus although an atrial nodal re-entrant tachycardia could not be ruled out. The adult cardiologist interpreted the Holter ECG as falling into the “bin” of supraventricular tachycardias, most likely an ectopic atrial tachycardia, or less likely atrioventricular-nodal or atrioventricular-accessory-pathway reentrant tachycardia. Both cardiologists did not believe the tachycardia was likely caused by nedosiran.
- Although there appears to be a temporal relationship between the participant’s second dose of nedosiran and intermittent self-resolving tachycardia, other factors could have contributed to the tachycardia in this patient, e.g., anxiety (according to the Clinical Study Report, the patient reported anxiety) or possibly a panic attack. The participant had also begun exercising, although it is not clear that the patient was exercising during the episodes of tachycardia. It is also not clear that the patient had an arrhythmia; there appeared to be disagreement between the two cardiology experts. As noted, the pediatric cardiologist’s assessment was that the tachycardia was likely sinus. Even if the participant did have supraventricular tachycardia, this is the most common rhythm disturbance in children, commonly due to an atrial nodal re-entrant tachycardia in this age group, and unlikely related to nedosiran. Further, because study drug was discontinued, the participant was not rechallenged with nedosiran to see if the tachycardia would recur. No other participant in the safety database has had an AE of tachycardia or arrhythmia.

One participant in the placebo group (b) (6) with PH1 discontinued study drug on Day 112 because of an SAE of blood creatinine increased, progression of chronic kidney disease (CKD) and initiation of dialysis.

7.6.2.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, DCR-PHXC-201

One participant in each treatment arm discontinued study drug because of an AE ([Table 27](#)). See [Section 7.6.2.3](#) for additional information on participant (b) (6), who discontinued nedosiran and participant (b) (6), who discontinued placebo.

Table 27. Participants With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, DCR-PHXC-201

System Organ Class Preferred Term	Nedosiran N=23 n (%)	Placebo N=12 n (%)	Nedosiran vs. Placebo Risk Difference (%) (95% CI)
Any AE leading to discontinuation	1 (4.3)	1 (8.3)	-4.0 (-21.7, 13.7)
Cardiac disorders (SOC)	1 (4.3)	0	4.3 (-4.0, 12.7)
Tachycardia	1 (4.3)	0	4.3 (-4.0, 12.7)
Investigations (SOC)	0	1 (8.3)	-8.3 (-24.0, 7.3)
Blood creatinine increased	0	1 (8.3)	-8.3 (-24.0, 7.3)

Source: adae.xpt; software: R

Treatment-emergent adverse events defined as any AE with an onset date/time on or after administration (including any partial administration) of the first dose of study intervention and through the study completion date from the end of study case report form. Duration is the 6-month treatment period.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

7.6.2.5. Treatment-Emergent Adverse Events, DCR-PHXC-201

[Table 28](#) shows TEAEs by System Organ Class and narrow FMQs that occurred in two or more participants and with a risk difference of >5% in the nedosiran group compared with placebo. The most common TEAEs were local administration reactions (injection site reactions) followed by hemorrhage, nausea, and bacterial infection. The size of the safety database is limited and some events, e.g., bacterial infections, were infrequent, hence, limiting conclusions regarding their relationship to nedosiran.

TEAEs that mapped to the narrow FMQ Hemorrhage were reported in three participants in the nedosiran group and none in placebo. These TEAEs included hematuria, injection site bruising, and metrorrhagia. Except for the TEAE of injection site bruising, the other events of hematuria (common in patients with kidney stones) and metrorrhagia were likely not related to nedosiran. Similarly, TEAEs that mapped to the narrow FMQ of Bacterial Infection included urinary tract infections, which are frequently associated with kidney stones in patients with PH, and tooth abscess, were likely not related to nedosiran. There is no obvious mechanistic basis by which nedosiran could cause hematuria, metrorrhagia, urinary tract infection, or tooth abscess; therefore, those events will not be discussed further.

Review of all TEAEs by Preferred Term ([Table 90](#)) identified one additional TEAE of neutrophil count decreased in two participants (9%) in the nedosiran group and none in placebo, for a risk difference of 9% (95% CI -3, 20). Participants (b) (6) and (b) (6) had a decrease in neutrophil count to 1.5 and 0.5x10⁹/L on a single assessment on Day 15 and Day 90, respectively. In both participants, the neutrophil counts returned to the normal range at the next assessment despite the participants remaining on nedosiran, suggesting that nedosiran did not play a causative role.

Table 28. Participants With Treatment-Emergent Adverse Events¹ by System Organ Class, FDA Medical Query (Narrow), and Preferred Term Occurring in at Least 2 Participants (Narrow FMQ), and With a Risk Difference >5% Above Placebo, Safety Population, DCR-PHXC-201

System Organ Class FMQ (Narrow) Preferred Term	Nedosiran N=23 n (%)	Placebo N=12 n (%)	Nedosiran vs. Placebo Risk Difference (%) (95% CI)
Gastrointestinal disorders (SOC)			
Nausea	4 (17.4)	1 (8.3)	9.1 (-13.0, 31.1)
General disorders and administration site conditions (SOC)			
Local administration reaction	8 (34.8)*	0	34.8 (15.3, 54.2)
Injection site erythema	5 (21.7)	0	21.7 (4.9, 38.6)
Injection site pain	2 (8.7)	0	8.7 (-2.8, 20.2)
Injection site bruising	1 (4.3)	0	4.3 (-4.0, 12.7)
Injection site rash	1 (4.3)	0	4.3 (-4.0, 12.7)
Vaccination site pain	1 (4.3)	0	4.3 (-4.0, 12.7)
Infections and infestations (SOC)			
Bacterial infection	2 (8.7)	0	8.7 (-2.8, 20.2)
Tooth abscess	1 (4.3)	0	4.3 (-4.0, 12.7)
Urinary tract infection	1 (4.3)	0	4.3 (-4.0, 12.7)
Skin and subcutaneous tissue disorders (SOC)			
Erythema	5 (21.7)	0	21.7 (4.9, 38.6)
Injection site erythema	5 (21.7)	0	21.7 (4.9, 38.6)
Vascular disorders (SOC)			
Hemorrhage	3 (13.0)	0	13.0 (-0.7, 26.8)
Hematuria	1 (4.3)	0	4.3 (-4.0, 12.7)
Injection site bruising	1 (4.3)	0	4.3 (-4.0, 12.7)
Metrorrhagia	1 (4.3)	0	4.3 (-4.0, 12.7)

Source: adae.xpt; software: R.

¹Treatment-emergent adverse events defined as any AE with an onset date/time on or after administration (including any partial administration) of the first dose of study intervention and through the study completion date from the end of study case report form. Duration is the 6-month treatment period.

* The narrow FMQ Local Administration Reaction includes one patient with vaccination site reaction after COVID-19 vaccine. Excluding the patient with vaccination site reaction, injection site reactions occurred in 7 patients (30%) in the nedosiran group. Abbreviations: AE, adverse event; CI, confidence interval; COVID-19, coronavirus disease 2019; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Local Administration Reactions (Injection Site Reactions)

Local administration reactions occurred more frequently in the nedosiran group (seven participants, 30%) compared with placebo (zero participants). Participants could receive up to six injections during the 6-month placebo-controlled period. Three of the seven participants (43%) experienced a reaction with one dose, and two participants (29%) had a reaction with all six doses. Local administration reactions included erythema, pain, bruising, and rash. The reactions were generally mild and did not lead to treatment discontinuation. A total of 23 reactions were reported, of which 5 (22%) resolved within 1 day of the injection. The median time for resolution was 12 days after the injection (range 0 to 99 days).

Nausea

Four participants (17%) in the nedosiran group and one (8%) in the placebo group reported AEs of nausea. Of the participants in the nedosiran group with nausea, three participants reported nausea within two days after a nedosiran dose, and one reported nausea 10 days after the nedosiran dose. The median duration of nausea was 8 days (range 1 to 152 days). All episodes were mild, did not lead to study drug interruption or discontinuation, and all resolved (it is not clear if additional treatments were administered for the nausea). Additional details are provided below for the participants randomized to nedosiran who developed nausea. There is no obvious mechanistic basis for such an effect and based on the provided information, including the time course for the events relative to nedosiran administration, it seems unlikely that nedosiran played a role.

- *Participant* (b) (6): A 10-year-old female with a history of PH2, gastrostomy, attention deficit hyperactivity disorder, and seizure. The participant was on concomitant potassium and sodium phosphate, ethosuximide, and diazepam. The participant had an AE of nausea on Day 58, the same day as the third nedosiran dose. The participant continued nedosiran dosing, the last dose in DCR-PHXC-201 was administered on Day 149 (b) (6). The nausea was reported to have resolved on Day 209 (b) (6) i.e., a duration of 152 days. The participant continued to receive nedosiran in the extension Study (DCR-PHXC-301).
- *Participant* (b) (6): A 46-year-old female with a history of PH1, kidney stones, angiomyolipoma, cystitis, drug hypersensitivity, hypertension, mumps, kidney cyst, rubella, ureteral stent insertion, and varicella. The participant was on concomitant amiloride/hydrochlorothiazide, magnesium, metamizole, paracetamol, potassium citrate, telmisartan, and pyridoxine hydrochloride. The participant experienced an AE of nausea on Day 3 (b) (6), 2 days after the first dose of nedosiran (on (b) (6)). The episode was reported as resolved after 2 days, on Day 4 (b) (6). The participant remained on nedosiran and completed the study.
- *Participant* (b) (6): A 17-year-old female with a history of PH2, and lithotripsy. The participant was on concomitant potassium citrate and paracetamol as needed. On Day 96 (b) (6) 10 days after her fourth nedosiran dose, the participant reported an AE of nausea, which resolved on the same day. The participant remained on nedosiran and completed the study.
- *Participant* (b) (6): A 36-year-old female with a history of PH1, asthma, irritable bowel syndrome, migraine, muscle spasms, ureteral stent insertion, and urethral cyst. The participant was on concomitant magnesium, krill oil, betamethasone dipropionate, budesonide, formoterol fumarate, codeine, drospirenone, and ethinylestradiol betadex. The participant experienced an AE of nausea on Day 3 (b) (6), 2 days after the first dose of nedosiran (on (b) (6)). The episode lasted for 13 days and was reported as resolved on Day 15 (b) (6). The participant remained on nedosiran and completed the study.

Hepatic Adverse Events

No participant in the nedosiran group and one participant (8%) in the placebo group had AEs mapping to the System Organ Class Hepatobiliary Disorders and narrow FMQ Hepatic Injury.

Kidney Adverse Events

As shown in Table 29, a higher proportion of participants in the placebo group reported AEs that mapped to the Renal and Urinary Disorders System Organ Class (seven patients in the nedosiran group [30%] and five in the placebo [42%] group). No AEs of glomerulonephritis or acute kidney injury were reported.

Table 29. Adverse Events Mapping to the Renal and Urinary Disorders System Organ Class, Safety Population, DCR-PHXC-201

Body System or Organ Class Preferred Term	Nedosiran N=23 n (%)	Placebo N=12 n (%)	Nedosiran vs. Placebo Risk Difference (%) (95% CI)
Renal and urinary disorders	7 (30)	5 (42)	-12 (-22, 45)
Nephrolithiasis	4 (17)	3 (25)	-7 (-21, 41)
Calculus urinary	2 (9)	1 (8)	-1 (-22, 30)
Renal colic	1 (4)	2 (17)	-13 (-10, 44)
Hematuria	2 (9)	0	9 (-28, 18)
Hydronephrosis	0	1 (8)	-1 (-8, 38)
Renal pain	1 (4)	0	1 (-23, 23)
Urethral discharge	1 (4)	0	1 (-23, 23)

Source: adae.xpt; software: JMP Clinical.

Risk difference (with 95% CI) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event

Muscle Pain or Weakness

Muscle pain or weakness was an adverse event of special interest. No participants reported muscle pain or weakness. TEAEs of increased blood creatine phosphokinase (CPK) were reported in one participant in each treatment group (4% in nedosiran and 8% in placebo). One participant (4%) in the nedosiran group and none in the placebo group reported muscle spasms; two participants (9%) in the nedosiran group and 1 (8%) in the placebo group reported AEs of pain in extremity. The narrative for AE of muscle spasms is provided below. Based on the provided information, it is not clear that nedosiran played a role.

- **Participant (b) (6)**: A 36-year-old male with a history of PH1, hypertension, kidney stones, kidney stone removal, and ureteral stent placement. The participant was on concomitant magnesium, potassium citrate, ramipril, and pyridoxine. The participant developed muscle spasms (cramps in the hands) on Day 77, 14 days after the participant's third dose of nedosiran. The AE was reported as mild. It is not known when the event resolved; the final outcome of the AE was reported as unknown. The participant experienced intermittent increases of creatine kinase (CK) levels (see additional details [below](#)). CK was normal when

assessed on Days 45, 60, and 90. Nedosiran dosing was not interrupted or discontinued and the patient continued to receive nedosiran in the extension study (DCR-PHXC-301).

7.6.2.6. Laboratory Findings, DCR-PHXC-201

Kidney Tests

The proportion of participants with a serum creatinine ≥ 1.5 x Baseline was similar in the two groups (Table 30). eGFR decreased by 25% or more in three participants (30%) in the placebo group and none in the nedosiran group.

Table 30. Participants With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Trial DCR-PHXC-201

Laboratory Parameter	Nedosiran N=23 n/N_w (%)	Placebo N=12 n/N_w (%)	Nedosiran vs. Placebo Risk Difference (%) (95% CI)
Creatinine, high (mg/dL)			
Level 1 (≥ 1.5 x baseline)	2/23 (8.7)	1/12 (8.3)	0.4 (-19.1, 19.8)
Level 2 (≥ 2 x baseline)	0/23 (0)	1/12 (8.3)	-8.3 (-24.0, 7.3)
Level 3 (≥ 3 x baseline)	0/23 (0)	0/12 (0)	0 (0, 0)
eGFR, low (mL/min/1.73 m ²)			
Level 1 (≥ 25 % decrease)	0/21 (0)	3/10 (30.0)	-30.0 (-58.4, -1.6)
Level 2 (≥ 50 % decrease)	0/21 (0)	1/10 (10.0)	-10.0 (-28.6, 8.6)
Level 3 (≥ 75 % decrease)	0/21 (0)	0/10 (0)	0 (0, 0)

Source: ad b.xpt; software: R.

Duration is the 6-month treatment period.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data

Creatine Phosphokinase / Creatine Kinase

Five participants (22%) in the nedosiran group and two (17%) in the placebo group had an increase in CPK above the ULN, as shown in [Table 31](#). Four of these participants in the nedosiran group (17%) and none in placebo had a CPK >3x ULN. None of the participants had symptoms of muscle pain or weakness, all remained on nedosiran treatment, and CPK in all but one participant ^{(b) (6)} returned to normal without additional intervention, suggesting that nedosiran did not play a role. Participant ^{(b) (6)} had fluctuating CK levels that could have been related to exercise (see the narrative below).

- *Participant ^{(b) (6)}*: An 18-year-old male with history of PH1, kidney stones, lithotripsy, gout, and stage 2 CKD. The participant was on concomitant allopurinol, colchicine, ibuprofen, potassium citrate, and pyridoxine. The participant was randomized to nedosiran. On ^{(b) (6)} the participant's Baseline CK was 100 U/L (ULN 200 U/L). On Day 45 ^{(b) (6)}, after receiving two doses of nedosiran, CK increased to 1416 U/L (7x ULN). AEs reported around the same time included non-cardiac chest pain and exacerbation of gout on Day 46 ^{(b) (6)}. The gout was treated with colchicine. On Day 60 ^{(b) (6)} repeat CK was 68 U/L and remained within the normal range thereafter until the end of the study. Nedosiran dosing was not changed or interrupted because of the elevated CK. The participant received five of six scheduled nedosiran doses in DCR-PHXC-201 from ^{(b) (6)} to ^{(b) (6)} (Day 90 dose missed because of coronavirus disease 2019 (COVID-19)-related travel restrictions). He rolled over to DCR-PHXC-301 and continued nedosiran from ^{(b) (6)} (Day 1) to Day 60 (3 doses). CPK remained normal during participation in DCR-PHXC-301. The participant discontinued participation in the study because he moved to another country and could not return to the United States because of COVID-19 travel restrictions.
- *Participant ^{(b) (6)}*: A 41-year-old male with history of PH1, urinary stones, lithotripsy, kidney stone removal, urethral repair, dry eye, hypertension, and Wolff-Parkinson-White syndrome on concomitant hyaluronate sodium eye drops, paracetamol, ramipril, and pyridoxine. On ^{(b) (6)} the participant's baseline CK was elevated at 355 U/L (ULN 200 U/L). On Day 15 ^{(b) (6)} 14 days after the first dose of nedosiran, CK transiently increased to 837 U/L (4x ULN) but decreased to 394 U/L on Day 30. On Day 120 ^{(b) (6)} CK transiently increased to 3099 U/L (15x ULN); it decreased to 605 U/L when rechecked on ^{(b) (6)} and had returned to around baseline at 377 U/L on Day 150 ^{(b) (6)} without intervention. The participant's end-of-study (Day 180, ^{(b) (6)} CK was 499 U/L. Nedosiran dosing was not changed or interrupted during the study.
 - The patient subsequently rolled over to DCR-PHXC-301; all available CK levels to data cutoff have been elevated at 419 U/L on Day 30, 310 U/L on Day 90, and 1225 U/L (6x ULN) on Day 180. The participant reported rock climbing and that he had started exercising.

- **Participant (b) (6)**: A 16-year-old male with a history of PH1, hypomagnesemia, vitamin D deficiency, post-traumatic stress disorder, tinea capitis, and obesity. The participant was on concomitant cholecalciferol, magnesium citrate, pyridoxine, topical ketoconazole, and topical betamethasone dipropionate-salicylic acid. The participant received six scheduled nedosiran doses in DCR-PHXC-201 from (b) (6) to (b) (6). The participant had an increase in CPK to >3x ULN while in DCR-PHXC-201.
 - Baseline CPK in DCR-PHXC-201 was mildly elevated at 268 U/L (normal range 2 to 251 U/L). One day after the first nedosiran dose, CPK was 142 U/L. On Day 30, CPK increased to 940 U/L (3.7x ULN) and was associated with an AE of fatigue, then down trended to normal by Day 45 and remained within the normal range thereafter, including from Baseline to Month 10 in DCR-PHXC-301. Nedosiran dosing was not interrupted.
- **Participant (b) (6)**: A 36-year-old male with history of PH1, hypertension, kidney stones, kidney stone removal, and ureteral stent placement. The participant was on concomitant magnesium, potassium citrate, ramipril, and pyridoxine. The participant had an increase in CPK to >3x ULN in DCR-PHXC-201 and to >10x ULN in DCR-PHXC-301.
 - The participant received six doses of nedosiran from (b) (6) to (b) (6) in DCR-PHXC-201. Baseline CK was 137 U/L (normal range 20 to 200 U/L). CK subsequently remained within the normal range until Day 120 when the level was 742 U/L (3.7x ULN). The patient had gone to the gym the day prior. On Day 150 (b) (6) CK was normal at 135 U/L. The participant also experienced an AE of muscle spasms (reported term for the AE was “hand cramps”) on Day 77 (b) (6) 14 days after the participant’s third dose of nedosiran (see details [above](#)). The duration of the AE was not reported. As noted, the participant’s CK was normal when assessed on Days 45, 60, and 90.
 - The participant subsequently rolled over to DCR-PHXC-301 where his baseline CK was normal at 151 U/L on (b) (6). On Day 30, CK was elevated to 2464 U/L (12x ULN). It is not clear if this episode was associated with exercise. Repeat CK on Day 90 was 242 U/L and on Day 120, 107 U/L. Nedosiran dosing was not interrupted or discontinued.

Table 31. Participants With Elevated CPK Values, Safety Population, DCR-PHXC-201

Laboratory Parameter	Nedosiran N=23 n/N _w (%)	Placebo N=12 n/N _w (%)	Nedosiran vs. Placebo Risk Difference (%) (95% CI)
CPK, high (U/L)			
Level 1 (>3x ULN)	4/23 (17.4)	0/12 (0)	17.4 (1.9, 32.9)
Level 2 (>5x ULN)	2/23 (8.7)	0/12 (0)	8.7 (-2.8, 20.2)
Level 3 (>10x ULN)	1/23 (4.3)	0/12 (0)	4.3 (-4.0, 12.7)

Source: ad b.xpt; software: R.

Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.

Duration is the 6-month treatment period.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; ULN, upper limit of normal

Antidrug Antibody (Immunogenicity)

The Office of Biotechnology Products reviewed the Applicant's ADA assay, and confirmed that it is suitable to detect ADAs against nedosiran. No participant had treatment-emergent ADAs to nedosiran. One participant had a positive ADA at screening before receiving nedosiran; the titer of the ADA decreased in the patient during the study.

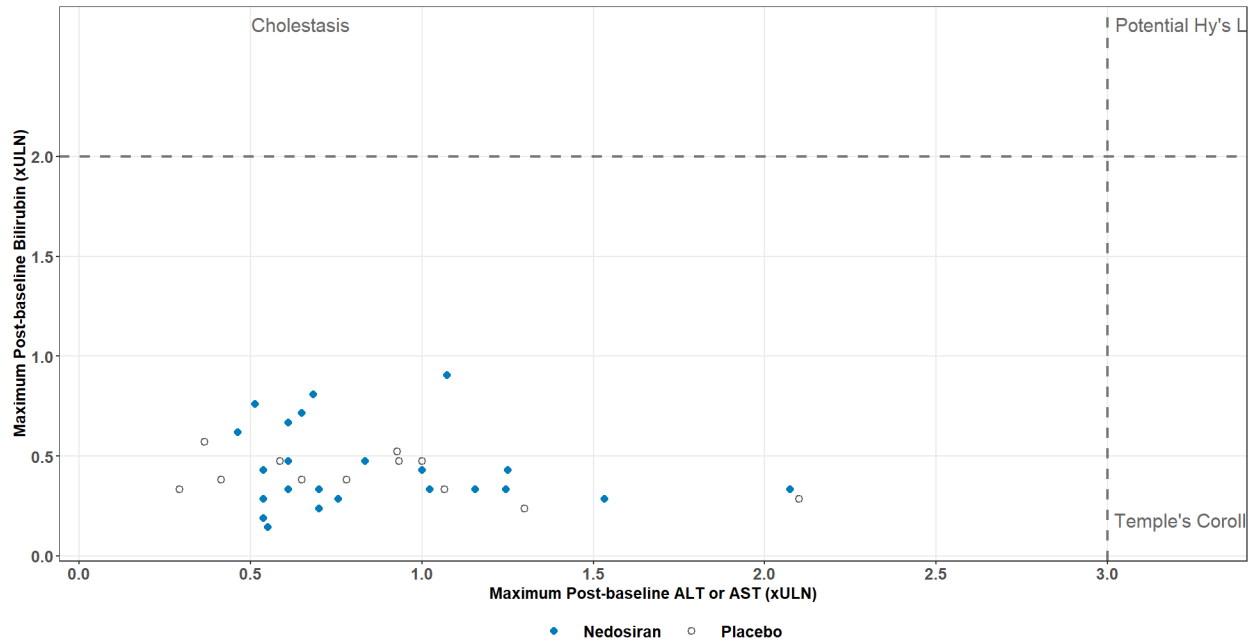
Low Neutrophil Counts

Four participants (17%) in the nedosiran group and none in the placebo group had low neutrophil counts of <500 cells/ μ L for a risk difference of 17% (95% CI 2, 33). All participants (b) (6) were from the same study site (101) and all episodes were transient and resolved despite continuation of nedosiran. None of the participants experienced infections during the time that the low neutrophil counts were reported. Given the findings at Site 101, the Applicant split samples from three participants for evaluation at both a local and central laboratory. According to the Applicant, neutrophil counts were within normal limits for all samples analyzed at the local laboratory, and were reported to be low for all samples analyzed at the central laboratory. The Applicant hypothesizes that "transportation issues may have affected the quality of the specimens, as literature describes issues with collection (i.e., cold tubes) and transport (i.e., taking too long to be analyzed) as a possible cause of low ANC ([Brigden and Dalal 1999](#); [Nagler et al. 2014](#))."

7.6.2.7. Assessment of Drug-Induced Liver Injury, DCR-PHXC-201

[Figure 5](#) shows a screening assessment for potential cases of drug-induced liver injury. Most participants in both groups maintained ALT, AST, and total bilirubin values within the normal range during the trial. No patient had an AST or ALT value >3x ULN, or total bilirubin >2x ULN.

Figure 5. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, DCR-PHXC-201



Source: ad b.xpt; software: R.

Each data point represents a patient plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.

A potential Hy's Law case (red circle) was defined as having any postbaseline total bilirubin equal to or exceeding 2x ULN within 30 days after a postbaseline ALT or AST equal to or exceeding 3x ULN, and ALP less than 2x ULN (note ALP values are not circled). All patients with at least one postbaseline ALT or AST and bilirubin are plotted.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; TB, total bilirubin; ULN, upper limit of normal

7.6.2.8. Vital Signs' Analyses, DCR-PHXC-201

There were no significant treatment-emergent changes from baseline in blood pressure, heart rate, or respiratory rate in either treatment group, or significant differences between the treatment groups.

7.6.2.9. Subgroup Analyses, DCR-PHXC-201

Review of the safety data in the subset of participants with PH1 did not identify additional safety concerns (additional information on safety data in patients with PH1 in [Section 17](#)). Overall, the safety data in the overall trial population was driven by the findings in participants with PH1. Subgroup analyses based on demographic factors were not conducted given the size of the study population and the safety profile seen in the larger study population.

7.6.3. Safety Results, DCR-PHXC-301

As shown in [Table 32](#), of the 51 participants enrolled in Study DCR-PHXC-301, twelve participants were on placebo prior to enrolling in Study DCR-PHXC-301. Among the 51 participants enrolled in the study, the median duration of exposure to nedosiran (not considering

the exposure in DCR-PHXC-201 prior to enrollment in DCR-PHXC-301) was 11 months (range 1 to 29 months). Eighteen participants (35%) received nedosiran for 18 months or longer.

Table 32. Duration of Exposure, Safety Population, DCR-PHXC-301

Parameter	Placebo To Nedosiran PH N=12 n (%)	Nedosiran To Nedosiran PH N=39 n (%)	Nedosiran Combined PH N=51 n (%)
Duration of treatment, months			
Mean (SD)	9.4 (5.4)	14.9 (8.1)	13.6 (7.8)
Median (Q1, Q3)	7.5 (6.6, 11.2)	15.6 (7, 22.2)	10.8 (6.9, 21.2)
Minimum, maximum	1, 20.1	1.9, 28.7	1, 28.7
Total exposure (person years)	9	49	58
Patients treated, by duration, n (%)			
<3 months	1 (8.3)	2 (5.1)	3 (5.9)
≥3 to <6 months	2 (16.7)	5 (12.8)	7 (13.7)
≥6 to <12 months	6 (50.0)	11 (28.2)	17 (33.3)
≥12 to <18 months	2 (16.7)	4 (10.3)	6 (11.8)
≥18 months	1 (8.3)	17 (43.6)	18 (35.3)

Source: adex.xpt and adsl.xpt; software: R.

Duration is a 36-month period.

Abbreviations: N, number of participants in treatment arm; n, number of participants with a given treatment duration; PH, primary hyperoxaluria; Q1, first quartile; Q3, third quartile; SD, standard deviation

7.6.3.1. Overview of Treatment-Emergent Adverse Events Summary, DCR-PHXC-301

Overall, 47 participants (92%) experienced a TEAE during Study DCR-PHXC-301, most of which were mild (Table 33). Four participants (8%), all previously on nedosiran in Study DCR-PHXC-201 experienced SAEs, and three participants (6%), all previously on nedosiran in Study DCR-PHXC-201, interrupted dosing because of an AE. No participant discontinued nedosiran because of AEs. There were no deaths.

Table 33. Overview of Treatment-Emergent Adverse Events, Safety Population, DCR-PHXC-301

Event Category	Placebo To Nedosiran PH N=12 n (%)	Nedosiran To Nedosiran PH N=39 n (%)	Nedosiran Combined PH N=51 n (%)
SAE	0	4 (10.3)	4 (7.8)
SAEs with fatal outcome	0	0	0
Life-threatening SAEs	0	0	0
AE leading to permanent discontinuation of study drug	0	0	0
AE leading to dose modification of study drug	0	3 (7.7)	3 (5.9)
AE leading to interruption of study drug	0	3 (7.7)	3 (5.9)
AE leading to reduction of study drug	0	0	0
AE leading to dose delay of study drug	0	0	0
Other	0	0	0

Event Category	Placebo To Nedosiran PH N=12 n (%)	Nedosiran To Nedosiran PH N=39 n (%)	Nedosiran Combined PH N=51 n (%)
Any AE	12 (100)	35 (89.7)	47 (92.2)
Severe and worse	1 (8.3)	1 (2.6)	2 (3.9)
Moderate	3 (25.0)	12 (30.8)	15 (29.4)
Mild	8 (66.7)	22 (56.4)	30 (58.8)

Source: adae.xpt; software: R.

Treatment-emergent adverse events defined as any AE with an onset date/time on or after administration (including any partial administration) of the first dose of study intervention and through the study completion date from the end of study case report form. Duration was a 36-month period.

Severity as assessed by the investigator.

Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with at least one event; PH, primary hyperoxaluria subtypes combined; PH, primary hyperoxaluria; SAE, serious adverse event

7.6.3.2. Deaths, DCR-PHXC-301

There were no deaths in Study DCR-PHXC-301 as of the data cutoff.

7.6.3.3. Serious Treatment-Emergent Adverse Events, DCR-PHXC-301

Four participants (8%) experienced SAEs in Study DCR-PHXC-301 ([Table 34](#)). These SAEs included abdominal pain, pyelonephritis, pain in extremity, acute kidney injury, calculus urinary, and nephrolithiasis. The SAEs of pyelonephritis, acute kidney injury, calculus urinary, and nephrolithiasis are events that are commonly seen in patients with PH and are not discussed further. The SAEs of abdominal pain and pain in the extremity were likely not caused by nedosiran as indicated in the narratives below.

- *Participant* ^{(b) (6)}: A 37-year-old male with PH1 was admitted for one day for transient epigastric abdominal pain 16 days after the second dose of nedosiran. The pain resolved after a few hours and did not lead to interruption or discontinuation of nedosiran.
- *Participant* ^{(b) (6)}: A 26-year-old female with PH1 was admitted for an SAE of pain in extremity because of infiltration of an intravenous infusion.

Table 34. Patients With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, DCR-PHXC-301

System Organ Class Preferred Term	Placebo To Nedosiran PH N=12 n (%)	Nedosiran To Nedosiran PH N=39 n (%)	Nedosiran Combined PH N=51 n (%)
Any SAE	0	4 (10.3)	4 (7.8)
Gastrointestinal disorders (SOC)	0	1 (2.6)	1 (2.0)
Abdominal pain	0	1 (2.6)	1 (2.0)
Infections and infestations (SOC)	0	1 (2.6)	1 (2.0)
Pyelonephritis	0	1 (2.6)	1 (2.0)
Musculoskeletal and connective tissue disorders (SOC)	0	1 (2.6)	1 (2.0)
Pain in extremity	0	1 (2.6)	1 (2.0)

System Organ Class Preferred Term	Placebo To Nedosiran PH	Nedosiran To Nedosiran PH	Nedosiran Combined PH
	N=12 n (%)	N=39 n (%)	N=51 n (%)
Renal and urinary disorders (SOC)	0	2 (5.1)	2 (3.9)
Acute kidney injury	0	1 (2.6)	1 (2.0)
Calculus urinary	0	1 (2.6)	1 (2.0)
Nephrolithiasis	0	2 (5.1)	2 (3.9)

Source: adae.xpt; software: R.

Treatment-emergent adverse events defined as any AE with an onset date/time on or after administration (including any partial administration) of the first dose of study intervention and through the study completion date from the end of study case report form.

Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Duration is a 36-month period.

Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with adverse event; PH, primary hyperoxaluria subtypes combined; SOC, system organ class

7.6.3.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation or Dose Interruptions, DCR-PHXC-301

No participants discontinued study treatment because of AEs.

Dose Interruptions

The dose of nedosiran was interrupted in three participants (6%) because of AEs, including in one participant because of hospitalization for SAEs of nephrolithiasis and pyelonephritis (b) (6), one participant for elevated AST, ALT, and bilirubin (b) (6), and one patient because of COVID-19 (b) (6). All the AEs resolved, and all patients continued to receive nedosiran treatment as of data cut-off.

- **Participant (b) (6):** A 28-year-old male with a history of PH1, nephrolithotomies, and ureteroscopy with stent insertion, on concomitant magnesium and potassium citrate. The participant received a single dose of nedosiran 3 mg/kg on (b) (6), in Study DCR-PHXC-101. He received his first dose of nedosiran in Study DCR-PHXC-301 on (b) (6) (Day 1). On Day 55 (25 days after the second dose of nedosiran in Study DCR-PHXC-301), the participant was admitted to the hospital with SAEs of nephrolithiasis and pyelonephritis (symptoms included right flank pain, fever, right lower back pain, blood in urine and renal colic). The participant was found to have a large right uretero-pelvic junction kidney stone requiring nephrostomy to relieve obstruction, and *Staphylococcus aureus* bacteremia and pyelonephritis. The infection was treated with intravenous meropenem and vancomycin. The participant missed the third nedosiran dose (Day 60), which was due while he was being treated in the hospital. Nedosiran dosing was resumed on Day 90, after discharge from the hospital. The participant remains on nedosiran as of data cutoff. No additional delays or dosing interruptions occurred as of data cutoff.

- Participant** (b) (6): A 21-year-old male with history of PH1, stage 2 to 3 CKD, hypertension, vitamin D deficiency, Gilbert syndrome, and nonalcoholic steatohepatitis. The participant was on concomitant citric acid, potassium bicarbonate, sodium citrate, cholecalciferol, magnesium aspartate and pyridoxine. The participant received one dose of nedosiran 6 mg/kg on (b) (6) in Study DCR-PHXC-101. The participant's baseline ALT, AST, total bilirubin, and direct bilirubin were 60 U/L (reference range 13 to 67 U/L), 30 U/L (reference range 16 to 45 U/L), 2.2 mg/dL (reference range 0.3 to 2 mg/dL), and 0.6 mg/dL (reference range 0.05 to 0.5 mg/dL), respectively. On Day 2 of Study DCR-PHXC-101, the participant had a TEAE of blood bilirubin increased (total bilirubin 2.3 mg/dL) that resolved on Day 8 (total bilirubin 1.8 mg/dL). On Day 29 of DCR-PHXC-101, the participant experienced TEAEs of alanine aminotransferase increased (ALT 86 U/L) and blood bilirubin increased (total bilirubin 2.1 mg/dL, direct bilirubin lower than baseline at 0.5 mg/dL). The blood bilirubin increased resolved on Day 46 and the 'alanine aminotransferase increased' was ongoing at the end of the study. At the end of the study (Day 57), the participant's ALT was 106 U/L, AST 48 U/L, total bilirubin 1.8 mg/dL, and direct bilirubin was 0.5 mg/dL.

 - The participant began monthly dosing with nedosiran in Study DCR-PHXC-301 on (b) (6) (Day 1). At Baseline in Study DCR-PHXC-301, ALT was 72 U/L (reference 0 to 45 U/L), AST 52 U/L (reference 0 to 41 U/L), total bilirubin 1.3 mg/dL (reference 0 to 1.2 mg/dL), direct bilirubin 0.41 mg/dL, and alkaline phosphatase (ALP) was 70 U/L. On Day 2, AEs of AST increase and blood bilirubin increased were reported. On Day 2, liver assessments included ALT of 101 U/L, AST 54 U/L, total bilirubin 1.6 mg/dL, direct bilirubin 0.6 mg/dL, and ALP of 63 U/L. The participant remained on nedosiran; ALT fluctuated from 94 to 99 U/L, AST ~45 U/L, and total bilirubin 1.1 to 1.6 mg/dL. On Day 45 (b) (6) AEs of aminotransferase increased [worsening of AST elevation], alanine aminotransferase increased [worsening of ALT elevation], and blood bilirubin increased [worsening of bilirubin elevation] were reported. Evaluation of the participant's liver assessments revealed an increase in ALT to a maximum of 156 U/L on Day 48, ranging from 143 to 98 U/L thereafter; the last available ALT was 115 U/L at Month 21. AST was 57 U/L on Day 45, varied between 57 to 48 U/L from Day 48 to Month 9, increased transiently to 70 U/L at Month 12, then decreased to 47 U/L at Month 15; the last AST was 49 U/L at Month 21. Total bilirubin peaked at 2.1 mg/dL on Day 28 then decreased to 1.4 mg/dL on Day 30 and ranged from 1.3 to 1.9 mg/dL thereafter; the last available result at Month 21 was 1.8 mg/dL.
 - The participant's ALT was >3x ULN on Day 45, Month 6, and Month 12 (156 U/L, 138 U/L, and 143 U/L, respectively) and bilirubin was >1.5x ULN (ULN 1.2 mg/dL) at Month 4 (1.9 mg/dL). The patient did not meet criteria for nedosiran discontinuation (ALT or AST >5x baseline, with baseline <2x ULN); however, nedosiran dosing was delayed while an evaluation of the elevations on Day 45 was undertaken.
 - The participant was evaluated by a gastroenterologist on (b) (6) (~Month 19) who concluded based on additional investigation including elastography, that the participant had nonalcoholic fatty liver disease.
 - This participant's fluctuations in liver assessments were likely secondary to other factors including Gilbert syndrome and nonalcoholic fatty liver disease. A causal relationship with nedosiran is unlikely given that the liver assessments did not continue to worsen while the participant remained on nedosiran for 21 months in Study DCR-PHXC-301.

- **Participant** ^{(b) (6)}: A 45-year-old male with PH2. Nedosiran dosing was temporarily interrupted when the participant developed COVID-19 at Month 17. Dosing was resumed at Month 18 and the participant remained on nedosiran as of data cutoff.

7.6.3.5. Treatment-Emergent Adverse Events, DCR-PHXC-301

AEs by Preferred Term that occurred in two or more patients are shown in [Table 35](#). Of the 51 patients enrolled, 47 (92%) reported AEs. The most common AEs were injection site reactions. Two patients (4%), one with PH1, the other with PH2, had AEs of lipoatrophy at the injection site; this injection site reaction was not reported in Study DCR-PHXC-201.

Table 35. Participants With Common Adverse Events Occurring in Two or More Participants, Safety Population, DCR-PHXC-301

Preferred Term	Placebo To Nedosiran PH N=12 n (%)	Nedosiran To Nedosiran PH N=39 n (%)	Nedosiran Combined PH N=51 n (%)
Any AE	12 (100)	35 (89.7)	47 (92.2)
Injection site pain	3 (25.0)	8 (20.5)	11 (21.6)
Nephrolithiasis	3 (25.0)	7 (17.9)	10 (19.6)
Adverse event following immunization	2 (16.7)	9 (23.1)	11 (21.6)
Vaccination site pain	2 (16.7)	4 (10.3)	6 (11.8)
Alanine aminotransferase increased	1 (8.3)	2 (5.1)	3 (5.9)
Cough	1 (8.3)	4 (10.3)	5 (9.8)
Fatigue	1 (8.3)	3 (7.7)	4 (7.8)
Flank pain	1 (8.3)	2 (5.1)	3 (5.9)
Hematuria	1 (8.3)	3 (7.7)	4 (7.8)
Headache	1 (8.3)	8 (20.5)	9 (17.6)
Injection site discoloration	1 (8.3)	4 (10.3)	5 (9.8)
Injection site erythema	1 (8.3)	13 (33.3)	14 (27.5)
Injection site pruritus	1 (8.3)	2 (5.1)	3 (5.9)
Nausea	1 (8.3)	4 (10.3)	5 (9.8)
Rhinitis	1 (8.3)	2 (5.1)	3 (5.9)
Upper respiratory tract infection	1 (8.3)	3 (7.7)	4 (7.8)
Urinary tract infection	1 (8.3)	5 (12.8)	6 (11.8)
Abdominal pain	0	3 (7.7)	3 (5.9)
Aspartate aminotransferase increased	0	3 (7.7)	3 (5.9)
Bladder pain	0	2 (5.1)	2 (3.9)
Calculus urinary	0	3 (7.7)	3 (5.9)
Constipation	0	2 (5.1)	2 (3.9)
COVID-19	0	7 (17.9)	7 (13.7)
Cystitis	0	4 (10.3)	4 (7.8)
Diarrhea	0	3 (7.7)	3 (5.9)
Dizziness	0	2 (5.1)	2 (3.9)
Dysmenorrhea	0	3 (7.7)	3 (5.9)
Enterobiasis	0	2 (5.1)	2 (3.9)
Glomerular filtration rate decreased	0	2 (5.1)	2 (3.9)
Glutamate dehydrogenase increased	0	2 (5.1)	2 (3.9)
Hypertension	0	2 (5.1)	2 (3.9)
Injection site atrophy	0	2 (5.1)	2 (3.9)
Injection site discomfort	0	7 (17.9)	7 (13.7)
Injection site hematoma	0	3 (7.7)	3 (5.9)

	Placebo To Nedosiran PH N=12 n (%)	Nedosiran To Nedosiran PH N=39 n (%)	Nedosiran Combined PH N=51 n (%)
Preferred Term			
Injection site induration	0	2 (5.1)	2 (3.9)
Injection site rash	0	3 (7.7)	3 (5.9)
Nasopharyngitis	0	10 (25.6)	10 (19.6)
Oropharyngeal pain	0	4 (10.3)	4 (7.8)
Pyrexia	0	4 (10.3)	4 (7.8)
Renal colic	0	5 (12.8)	5 (9.8)
Renal pain	0	2 (5.1)	2 (3.9)
Urethritis	0	2 (5.1)	2 (3.9)
Vomiting	0	5 (12.8)	5 (9.8)

Source: adae.xpt; software: R.

Treatment-emergent adverse events defined as any AE with an onset date/time on or after administration (including any partial administration) of the first dose of study intervention and through the study completion date from the end of study case report form. Duration was a 36-month period.

Coded as Medical Dictionary for Regulatory Activities preferred terms.

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; N, number of patients in treatment arm; n, number of patients with adverse event; PH, primary hyperoxaluria subtypes combined

Other AEs of interest included three participants (6%) with ALT increased, three participants (6%) with AST increased, and one participant (2%) with bilirubin conjugated increased (Table 36).

Table 36. Adverse Events of Special Interest Assessment, Safety Population, DCR-PHXC-301

	Placebo To Nedosiran PH N=12 n (%)	Nedosiran To Nedosiran PH N=39 n (%)	Nedosiran Combined PH N=51 n (%)
Drug-Induced Liver Injury Assessment			
AE grouping related to AESI	1 (8.3)	3 (7.7)	4 (7.8)
Alanine aminotransferase increased	1 (8.3)	2 (5.1)	3 (5.9)
Aspartate aminotransferase increased	0	3 (7.7)	3 (5.9)
Bilirubin conjugated increased	0	1 (2.6)	1 (2.0)
Maximum severity			
Death	0	0	0
Life-threatening	0	0	0
Severe	0	0	0
Moderate	0	0	0
Mild	1 (8.3)	3 (7.7)	4 (7.8)
Serious	0	0	0
Deaths	0	0	0
Resulting in discontinuation	0	0	0

Source: adae.xpt; software: R.

Treatment-emergent adverse events defined as any AE with an onset date/time on or after administration (including any partial administration) of the first dose of study intervention and through the study completion date from the end of study case report form. Duration is a 36-month period.

Relatedness is determined by investigator.

Abbreviations: AE, adverse event; AESI, adverse event of special interest; N, number of patients in treatment arm; n, number of patients with adverse event; PH, primary hyperoxaluria subtypes combined

Review of these events did not suggest that nedosiran played a role. Information on additional testing to evaluate the cause of these abnormalities, where available, is provided in the narratives below.

- *Participant* (b) (6): See patient narrative in [Section 7.6.3.4](#) under Dose Interruptions. This patient had TEAEs of ALT increased, AST increased, and blood bilirubin increased.
- *Participant* (b) (6): A 22-year-old female with a history of PH1, nephrolithiasis, CKD, musculoskeletal chest pain, and vitamin D deficiency. The patient received a single dose of nedosiran 6 mg/kg on (b) (6) in Study DCR-PHXC-101. The patient began monthly nedosiran in Study DCR-PHXC-301 on (b) (6). She was on concomitant citric acid, potassium bicarbonate, sodium citrate, oral contraception, ibuprofen/paracetamol for intermittent headache, and magnesium. At Month 21, the patient developed TEAEs of alkaline phosphatase increased, alanine aminotransferase increased, aspartate aminotransferase increased, bilirubin conjugated increased, and blood lactate dehydrogenase increased. The AEs were mild and resolved approximately 2 weeks later.
 - Review of the participant's laboratory assessments revealed that from Month 18 to Month 21, there was an increase of ALT from 24 to 113 U/L, AST from 24 to 103 U/L, LDH from 186 to 337 U/L, and ALP from 89 to 117 U/L. Total bilirubin increased from 0.7 mg/dL at Month 15 to 1 mg/dL at Month 18, then decreased to 0.5 mg/dL at Month 21. When rechecked approximately 2 weeks later (last available assessments), AST was 36 U/L, ALT 34 U/L, bilirubin 0.6 mg/dL, LDH 199 U/L, and ALP 91 U/L.
 - Nedosiran dosing was not interrupted or delayed and the patient remained on nedosiran as of data cutoff.
- *Participant* (b) (6): A 30-year-old male with a history of PH1, kidney stones, obesity, dizziness, tendonitis, and Hashimoto thyroiditis. The participant was on concomitant levothyroxine, sodium bicarbonate, and pyridoxine. The participant was on placebo in Study DCR-PHXC-201 and began treatment with nedosiran in Study DCR-PHXC-301 on (b) (6) (Day 1). At Month 3, the participant had an AE of ALT increased. Review of the participant's liver assessments revealed that the baseline ALT was 29 U/L, increased to 53 U/L at Month 3, then decreased to 45 U/L at Month 6 and 32 U/L at Month 9 (last available assessment as of data cutoff). There were no significant changes from Baseline to Month 3 in AST or bilirubin.
 - The AE was reported to be mild, nedosiran dosing was not interrupted, and the AE was reported as resolved at Month 6.
- *Participant* (b) (6): A 27-year-old female with a history of PH2, lithotripsy, hypertonionia, arthritis, and hypertension. The participant was on concomitant hydrochlorothiazide and ramipril. She received a single dose of nedosiran in Study DCR-PHXC-101 on (b) (6) and began monthly nedosiran in Study DCR-PHXC-301 on (b) (6) (Day 1). Three AEs of aspartate aminotransferase increased were reported on Day 15 (resolved on Day 29), Month 3 (resolved at Month 11), and Month 15 (resolved at Month 18). All TEAEs were considered mild in severity.
 - The participant was asymptomatic, no new medications were introduced, and liver ultrasound was normal. Evaluation of liver assessments reveals that the patient had an elevated AST at screening of 51 U/L and at Baseline of 45 U/L (reference range

0 to 41 U/L). On Day 15, AST increased to 73 U/L (maximum level while in the Study), then fluctuated from 42 to 53 U/L from Day 30 to Month 12, increased to 58 U/L at Month 15, and fluctuated from 40 to 51 U/L from Months 18 to 24. There were no significant changes in ALT or bilirubin during this time. Nedosiran dosing was not interrupted or delayed.

7.6.3.6. Laboratory Findings, DCR-PHXC-301

Kidney Tests

Three participants (6%) had an increase in serum creatinine to ≥ 1.5 x baseline, including one participant (2%) with an elevation ≥ 2 x baseline but < 3 x baseline. No participant had a $\geq 25\%$ decrease in eGFR (Table 37). These are expected events in participants with PH, and as noted in Section 7.6.2.6, these laboratory findings occurred with equal or lower frequency in patients on nedosiran compared with participants on placebo in DCR-PHXC-201.

Table 37. Participants With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, DCR-PHXC-301

Laboratory Parameter	Placebo To Nedosiran PH N=12 n/N _w (%)	Nedosiran To Nedosiran PH N=39 n/N _w (%)	Nedosiran Combined PH N=51 n/N _w (%)
Creatinine, high (mg/dL)			
Level 1 (≥ 1.5 x baseline)	0/12 (0)	3/39 (7.7)	3/51 (5.9)
Level 2 (≥ 2 x baseline)	0/12 (0)	1/39 (2.6)	1/51 (2.0)
Level 3 (≥ 3 x baseline)	0/12 (0)	0/39 (0)	0/51 (0)
eGFR, low (mL/min/1.73 m ²)			
Level 1 ($\geq 25\%$ decrease)	0/0 (NA)	0/15 (0)	0/15 (0)
Level 2 ($\geq 50\%$ decrease)	0/0 (NA)	0/15 (0)	0/15 (0)
Level 3 ($\geq 75\%$ decrease)	0/0 (NA)	0/15 (0)	0/15 (0)

Source: ad b.xpt; software: R.

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is a 36-month period.

Abbreviations: eGFR, estimated glomerular filtration rate; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; PH, primary hyperoxaluria subtypes combined

Creatine Phosphokinase/Creatine Kinase

As shown in Table 38, 7 participants (14%) had an increase in CPK > 3 x ULN, including 4 participants (8%) with levels > 5 x ULN, and 2 participants (4%) with levels > 10 x ULN. None of the participants had symptoms of muscle pain or weakness, all remained on nedosiran, and CPK levels returned to the normal range without additional intervention in all but one participant ((b) (6)); as noted in Section 7.6.2.6, Participant ((b) (6)) had fluctuating CK levels that could have been related to exercise). The narratives for these participants are provided below.

Table 38. Participants With Elevated Creatine Phosphokinase Levels, Safety Population, DCR-PHXC-301

Laboratory Parameter	Placebo To Nedosiran PH N=12 n/N _w (%)	Nedosiran To Nedosiran PH N=39 n/N _w (%)	Nedosiran Combined PH N=51 n/N _w (%)
CPK, high (U/L)			
Level 1 (>3x ULN)	0/12 (0)	7/39 (17.9)	7/51 (13.7)
Level 2 (>5x ULN)	0/12 (0)	4/39 (10.3)	4/51 (7.8)
Level 3 (>10x ULN)	0/12 (0)	2/39 (5.1)	2/51 (3.9)

Source: ad b.xpt; software: R.

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is a 36-month period.

Abbreviations: CPK, creatine phosphokinase; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; PH, primary hyperoxaluria subtypes combined; ULN, upper limit of normal

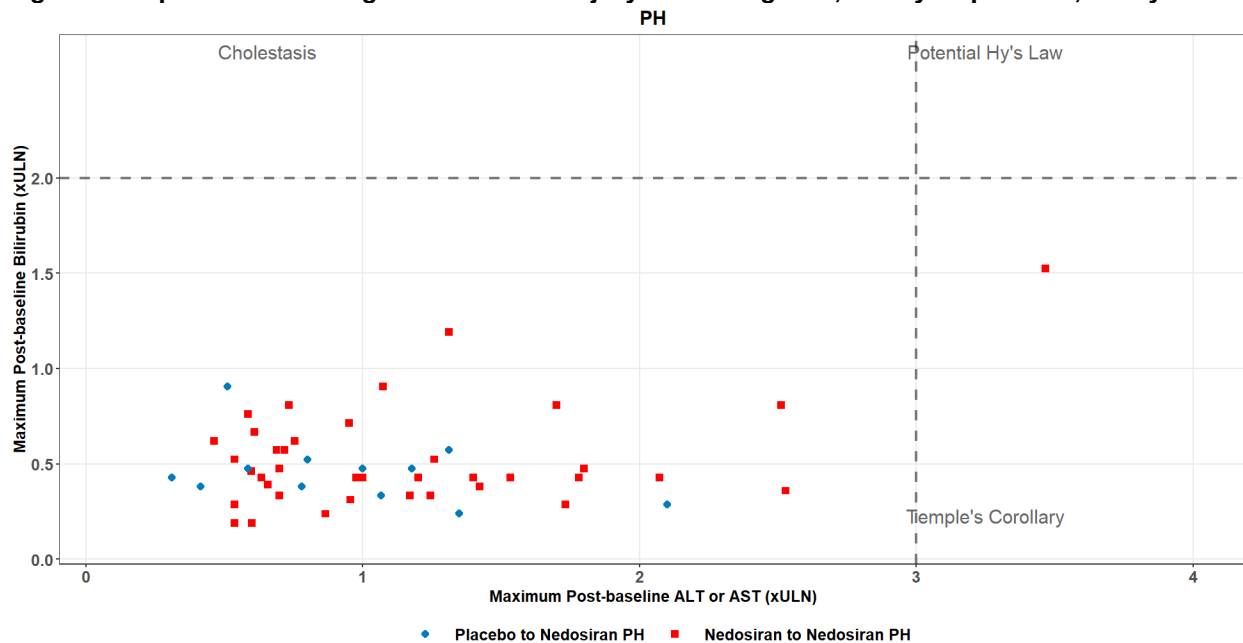
- **Participant** ^{(b) (6)}: A 32-year-old female with a history of PH1, lithotripsy, hypertension, and psoriasis. The participant was on concomitant topical betamethasone, desogestrel (oral contraception), doxylamine, and ramipril. She received a single dose of nedosiran 3 mg/kg in Study DCR-PHXC-101 on ^{(b) (6)}, and began monthly nedosiran in Study DCR-PHXC-301 on ^{(b) (6)} (Day 1). The participant's baseline CPK in DCR-PHXC-101 was 2456 U/L (11x ULN; normal range 35 to 228 U/L), and also the highest CPK for this participant. The CPK subsequently down-trended to 1001 U/L on Day 2 and remained normal thereafter. In DCR-PHXC-301, the CPK levels remained within normal (20 to 180 U/L) up to data cutoff, with the exception of a slightly higher CK value of 183 U/L on Day 30.
- **Participant** ^{(b) (6)}: A 16-year-old male with a history of PH1 on concomitant potassium citrate/sodium citrate and pyridoxine. He received a single dose of nedosiran 6 mg/kg on ^{(b) (6)}, in Study DCR-PHXC-101 and began monthly nedosiran in Study DCR-PHXC-301 on ^{(b) (6)} (Day 1). The participant's CPK was normal throughout DCR-PHXC-101. The participant's baseline CPK in DCR-PHXC-301 was elevated to >13x ULN at 3691 U/L (normal range 2 to 251 U/L) before receiving nedosiran. On Day 2, CPK trended down to 1875 U/L, and subsequently, except for one mildly elevated level of 274 U/L at Month 18, remained within normal from Day 15 to Month 21.
- **Participant** ^{(b) (6)}: A 26-year-old male with a history of PH2, chronic back and flank pain, and nephrolithiasis. The participant was on concomitant ibuprofen, hydromorphone, and medical marijuana. He received a single dose of nedosiran 3 mg/kg on ^{(b) (6)}, in Study DCR-PHXC-101 and began monthly nedosiran in Study DCR-PHXC-301 on ^{(b) (6)} (Day 1). The participant's baseline CPK was 74 U/L (normal range 20 to 200 U/L) in DCR-PHXC-101. On Day 29, 28 days after the single dose of nedosiran, CPK transiently increased to 686 U/L (3.4x ULN), then remained within the normal range from Day 43 to the end of the study (Day 57).
 - The participant's baseline CPK in DCR-PHXC-301 was mildly elevated at 368 U/L (normal range 20 to 200 U/L), and despite nedosiran dosing on Day 1, CPK down-trended to 242 U/L on Day 2. All subsequent CPK levels to Month 21 were within the normal range.

- Of note, this participant experienced 24 episodes of severe renal colic, frequently accompanied by severe nausea. One such episode led to an SAE of hospitalization for severe renal colic requiring right extracorporeal shock wave lithotripsy.
- Participant (b) (6): See the narrative in [Section 7.6.2.6](#) for an isolated one-time increase of CPK to >7x ULN while in DCR-PHXC-201. CPK remained normal during participation in DCR-PHXC-301.
- Participant (b) (6): See the narrative in [Section 7.6.2.6](#).
- Participant (b) (6): See the narrative in [Section 7.6.2.6](#) for fluctuating CPK levels (elevated to 6x ULN in DCR-PHXC-301).
- Participant (b) (6): See the narrative in [Section 7.6.2.6](#).

7.6.3.7. Assessment of Drug-Induced Liver Injury, DCR-PHXC-301

[Figure 6](#) shows a screening assessment for potential cases of drug-induced liver injury. One participant (b) (6) had an increase in ALT >3x ULN and a total bilirubin >1.5x ULN. As discussed in [Section 7.6.3.4](#), review of the case did not suggest that nedosiran played a role.

Figure 6. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Study/Trial B



Source: ad b.xpt; software: R.

Each data point represents a patient plotted by their maximum ALT or AST versus their maximum total bilirubin values in the post-baseline period.

A potential Hy's Law case (red circle) was defined as having any postbaseline total bilirubin equal to or exceeding 2x ULN within 30 days after a postbaseline ALT or AST equal to or exceeding 3x ULN, and ALP less than 2x ULN (note ALP values are not circled). All patients with at least one postbaseline ALT or AST and bilirubin are plotted.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; PH, primary hyperoxaluria subtypes combined; PH1, primary hyperoxaluria 1; TB, total bilirubin; ULN, upper limit of normal

7.6.3.8. Vital Signs Analyses, DCR-PHXC-301

There were no significant treatment-emergent changes from baseline in blood pressure, heart rate, or respiratory rate.

7.6.3.9. Subgroup Analyses, DCR-PHXC-301

No differences were noted in the safety findings in patients with PH1 compared with the overall trial population.

7.7. Key Safety Review Issues

No safety finding rose to the level of a key safety review issue.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Renal Impairment

The Applicant has proposed (b) (4) as shown in [Table 39](#), and no dose adjustment for patients with mild or moderate renal impairment. The Applicant also proposed to (b) (4)

Table 39. (b) (6)

(b) (6)

Studies DCR-PHXC-101 and DCR-PHXC-201 enrolled participants with normal renal function as well as those with mild to moderate renal impairment. Of 18 participants with PH1 enrolled in DCR-PHXC-101, 10, and 3 participants had mild and moderate renal impairment, respectively. The differences in exposure (C_{max} , AUC_{0-last}) between participants with renal impairment and those with normal renal function were dose dependent; no PK differences were observed among participants with normal renal impairment and those with mild-to-moderate renal impairment.

Of the 23 participants (PH1 and PH2) randomized to active treatment in DCR-PHXC-201, 12, 7, and 4 participants had normal, mild, and moderate renal impairment, respectively. Two participants with moderate renal impairment were adolescents; all other participants with renal impairment were adults. PK sampling for nedosiran in DCR-PHXC-201 was conducted on

Days 1, 30 and 150, and did not extend beyond 24 h (Days 1, 30) or 12 h (Day 150). No differences in the PK profiles were observed between participants with normal renal function and those with mild to moderate renal impairment during this initial 12 to 24 h ($C_{\max}$) sampling period (see [Section 14.2](#)); however, the complete elimination profile ($AUC_{0-\text{last}}$) was not obtained. Given the small number of participants enrolled in the study and incomplete PK sampling, the observed total AUCs could not be calculated; hence, population PK/PD predictions were used to assess the impact of renal impairment on PK and PD. Based on the population PK/PD predictions, mild and moderate renal impairment is not expected to have a clinically significant effect on the PK or the PD (24 h urinary oxalate excretion) of nedosiran (see [Section 14.5](#)).

PH patients with severe renal impairment (an eGFR <30 mL/min/1.73 m²) and those with kidney failure being treated with dialysis were not enrolled in the trials that were submitted to support the marketing application. (b) (4)

The review team agrees that labeling should indicate that no dose adjustment is needed in patients with (b) (4) (≥ 30 mL/min/1.73 m²). (b) (4)

Hepatic Impairment

The Applicant has proposed the following language for use of nedosiran in patients with hepatic impairment (HI):

No dose adjustment of nedosiran is recommended for patients with mild hepatic impairment (total bilirubin $\leq$ upper limit of normal (ULN) and aspartate aminotransferase [AST] $>$ ULN or total bilirubin >1 to 1.5 times ULN and any AST). Nedosiran has not been studied in patients with moderate or severe hepatic impairment (total bilirubin >1.5 ULN with any AST).

Trials for nedosiran enrolled five participants with mild HI based on the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria. Two patients were from the single dose study (DCR-PHXC-101) and three patients were from multiple dose studies (DCR-PHXC-201 and DCR-PHXC-301). No patients with moderate or severe HI were enrolled in the studies. The nedosiran concentration-time and 24 h urinary oxalate-time profiles were comparable between the normal hepatic function group and mild HI group (see [Section 14.2](#)) and HI status (normal versus mild) was not a significant covariate in the population PK/PD model of nedosiran.

The review team agrees with the proposed labeling that no dose adjustment of nedosiran is required in patients with mild HI and that nedosiran has not been studied in patients with moderate or severe HI (total bilirubin >1.5 ULN with any AST) (see [Section 14.2](#)).

Body Weight

The proposed dosing regimen includes a body weight band-based dosing regimen in adults and adolescents (160 mg once monthly if age 12 years or above with weight ≥ 50 kg, 128 mg once monthly if age 12 years or above with weight <50 kg) (b) (4)

Body weight was incorporated in the PK model by scaling the clearance and volume parameters allometrically. Body weight was not a significant covariate for the PD model. For an overview of the results supporting the proposed dosing regimen see [Section 14.5](#). The review team recommends including a dose cap of 128 mg for pediatric patients 9 to <12 years of age with body weight <50 kg, to prevent a potential decrease in dose when 11-year-old patients turn 12 years of age (see [Section 6.1](#)). This approach does not compromise efficacy in this age and weight group.

Other Intrinsic Factors

Based on population PK modeling, age and gender are not significant covariates that influence the PK of nedosiran. Across the studies, the proportion of male patients enrolled ranged from 44 to 47%. In Study DCR-PHXC-103, the PK of nedosiran was similar in healthy Japanese versus Caucasian participants, across the dose range of (1.5 to 6 mg/kg). In addition, race (white/Asian/black/unknown/other) was not found to be a significant covariate in the population PK model.

No dose adjustment is needed for nedosiran based on age, gender, or race.

8.2. Extrinsic Factors

Drug Interactions

The drug-drug interaction potential of nedosiran involving cytochrome P450 (CYP) enzymes and human transporter proteins was investigated in vitro. Based on the in vitro evaluation, no clinically relevant drug-drug interactions are expected for nedosiran, and no drug-drug interaction-based dose adjustment is necessary.

Nedosiran as a Victim

Nedosiran was stable in human hepatocytes and is not metabolized by CYP/uridine 5'-diphospho-glucuronosyl transferase enzymes. Nedosiran was not found to be a substrate of human multidrug and toxin extrusion (MATE) 1, MATE2-K, ornithine aminotransferase (OAT) 1, OAT3, OATP1B1, OATP1B3, ornithine carbamoyltransferase 1, or ornithine carbamoyltransferase 2 uptake transporters. Nedosiran was not found to be a substrate of human breast cancer resistance protein, multidrug resistance-associated protein 1, bile salt export pump, MRP2, MRP3, MRP4, MATE1 or MATE2-K efflux transporters (see [Section 14.1](#)). The concomitant use of vitamin B6 (pyridoxine) was not found to be a statistically significant covariate in the PK model of nedosiran (see [Section 14.5](#)), however caution is warranted in interpreting this result given the limited sample size for this analysis (only 8 PH1 patients of a total of 143 participants in the pooled study population were on concomitant pyridoxine).

Nedosiran as a Perpetrator

Nedosiran did not inhibit any major CYP enzymes or any of the human uptake or efflux drug transporters at clinically relevant concentrations. No time-dependent inhibition of CYP enzymes or CYP induction potential was identified (see [Section 14.1](#)).

8.3. Plans for Pediatric Drug Development

On May 15, 2018, FDA granted nedosiran orphan drug designation (designation request number DRU-2018-6354) for the treatment of PH; therefore, the product is exempt from Pediatric Research Equity Act requirements for the indication. Study DCR-PHXC-201 enrolled participants down to 9 years of age; hence, the initial approval of nedosiran for the treatment of PH1 will be extended to patients down to 9 years of age. Juvenile toxicology data are summarized in [Section 7.1](#).

8.4. Pregnancy, Lactation, and Females / Males of Reproductive Potential

Animal Data

Developmental and reproductive toxicity studies supporting labeling are summarized below.

Nonclinical Data Supporting Labeling on Fertility, Pregnancy and Lactation

Table 40. Nonclinical Data on Fertility, Pregnancy, and Lactation

Labeling Section	Nonclinical Data
8.1 Pregnancy	In mice, subcutaneous administration of nedosiran at doses up to 2000 mg/kg (approximately 58-fold the MRHD based on body surface area) or a mouse-specific (pharmacologically active) analog (10 mg/kg/dose) during organogenesis (dosing on GD 6, 8, 10, 12, and 14 for nedosiran; GD 3 and 10 for the analog) did not have adverse effects on embryo-fetal development. Subcutaneous administration of nedosiran (0, 2, 6 or 20 mg/kg/dose based on BSA) to pregnant New Zealand White rabbits during organogenesis (dosing on GD 7, 9, 11, 13, 15, 17, and 19) resulted in maternal toxicity on the basis of body weight loss up to 6.5% following the first dose in the 6 and 20 mg/kg/dose groups. Higher postimplantation loss and lower numbers of live fetuses occurred at ≥ 6 mg/kg/dose (exposures equivalent to the MRHD based on BSA), and fetal cardiovascular and skeletal malformations occurred at the 20 mg/kg/dose (2-fold the MRHD based on BSA). At the 2 mg/kg/dose, which is below the MRHD, no adverse findings were seen. In a pre- and postnatal study in mice, subcutaneous administration of nedosiran (0, 250, 500, or 1000 mg/kg/dose) or a mouse-specific (pharmacologically active) analog (10 mg/kg/dose) from implantation to weaning did not have adverse effects on the growth, viability, development, and reproductive performance of the offspring.
8.2 Lactation	No animal studies were conducted to assess placental transfer.
8.3 Females and males of reproductive potential	See animal studies in Labeling Section 13.1, below.
13.1 Fertility	Weekly subcutaneous administration of nedosiran at doses of 500, 1000, or 2000 mg/kg or of a mouse-specific analog (pharmacologically active) at a dose of 10 mg/kg to male mice for 4 weeks prior to and throughout mating, and to female mice for 2 weeks prior to and throughout mating and to GD 7 did not affect male or female fertility or early embryonic development.

Source: Applicant's Nonclinical Study Report

Abbreviations: BSA, body surface area; GD, gestational day; MRHD, minimum recommended human dose

Clinical Experience

One pregnancy was reported in Study DCR-PHXC-301. The participant received nedosiran from (b) (6), to (b) (6). Screening pregnancy test was negative before the nedosiran dose on (b) (6). On (b) (6), serum beta-human chorionic gonadotropin pregnancy test was positive (checked because of late menses) and nedosiran was discontinued. The patient had a spontaneous abortion at approximately 5 weeks of pregnancy. According to the Division of Pediatric and Maternal Health's consultation by Drs. Katherine Kratz and Miriam Dinatale, the spontaneous abortion was not likely related to nedosiran's effect on the fetus because (1) based on the PK profile, nedosiran would likely not have been present in the plasma by the time of conception; (2) the asialoglycoprotein receptor is not appreciably expressed in the fetal liver; hence, fetal uptake and toxicity is unlikely; and (3) preclinical studies in mice demonstrated that the active mouse analog of nedosiran, DCR-m355a, reduced maternal expression of LDHA but did not change LDHA expression in pup livers and did not cause embryonic toxicity.

There are no human data regarding the use of nedosiran in lactating women. Drs. Kratz and Dinatale note that based on the drug's large molecular size, it is unlikely that nedosiran will accumulate in human milk.

9. Product Quality

Approval

The Office of Pharmaceutical Quality has determined that the NDA meets all applicable standards to support the identity, strength, quality, and purity that it purports the drug product to have. As such, the Office of Pharmaceutical Quality recommends approval of this NDA from a quality perspective. A shelf life of 36 months is granted for the drug product in a single-dose 0.5 mL glass vial (80 mg) when stored at 2°C to 8°C. A shelf-life of 30 months is granted for the drug product in a 0.8 mL prefilled syringe (128 mg) and the drug product in a 1.0 mL prefilled syringe (160 mg) when stored at 2°C to 8°C.

9.1. Device or Combination Product Considerations

Two of the drug product presentations, the 0.8 mL prefilled syringe (128 mg) and 1.0 mL prefilled syringe (160 mg), are combination products. The single dose syringe system for both comprises a (b) (4) glass barrel with a (b) (4) staked needle and rigid needle shield, (b) (4) rubber plunger, and carton. The information supporting the combination product components was reviewed by the Office of Pharmaceutical Quality and found to be adequate.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

FDA Inspections

FDA requested an inspection of clinical investigator Site #101. The site enrolled the greatest number of participants in Study DCR-PHXC-201 (7 of 35 enrolled participants) and the size of the treatment effect on the primary endpoint in patients with PH1 decreases substantially when this site is removed from the analysis (though the endpoint remains statistically significant). Of note, it appears that the placebo arm did worse at this site compared with other sites. According to the Clinical Inspection Summary by Dr. Tina Chang in the Division of Clinical Compliance Evaluation, Office of Scientific Investigations, the study appears to have been conducted adequately at Site #101, and the data generated by the clinical investigator site appears acceptable.

No inspections were requested based on financial disclosures. Three investigators at one site in (b) (6) reported financial disclosures exceeding (b) (6) for Study DCR-PHXC-101 (collectively the site investigators received (b) (6) in “direct fees” and (b) (6) for “indirect fees” for an investigator-initiated grant for (b) (6). This site and

principal investigator also enrolled participants in Study DCR-PHXC-201 (Study Site (b) (6)). Collectively, Site (b) (6) enrolled one participant who was randomized to placebo in Study DCR-PHXC-201 and removal of this patient from the efficacy analysis did not alter the study results.

Site Audits and Data Quality Assurance

The Applicant's "quality group" monitored the Study and conducted investigator site audits to ensure the accuracy and reliability of clinical Study data. According to the DCR-PHXC-201 Clinical Study Report, electronic case report forms were completed from source documents. Investigators were responsible for verifying that data entries were accurate and correct. Study monitors verified electronic case report form data entries for accuracy and completeness.

Protocol Deviations

The Applicant refers to major protocol deviations as "important" deviations. "Important" protocol deviations were defined as those that could potentially affect the safety of the participant, substantially alter risks to the participant, and/or effect the ethics or the integrity of study data; all others were considered "non-important" (i.e., minor).

Eighty-seven major protocol deviations were reported in 30 participants (21 in the nedosiran group and 9 in placebo):

- The most common major protocol deviations were related to efficacy assessments and reported in 20 participants (14 in the nedosiran group, 6 in placebo). These included efficacy assessments not completed or not completed within the protocol-specified timeframe:
 - Twenty-four-hour urine collections for Uox were not collected/recollected, incorrectly collected, or not processed because of improper labeling of the sample for six participants;
 - Spot urine collections were not obtained at various timepoints for seven participants;
 - The PedsQL questionnaire was not completed for seven participants;
 - The PedsQL Family Impact Module was not completed for three participants;
 - Kidney ultrasound assessments were not obtained for three participants;
 - One participant's fluid intake information was not collected.
- Four participants missed one dose of Study drug (3 in the nedosiran group, 1 in placebo):
 - Participant (b) (6): A participant with PH1 randomized to nedosiran missed the Day 90 dose (and the study visit) for reasons related to the COVID-19 pandemic;
 - Participant (b) (6): A participant with PH1 randomized to nedosiran did not receive Study drug from Day 60 onward. Dosing was discontinued at the recommendation of the Data Safety and Monitoring Committee because of an AE of tachycardia;
 - Participant (b) (6): A participant with PH1 randomized to nedosiran – the pharmacist threw away one of the kits for this participant on Day 90. This was after the correct dose was prepared for this participant. It is not clear if the patient subsequently received Study drug on/within the Day 90 window;
 - Participant (b) (6): A participant with PH1, randomized to placebo, the dose was not increased for weight on Day 120.

- Laboratory/endpoint data were not collected or not evaluable in eight participants (six in the nedosiran group, two in placebo):
 - Serum vitamin B6 levels were not collected or not evaluable for seven patients;
 - Plasma oxalate was not collected for one patient;
 - PK samples were incorrectly collected for one patient.
- The visit window was missed for six participants (five participants in the nedosiran group, one in placebo):
 - Five participants missed a study visit for reasons related to the COVID-19 pandemic;
 - One patient missed a study visit because of their work schedule.
- Safety assessments were not collected in five participants (three nedosiran, two placebo):
 - Two participants missed one to two safety assessments related to the COVID-19 pandemic;
 - An ECG was not obtained for one participant;
 - One participant missed a telemedicine safety assessment;
 - One participant missed hematology laboratory assessments for one visit.
- Two participants were not reconsented when appropriate and one participant was consented using an obsolete consent form.
- Six participants had other major protocol deviations (two in the nedosiran group, four in placebo):
 - Kidney ultrasound not anonymized for four participants;
 - For one participant, weight and height assessments were obtained verbally from the participant (not measured in clinic);
 - For one participant a prescription form was signed by a “nonauthorized” physician.

Of note, all missed 24 h Uox samples were imputed for the primary efficacy analysis, as specified in the Statistical Analysis Plan. No participant missed more than one Uox assessment after Day 90. It is possible that missed doses in the nedosiran group could have led to an attenuation of the treatment effect in those participants; however, despite this the treatment effect in the overall trial population remained significant. It is unlikely that the protocol deviations affected participant safety.

All other protocol deviations were minor.

11. Advisory Committee Summary

The application does not raise significant issues regarding the safety or effectiveness of the drug requiring external expert advice; hence, no Advisory Committee meeting was held.

III. Additional Analyses and Information

12. Summary of Regulatory History

U.S. Regulatory Actions and Marketing History

Nedosiran is not marketed in the United States, and there have been no previous regulatory actions.

Summary of Presubmission/ Submission Regulatory Activity

There were several interactions with FDA over the course of development; a summary of key regulatory milestones, agreements, and advice is provided in [Table 41](#).

Table 41. Key Regulatory Milestones, Agreements, and Advice

Date/Source	Advice From Agency/Regulatory Action
December 13, 2016 Pre-IND Meeting	The Division indicated that it may be willing to accept a substantial change in Uox in patients with very high baseline levels as a surrogate endpoint in patients with primary hyperoxaluria and a prior history of kidney stones, but to do so additional data were needed to support Uox as a surrogate endpoint in this disease, e.g., data indicating that treatment effects on Uox reliably predicted treatment effects on clinical outcomes in PH and information on the magnitude of a treatment's effect on Uox that could be considered clinically meaningful.
December 10, 2018 End-of-Phase 1 Meeting	The Division noted that based on the provided data from the Rare Kidney Stone Consortium Registry on the relationship between Uox and progression to kidney failure as well as data on the effects of reduction of Uox on nephrocalcinosis and rate of kidney function decline in patients with PH1 after pre-emptive liver transplantation, a substantial change in Uox could be used as a basis for traditional approval of nedosiran in patients with PH1 and relatively preserved kidney function, no signs of systemic oxalosis, and high baseline Uox levels. The Division requested more information on typical Uox levels in patients with PH2 and patients with PH3, as well as the relationship between Uox levels and clinical manifestations in patients with PH3.
March 19, 2019 Type A Meeting	The Division agreed with the Applicant's proposed primary endpoint for Study DCR-PHXC-201, i.e., measurement of 24 h urinary oxalate burden, expressed as time-weighted standardized (TWS) area under the curve (AUC) from Day 90 to 180, based on percentage change from baseline. However, the Division also indicated that achieving a statistically significant treatment effect would not be sufficient for approval and reiterated that the trial would also need to enroll a sufficient number of patients with markedly elevated Uox levels at baseline and show a substantial reduction in Uox in this population.
July 2, 2019 Breakthrough Therapy Designation	The Agency granted nedosiran Breakthrough Therapy designation for the treatment of PH1 based on marked and sustained reductions in Uox levels in patients with PH1 treated with nedosiran in a Phase 2 study.

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Date/Source	Advice From Agency/Regulatory Action
November 4, 2019 Initial Comprehensive Multidisciplinary Breakthrough Therapy meeting	(b) (4)
November 2, 2020 Meeting Written Responses (Contents of a Future NDA Submission)	• The Division agreed to a rolling NDA submission • The Division indicated that DCR-PHXC-201 could support an indication for PH1
December 30, 2020 Breakthrough Therapy Designation	The Agency denied the Applicant's request for Breakthrough Therapy designation for PH2.
August 11, 2021 Email Communication	The Applicant informed the Agency by email that based on their review of the completed trial data of DCR-PHXC-201, they will seek approval for PH1 only (b) (4) Given the new information, the Agency requested that the Applicant share the topline results of Study DCR-PHXC-201 and request another pre-NDA meeting to discuss further.
October 21, 2021 Type C Meeting (Topline Results)	The Division raised the following concerns regarding the topline results of Study DCR-PHXC-201 and recommended that the Applicant address these concerns before submission of a marketing application: • The impact on efficacy of imbalances in baseline characteristics between the two study arms (e.g., PH type, 24 h Uox levels, and proportion of patients with high baseline Uox levels); the Division encouraged additional analyses to address these imbalances • The data that the Applicant will provide to address substantial evidence of effectiveness for PH1 • The evidence that the Applicant will provide to demonstrate that the treatment effect on Uox is durable in patients with PH1; the Division indicated that the Applicant should provide follow-up data for patients with PH1 who were enrolled in DCR-PHXC-201 who also enrolled in DCR-PHXC-301 to help address this issue

Date/Source	Advice From Agency/Regulatory Action
January 26, 2022 Pre-NDA Meeting	The Applicant requested this meeting to obtain Agency feedback on their plans to address the concerns raised by the Division during the October 21, 2021, meeting. • The Agency indicated that the additional analyses proposed by the Applicant were reasonable to support efficacy in PH1. The Applicant's proposal included: - Conducting all prespecified efficacy analyses outlined in the SAP for DCR-PHXC-201 for the primary endpoint including sensitivity and subgroup analyses, and for the secondary endpoints for patients with PH1 and PH2 (i.e., the trial population as a whole), and the subgroup of patients with PH1 - Assessing the percentage change in 24 h Uox from baseline to Day 180 (averaged from Day 90 to 180) in patients with PH1 - Evaluating the proportion of patients with PH1 with normal 24 h Uox at Day 180 • The Agency requested additional analyses including the percent change in 24 h Uox from baseline to Day 180 (averaged from Day 90 to 180) and the proportion of patients with normal 24 h Uox at Day 180 for the trial population as a whole. • The Agency indicated that the Applicant's proposed subgroup, sensitivity, and post hoc analyses to address the impact of the baseline imbalances in 24 h Uox levels and the proportion of patients with high baseline Uox levels between the two study arms were reasonable. These analyses included: - The primary endpoint analysis with baseline Uox as a covariate in the ANCOVA model (prespecified primary endpoint analysis). - The primary endpoint analysis in the subgroup of patients with "high" baseline Uox >1600µmol/24 h in the overall population (prespecified subgroup analysis) and patients with PH1 only. - A post hoc primary endpoint analysis in the subgroup of patients with baseline Uox <1600µmol/24 h in patients with PH1 (sample size of each treatment group not provided with topline results). - A post hoc primary endpoint analysis of patients with PH1 excluding two placebo patients with 24 h Uox >2800µmol/24 h (>6x the upper limit of normal and "significantly higher" than the mean for the placebo group). - A post hoc analysis of percentage change from baseline in 24 h Uox in DCRPHXC-301 for patients with PH1 who were previously in the placebo arm in DCR-PHXC-201. • The Agency indicated that the Applicant's proposed analyses of Study DCR-PHXC-301 could serve as confirmatory evidence of effectiveness including - Changes in Uox in patients with PH1 who rolled over from single dose study DCR-PHXC-101 to demonstrate changes whilst on treatment, off-treatment, and on-treatment again - Analyses of the percentage change in 24 h Uox from DCR-PHXC-201 baseline to Month 3 and Month 6 in DCRPHXC-301, based on the available data at data cutoff, for patients with PH1 previously randomized to placebo in DCR-PHXC-201. Additional 6-month Uox data for the remaining patients would be provided at the time of the safety update. • The Agency indicated that the Applicant's proposed analyses to support the durability of the treatment effect were reasonable and requested that the Applicant submit at least 6 months of Uox data for all placebo patients with PH1 from Study DCR-PHXC-201 who had rolled over to receive nedosiran in DCR-PHXC-301 and submit all available Uox data beyond 6 months until data cutoff.

Source: Table generated by the clinical reviewer from a review of Agency communications with the Applicant.
Abbreviations: ANCOVA, analysis of covariance; IND, investigational new drug; NDA, new drug application; PH1/2/3, primary hyperoxaluria type 1/2/3; SAP, statistical analysis plan; Uox, urinary oxalate

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

13.1.1. Pharmacology

13.1.1.1. Primary Pharmacology

- Nedosiran is a dicer-substrate small interfering ribonucleic acid (siRNA) oligonucleotide conjugated to N-acetyl-D-galactosamine (GalNAc) to enable uptake by the asialoglycoprotein receptor, which is highly expressed in the hepatocytes. It is designed to silence the expression of lactate dehydrogenase A (LDHA) messenger ribonucleic acid (mRNA), and thereby reduce production of oxalate in the liver.
- The target sequence of nedosiran in LDHA mRNA is conserved in humans and nonhuman primates, but not in mice, and thus, nedosiran is fully active in cynomolgus monkeys but inactive in mice.
- Administration of nedosiran (1, 3, 6 mg/kg) to a knock-in mouse model expressing human LDHA mRNA resulted in dose-dependent knockdown of LDHA mRNA in the liver that was sustained for 4 weeks postdose.
- A single subcutaneous (SC) dose of nedosiran (1, 3 mg/kg) in cynomolgus monkeys resulted in reduction of LDHA mRNA by 28% and 72%, indicating that a single low dose of 1 mg/kg (human equivalent dose 0.3 mg/kg) is a pharmacologically active dose.
- In a mouse model of PH1 induced by knockout of the alanine-glyoxylate aminotransferase 1 gene, a single SC dose of 0.5, 1, or 5 mg/kg DCR-m355 (the mouse active analog of nedosiran) reduced urinary oxalate concentration (normalized to creatinine); the reduction was sustained for 4 weeks, indicating that suppression of LDHA mRNA correlates with reduction of oxalate to near normal levels.
- In a mouse model of PH2 generated using siRNA-mediated knockdown of the *Grhpr* gene, urinary oxalate concentration was reduced to baseline levels after three weekly doses of DCR-m355 (10 mg/kg), indicating that inhibition of hepatic LDHA mRNA expression reduces oxalate production.

- In a mouse model of PH3 generated by drinking 1% hydroxyproline, SC administration of DCR-m355 at a dose level of 5 mg/kg weekly for 3 weeks prevented a hydroxyproline-induced elevation of creatinine-normalized urinary oxalate concentration, demonstrating the potential of LDHA mRNA knockdown for the treatment of PH.
- In CD-1 mice subjected to running on a treadmill, administration of DCR-m355 (5 mg/kg) once per week for 4 weeks resulted in significant LDHA mRNA knockdown (>95%) in the liver, with no effect on skeletal muscle LDHA mRNA expression or changes in circulating lactate, pyruvate and creatine kinase levels, demonstrating selective inhibition of LDHA mRNA in the liver without alterations of skeletal muscle LDHA isoenzyme activity.

13.1.1.2. Secondary Pharmacology

The potential for off-target activity of nedosiran was assessed via an in silico bioinformatics analysis of the human genome database using basic local alignment tools to identify sequences that may be homologous with the full-length or shortened chain portions of the antisense and sense strands of nedosiran. The in silico analysis showed minimal potential for RNAi-mediated hybridization to nontarget RNAs. The half-maximal inhibitory concentration for nedosiran against its target transcript LDHA is approximately 25pM in an in vitro human cell line assay, which is >10,000-fold lower than the potential for nontarget transcripts, indicating that none of the selected genes with complementarity to the guide strand are likely off-targets for nedosiran. Overall, the sequence of nedosiran has specificity for the intended target LDHA mRNA with low likelihood of hybridization to off-target RNAs.

13.1.1.3. Safety Pharmacology

- Nedosiran did not inhibit human ether-a-go-go related gene channel current up to a concentration of 48 µg/mL.
- Nedosiran had no significant adverse effect on central nervous system, respiratory, or cardiovascular function of cynomolgus monkeys at doses up to 300 mg/kg.

Table 42. Safety Pharmacology Studies

Study Information	Findings
Study No./Study Title	19-L1360-V-020 / Nedosiran on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells
Cell culture: HEK-293 stably transfected with hERG cDNA. Concentration: 1.6, 16, 48 µg/mL. Positive control: Terfenadine	As determined by in vitro hERG assay, nedosiran at concentrations up to 48 µg/mL showed no inhibition of hERG potassium channels.
Study No./Study Title	17-DEV-006/Central Nervous System Safety Study in Conscious Cynomolgus Monkeys
Species: Cynomolgus monkey Number: 4 males/dose group Dose: 30, 300 mg/kg, single SC injection	Nedosiran had no adverse effect on the CNS function in conscious cynomolgus monkeys following a single dose of SC injection up to 300 mg/kg.

Study Information	Findings
Study No./Study Title	17-DEV-006/Respiratory Safety Study in Conscious Cynomolgus Monkeys
Species: Cynomolgus monkey Number: 4 males/dose group Dose: 30, 300 mg/kg, single SC injection	Nedosiran had no adverse effect on respiratory function in conscious cynomolgus monkeys following a single dose of SC injection up to 300 mg/kg.
Study No./Study Title:	17-DEV-006/Cardiovascular Safety Study in Conscious Cynomolgus Monkeys
Species: Cynomolgus monkey Number: 4 males/dose Dose: 30, 300 mg/kg Single SC injection	Nedosiran caused minor increases in heart rate, decrease in mean RR interval, and fluctuations in mean blood pressure at a dose level of 300 mg/kg (plasma concentration 52,818 ng/mL at 8 h), which is estimated to be 81-fold the MRHD of 2.8 mg/kg (C_{max} 649 ng/mL).

Source: Applicant's nonclinical study report

Abbreviations: cDNA, complementary deoxyribonucleic acid; C_{max} , maximum plasma concentration; CNS, central nervous system; HEK, human embryonic kidney; hERG, human ether-a-go-go-related gene; MRHD, maximum recommended human dose; SC, subcutaneous

13.1.2. Pharmacokinetics / ADME / Toxicokinetics

General pharmacokinetics (PK) including absorption, distribution, metabolism, and excretion, and toxicokinetics of nedosiran were characterized in mice and monkeys ([Table 43](#)).

Table 43. Major Findings of PK Studies

Study No / Study Title	Major Findings
Study Title	Absorption
Study No: 17-DEV-002, 17-DEV-003 Species: Mice (3M/3F per dose group), Cynomolgus monkey (4-6 M/4-6 F/dose group). Dose: Mice 3, 100 mg/kg; Monkey 3, 100, 300 mg/kg Repeated dose SC injection.	Nedosiran is absorbed rapidly with a T_{max} of 0.5 to 2 h and 1.5 to 8 h in mice and monkeys, respectively. Peak plasma concentration rapidly declined in a multiexponential manner, with an initial rapid distribution phase to tissues, followed by a much slower terminal elimination phase, indicating equilibrium between plasma and tissue concentration. Subcutaneous bioavailability was 4% in mice and 8% in monkeys at a dose of 3 mg/kg. Plasma elimination half-life was approximately 4 h.
Study Title:	Distribution
Study No: 17-DEV-007, 17-DEV-003, 20-L1360-M-0067. Species: Mice (3 M/3 F), Cynomolgus monkey (4-6 M/4-6 F/dose group), Dose Nedosiran: Mice 3, 30, 100 mg/kg; Monkey 30, 100, 300 mg/kg [^3H]-Nedosiran mice 5 mg/kg	Nedosiran is distributed primarily to the liver, and to a lesser extent to the kidney. The mean liver-to-kidney concentration ratios at 48 h after the second dose were 30.3 (dose 30 mg/kg), 13.9 (dose 100 mg/kg), and 7.5 (dose 300 mg/kg). Concentrations in other organs, including skeletal muscle, brain, and reproductive tissues, were less than 2% of those in the liver. [^3H]-nedosiran (5 mg/kg) administered to mice by SC injection distributed primarily to the liver and urinary bladder. Tissues with measurable radioactivity were kidney, lung, bone marrow, spleen, lymph node, salivary gland, and thyroid gland. No apparent differences in plasma protein binding were observed among the species tested (mouse, cynomolgus monkey, and human). Plasma protein binding ranged from 86% to 88% at 5 μ g/mL, 74% to 85% at 10 μ g/mL, and 46% to 51% at 20 μ g/mL.

Study No / Study Title	Major Findings
Study Title:	Metabolism
Study No: 17-DEV-007, 17-DEV-005 Species: Mice (3 M/3 F), Cynomolgus monkey (4-6 M/ 4-6 F/dose group), Dose: Mice 3, 100 mg/kg; Monkey 30, 100, 300 mg/kg.	Nedosiran is metabolized by sequential removal of the four GalNAcs and four pentanamido linker moieties in the lysosomes. The presence of all 4 GalNAc ligands in the urine indicate nedosiran that had not been taken up into cells and metabolized, but instead was cleared from systemic circulation directly via renal excretion.
Study Title:	Excretion
Study No: 17-DEV-007, 19-DEV-014 Species: Mice (3 M/3 F), Cynomolgus monkey (5/dose group) Dose: Mice 3, 100 mg/kg Monkey 3 mg/kg	Nedosiran and its metabolites are excreted rapidly in the urine. The major products in the urine are full-length intact nedosiran that has not been taken up into cells and metabolized.

Source: Applicant's Nonclinical Study Report.

Abbreviations: F, female; M, male; SC, subcutaneous; T_{max}, time to maximum plasma concentration

13.1.3. Toxicology

13.1.3.1. General Toxicology

Repeat dose toxicology studies were conducted in mice for up to 26 weeks and monkeys for up to 39 weeks. Key results from these pivotal chronic toxicology studies are summarized in the following subsections. The monkey is considered a pharmacologically relevant model because the LDHA mRNA target sequence has 100% homology with humans. Nedosiran is inactive in the mouse because the LDHA mRNA sequence is different from humans, and hence, the toxicology of nedosiran was studied in the mouse to assess off-target hybridization effects. The animals were dosed once every 4 weeks to mimic the clinical monthly dosing frequency.

Study Title: 6-Month Repeat-Dose Study of Nedosiran in Juvenile Mice

Key Study Findings:

- In the chronic 6-month study in juvenile mice ([Table 44](#)), nedosiran administered SC once every 4 weeks at a dose level of 300 mg/kg was associated with a greater incidence and severity of injection site reactions consisting of mononuclear cell infiltration, fibroplasia, and macrophage hypertrophy which were resolved at the end of the 8-week recovery period ([Table 45](#)).
- Macrophagic hypertrophic changes at the injection sites are attributed to accumulation of the test article and are considered a class effect of oligonucleotides.
- The no observable adverse effect level (NOAEL) in the juvenile mouse was considered to be 300 mg/kg, with a corresponding mean area under the concentration-time curve from dosing to the time of the last measured concentration (AUC_{last}) of 526 µg·h/mL on Day 169, which is approximately 38-fold the exposures at a human dose of 2.8 mg/kg, with a corresponding AUC_{last} of 13.6 µg·h/mL.

Table 44. Study Information

Study Features and Methods	Details
Study number	17-DEV-004
Methods	Animals were dosed by SC injection in the interscapular area of the back with a total of 7 doses over a 6-month period.
GLP compliance	Yes
Dose and frequency of dosing	30, 100, 300 mg/kg, once every 4 weeks
Route of administration	Subcutaneous injection
Formulation/vehicle	0.9% sodium chloride Injection, USP
Species/strain	CD-1 mice
Number/sex/group	10/sex/dose group
Age	6 weeks (developmentally close to human puberty)
Satellite groups/unique design	Toxicokinetics cohort n=51/sex/dose group Recovery: n=6/sex for 100 and 300 mg/kg
Deviation from study protocol affecting interpretation of results	All protocol deviations and any circumstances that could affect the quality or integrity of the data were assessed to have no impact on the integrity of the data or the interpretations of the study.

Source: Applicant's Nonclinical Study Report.

Abbreviations: GLP, good laboratory practices; SC, subcutaneous; USP, United States Pharmacopeia

Table 45. Observations and Results

Parameter	Major Findings
Mortality	Two animals in the high dose group of 300 mg/kg were euthanized on Day 77 due to declining condition. One animal in the control group was found dead on Day 164. Gross examination showed a mass in the thymus at necropsy, and microscopic examination revealed lymphoma derived from thymic lymphocytes. The rest of the animals survived to scheduled sacrifice.
Clinical signs	No changes in clinical signs were observed.
Body weights	No test article-related changes in body weights were observed.
Clinical chemistry	No changes in hematology, serum chemistry and urinalysis parameters were observed. One animal in the mid-dose group exhibited an increase in liver enzymes (alanine aminotransferase, aspartate aminotransferase) and creatine kinase. Sporadic increases in these enzymes are common in mice and are considered secondary to handling. Minor wounds, abrasions, and hair loss were noted sporadically throughout the study, and were considered incidental.
Gross pathology	No changes were observed during the assessment of gross pathology at terminal or recovery necropsies.
Organ weights	No test article-related changes in organ weights were noted at terminal necropsy.
Histopathology	Test article-related findings at terminal necropsy were limited to the injection sites and consisted of mild subcutaneous mononuclear cell infiltrates, fibroplasia and macrophage hypertrophy in the 300 mg/kg dose group. All findings were resolved by the end of the 8-week recovery period.
Adequate battery: Yes	
Peer reviewed: Yes	

Parameter	Major Findings
Toxicokinetics	On Day 1, maximum plasma concentration (C_{max}) increased in a dose-proportional manner from 30 mg/kg to 100 mg/kg (3.9-fold for a 3.3-fold increase in dose) and 300 mg/kg (9.3-fold for a 10-fold increase in dose). On Day 169, C_{max} was dose proportional at 100 mg/kg (3.2-fold) and less than dose proportional at 300 mg/kg (6.8-fold). Total exposure (AUC_{last}) on Days 1 and 169 was greater than dose proportional over the dose range evaluated (100 mg/kg: 4.8- and 4.6-fold, respectively; 300 mg/kg: 20.5- and 17.2-fold, respectively). Group mean accumulation ratios for C_{max} ranged from 1.34 to 1.85 and for AUC_{last} ranged from 1.68 to 1.99. T_{max} was observed at the first (1 h) or second (2 h) time point postdose. Plasma elimination half-life could not be determined in mice. No sex-related difference in plasma concentration of nedosiran was apparent.
Tissue concentration	The tissue concentration of nedosiran was higher in the liver than the kidney. The concentration of nedosiran in both tissues increased with increasing dose and was less than dose proportional in the liver and greater than dose proportional in the kidney. Over a 10-fold dose range, mean nedosiran concentration increased 3-fold in the liver and up to 17-fold in the kidney.

Source: Applicant's Nonclinical Study Report.

Abbreviations: AUC_{last} , area under the concentration-time curve from dosing to the time of the last measured concentration; T_{max} , time to maximum plasma concentration

Study Title: 39-Week Repeat-Dose Study of Nedosiran in Juvenile and Adult Monkey

Key Study Findings

- In the chronic 9-month study in the cynomolgus monkey ([Table 46](#)), nedosiran administered SC once every 4 weeks was associated with minimal to moderate basophilic macrophage hypertrophy in the liver Kupffer cells, mesenteric lymph node, and injection sites at doses ≥ 30 mg/kg, and in the mandibular lymph nodes and testes at a dose of 300 mg/kg. Microscopy evaluation of the liver revealed an increase in the number and size of clear vacuoles and lysosomes within hepatocytes in the 300 mg/kg dose group, but there was no degeneration or necrosis ([Table 47](#)).
- During the 8-week recovery period, the findings of macrophage basophilic hypertrophy were partially reversed at the injection site; however, the findings in the liver, lymph nodes and testes were still evident in the 300 mg/kg dose group.
- Hypertrophic, basophilic changes in the Kupffer cell/macrophage in the liver and lymph nodes could be due to accumulation of the test article and have been reported with this class of oligonucleotides.
- Findings of basophilic hypertrophy of macrophages in sexually mature monkeys may not suggest adverse effects on fertility because in a dedicated study on fertility and embryonic development study in male mice, there were no nedosiran- or DCR-m355a-related effects on mating and fertility parameters, sperm motility, sperm density, or sperm morphology, reproductive organ weights (testes, epididymides, prostate, and seminal vesicles), and no macroscopic observations were detected at necropsy examination.
- In the juvenile monkey, the histological findings in the liver, lymph nodes and testes were still evident in the 300 mg/kg dose group, and hence, the NOAEL for nedosiran was considered to be 100 mg/kg, with corresponding AUC_{0-48h} 400 $\mu\text{g}\cdot\text{h/mL}$, which is

approximately 29-fold the exposures in humans dosed 2.8 mg/kg with a corresponding AUC_{last} 13.6 $\mu\text{g}\cdot\text{h/mL}$.

Table 46. Study Information

Study Features and Methods	Details
Study number	17-DEV-005
GLP compliance	Yes
Methods	Animals were dosed by SC injection in the interscapular area of the back with a total of ten doses over a 39-week period
Dose and frequency of dosing	Juvenile: 30, 100, 300 mg/kg once every 4 weeks. Young adult: 300 mg/kg once every 4 weeks
Route of administration	Subcutaneous injection
Formulation/vehicle	0.9% sodium chloride injection, USP
Species/strain	Cynomolgus monkey
Number/sex/group	4/sex/dosage group
Age	Juvenile age: 13 to 16 months (developmentally between 2 to 12 years of human age).
Satellite groups/ unique design	Recovery n=2/sex
Deviation from study protocol affecting interpretation of results	All protocol deviations and any circumstances that could affect the quality or integrity of the data were assessed to have no impact on the integrity of the data or the interpretations of the study.

Source: Applicant's Nonclinical Study Report.

Abbreviations: GLP, good laboratory practices; SC, subcutaneous; USP, United States Pharmacopeia

Table 47. Observations and Results

Parameter	Major Findings
Mortality	All animals survived to scheduled sacrifice.
Clinical signs	No changes were observed in clinical signs, physical examinations, ECG, and ophthalmology.
Body weights	No changes in body weights were observed.
Injection site observations	Incidental and procedural findings included pink discoloration and/or scab/crust at the injection site but did not increase in severity after repeated dosing.
Hematology	No changes were observed in clinical pathology parameters (including hematology, coagulation, and urinalysis).
Clinical chemistry	No effect on platelet count or mean platelet volume was observed. Sporadic increases in ALT, AST, CK, and LDH were not considered test article related due to their small magnitude and were attributed to handling and restraint.
Urinalysis	Analysis of urine revealed detectable levels of nedosiran and metabolites 48 h postdose on Days 3, 87, and 255 in animals receiving 100 or 300 mg/kg. Among these, intact full-length antisense strand, and sense strands with all four GalNAc groups intact were the most abundant.
Cytokine analysis	No test article-related effect on cytokine activation was evident at any time point evaluated. Cytokine levels, such as G-CSF, IFN- α 2a, IFN- γ , IL-1 β , IL-6, IL-8, and TNF- α , were low to undetectable.
Complement analysis	No test article-related effect on complement activation (Bb or C3a) was evident at any time point evaluated.
Gross pathology	No changes attributed to administration of nedosiran were seen in gross pathology at terminal or recovery necropsies.
Organ weights	No test article-related organ weight changes were observed at terminal or recovery necropsies in the juvenile or young adult animals.

Parameter	Major Findings
Histopathology Adequate battery: Yes Peer reviewed: Yes	At terminal necropsy, increases in the incidence and/or severity of the Kupffer cell basophilic hypertrophy and hepatocyte basophilia in the liver and macrophage basophilic hypertrophy in the mesenteric lymph node were noted in both the juvenile and young-adult animals. Minimal to mild basophilic hypertrophy of the Kupffer cells/macrophages in the liver, mesenteric lymph node, and injection sites was noted at doses ≥ 30 mg/kg. Additional findings included minimal hepatocyte hypertrophy and mixed inflammatory cell infiltration in the liver (juvenile monkey), and macrophage basophilic hypertrophy in the mandibular lymph nodes and testes in the 300 mg/kg dose group. Transmission electron microscopy revealed an increase in the number and size of lysosomes, which contained amorphous electron-dense material, which were not consistent with phospholipidosis. The absence of degeneration or necrosis, or effects on other features of the cell and subcellular organelles, suggests that the observed changes were not adverse. At recovery necropsy, macrophage basophilic hypertrophy was still evident in the liver, lymph nodes, and testes in juveniles dosed with 100 and 300 mg/kg and in young adults dosed with 300 mg/kg, whereas the findings at the injection sites and mixed inflammatory cell infiltrates in the liver were resolved.
Toxicokinetics	C_{max} increased in an approximately dose-proportional manner with a 10-fold increase in dose resulting in a 9.0-fold and 9.3-fold increase in C_{max} on Days 1 and 253, respectively. AUC_{0-48} increased in a greater than dose-proportional manner, i.e., a 10-fold increase in dose from 30 to 300 mg/kg resulted in 24- and 23-fold increases in AUC_{0-48} on Days 1 and 253, respectively. Accumulation ratios were similar across dose levels and ranged from 0.993 to 1.29 for C_{max} and from 1.25 to 1.44 for AUC_{0-48} . Accumulation was similar in juvenile and young adult animals at the 300 mg/kg dose, with AUC_{0-48} accumulation ratios of 1.25 and 1.36, respectively. T_{max} values ranged from 1.8 to 11 h and tended to increase with dose. The plasma elimination half-life was approximately 4 h. No remarkable sex-related differences in exposure were observed on Day 1 or 253. No age-related differences in toxicokinetics were evident.
Tissue concentration	The tissue concentration of nedosiran increased with dose, although the increases were less than dose proportional. Concentration of nedosiran at terminal sacrifice (Day 255) were higher in the liver than in the kidney. On Day 309 (8 weeks after the last dose), the tissue concentrations of nedosiran were 40.0 to 77.8% (liver) and 7.35 to 16.0% (kidney) of those on Day 255, with the apparent rate of decrease more rapid in the kidney than in the liver.
Pharmacodynamic analysis	By Day 255, nedosiran induced significant reduction in LDHA mRNA expression (92% reduction), and this reduction persisted for at least 8 weeks post-dose (Day 309), with no recovery of LDHA mRNA expression. No age-related difference in the concentration of RNA-induced silencing complex-loaded nedosiran was observed between juvenile and young-adult animals at the 300 mg/kg dose level.

Source: Applicant's Nonclinical Study Report.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC_{0-48} , area under the concentration-time curve from time 0 to 48 h; CK, creatinine kinase; C_{max} , maximum plasma concentration; G-CSF, granulocyte colony stimulating factor; IFN, interferon; IL, interleukin; LDH, lactate dehydrogenase; LDHA, lactate dehydrogenase A; T_{max} , time to maximum plasma concentration; TNF, tumor necrosis factor

13.1.3.2. Genetic Toxicology

Nedosiran was negative in the bacterial reverse mutation assay and did not induce micronuclei in mammalian cells in vitro or in vivo ([Table 48](#)).

Table 48. Key Study Findings

Study Information	Key Findings
Study Title	In vitro reverse mutation assay in bacterial cells
Study No. 16-DEV-008	No cytotoxic effects were observed in a 5000 µg/plate of nedosiran.
Strains: <i>Salmonella typhimurium</i> (TA 98, TA 100, TA 1535, TA 1537) and WP2 uvrA	There was no increase in the incidence of histidine-independent revertant mutant colonies in any of the bacterial strains in the absence or presence of metabolic activation using rat liver fraction. Positive controls (sodium azide 1 µg/plate, 2-aminoanthracene 2.5 µg/plate) showed an increase in revertant colony incidence. Nedosiran was non-mutagenic in an in vitro bacterial reverse mutation assay.
GLP compliance: Yes.	
Study validation: Positive controls showed increase in revertant colony incidence.	
Study Title	In vitro mammalian cell micronucleus assay
Study No. 17-DEV-010	No cytotoxicity was observed at a concentration level 500 µg/mL of nedosiran. The percentage of cells with micronucleated binucleated cells in the presence and absence of metabolic activation was not significantly increased relative to vehicle control. The results from positive controls (cyclophosphamide 15 µg/mL, mitomycin 0.4 µg/mL) demonstrated the validity and sensitivity of the test system for detecting chemical clastogens and aneugens in the presence and absence of metabolic activation. Nedosiran is considered negative for inducing micronuclei in human peripheral blood lymphocytes.
Cell culture: Human peripheral blood lymphocytes	
GLP compliance: Yes	
Study validation: Positive controls demonstrated validity and sensitivity for detecting chemical clastogens and aneugens.	
Study Title	In vivo micronucleus assay in mice
Study No. 18-DEV-004	Subcutaneous injection of nedosiran at doses of 500, 1000, and 2000 mg/kg once daily for two consecutive days did not cause an increase in the number of micronucleated polychromatic erythrocytes at any dose level as compared with the negative control. No bone marrow cytotoxicity was noted at any dosage. The positive control cyclophosphamide 60 mg/kg caused a significant increase in the number of micronucleated polychromatic erythrocytes. Nedosiran is considered to be negative for inducing bone marrow micronuclei in in vivo genotoxicity test.
Strain: CD-1 mice	
GLP compliance: Yes	
Study validation: Positive controls using a known clastogen demonstrated the validity and sensitivity of the test system for detecting bone marrow micronucleated polychromatic erythrocytes.	

Source: Applicant's Nonclinical Study Report.
Abbreviation: GLP, good laboratory practices

13.1.3.3. Carcinogenicity

The carcinogenic potential of nedosiran has not been assessed. The Agency agrees that carcinogenicity studies can be conducted postmarketing. The available data do not raise concern for a risk of carcinogenicity that should delay approval given the serious nature of the disease and limited therapeutic options.

13.2. Individual Reviews of Studies Submitted With the New Drug Application

13.2.1. Reproductive Toxicology

13.2.1.1. Fertility and Early Embryonic Development

Study Number/Title: 19-DEV-001/Fertility and Early Embryonic Development Study in Mice

Good laboratory practices (GLP) compliance: Yes

Key Study Findings

- In the male fertility study in mice ([Table 49](#)), there were no nedosiran- or DCR-m355a-related effects on any mating and fertility parameter, sperm motility, sperm density, sperm morphology, or reproductive organ weights (testes, epididymides, prostate, and seminal vesicles), and no macroscopic observations were detected at necropsy examination.
- In female mice, there were no nedosiran- or DCR-m355a-related effects on estrous cycling, mating, fertility, or ovarian or uterine parameters, and there were no macroscopic observations.
- The NOAEL for fertility and early embryonic development for nedosiran was 2000 mg/kg (about 58-fold the maximum recommended human dose (MRHD) based on body surface area) ([Table 50](#)).

Table 49. Methods Used in the Fertility and Early Embryonic Development Study in Mice

Parameter	Method Details
Dose and frequency of dosing	Nedosiran 500, 1000, 2000 mg/kg, DCR-m355a (mouse analog) 10 mg/kg, once weekly before, during, and after cohabitation through Week 7 for males and through GD 7 for females.
Route of administration	Subcutaneous injection
Formulation/vehicle	0.9% sterile sodium chloride for injection, USP
Species/strain	CrI:CD(ICR) mice
Number/sex/group	25 mice/sex/group
Study design	Male mice were dosed once weekly beginning 28 days before cohabitation, during cohabitation, and continuing through the day before euthanasia (up to Day 52; 7 doses). Female mice were dosed once weekly beginning 15 days before cohabitation, during cohabitation, and continuing until GD 7 (4 doses).
Deviation from study protocol affecting interpretation of results	There were no deviations that affected the overall integrity of the study or the interpretation of the study results and conclusions.

Source: Applicant's Nonclinical Study Report.

Abbreviations: GD, gestational day; ICR, Institute for Cancer Research; USP, United States Pharmacopeia

Table 50. Observations and Results

Parameter	Major Findings
Mortality	There were no nedosiran or DCR-m355a-related mortalities.
Clinical signs	There were no nedosiran or DCR-m355a-related clinical observations.
Body weights	There was no effect on body weight gains in males and females treated with nedosiran. Administration of DCR-355a resulted in decreased body weight gains in males and females during study Days 1 to 8; thereafter, mean body weight gains were similar to or higher than controls during the premating dose period. There were no nedosiran or DCR-m355a-related effects on mean maternal body weight gains, mean maternal body weights, or mean gravid uterine weights in females during the gestation period.
Fertility parameters	In males, there were no nedosiran- or DCR-m355a-related effects on mating and fertility parameters, sperm motility, sperm density, or sperm morphology, reproductive organ weights (testes, epididymides, prostate, and seminal vesicles), and no macroscopic observations detected at necropsy examination. In females, there were no nedosiran- or DCR-m355a-related effects on estrous cycling, mating, fertility, or ovarian or uterine parameters, and there were no macroscopic observations.
Necropsy	There were no nedosiran or DCR-m355a-related macroscopic observations detected at necropsy examination. There were no nedosiran or DCR-m355a-related effects on terminal body weights or the absolute or relative (to terminal body weight) weight of the testes, epididymides, seminal vesicles or prostate gland.

Source: Applicant's Nonclinical Study Report.

13.2.1.2. Embryo-Fetal Development

Study Number/Title: 18-DEV-013/Embryo-Fetal Development Study in Mice

GLP compliance: Yes

Key Study Findings

- In an embryofetal development study in pregnant mice ([Table 51](#)), no maternal or developmental toxicity was observed at doses of nedosiran up to 2000 mg/kg, which is 58-fold the MRHD of 2.8 mg/kg based on body surface area ([Table 52](#)).
- No developmental adverse effects were observed for the active mouse analog (DCR-m355a) at 10 mg/kg, a dose level which reduced LDHA mRNA expression by approximately 75%.

Table 51. Methods Used in the Embryo-Fetal Developmental Study in Mice

Parameter	Method Details
Dose and frequency of dosing	Nedosiran 500, 1000, 2000 mg/kg, DCR m355a 10 mg/kg, once every other day
Route of administration	Subcutaneous injection
Formulation/vehicle	0.9% sterile sodium chloride for injection, USP
Species/strain	Crl:CD1(ICR) female mice
Number/sex/group	25 females/group
Satellite groups	4/group for toxicokinetics
Study design	Nedosiran was administered once every other day on GD 6, 8, 10, 12, and 14. Because nedosiran is not pharmacologically active in mice, the study included the mouse analog DCR-m355a to assess effects related to pharmacological activity.
Deviation from study protocol affecting interpretation of results	The deviations were addressed in the finalized amended protocol and did not impact the overall integrity of the study or the interpretation of the study results and conclusions.

Source: Applicant's Nonclinical Study Report.

Abbreviations: GD, gestational day; ICR, Institute for Cancer Research; USP, United States Pharmacopeia

Table 52. Observations and Results

Parameter	Major Findings
Mortality	There were no nedosiran or DCR-m355a-related mortalities at any dose.
Clinical signs	There were no nedosiran- or DCR-m355a-related clinical signs at any dose level.
Body weights	There were no test article-related effects on mean maternal body weight gains or mean maternal body weights.
Necropsy findings: Cesarean section data	There were no nedosiran or DCRm355a-related fetal skeletal malformations or variations at any dose. Skeletal examination revealed a misshapen supraoccipital, a malformation in skull development, in a single fetus in mice treated with DCR m355a 10 mg/kg. However, because it occurred in only a single fetus and litter, it was not considered to be related to DCR-m355a.
Necropsy findings: Offspring	There were no test article-related macroscopic findings or effects on any ovarian and uterine parameters or litter size at any dose level.

Source: Applicant's Nonclinical Study Report.

Study Number/ Title: 19-L1360-L-018 / Embryo-Fetal Development Study in Rabbit

GLP compliance: Yes

Key Study Findings

- In an embryofetal development study in New Zealand White rabbits ([Table 53](#)), subcutaneous administration of nedosiran on gestational day (GD) 7, 9, 11, 13, 15, 17, and 19 at doses of 2, 6, or 20 mg/kg/dose resulted in maternal toxicity in the form of body weight loss and lower food consumption in the 6 and 20 mg/kg/dose groups following administration of the first dose on GD 8. Thereafter, absolute body weight and body weight gains were comparable to controls beginning on GD 9 to the end of dosing (GD 20). Higher post-implantation loss and lower numbers of live fetuses occurred at ≥ 6 mg/kg/dose (0.7x the MRHD), and fetal cardiovascular and skeletal malformations occurred at the 20 mg/kg/dose (2x the MRHD). A dose level of 2 mg/kg/dose (0.2x the MRHD) was considered to be the NOAEL for maternal toxicity and for embryo/fetal development in rabbits. Based on exposures, a dose level of 2 mg/kg in rabbits achieved AUC_{last} 1220 h·ng/mL at GD 19, which is approximately 0.1x the human exposure (AUC 13,600 h·ng/mL) at the MRHD ([Table 54](#)).
- Nedosiran administration did not reduce LDHA mRNA expression in maternal or fetal liver, and thus, it is not pharmacologically active in rabbits. The cause for the embryo-fetal toxicities observed in the rabbit is unclear, but it may be related to the inhibition of citrate synthase mRNA expression, which is the last step in the Krebs cycle ATP generation and is crucial for organ development.
- Similar findings of maternal toxicity and post-implantation loss were observed with a scrambled sequence of chemically comparable GalNAc-conjugated siRNA, indicating that the embryo-fetal toxicity observed in the rabbit may be associated with the bulk chemical and physical properties (e.g., high molecular weight, polyanionic polymer) of the molecule and/or extrahepatic silencing of the mRNA.

Table 53. Methods Used in the Embryo-Fetal Development Study in Rabbit

Parameter	Method Details
Dose and frequency of dosing	Nedosiran 2, 6, 20 mg/kg, single injection during organogenesis on GD 7, 9, 11, 13, 15, 17, and 19
Route of administration	Subcutaneous injection
Formulation/vehicle	0.9% sterile sodium chloride for injection, USP
Species/strain	Pregnant New Zealand White rabbits
Number/sex/group	25/dose group
Satellite groups:	3/dose group toxicokinetics
Study design	Female rabbits were administered nedosiran 0, 2, 6 or 20 mg/kg/dose subcutaneously on GD 7, 9, 11, 13, 15, 17, and 19.
Deviation from study protocol affecting interpretation of results	None of the deviations were considered to have impacted the overall integrity of the study or the interpretation of the study results and conclusions.

Source: Applicant's Nonclinical Study Report.

Abbreviations: GD, gestational day; USP, United States Pharmacopeia

Table 54. Observations and Results

Parameter	Major Findings
Mortality	All animals survived to the scheduled necropsy on GD 29.
Clinical signs	No nedosiran-related clinical observations were noted at any dose level.
Body weights	Following the first dose (GD 7-8), nedosiran-related mean maternal body weight losses of up to 6.5% and 6.1% compared to the control group were noted in the 6 and 20 mg/kg dose groups, respectively. Mean body weight gains in the 6 and 20 mg/kg dose groups remained higher than the control group during GD 10-11, and thereafter, mean body weight gains were generally comparable to the control group. In addition, mean absolute body weights in the 6 and 20 mg/kg/dose groups were comparable to the control group beginning on GD 9 and continuing to the end of the dosing period (GD 20).
Necropsy findings: Cesarean section data	At the scheduled necropsy on GD 29, no nedosiran-related internal findings were observed at any dose level.
Necropsy findings: Offspring	<u>Low dose 2 mg/kg</u>: No nedosiran-related developmental variations were noted at 2 mg/kg. <u>Mid dose 6 mg/kg</u>: Nedosiran-related higher mean litter proportions of post-implantation loss (primarily early resorptions) were noted at doses ≥ 6 mg/kg, resulting in lower mean numbers of live fetuses. <u>High dose 20 mg/kg</u>: Nedosiran-related lower mean gravid uterine weight was noted in the 20 mg/kg/dose group. Nedosiran-related external, visceral, and skeletal fetal malformations were noted in the 20 mg/kg/dose group. Three fetuses had a short or thread-like tail with corresponding skeletal malformations of absent caudal and/or sacral vertebrae. Three different fetuses had a malpositioned posterior vena cava. In addition, one fetus had an overriding aorta and pulmonary trunk atresia, and two fetuses had caudally malpositioned right kidneys. Three fetuses (one of which had a short tail) also had fused thoracic centra.
Toxicokinetics	Peak plasma concentration of nedosiran were observed at 0.5 to 4 h postdose (increasing with dose level) on GD 7 and GD 19. At 48 h postdose, nedosiran concentrations were quantifiable in maternal kidney and liver, fetal plasma, and placenta at all dose levels, and in amniotic fluid (1 litter/dose group) at doses ≥ 6 mg/kg, but not in fetal kidney or liver. Concentrations were highest in maternal liver followed by maternal kidney. Placenta concentration was 24- to 54-fold higher than maternal plasma concentration. Mean fetal plasma concentration was 2- to 8-fold lower than maternal plasma concentration.

Parameter	Major Findings
Effects on citrate synthase mRNA expression	In silico complementarity analysis indicated that nedosiran may knockdown rabbit citrate synthase mRNA, and hence, maternal and fetal liver tissues were analyzed for mRNA expression of citrate synthase. Nedosiran at a dose level of 20 mg/kg reduced citrate synthase mRNA expression (up to 50%) in rabbit maternal liver, but not in fetal liver. Since citrate synthase catalyzes the last step in the Krebs cycle, the inhibition could reduce ATP generation and lead to alterations in high energy dependent organs, such as the heart and skeletal muscle. However, lack of seed sequence complementarity of nedosiran in the maternal and fetal genes indicate that non-RNAi mechanisms may account for the higher post-implantation loss and lower number of live fetuses that occurred at ≥ 6 mg/kg, and fetal cardiovascular and skeletal malformations at 20 mg/kg/dose. Human citrate synthase mRNA does not have sequence homology with nedosiran, but in humans, nedosiran inhibits LDHA, a key enzyme in the conversion of lactate to pyruvate, involved in glycolysis in the generation of ATP, and thus, theoretically, knockdown of LDHA and reduction of ATP generation in off-target organs could lead to crucial developmental abnormalities.

Source Applicant's Nonclinical Study Report.

Abbreviations: ATP, adenosine triphosphate; GD, gestational day; LDHA, lactate dehydrogenase A; RNA, RNA interference

13.2.1.3. Pre- and Postnatal Development Study

Study Number/Title: 19-L1360-M-027/ Pre- and Postnatal Development Study in Mice

GLP compliance: Yes

Key Study Findings

- In a pre- and postnatal development study ([Table 55](#)), administration of nedosiran to pregnant female mice on gestational and lactation days at doses up to 1000 mg/kg (29-fold the MRHD based on body surface area) or the mouse active analog DCR-m355a (10 mg/kg) did not have adverse effects on the growth, viability, development and reproductive performance of the offspring ([Table 56](#) and [Table 57](#)).
- Maternal livers from DCR-m355a administered mice had a reduction of 5.8% in LDHA mRNA expression relative to controls, but there was no reduction in pup liver LDHA mRNA expression, suggesting no fetal or lactation exposure to DCR-m355a.

Table 55. Methods Used in the Pre- and Postnatal Development Study in Mice

Parameter	Method Details
Dose and frequency of dosing	Nedosiran 250, 500, 1000 mg/kg, DCR-m355a 10 mg/kg. Nedosiran was injected on GD 6, 8, 10, 12, 14, and 16, and on LD 1, 8, 15, and 20. DCR-m355a was injected on GD 3, 10, and 17 and on LD 5, 12, and 19.
Route of administration	Subcutaneous injection
Formulation/vehicle	0.9% sterile sodium chloride for injection, USP
Species/strain	Crl:CD1(ICR) female mice
Number/sex/group	25/dose group

Parameter	Method Details
Study design	Time-mated female mice were administered nedosiran by SC injection in the dorsal scapular every other day on gestation days, and weekly on lactation days. DCR-m355a was injected weekly on gestation days and lactation days.
Deviation from study protocol affecting interpretation of results	None of the deviations were considered to have impacted the overall integrity of the study or the interpretation of the study results and conclusions.

Source: Applicant's Nonclinical Study Report.

Abbreviations: GD, gestational day; ICR, Institute for Cancer Research; LD, lactation day; SC, subcutaneous; USP, United States Pharmacopeia

Table 56. Observations and Results

Parameter	Major Findings
Mortality	There were no nedosiran or DCR-m355a-related deaths in the F ₀ females. In the F ₁ generation offspring, one female in the 500 mg/kg nedosiran dose group was found dead on PND 35. No clinical observations were noted prior to death; at necropsy, dark red contents were noted in the stomach duodenum, jejunum, and ileum.
Clinical signs	No nedosiran or DCR-m355a-related clinical observations were observed.
Body weights	No nedosiran or DCR-m355a related effects on body weight gains, mean gestation lengths or the process of parturition for F ₀ and F ₁ generation offspring were noted.
Necropsy observation	No nedosiran or DCR-m355a-related internal findings, effects on the mean number of implantation sites and unaccounted-for sites, number of F ₁ pups born, live litter size, percentage of males at birth, postnatal survival, pup clinical observations, and pup body weights were observed.
Gestation length	No nedosiran or DCR-m355a-related effects were noted on mean gestation lengths or the process of parturition at any dosage level. Mean F ₀ gestation lengths in the nedosiran or DCR-m355a-treated groups were similar to the values in the control group.
Physical development	In the F ₁ generation, there were no effects on developmental landmarks (balanopreputial separation and vaginal patency), neurobehavior, reproductive performance, intrauterine survival and mean numbers of corpora lutea, or necropsy findings attributable to F ₀ maternal in response to nedosiran or DCR-m355a administration.
Neurological assessment	Motor activity patterns (total activity and ambulatory activity counts) in F ₁ animals were unaffected by administration of test article to F ₀ maternal when evaluated on PND 61.
Reproduction	No effects on F ₁ reproductive performance were observed at any dosage that could be attributed to F ₀ maternal administration of nedosiran or DCR-m355a.
F ₂ Generation	Mean numbers of corpora lutea, implantation sites, and intrauterine survival of the F ₂ embryos were unaffected by administration of the test article to F ₀ maternal animals. Only a single female in the 1000 mg/kg dose group had a higher mean post-implantation loss.

Source: Applicant's Nonclinical Study Report.

Abbreviation: PND, postnatal day

Table 57. Reproductive Toxicity Safety Margins by Body Surface Area

Study	NOAEL (mg/kg)	HED (mg/kg)	MRHD 2.8 mg/kg Safety Multiple
Fertility (male mouse)	2000	162	58
Fertility (female mouse)	2000	162	58
EFD mouse	2000	162	58
EFD rabbit	2	0.65	0.2
PPND mouse	1000	81	29

Source: Nonclinical review analysis.

Abbreviations: EFD, embryo-fetal development; NOAEL, no observed adverse effect level; PPND, peri- and postnatal development

13.3. Other Toxicology / Specialized Studies

13.3.1. Platelet Activation

Due to concerns regarding platelet activation induced by the phosphorothioate oligonucleotides, the potential of nedosiran to activate human platelets was assessed ex vivo in whole blood using flow cytometry. Nedosiran at concentrations up to 200 µg/mL did not induce human platelet activation as shown by the absence of expression of CD62P. In addition, nedosiran did not affect platelet counts, prolong the activated thromboplastin time or activate complement in the in vivo toxicology studies in mice and monkeys.

13.3.2. Antidrug Antibodies (ADA)

ADA analysis has not been conducted with samples from the nonclinical studies; however, PK and pharmacodynamics (PD) data from the nonclinical studies suggest that neutralizing ADAs against nedosiran were not formed. Repeat-dosing of nedosiran in monkeys showed robust reduction of the target LDHA mRNA. In addition, repeat dosing in mice and monkeys achieved similar maximum plasma concentration (C_{max}) and AUC after first and last dosing of nedosiran. Moreover, immune complex deposition in tissues was not observed in the repeat-dose toxicity studies of nedosiran in mice and monkeys.

13.3.3. Impurities / Degradants

- The nedosiran drug substance tested in the toxicology studies was from batches used in the clinical drug product or manufactured using a similar process. The impurity levels in the pivotal repeat-dose toxicity studies were greater than those potentially present in the commercial product for clinical use based on the proposed drug substance specifications; therefore, the impurities and their proposed specifications are considered qualified.
- The (b) (4) impurities, and (b) (4) impurity that may be present as a degradation product in the drug product are qualified in the toxicology studies up to the proposed specifications. No more than (b) (4) % are proposed as (b) (4) acceptance criteria for qualification threshold. (b) (4)

(b) (4) Overall, the drug substance-related impurities are considered qualified.

13.4. Individual Reviews of Studies Submitted With the New Drug Application

Not applicable.

14. Clinical Pharmacology

14.1. In Vitro Studies

14.1.1. Plasma Protein Binding

The plasma protein binding for nedosiran was determined using an electrophoretic mobility shift assay, which is based on the principle that an oligonucleotide-protein complex and an unbound oligonucleotide will have different mobility during electrophoresis. The conventional methods to determine binding were reported to have issues related to nonspecific adsorption. Though plasma protein binding was carried out with nedosiran concentrations ranging from 1 to 10 µg/mL, the electrophoretic mobility shift assay was not sensitive enough to quantify concentrations below 5 µg/mL. The incubations were done for 60 min at 37°C and 90% human plasma. Plasma protein binding was dependent on concentrations with the mean percentage binding decreasing from 85.6% to 73.9% for nedosiran concentrations of 5 and 10 µg/mL, respectively. These concentrations are approximately 5- to 10-fold higher than the clinical C_{max} of nedosiran.

14.1.2. Metabolism of Nedosiran

The in vitro metabolism studies for nedosiran were carried out using human hepatocyte suspension. Nedosiran was stable without any metabolite formation after a 24 min incubation with human hepatocytes at concentrations ranging between 0.25 and 75 µg/mL, indicating no role for cytochrome P450 (CYP) or uridine 5'-diphospho-glucuronosyltransferase metabolism.

14.1.3. Inhibition and Induction of CYP Isozymes by Nedosiran

The in vitro assessment of CYP enzyme inhibition was carried out in human hepatocytes with or without a 30 min preincubation of nedosiran at concentrations ranging between 0.25 µg/mL to 75 µg/mL. A cocktail of CYP substrates was added and CYP activity analysis was performed after 24 or 54 min (for 30 min preincubation).

The induction potential of nedosiran on CYP enzymes were assessed at concentrations ranging from 0.25 to 75 µg/mL after a 48 h and 72 h incubation for mRNA and CYP activity evaluations, respectively.

The results for inhibition and induction of CYP enzyme activity by nedosiran and positive controls are summarized in [Table 58](#). Nedosiran is unlikely to be an inhibitor or inducer of CYP enzymes at clinically relevant plasma concentrations.

Table 58. In Vitro Assessments for Nedosiran as an Inhibitor or Inducer of CYPs

Enzyme Tested	Substrate	Substrate Concentration (μM)	Metabolite	Positive Controls	% Inhibition or Induction by Positive Control	% Inhibition or Induction by Nedosiran*	Conclusion for Nedosiran
CYP1A2	Phenacetin	20	Acetaminophen	2μM Furafllyline	55	16	Not an inhibitor
CYP2B6	Bupropion	5	OH-bupropion	0.1μM Ticlopidine	55	-2	Not an inhibitor
CYP2C8	Repaglinide	25	OH-repaglinide	100μM Gemfibrozil	93	-6	Not an inhibitor
CYP2C9	Diclofenac	5	OH-diclofenac	10μM Tienilic acid	59	-6	Not an inhibitor
CYP2C19	Omeprazole	20	5-OH-omeprazole	10μM Fluoxetine	19	3	Not an inhibitor
CYP2C19	Omeprazole	20	Desmethyl omeprazole	10μM Fluoxetine	15	-5	Not an inhibitor
CYP2D6	Dextromethorphan	1	O-desmethyl dextromethorphan	0.5μM Paroxetine	85	-3	Not an inhibitor
CYP3A4	Omeprazole	20	Sulfoxidation	20μM Verapamil	63	-2	Not an inhibitor
CYP3A4	Omeprazole	20	3-hydroxylation	20μM Verapamil	66	4	Not an inhibitor
CYP3A4	Testosterone	100	6β-OH-testosterone	20μM Verapamil	71	-1	Not an inhibitor
CYP3A4	Midazolam	20	1'-OH-midazolam	20μM Verapamil	62	14	Not an inhibitor
CYP1A2 induction	Phenacetin	20	Acetaminophen	50μM Omeprazole	100	0	Not an inducer
CYP2B6 induction	Bupropion	5	OH-bupropion	1000μM Phenobarbital	100	-1	Not an inducer
CYP3A4 induction	Testosterone	100	6β-OH-testosterone	10μM Rifampicin	100	0	Not an inducer
CYP3A4 induction	Midazolam	20	1'-OH-midazolam	50μM Omeprazole	100	-2	Not an inducer

Source: Module 5.3.2.2; in vitro report no. 18-DEV-007.

* In the presence of the highest tested concentration of 75 μg/mL.

Abbreviation: CYP, cytochrome P450

14.1.4. Evaluation of Drug Transporters Involved in the Disposition of Nedosiran

The substrate nature of nedosiran (0.075, 1.5, 3.75, and 37.5 µg/mL) was investigated in Madin-Darby canine kidney II-cell monolayer assays for multidrug resistance protein 1 and breast cancer resistance protein efflux transporters and in transporter overexpressing and control cells in the uptake substrate assays for uptake transporters. Nedosiran was not found to be a substrate for any of the major efflux or uptake drug transporters ([Table 59](#)).

Table 59. In Vitro Assessments for Nedosiran as Substrate of Transporter

Transporter	Compound	Dosing Concentration ^a	Intracellular Fold Accumulation
OAT1	Nedosiran	37.5 µg/mL	1.1
	Tenofovir (positive control substrate for OAT1)	5µM	123.64
OAT3	Nedosiran	37.5 µg/mL	0.76
	E3S (positive control substrate for OAT3)	1µM	55.48
OATP1B1	Nedosiran	37.5 µg/mL	NA ^b
	E217βG (positive control substrate for OATP1B1)	1µM	81.91
OATP1B3	Nedosiran	37.5 µg/mL	NA ^b
	CCK-8 (positive control substrate for OATP1B3)	1µM	82.33
OCT2	Nedosiran	37.5 µg/mL	0.76
	Metformin (positive control substrate for OCT2)	10µM	26.19
MATE1	Nedosiran	37.5 µg/mL	NA ^b
	Metformin (positive control substrate for MATE1)	10µM	21.79
MATE2-K	Nedosiran	37.5 µg/mL	NA ^b
	Metformin (positive control substrate for MATE2-K)	10µM	15.63
MDCKII-MDR1	Nedosiran apical-to basolateral	37.5 µg/mL	NA ^b
	Nedosiran basolateral-to apical		
	Digoxin efflux ratio-ER (positive control for BCRP)		
MDCKII-BCRP	Digoxin ER (in presence of inhibitor Valspodar)	5µM	14.4
		5+10µM	0.1
MDCKII-MDR1	Nedosiran apical-to basolateral	37.5 µg/mL	NA ^b
	Nedosiran basolateral-to apical		
	Prazosin efflux ratio (positive control for BCRP)		
MDCKII-BCRP	Prazosin efflux ratio (in presence of inhibitor Ko134)	1µM	15.4
		1+1µM	-0.4

Source: Module 5.3.2.2; in vitro report no.18-DEV-007 Tables 29-39.

^a Results from the highest dosing concentration of nedosiran are presented.

^b The fold accumulation could not be estimated as the intracellular concentration or concentration in receiver compartment was BLQ. Abbreviations: BCRP, breast cancer resistance protein; BLQ, below the limit of quantification; CCK-8, cell counting kit-8; ER, extended release; MATE, multidrug and toxin extrusion; MDCKII-BCRP, Madin-Darby canine kidney-breast cancer resistance protein; MDCKII-MDR1, Madin-Darby canine kidney-multidrug resistance 1; NA, not applicable; OAT, ornithine aminotransferase; OCT, ornithine transcarbamoylase

14.1.5. Evaluation of Inhibition of Drug Transporters by Nedosiran

The inhibition potential of nedosiran (3.75 and 37.5 µg/mL) on transporter-mediated probe substrate accumulation was investigated in transporter-containing vesicles in the vesicular transport inhibition assays for efflux transporters and in transporter-expressing and control cells in the uptake inhibition assays for uptake transporters. Nedosiran was not found to be an inhibitor for any of transporters at the highest concentrations tested (37.5 µg/mL).

Table 60. In Vitro Assessments for Nedosiran as an Inhibitor of Transporters

Transporter	Compound	Dosing Concentration	Relative Inhibition (%)
BCRP	Nedosiran	37.5 µg/mL	8
	Kol43 (positive control for BCRP inhibition)	1µM	97
BSEP	Nedosiran	37.5 µg/mL	-3
	Cyclosporin A (positive control for BSEP inhibition)	10µM	95
MDR-1	Nedosiran	37.5 µg/mL	4
	Valspodar (positive control for MDR-1 inhibition)	1µM	97
MRP-2	Nedosiran	37.5 µg/mL	-7
	Benzbromarone (positive control for MRP-2 inhibition)	200µM	99
MRP-3	Nedosiran	37.5 µg/mL	5
	MK571 (positive control for MRP-3 inhibition)	150µM	94
MRP-4	Nedosiran	37.5 µg/mL	0
	MK571 (positive control for MRP-4 inhibition)	150µM	99
OAT1	Nedosiran	37.5 µg/mL	16
	Probenecid (positive control for OAT1 inhibition)	300µM	97
OAT-3	Nedosiran	37.5 µg/mL	9
	Probenecid (positive control for OAT3 inhibition)	500µM	98
OATP1B1	Nedosiran	37.5 µg/mL	5
	Rifampicin (positive control for OATP1B1 inhibition)	50µM	98
OATP1B3	Nedosiran	37.5 µg/mL	15
	Rifampicin (positive control for OATP1B3 inhibition)	10µM	89
OCT-1	Nedosiran	37.5 µg/mL	-6
	Verapamil (positive control for OCT-1 inhibition)	100µM	98
OCT-2	Nedosiran	37.5 µg/mL	-21
	Verapamil (positive control for OCT-2 inhibition)	300µM	96
MATE-1	Nedosiran	37.5 µg/mL	8
	Pyrimethamine (positive control for MATE-1 inhibition)	1µM	92
MATE-2	Nedosiran	37.5 µg/mL	0
	Pyrimethamine (positive control for MATE-2 inhibition)	10µM	93

Source: Module 5.3.2.2; In vitro report no. 18-DEV-007 Tables 15-28.

Results are for highest tested concentration of nedosiran.

Abbreviations: BCRP, breast cancer resistance protein; BSEP, bile salt export pump; MATE, multidrug and toxin extrusion; MDR, multidrug resistance; MRP, multidrug resistance-associated protein; OAT, ornithine aminotransferase; OCT, ornithine transcarbamoylase

14.2. In Vivo Studies

DCR-PHXC-101 (Part A): Single Ascending Dose PK and PD Study in Healthy Volunteers and DCR-PHXC-101 (Part B): Single Ascending Dose PK and PD Study in PH1 Patients

Study Design

This was a phase 1, placebo-controlled, single-blind, single-center study in normal healthy volunteers (Group A, N=25) and open-label multicenter study in patients with PH (Group B, N=18) to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of single ascending subcutaneous doses of nedosiran. There were five cohorts in Group A, each of which comprised 5 healthy participants (3 active, 2 placebo) randomized to receive one of the following nedosiran sodium doses: 0.3, 1.5, 3, 6 or 12.0 mg/kg (0.28, 1.4, 2.8, 5.6, or 11.3 mg/kg free acid equivalent [FAE], respectively). There were three cohorts in Group B, in which 18 PH patients

were assigned into cohorts of 6, 8 and 4 to receive single nedosiran sodium doses of 1.5, 3 and 6 mg/kg, respectively (1.4, 2.8 and 5.6 mg/kg FAE, respectively).

Plasma PK was analyzed at predose, 0.083, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 168, 336, 504, and 696 h (Day 29) postdose. Pooled urine was collected at 0 to 6, >6 to 12, and >12 to 24 h postdose and on Days 8, 15, 22, 43, 57, and every 28 days until urine oxalate returned to 80% of baseline values.

Results

In Group A (healthy participants), the peak, as well as the total exposure of nedosiran, was greater than dose-proportional with increase in dose in the 0.3 to 12 mg/kg dose range. In Group B (participants with PH), the exposure of nedosiran was dose proportional with mean $C_{\max}$ increasing 3.8-fold and mean $AUC_{0-\text{last}}$ increasing 4.5-fold with a 4-fold change in dose from 1.5 mg/kg to 6 mg/kg. The amount of dose excreted unchanged in urine ranged between ~15% to 30% and ~22% to 35%, in Groups A and B, respectively. In Group B, the mean maximum percentage reduction in 24 h excretion of urinary oxalate from baseline across cohorts was 51%, 74%, and 78% for the 1.5, 3, and 6 mg/kg doses, respectively.

Table 61. PK Parameters for Nedosiran Following Single Subcutaneous Doses in Healthy Participants (Group a) and PH Patients (Group B)

Group	Dose (mg/kg)	N	C _{max} ^a (ng/mL)	T _{max} ^a (h)	AUC _{0-last} ^a (h·ng/mL)	AUC _{0-∞} ^a (h·ng/mL)	t _{1/2} ^a (h)	CL/F ^a (L/h)	VZ/F ^a (L)	CL _R ^a (L/h)	F _e ^a (%)
A	0.3 (0.28 FAE)	3	62.0 (24.8)	8.00 (6.00, 8.00)	1190 (22.9)	1440 ^b (6.41)	7.12 ^b (6.66)	19.0 ^b (1.74)	195 ^b (8.41)	3.62 (21.5)	15.2 (7.64)
A	1.5 (1.4 FAE)	3	389 (24.7)	6.00 (4.00, 8.00)	6160 (29.9)	6380 (27.1)	5.34 (13.4)	17.3 (9.96)	134 (22.2)	2.94 (19.4)	15.0 (2.78)
A	3.0 (2.8 FAE)	3	649 (50.8)	12.0 (0.50, 24.0)	15,500 (25.0)	13,100 ^c	12.1 ^c	14.3 ^c	250 ^c	3.36 (17.9)	16.5 (23.3)
A	6.0 (5.6 FAE)	3	1570 (8.77)	6.00 (2.02, 12.0)	35,700 (24.8)	35,800 (24.5)	13.8 (45.0)	11.5 (23.2)	226 (51.2)	3.32 (43.9)	21.2 (53.2)
A	12.0 (11.3 FAE)	3	4010 (6.20)	12.0 (6.02, 12.0)	84,500 (3.32)	NC	NC	NC	NC	3.48 (17.6)	29.4 (11.8)
B	1.5 (1.4 FAE)	6	547 (29.7)	8.00 (0.550, 12.0)	9990 (16.3)	10700 ^d (6.06)	4.57 ^d (10.8)	12.6 ^b (14.6)	83.6 ^d (23.6)	3.42 (38.1)	21.5 (45.2)
B	3.0 (2.8 FAE)	8	1050 (46.9)	8.03 (6.00, 12.0)	20,400 (35.9)	15900 ^e	5.45 ^e	12.2 ^e	96.3 ^e	3.47 (68.3)	26.6 (55.4)
B	6.0 (5.6 FAE)	4	2090 (33.6)	8.00 (7.92, 12.0)	45,200 (32.2)	28200 ^e	7.27 ^e	9.97 ^e	105 ^e	3.94 (81.3)	34.5 (80.5)

Source: Study DCR-PHXC-101 CSR.

^a Arithmetic mean and %CV are reported for all parameters except for T_{max}, which is shown as median and minimum, maximum.

^b n=2.

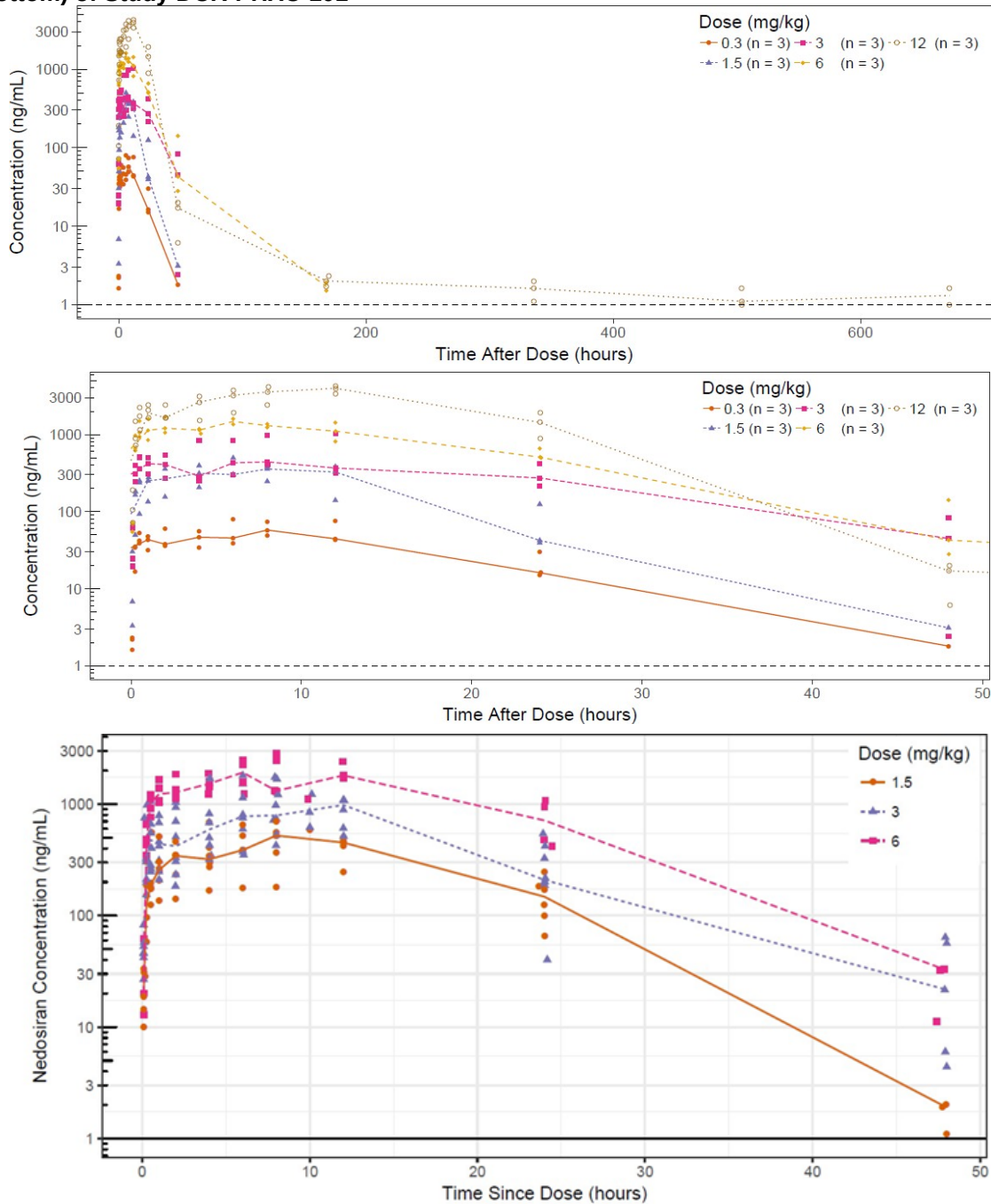
^c n=1.

^d n=4.

^e n=1.

Abbreviations: CV, coefficient of variation; AUC_{0-∞}, area under the concentration-time curve from time 0 to infinity; AUC_{0-last}, area under the concentration-time curve from time 0 to last quantifiable time point; CL/F, apparent clearance; CL_R, renal clearance; C_{max}, maximum observed concentration; FAE, free acid equivalent; F_e, fraction excreted unchanged in the urine; N, number of participants; NC, not calculated; t_{1/2}, half-life; T_{max}, time to maximum observed concentration, V_Z/F, apparent volume of distribution (terminal phase)

Figure 7. Median Plasma Concentration-Time Profiles in Healthy Participants for 672 h (Top), First 48 h in Patients With PH in Group A (Middle), and First 48 h in Patients With PH in Group B (Bottom) of Study DCR-PHXC-101



Source: Study DCR-PHXC-101 CSR.

LLOQ (1 ng/mL) indicated by horizontal line; X-axis truncated at 50 h in lower panels.

Abbreviations: CSR, clinical study report; LLOQ, lower limit of quantification; PH, primary hyperoxaluria

DCR-PHXC-102 (Intrinsic factor PK): Single Dose Study in Participants With Severe Renal Impairment and End-Stage Renal Disease (ESRD)

Study Design

Study DCR-PHXC-102 was an open-label study conducted to characterize the effects of severe renal impairment and hemodialysis (in patients with ESRD) on the PK of nedosiran. The control group was healthy participants with normal renal function and was matched for gender, age (± 10 years), and weight ($\pm 20\%$) with the other test groups (Table 62). The participants received a single dose of nedosiran sodium (170 mg) by SC injection on Day 1 and serial PK samples were collected at predose, 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 48, 72, 96, 168, 336, and 672 h (Day 28) postdose. In Group 1a, blood samples collected during hemodialysis for PK assessment were drawn from both the line entering and the line exiting the dialyzer (representing arterial and venous blood samples, respectively). Dialysate samples in Group 1a were obtained every 30 min for the duration of dialysis on Day 1. Pooled urine (for participants with urine output) was obtained at predose (single void), 0 to 6, >6 to 12, >12 to 24, >24 to 48, >48 to 72, and >72 to 96 h postdose.

Table 62. Study Design of DCR-PHXC-102

Group	Number of Participants Enrolled	Hemodialysis / Renal Function Status	eGFR ^a at Screening (mL/min/1.73 m ²)	Dosing Schedule	Pharmacokinetic Sample Type
Group 1a	8	Stable hemodialysis Severe RI/ESRD ^b	<30	On Day 1, 8 h before dialysis	Plasma, urine, dialysate
Group 1b	8	Stable hemodialysis Severe RI/ESRD ^b	<30	On Day 1, 2 h after dialysis	Plasma, urine
Group 2	8	No hemodialysis Severe RI/ESRD ^b	<30	On Day 1	Plasma, urine
Group 3	10 ^c	Normal renal function	≥ 90	On Day 1	Plasma, urine

Source: Study DCR-PHXC-102 Clinical Study Report Section 10.1.

^a eGFR estimated using the CKD-EPI equation.

^b Severe RI is defined as eGFR <30 mL/min/1.73 m²; ESRD is defined as an eGFR <15 mL/min/1.73 m².

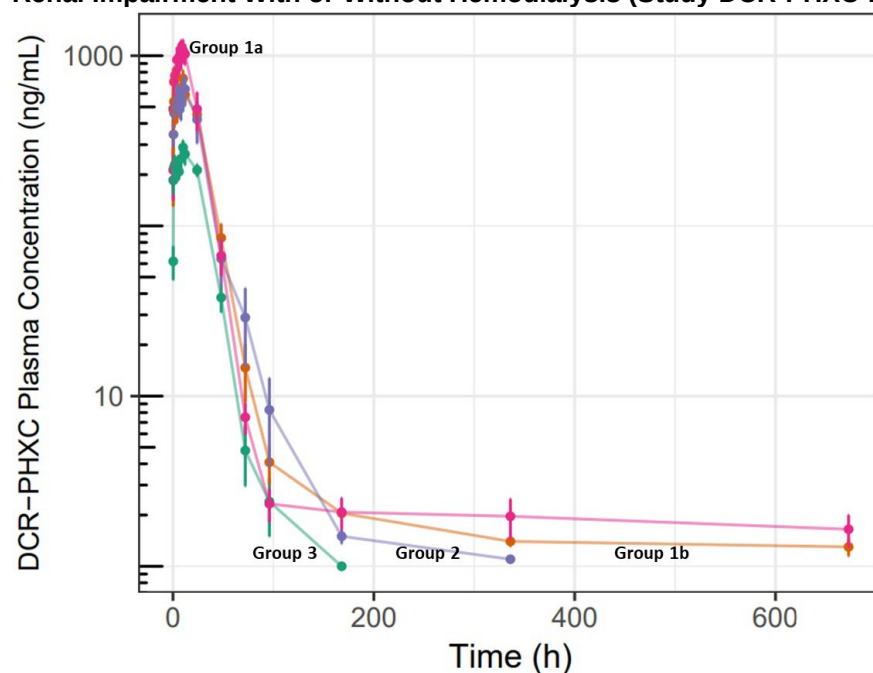
^c Due to matching requirements, 2 additional participants were enrolled in Group 3, for a total of 10, rather than the 8 prespecified in the protocol.

Abbreviations: CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; RI, renal impairment

Results

In participants with normal renal function, mean renal clearance was 3.2 L/h, and the mean unchanged drug eliminated over the first 96 h was 15.2%. Exposures increased with impairment of renal function, but the time to the maximum plasma concentration was not affected. During the 4 h dialysis period only 4% of drug was eliminated; however, overall exposure (AUC and C_{max}) was 30% lower in Group 1a (participants who were dosed 8 h before hemodialysis), as compared to Group 1b (those dosed 2 h after hemodialysis) and the reasons for these observations are not clear.

Figure 8. Mean ($\pm$ SEM) Plasma Nedosiran Concentration-Time Profiles in Patients With Severe Renal Impairment With or Without Hemodialysis (Study DCR-PHXC-102)



Source: DCR-PHXC-102 CSR, Section 16.1.13.

Log y-axis; Observations BLQ were removed; Group1a: Severe RI/ESRD participants stable on hemodialysis given nedosiran 8 h before dialysis; Group 1b: Severe RI/ESRD participants stable on hemodialysis given nedosiran 2 h after dialysis; Group 2: Severe RI/ESRD participants who do not require hemodialysis; Group 3: Participants with normal renal function.

Abbreviations: BLQ, below the limit of quantification; CSR, clinical study report; ESRD, end-stage renal disease; RI, renal impairment; SEM, standard error of the mean

Table 63. PK Parameters of Nedosiran Following a Single Dose in Patients With Severe Renal Impairment With or Without Hemodialysis (Study DCR-PHXC-102)

Group ^a	Dose ^b (mg)	C _{max} (ng/mL)		T _{max} (h)		AUC _{0-last} (h·ng/mL)		AUC _{0-∞} (h·ng/mL)		t _{1/2} (h)		CL/F (L/h)		Vz/F (L)		CLR (L/h)		Fe (%)	
		N	Mean (%CV)	N	Median (Min, Max)	N	Mean (%CV)	N	Mean (%CV)	N	Mean (%CV)	N	Mean (%CV)	N	Mean (%CV)	N	Mean (%CV)	N	Mean (%CV)
1a	170	8	757 (47.2)	8	11.0 (4.00, 24.0)	8	18300 (44.8)	5	15200 (32.3)	5	13.6 (53.2)	5	12.1 (29.6)	5	223 (51.1)	1	0.0396 (NA)	1	0.344 (NA)
1b	170	8	1190 (45.1)	8	9.00 (2.00, 12.0)	8	25500 (40.8)	4	26800 (32.8)	4	43.2 (163)	4	6.79 (26.9)	4	297 (141)	1	0.0924 (NA)	1	1.07 (NA)
2	170	8	982 (83.5)	8	10.0 (0.25, 24.0)	8	19800 (24.7)	0	NC	0	NC	0	NC	0	NC	7	0.417 (76.6)	7	4.27 (49.0)
3	170	10	315 (35.6)	10	10.0 (0.50, 12.0)	10	8390 (23.2)	9	8410 (24.4)	9	8.27 (28.5)	9	21.9 (36.5)	9	280 (75.3)	7	3.15 (22.0)	7	15.2 (19.8)

Source: DCR-PHXC-102 CSR, Section 16.1.13.

^a Group 1a: Severe RI/ESRD participants stable on hemodialysis given nedosiran 8 h before dialysis; Group 1b: Severe RI/ESRD participants stable on hemodialysis given nedosiran 2 h after dialysis; Group 2: Severe RI/ESRD participants who do not require hemodialysis; Group 3: Participants with normal renal function.

^b Dose expressed in sodium salt weight.

Abbreviations: AUC_{0-∞}, area under the concentration-time curve from time 0 to infinity; AUC_{0-last}, area under the concentration-time curve from time 0 to last quantifiable time point; CL/F, apparent clearance; CLR, renal clearance (calculated as CLR(0-last)); C_{max}, maximum observed concentration; CV, coefficient of variation; FAE, free acid equivalent; fe, fraction excreted unchanged in urine; N, number of participants; NA, not applicable; NC, not calculated; PK, pharmacokinetics; t_{1/2}, half-life; T_{max}, time to maximum observed concentration, Vz/F, apparent volume of distribution (terminal phase)

Table 64. Statistical Analysis of PK Parameters in Study DCR-PHXC-102

Grouping ^a (Test vs. Reference)	PK Parameter (Unit)	Test Group		Reference Group		Ratio of Geometric Means	90% CI of Ratio of Geometric Means
		Geometric Mean	N	Geometric Mean	N		
Group 2 vs. Group 3	AUC _{0-last} (h·ng/mL)	19,280	8	8137	10	2.37	(1.90, 2.96)
	AUC _{0-∞} (h·ng/mL)	NC	0	8129	9	NC	NC
	C _{max} (ng/mL)	811	8	289	10	2.81	(1.79, 4.40)
Group 1a vs. Group 3	AUC _{0-last} (h·ng/mL)	16,831	8	8137	10	2.07	(1.54, 2.78)
	AUC _{0-∞} (h·ng/mL)	14,583	5	8129	9	1.79	(1.33, 2.42)
	C _{max} (ng/mL)	673	8	289	10	2.33	(1.51, 3.58)
Group 1b vs. Group 3	AUC _{0-last} (h·ng/mL)	23,544	8	8137	10	2.89	(2.15, 3.89)
	AUC _{0-∞} (h·ng/mL)	25,847	4	8129	9	3.18	(2.31, 4.38)
	C _{max} (ng/mL)	1058	8	289	10	3.66	(2.36, 5.69)
Group 1a vs. Group 1b	AUC _{0-last} (h·ng/mL)	16,831	8	23,544	8	0.72	(0.49, 0.11)
	AUC _{0-∞} (h·ng/mL)	14,583	5	25,847	4	0.56	(0.38, 0.83)
	C _{max} (ng/mL)	673	8	1058	8	0.64	(0.39, 1.04)

Source: DCR-PHXC-102 Clinical Study Report, Section 16.1.13.

^a Group 1a: Severe RI/ESRD participants stable on hemodialysis given nedosiran 8 h before dialysis; Group 1b: Severe RI/ESRD participants stable on hemodialysis given nedosiran 2 h after dialysis; Group 2: Severe RI/ESRD participants who do not require hemodialysis; Group 3: Participants with normal renal function.

Abbreviations: AUC_{0-∞}, area under the concentration-time curve from time 0 to infinity; AUC_{0-last}, area under the concentration-time curve from time 0 to last quantifiable time point; CI, confidence interval; C_{max}, maximum observed concentration; CSR, clinical study report; ESRD, end-stage renal disease; N, number of participants; NC, not calculated; PK, pharmacokinetics; RI, renal impairment

Conclusion

The mean nedosiran plasma exposures increased approximately two-to-three-fold in severe renal impairment groups as compared to participants with normal renal function. According to the clinical team, the available data are not sufficient to provide dosing recommendations for patients with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m² or patients with kidney failure receiving dialysis because data on the effect of nedosiran on reducing plasma oxalate (i.e., an appropriate surrogate endpoint for the systemic manifestations of PH1 in patients with such low levels of kidney function) would be needed to do so.

DCR-PHXC-103 (Intrinsic Factor PK): Single Dose Study in Healthy Japanese and Caucasian Participants

Study Design

Study DCR-PHXC-103 was an open-label, parallel-group, uncontrolled, single SC dose study to compare the PK of nedosiran between 18 Japanese and 18 Caucasian healthy participants (done as a part of market application in Japan). The participants were assigned to receive one of three dose levels of nedosiran sodium (FAE) as follows: 1.5 (1.4 FAE) mg/kg, 3.0 (2.8 FAE) mg/kg, or 6.0 (5.6 FAE) mg/kg with six participants per group per dose.

Blood for determination of nedosiran concentrations and PK parameters was collected before dosing and at 5 min and at 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 168 (Day 8), and 336 (Day 15) h postdose. Urine for determination of nedosiran concentrations and PK parameters was collected predose (single void) and over the intervals of 0 to 6 h, >6 to 12 h, >12 to 24 h, >24 to 48 h (24 h urine collection), and >48 to 72 h (24 h urine collection).

Results

The PK of nedosiran was similar between healthy Japanese and Caucasian participants for the tested dose range of 1.5 to 6 mg/kg ([Table 65](#)). The 90% confidence interval for the slope of the relationship between the log-transformed PK parameters and log-transformed dose contained 1 for both races and there was no evidence to exclude dose proportionality. Approximately 20% of the dose was excreted unchanged in the urine and the renal clearance or fraction excreted unchanged in urine were independent of dose and ethnicity. The renal clearance ranged between 2.3 to 3.9 L/h across the cohorts.

Table 65. PK Parameters of Nedosiran Following a Single Dose in Japanese and Caucasian Healthy Participants

Dose (mg/kg)	Cohort	N	C _{max} ^a (ng/mL)	T _{max} ^a (h)	AUC _{0-last} ^a (h·ng/mL)	AUC _{0-∞} ^a (h·ng/mL)	t _{1/2} ^a (h)	CL/F ^a (L/h)	VZ/F ^a (L)	CLR ^a (L/h)	fe ^a (%)
1.5 (1.4 FAE)	Caucasian	6	323 (22.6)	10.0 (4.00, 12.0)	7290 (17.4)	7180 ^b (15.0)	5.89 ^b (21.1)	17.1 ^b (30.3)	147 ^b (38.7)	3.25 ^b (35.1)	18.4 (6.68)
	Japanese	6	326 (32.3)	8.00 (0.50, 24.0)	6910 (9.93)	7180 ^c (5.10)	6.54 ^c (19.2)	16.0 ^c (15.1)	154 ^c (35.3)	3.7 ^c (21.4)	22.2 (7.33)
3.0 (2.8 FAE)	Caucasian	6	684 (23.8)	7.99 (1.00, 12.0)	13700 (8.61)	13400 ^c (9.91)	6.79 ^c (5.08)	17.8 ^c (8.15)	175 ^c (10.3)	2.87 ^c (19.3)	17.7 (21.2)
	Japanese	6	497 (37.3)	7.00 (1.00, 12.0)	12300 (12.7)	12400 (12.9)	7.09 (17.3)	15.6 (23.6)	161 (30.1)	3.47 (30.4)	22.3 (21.9)
6.0 (5.6 FAE)	Caucasian	6	1350 (26.9)	8.00 (4.00, 12.0)	30100 (16.9)	27100 ^d (28.6)	5.89 ^d (12.7)	12.7 ^d (7.64)	108 ^d (20.2)	2.27 ^d (6.42)	18.8 (13.7)
	Japanese	6	1140 (21.4)	8.00 (6.00, 12.0)	29900 (20.6)	26100 ^d (22.2)	10.7 ^d (66.4)	13.9 ^d (15.6)	204 ^d (53.6)	3.85 ^d (10.9)	26.8 (20.5)

Source: Study DCR-PHXC-103 CSR, Section 16.1.13 PK report.

^a Arithmetic mean and %CV are reported for all parameters except for T_{max}, which is shown as median and minimum, maximum.

^b n=3.

^c n=4.

^d n=2.

Abbreviations: AUC_{0-∞}, area under the concentration-time curve from time 0 to infinity; AUC_{0-last}, area under the concentration-time curve from time 0 to last quantifiable time point; CL/F, apparent clearance; CL_R, renal clearance; C_{max}, maximum observed concentration; CV, coefficient of variation; FAE, free acid equivalent; fe, fraction excreted unchanged in urine; N, number of participants; PK, pharmacokinetics; t_{1/2}, half-life; T_{max}, time to maximum observed concentration, Vz/F, apparent volume of distribution (terminal phase)

Table 66. Statistical Analysis of PK Parameters in Japanese vs. Caucasian Healthy Participants

Dose (mg/kg)	PK Parameter (Unit)	Ratio (%) of Geometric Means (Japanese vs. Caucasian)	90% CI of Ratio of Geometric Means	No. of Participants (Japanese, Caucasian)
1.5 (1.4 FAE)	AUC _{0-last} (h·ng/mL)	95.6	(81.8, 111.8)	6, 6
	AUC _{0-∞} (h·ng/mL)	100.7	(85.4, 118.7)	4, 3
	C _{max} (ng/mL)	97.3	(69.1, 136.9)	6, 6
3.0 (2.8 FAE)	AUC _{0-last} (h·ng/mL)	89.7	(79.9, 100.7)	6, 6
	AUC _{0-∞} (h·ng/mL)	92.2	(79.8, 106.4)	6, 4
	C _{max} (ng/mL)	71.2	(52.4, 96.9)	6, 6
6.0 (5.6 FAE)	AUC _{0-last} (h·ng/mL)	98.8	(80.7, 121)	6, 6
	AUC _{0-∞} (h·ng/mL)	97.1	(45.6, 207.1)	2, 2
	C _{max} (ng/mL)	85.5	(64.3, 113.6)	6, 6

Source: Study DCR-PHXC-103 Clinical Study Report, Section 16.1.13 PK Report.

Abbreviations: AUC_{0-∞}, area under the concentration-time curve from time 0 to infinity; AUC_{0-last}, area under the concentration-time curve from time 0 to last quantifiable time point; CI, confidence interval; C_{max}, maximum observed concentration; FAE, free acid equivalent; PK, pharmacokinetics

DCR-PHXC-201 (Double-Blind Efficacy Study): Multiple Dose Study with PK and PD in PH Patients (Children and Adults)

Study Design

The study design is described in [Section 6.2.1.1](#). Adult and adolescent participants weighing at least 50 kg received 6 nedosiran doses of 170 mg (160 mg FAE) administered monthly (or matching placebo), while those weighing less than 50 kg received nedosiran doses of 136 mg (128 mg FAE) administered monthly (or matching placebo). Participants who were 6 to 11 years old received a monthly nedosiran dose of 3.5 mg/kg (3.3 mg/kg FAE), but not to exceed 136 mg (128 mg FAE) in total dose (or matching placebo). The blood samples for PK were obtained as per the following schedules:

- Age ≥18 years: Days 1 and 30: predose and at 5, 15, and 30 min and 1, 2, 4, 6, 10, and 12 h postdose; Days 2 and 31: 24 h postdose; Day 150: Predose and at 2, 6, and 12 h postdose.
- Age 6 to 17 years: Days 1 and 30: predose and at 30 min and 2 and 10 h postdose; Days 2 and 31: 24 h postdose; Day 150: predose and at 2 and 10 h postdose.

Results

The median body weight in adults, adolescent, and pediatric participants were 66, 59.6, and 33 kg, respectively. The median eGFR was higher in adolescent and pediatric patients (94 and 142 mL/min/m², respectively) compared with the median eGFR in adult patients (79 mL/min/m²). Overall, there were 4 patients with moderate renal impairment (RI) and 7 patients with mild RI. Of these 11 patients with renal impairment, only 2 patients were adolescent patients with mild RI. A total of 33 participants completed study treatment and continued into the long-term extension study, Study DCR-PHXC-301.

Table 67. Mean (%CV) PK Parameters of Nedosiran in Adult and Adolescent Participants After Dosing With 170 mg of Nedosiran Sodium (FAE of 160 mg) and Pediatric Patients After Dosing With 3.5 mg/kg (FAE of 3.3 mg/kg)

Day	N	C _{max} (ng/mL)	T _{max} ^a (h)	AUC _{0-last} (h·ng/mL)	R _{ac} (C _{max})	R _{ac} (AUC)	t _{1/2} (h)	V _z /F (L)
Adults^b								
1	12	821 (34.1)	10.8 (0.967, 12.1)	13000 (28.3)	NA	NA	11.9 ^c (NC)	126 ^c (NC)
30	11	844 (44.1)	6.00 (2.00, 11.6)	13600 (36.3)	1.03 ^d (24.6)	1.03 ^e (20.9)	15.0 ^f (68.1)	NA
150	8	742 (64.7)	11.6 (2.02, 12.0)	6690 (51.0)	1.40 (52.5)	0.948 ^g (38.2)	NA	NA
Adolescents^{b,h}								
1	5	435 (65.8)	2.00 (0.500, 10.0)	7080 (43.1)	NA	NA	NC	NC
30	5	381 (46.2)	9.65 (0.500, 10.0)	6870 (40.5)	1.01 ^d (30.8)	1.03 (15.4)	NC	NA
6 to 11 years oldⁱ								
1	2	614	6.2 (2.1, 10.2)	10100	NA	NA	NC	NC

Source: Tables 7 to 11 in Section 16.1.13 (PK and ADA report) of Study DCR-PHXC-201 Clinical Study Report.

^a Arithmetic mean and %CV are reported for all parameters except for T_{max}, which is shown as median and minimum, maximum.

^b For adult participants, PK samples were collected up to 24 h postdose on Days 1 and 30; and up to 12 h postdose on Day 150. For adolescent participants, PK samples were collected up to 24 h postdose on Days 1 and 30.

^c n=2.

^d Calculated as R_{ac}(C_{max})=C_{max} (Day 30 or Day 150)÷C_{max} (Day 1).

^e R_{ac}(AUC) on Day 30 was calculated as R_{ac}(AUC)=AUC₀₋₂₄ (Day 30)÷AUC₀₋₂₄ (Day 1).

^f n=5.

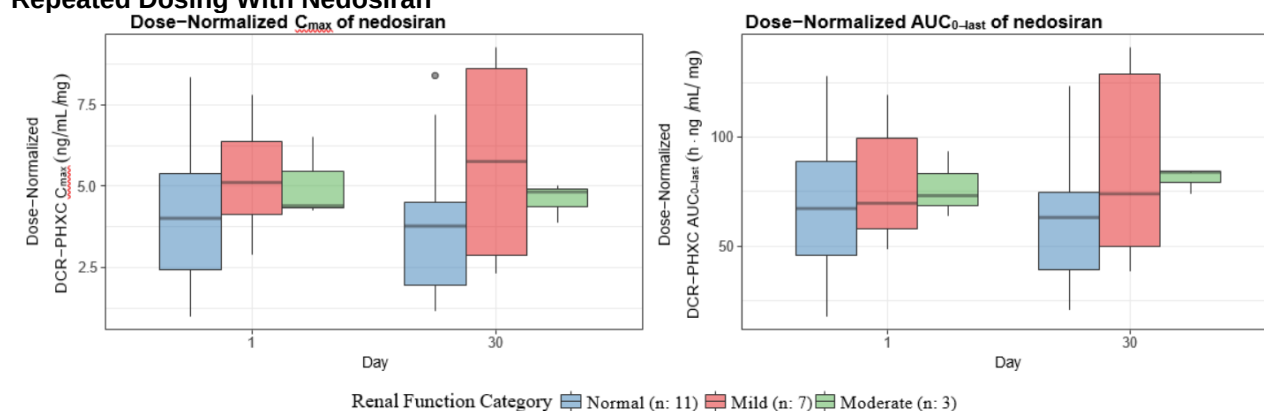
^g R_{ac}(AUC) on Day 150 was calculated as AUC₀₋₁₂ (Day 150)÷AUC₀₋₁₂ (Day 1).

^h Summary statistics for Day 150 in adolescent patients are not presented due to limited data.

ⁱ Summary statistics for Days 30 and 150 in pediatric patients are not presented due to limited data.

Abbreviations: AUC_{0-last}, area under the concentration-time curve from time 0 to last quantifiable time point; C_{max}, maximum observed concentration; CV, coefficient of variation; FAE, free acid equivalent; N, number of participants; NA, not applicable; NC, not calculated; PK, pharmacokinetics; R_{ac}(AUC), AUC accumulation ratio; R_{ac}(C_{max}), C_{max} accumulation ratio; t_{1/2}, elimination half-life; T_{max}, time to maximum observed concentration; V_z/F, apparent volume of distribution

Figure 9. Comparison of Exposures by Renal Function Category (Study DCR-PHXC-201) After Repeated Dosing With Nedosiran



Solid horizontal line = median, box heights = 25th and 75th percentiles (i.e the interquartile range (IQR)), symbols = outliers (1.5 * IQR).

Source: Figure 10 in Section 16.1.13 (PK and ADA report) of Study DCR-PHXC-201 Clinical Study Report.

Abbreviations: AUC_{0-last}, area under the concentration-time curve from time 0 to last quantifiable time point; C_{max}, maximum observed concentration

PK sampling for nedosiran in DCR-PHXC-201 did not extend beyond 24 h (Days 1, 30) or 12 h (Day 150). Given the limited PK sampling, the plasma exposure comparisons are limited to the first 12 to 24 h. In adults and adolescents, the plasma exposure of nedosiran did not seem to change with time suggesting no accumulation following repeated monthly dosing. There were very limited PK data in the 6- to 11-year-old pediatric participants. Based on the initial 12 to 24 h (C_{max}) sampling period, no differences in the exposures were observed between participants with normal renal function and those with mild to moderate renal impairment.

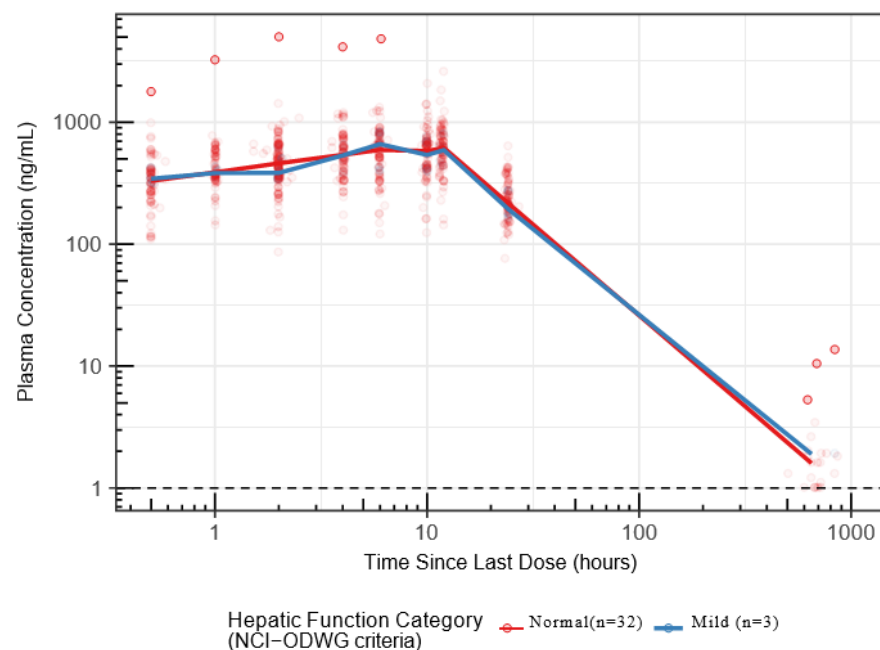
Nedosiran PK and PD in Patients With Mild Hepatic Impairment (HI) (Pooled Data From Studies DCR-PHXC-101, -201, and -301)

The single dose (-101) and multiple dose (-201 and -301) studies permitted enrollment of PH patients with normal hepatic function or mild HI, as defined by the National Cancer Institute Organ Dysfunction Working Group criteria:

- **Normal:** Total bilirubin (TB) and aspartate aminotransferase (AST) $\leq$ upper limit of normal (ULN)
- **Mild HI:** TB $\leq$ ULN and AST $>$ ULN; or ULN $<$ TB ≤ 1.5 x ULN with any AST
- **Moderate HI:** 1.5 x ULN $<$ TB ≤ 3 x ULN with any AST level
- **Severe HI:** TB > 3 x ULN with any AST level.

A total of five patients with mild HI were enrolled across these studies. No patients with moderate or severe HI were enrolled in these studies. Overall, the nedosiran plasma concentration-time profiles and the 24 h urinary oxalate-time profiles were similar in patients with normal hepatic function and mild HI, as shown in [Figure 10](#) and [Figure 11](#)

Figure 10. Comparison of Median Nedosiran Plasma Concentration-Time Profiles by Hepatic Function in Patients Dosed With 170 mg of Nedosiran Sodium

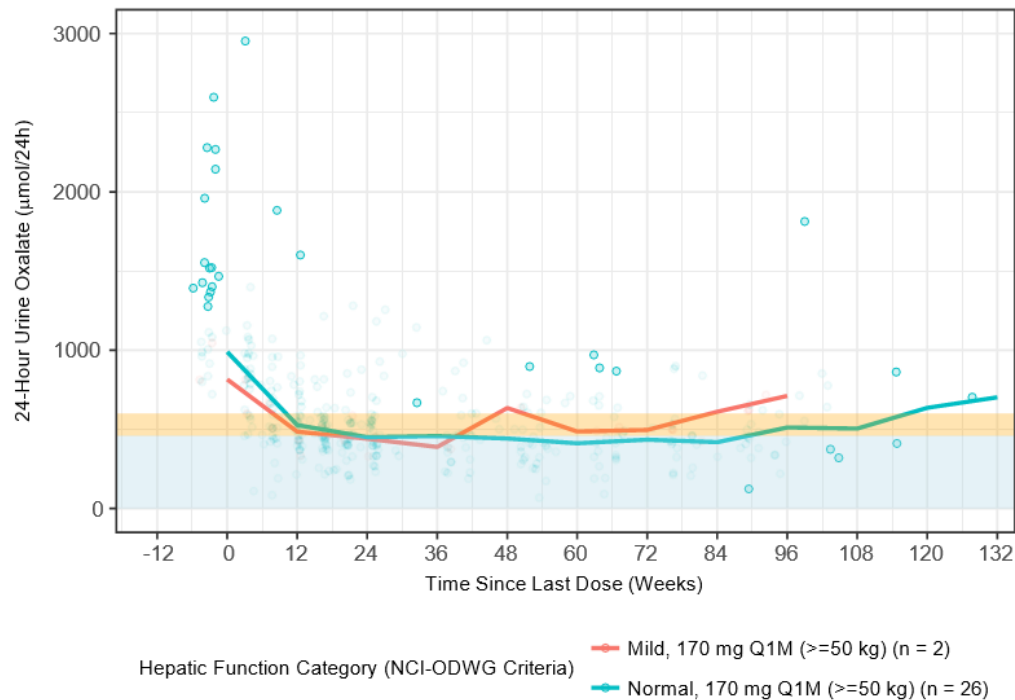


Source: Figure 20 in Population PK-PD Report [253335].

Solid lines show medians; filled circles represent observed data; and dashed line indicates the LLOQ (1 ng/mL). Data below the LLOQ (1 ng/mL) were excluded. X- and Y-axes on log scales. Participants with unknown hepatic function (n=34) were excluded from the plot. Data consisted of participants from study DCR-PHXC-201 and DCR-PHXC-301 who received 170 mg dose.

Abbreviations: LLOQ, lower limit of quantification; NCI-ODWG, National Cancer Institute Organ Dysfunction Working Group

Figure 11. Comparison of Median 24 h Urinary Oxalate Time Profiles by Hepatic Function in PH1 Participants (Study DCR-PHXC-201) After Repeated Dosing With Nedosiran



Source: Figure 9 in Supplement 1 of Population PK-PD Report [253335].

Solid circles are individual UO24 observations, solid lines are medians of subpopulations, and blue and orange shaded areas are the normal (<460 μmol/24 h) and near normal (<600 μmol/24 h) ranges of UO24, respectively.

Abbreviations: LLOQ, lower limit of quantification; NCI-ODWG, National Cancer Institute Organ Dysfunction Working Group; PH1, primary hyper oxaluria type 1; UO24, 24 h urinary oxalate

14.3. Bioanalytical Method Validation and Performance

Quantification of Nedosiran in Plasma, Urine, and Dialysate

A validated anion-exchange high-performance liquid chromatography method was used for determination of nedosiran in human plasma, urine, and dialysate. The same method was used for the quantification of nedosiran in all the clinical studies in this NDA submission, including DCR-PHXC-101, DCR-PHXC-102, DCR-PHXC-103, DCR-PHXC-201, and DCR-PHXC-301. The assay was based on hybridization of the antisense strand of nedosiran with a complementary peptide nucleic acid strand that was attached to a dye to enable fluorescence detection. The concentrations of nedosiran were evaluated by quantifying the antisense strand of nedosiran, and values were reported as the full-length double-stranded siRNA sodium salt. There was no analyte extraction or internal standard employed.

Table 68. Parameters of Method Validation for Analysis of Nedosiran in Human Plasma

Bioanalytical Method Validation Report Name Amendments	Validation of an AEX-HPLC Method for the Analysis of DCR-L1360 in Human Plasma, Amendment 01, Addendum 01	
Method description	Anion-exchange high-performance liquid chromatography with fluorescence detection	
Materials used for standard calibration curve and concentration	DCR-L1360, lot BCR 100000 (lyophilized powder)	
Validated assay range	1.0 to 2000.0 ng/mL	
Material used for QCs and concentration	DCR-L1360, lot BCR 100000 (lyophilized powder)	
Minimum required dilutions	Not applicable	
Source and lot of reagents	PNA probe: PNA-DCR-DP9247G-02 (b) (4) lots 170394, 180278, 181046	
Regression model and weighting	Linear, 1/x	
Validation Parameters	Method Validation Summary	
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	6
	Cumulative accuracy (%bias) from LLOQ to ULOQ	95.2% to 103.3%
	Cumulative precision (%CV) from LLOQ to ULOQ	≤5.0%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs:	
	1.0 ng/mL (LLOQ)	102.8%
	3.0 ng/mL	96.9%
	900.0 ng/mL	100.2%
	1800.0 ng/mL	99.4%
	Interbatch %CV:	
	1.0 ng/mL (LLOQ)	6.5%
	3.0 ng/mL	2.6%
	900.0 ng/mL	2.8%
	1800.0 ng/mL	1.9%
	Total error	Not applicable
Selectivity & matrix effect	Six lots tested, 100% to 120% observed bias	
Interference & specificity	Not performed	
Hemolysis effect	Not performed	
Lipemic effect	Not performed	
Dilution linearity & hook effect	100,000 ng/mL; diluted 1/100; 82.5% to 110.1% observed bias	
Bench-top/process stability	4 h on wet ice	
	QC low, 3.0 ng/mL: 94.4%	
	QC high, 1800.0 ng/mL: 96.0%	
Freeze-thaw stability	3 freeze-thaw cycles	
	QC low, 3.0 ng/mL: 87.8%	
	QC high, 1800.0 ng/mL: 95.7%	
Long-term storage	12 months at -20°C:	
	QC 1, 3.0 ng/mL: 110.0%	
	QC 2, 1800.0 ng/mL: 100.8%	
	QC 3, 100,000.0 ng/mL: 109.7%	
	12 months at -80°C:	
	QC 1, 3.0 ng/mL: 107.8%	
	QC 2, 1800.0 ng/mL: 103.0%	
	QC 3, 100,000.0 ng/mL: 102.0%	
Parallelism	Not applicable	
Carry over	Calculated concentration following injection of ULOQ was BLQ; percentage of LLOQ ranged from 0.0 to 9.6%	

Source: Table 2.7.1.6 in Module 2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods.

Abbreviations: AEX-HPLC, anion-exchange high-performance liquid chromatography; BLQ, below the limit of quantification; CV, coefficient of variation; LLOQ, lower limit of quantification; PNA, peptide nucleic acid; QC, quality control; ULOQ, upper limit of quantification

Long-term stability in plasma was established for 365 days and clinical study samples were analyzed within the stability period and by 210, 120, 164, 257, and 352 days for Studies 101, 102, 103, 201, and 301, respectively. The incurred sample reanalysis was performed in 6 to 39% of samples across the clinical studies and 78 to 94% of these samples met the prespecified acceptance criterion.

Table 69. Parameters of Method Validation for Analysis of Nedosiran in Human Urine

Bioanalytical Method Validation Report Name, Amendments	Validation of an AEX-HPLC Method for the Analysis of DCR-L1360 in Human Urine, Addendum 01	
Method description	Anion-exchange high-performance liquid chromatography with fluorescence detection	
Materials used for standard calibration curve and concentration	DCR-L1360, lot BCR 100000 (lyophilized powder)	
Validated assay range	1.0 to 2000.0 ng/mL	
Material used for QCs and concentration	DCR-L1360, lot BCR 100000 (lyophilized powder)	
Minimum required dilutions	Not applicable	
Source and lot of reagents	PNA probe: PNA-DCR-DP9247G-02 (b) (4); lots 170394, 180278, 181046	
Regression model and weighting	Linear, 1/x	
Validation Parameters	Method Validation Summary	
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators	6
	from LLOQ to ULOQ	
	Cumulative accuracy (%bias) from LLOQ to ULOQ	97.3% to 103.3%
Performance of QCs during accuracy and precision runs	Cumulative precision (%CV) from LLOQ to ULOQ	1.4% to 10.0%
	Cumulative accuracy (%bias) in 4 QCs:	
	1.0 ng/mL (LLOQ)	108.3%
	3.0 ng/mL	100.0%
	900.0 ng/mL	99.4%
	1800.0 ng/mL	98.8%
	Interbatch %CV:	
	1.0 ng/mL (LLOQ)	7.9%
	3.0 ng/mL	2.6%
	900.0 ng/mL	2.0%
	1800.0 ng/mL	1.7%
	Total error	Not applicable
Selectivity & matrix effect	6 lots tested, 110% to 120% observed bias	
Interference & specificity	Not performed	
Hemolysis effect	Not performed	
Lipemic effect	Not performed	
Dilution linearity & hook effect	100,000 ng/mL; diluted 1/100; 94.0% to 97.9% observed bias	
Bench-top/process stability	4 h on wet ice	
	QC low, 3.0 ng/mL: 90.0%	
	QC high, 1800.0 ng/mL: 97.0%	

Bioanalytical Method Validation Report Name, Amendments	Validation of an AEX-HPLC Method for the Analysis of DCR-L1360 in Human Urine, Addendum 01
Freeze-thaw stability	3 freeze-thaw cycles (repeated) QC low, 3.0 ng/mL: 88.9% QC high, 1800.0 ng/mL: 101.4%
Long-term storage	12 months at -20°C: QC 1, 3.0 ng/mL: 88.9% QC 2, 1800.0 ng/mL: 105.6% QC 3, 100,000.0 ng/mL: 104.1% 12 months at -80°C: QC 1, 3.0 ng/mL: 90.0% QC 2, 1800.0 ng/mL: 99.4% QC 3, 100,000.0 ng/mL: 103.3%
Parallelism	Not applicable
Carry over	Calculated concentration following injection of ULOQ was BLQ; percentage of LLOQ ranged from 0.0 to 0.0%

Source: Table 2.7.1.7 in Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods.

Abbreviations: AEX-HPLC, anion-exchange high-performance liquid chromatography; BLQ, below the limit of quantification; CV, coefficient of variation; LLOQ, lower limit of quantification; PNA, peptide nucleic acid; QC, quality control; ULOQ, upper limit of quantification

The clinical urine samples were analyzed within the stability period of 12 months, corresponding to 7, 4, and 2 months for Studies 101, 102, and 103, respectively. The incurred sample reanalysis was performed in 13 to 15% of samples across the above studies and 86 to 100% of these samples met the prespecified acceptance criterion.

Table 70. Parameters of Method Validation for Analysis of Nedosiran in Dialysate

Bioanalytical Method Validation Report Name, Amendments	Validation of an AEX-HPLC Method for the Analysis of DCR L1360 in Human Dialysate, Addendum 01	
Method description	Anion-exchange high-performance liquid chromatography with fluorescence detection	
Materials used for standard calibration curve and concentration	DCR L1360, lot BCR 100000 (lyophilized powder)	
Validated assay range	1.0 to 2000.0 ng/mL	
Material used for QCs and concentration	DCR L1360, lot BCR 100002 (lyophilized powder)	
Minimum required dilutions	Not applicable	
Source and lot of reagents	PNA probe: PNA-DCR-DP9247G-02 (b) (4); lot 190900 and 191939	
Regression model and weighting	Linear, 1/x	
Validation Parameter	Method Validation Summary	
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ 6	
	Cumulative accuracy (%bias) from LLOQ to ULOQ	99.3 to 100.9%
	Cumulative precision (%CV) from LLOQ to ULOQ	0.0 to 1.6%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs:	
	1.0 ng/mL (LLOQ)	101.7%
	3.0 ng/mL	98.3%
	900.0 ng/mL	103.0%
	1800.0 ng/mL	102.4%
	Interbatch %CV:	
	1.0 ng/mL (LLOQ)	3.8%
	3.0 ng/mL	2.1%
	900.0 ng/mL	2.1%
	1800.0 ng/mL	1.8%
	Total error	Not applicable
Selectivity & matrix effect	Six lots tested, 100 to 110% observed bias	
Interference & specificity	Not performed	
Hemolysis effect	Not performed	
Lipemic effect	Not performed	
Dilution linearity & hook effect	500,000 ng/mL; diluted 1/500; 88.5 to 91.8% observed bias	

Bioanalytical Method Validation Report Name, Amendments	Validation of an AEX-HPLC Method for the Analysis of DCR L1360 in Human Dialysate, Addendum 01
Bench-top/process stability	4 h on wet ice QC low, 3.0 ng/mL: 107.8% QC high, 1800.0 ng/mL: 110.6%
Freeze-thaw stability	3 freeze-thaw cycles QC low, 3.0 ng/mL: 106.7% QC high, 1800.0 ng/mL: 108.9%
Long-term storage	12 months at –20°C: QC 1, 3.0 ng/mL: 113.3% QC 2, 1800.0 ng/mL: 110.3% 12 months at –80°C: QC 1, 3.0 ng/mL: 108.9% QC 2, 1800.0 ng/mL: 107.7%
Parallelism	Not applicable
Carry over	Calculated concentration following injection of ULOQ was BQL; percentage of LLOQ ranged from 0.0 to 0.0%

Source: Table 2.7.1.8 in Module 2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods.
Abbreviations: AEX-HPLC, anion-exchange high-performance liquid chromatography; BLQ, below the limit of quantification; CV, coefficient of variation; LLOQ, lower limit of quantification; PNA, peptide nucleic acid; QC, quality control; ULOQ, upper limit of quantification

The dialysate samples in Study 102 were analyzed within 3 months which was within the 12-month stability period. The incurred sample reanalysis was not performed as none of the samples in Study 102 had quantifiable concentrations.

Overall, the accuracy and precision of calibration standards and quality controls for the analyte (antisense strand) were found to be within the acceptable limits ($\leq 15\%$) during analysis of plasma, urine, and dialysate samples, across the respective clinical studies.

Quantification of Oxalate in Urine

Validation was done for the use of a commercial assay kit (Trinity Biotech Oxalate kits) for the colorimetric determination of oxalate in human urine from 50 to 2000 μM . The determination of urinary oxalate is based on its enzymatic oxidation with oxalate oxidase, followed by measurement at 580 nm. The pH of human urine samples was adjusted to between 2.5 and 5.

Table 71. Bioanalytical Method Summary for Assay of Urinary Oxalate

Bioanalytical Method Validation Report Name, Amendments	Validation of a Colorimetric Method for the Quantitative Determination of Oxalate in Human Urine (Study No. Oxalate-MV-urine-R1)
Method description	Colorimetric method using Oxalate Kit 591
Materials used for standard calibration curve and concentration	Trinity Biotech oxalate standards (part number 591-11)
Validated assay range	50 to 2000 µmol/L
Material used for QCs and concentration	Trinity Biotech Accumark Oxalate urine control-N with Cat. No. 06627, and control-E with Cat. No. 06502
Minimum required dilutions	Not applicable
Source and lot of reagents	(b) (4)
Regression model and weighting	Not applicable
Validation Parameter	Method Validation Summary
Trueness	Average positive bias of 12.1 µmol/L
Accuracy	Bias of +1.5%
Repeatability	Average CVW 1.75%
Intermediate precision	Average CVB 1.78%
Precision	Average CVA 2.51%
Uncertainty of measurement	Low level range: 230-258 µmol/L High level range: 986-1074 µmol/L
Measurement interval	Deviation from target: ≤0.01% Precision: CV ≤0.52%
Recovery	92.7-100.0%
Linearity	Deviation from line of identity: 0.4%
Detection limit and quantification limit	Lowest level at which both accuracy and precision <20%: <100 µmol/L
Bench-top/process stability	At least 3 days at room temperature; 1 week at 2-8°C
Freeze-thaw stability	At least six cycles (-20°C)
Long-term storage	At least 1 year at -20°C
Carry over	Apparent oxalate in water after sample with oxalate 4400: <50 µmol/L
Bias against the Cobas Mira method	Bias: 6.80%

Source: Table 2.7.1.10 in Module 2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods.

Abbreviations: CV, coefficient of variation; CVA, among-samples coefficient of variation; CVB, between-sample coefficient of variation; CVW, within-sample coefficient of variation; QC, quality control

Conclusion

The methods for quantifying nedosiran in human plasma, urine, dialysate and for oxalate in human urine satisfied the method validation criterion in accordance with the FDA Guidance for Industry *M10 Bioanalytical Method Validation and Study Sample Analysis* (November 2022) and showed an acceptable performance during the sample analysis, as applicable, in clinical Studies-101, -102, -103, -201, and -301.

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

ADA to nedosiran were detected in serum samples using a validated enzyme-linked immunosorbent assay method. The method was used for detection and confirmation of ADAs using a 30 µL aliquot of human serum sample. Samples were analyzed in a tiered approach with a screening assay that identified ‘potential positive’ samples, followed by a confirmatory assay and titer assay on confirmed positive samples. The drug tolerances for 400 ng/mL and 1600 ng/mL of ADA were reported to be 1.00 µg/mL and 25.0 µg/mL of nedosiran (drug), respectively. No neutralizing assay was developed.

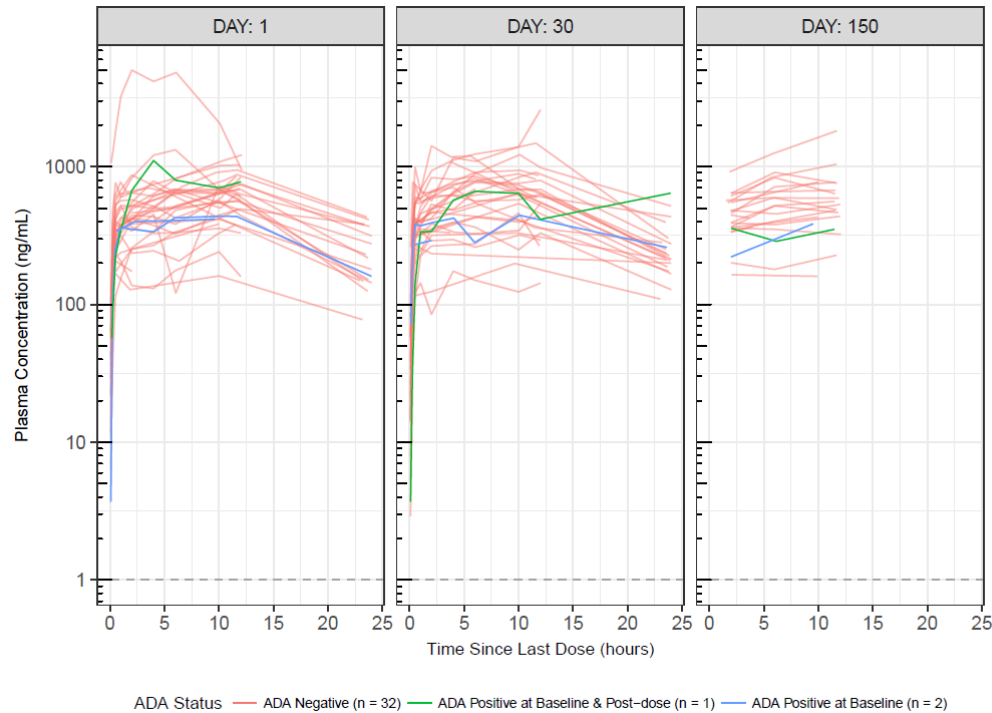
ADA sampling was obtained from PH patients, across the trials, as below.

- Study-101 (Part B): Days 1, 15, 57
- Study-201: Screening, Days 45, 180
- Study-301: Screening, Days 45, 180

A total of 59 patients were screened with the ADA assay and none were identified to have developed treatment-emergent ADA. Two patients tested positive for ADA only at baseline. Another patient tested positive both prior to dosing and post nedosiran dosing and therefore was not considered to have treatment-emergent ADA. The titer of this patient’s ADA test response continually reduced by 94% over the 12-month treatment period from 2560 at screening, to 1280 on Day 45, and 640 on Days 180 and 160 during the follow-up sample (in Month 12).

The PK profiles (on Days 1, 30, and 150) and PD response of nedosiran (24 h urinary oxalate excretion) following 170 mg one monthly dosing regimen in Studies -201 and -301 were compared between patients that screened positive for ADA and others. As shown in [Figure 12](#) and [Figure 13](#), the PK profiles and 24 h urinary oxalate excretion profiles of the three patients who tested positive for ADA at screening or any time point during the study were comparable to other patients that tested negative for ADA.

Figure 12. Overlay Plot of Median Plasma Concentration-Time Profiles in PH1 Patients With and Without ADA in Studies-201/-301

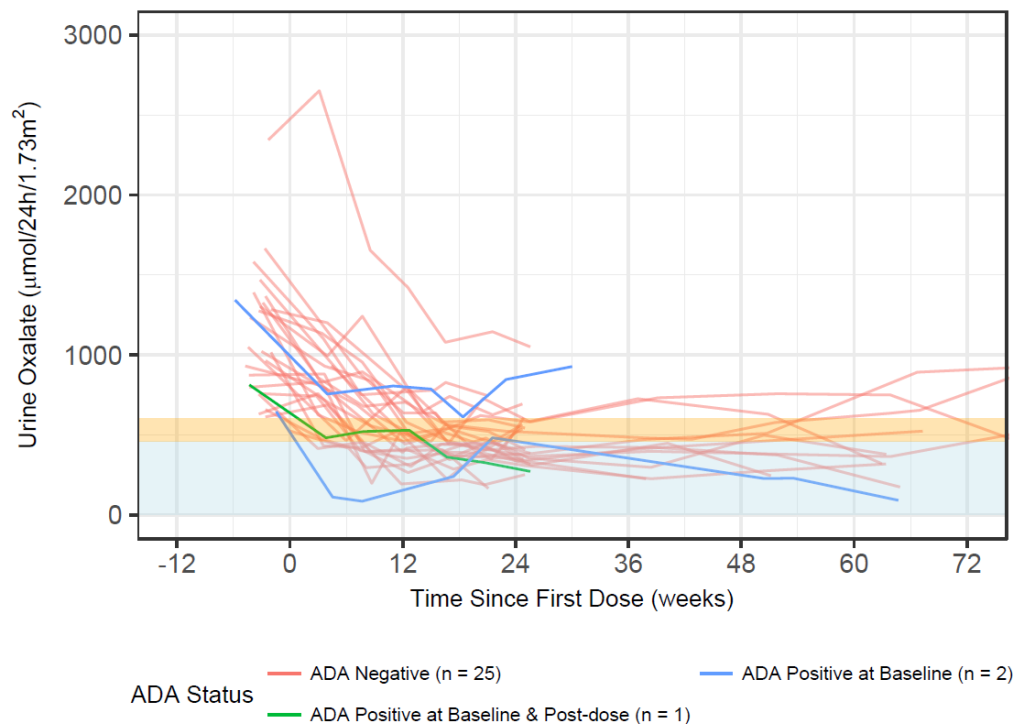


Source: Figure 22, Population PKPD model report DIC202005 [253335].

Dashed line represents the LLOQ (1 ng/mL). Time was truncated to 24 h postdose; data below the LLOQ (1.00 ng/mL) were excluded; Y-axis on log scale.

Abbreviations: ADA, antidrug antibodies; LLOQ, lower limit of quantification; PH1, primary hyperoxaluria type 1; PKPD, pharmacokinetics/pharmacodynamics

Figure 13. Overlay Plot of 24 H Urine Oxalate Time Profiles in PH1 Patients With and Without ADA in Studies-201/-301



Source: Figure 43, Population PKPD model report DIC202005 [253335].

The solid lines are the individual $\text{UO}_{24}/\text{BSA}$ profiles, shaded areas are the normal ($<460 \mu\text{mol}/24 \text{ h}/1.73 \text{ m}^2$) and near normal ($<600 \mu\text{mol}/24 \text{ h}/1.73 \text{ m}^2$) range of $\text{UO}_{24}/\text{BSA}$, respectively.

Abbreviations: ADA, antidrug antibodies; BSA, body surface area; PH1, primary hyperoxaluria type 1; PKPD, pharmacokinetics/pharmacodynamics; UO_{24} , 24 h urinary oxalate

Conclusion

The presence of nedosiran antibodies did not affect the PK of nedosiran or PD response to nedosiran. However, only one patient had ADA while on treatment, thus data are limited. All three patients who were positive for ADA were positive at baseline; no patients developed treatment-emergent ADA.

14.5. Pharmacometrics Assessment

Population PK Analysis

The Applicant submitted two population PK and PK-PD study reports, ‘Population PKPD Model Update and Simulations for Nedosiran (DCR-PHXC)’ (referred to as ‘main report’) and ‘Supplement 1 to Population PKPD Model Update and Simulations for Nedosiran (DCR-PHXC)’ (referred to as ‘Supplement 1’). An additional 138 urine oxalate observations and 219 dosing records beyond 24 months from the start of the study were included in Supplement 1. There were no changes in PK data from studies DCR-PHXC-101, DCR-PHXC-102, DCRPHXC-103, DCR-PHXC-201 and DCR-PHXC-301. The model described in Supplement 1 was regarded as the final model. The final model building population PK dataset consisted of 379, 469, 429, 363, and 338 plasma nedosiran concentrations from studies DCR-PHXC-101, DCR-PHXC-102, DCR-PHXC-103, DCR-PHXC-201, and DCR-PHXC-301, respectively, with a total of 143 participants 9 to 73 years old, with body weight ranging from 31.8 to 132 kg. The dataset included a total of 91 males and 52 females. The demographics summary for all studies is provided in [Table 72](#) and [Table 73](#).

Table 72. Summary of Demographics (PK) – All Studies (Categorical)

Sex	Race	PHSTAT	VITB	ADABL	HEPATC
Female: 52 (36.4%)	White: 80 (55.9%)	NHV: 85 (59.4%)	Not used: 65* (45.5%)	Not present: 55 (49%)	Normal: 68 (47.6%)
Male: 91 (63.6%)	Black: 17 (11.9%)	PH1: 46 (32.2%)	Used: 8 [†] (5.6%)	Present: 3 (2.1%)	Mild: 5 (3.5%)
	Asian: 24 (16.8%)	PH2: 12 (8.4%)	Unknown: 70 [‡] (49%)	No sample: 85 (49%)	Unknown: 70 (49%)
	Other: 7 (4.9%)				
	Unknown: 15 (10.5%)				

PHSTAT = PH status; VITB = vitamin B6 use at study start; ADABL = ADA presence at study start; HEPATC = hepatic function category based on NCI-ODWG.

Note rollover PH patients from study DCR-PHXC-101 (n=16) were treated as new PH patients in study DCR-PHXC-301. Rollover PH patients from study DCR-PHXC-201 to DCR-PHXC-301 were treated as a single PH patient for their participation in studies DCR-PHXC-201 and DCR-PHXC-301.

*Includes 15 normal healthy volunteers. [†]Only PH1 patients used vitamin B6 in these studies. PH patients were using vitamin B6 before the start of study and continued to use throughout the study. [‡]Includes normal healthy volunteers only.

Source: dic202005-253335-suppl, Table 6.

Abbreviation: PK, pharmacokinetics

Table 73. Summary of Demographics (PK) – All Studies (Continuous)

	Age (year)	Weight (kg)	Body surface area (m ²)	Body mass index (kg/m ²)	eGFR (mL/min/1.73m ²)	CRCL (mL/min)	ALT (IU/L)	AST (IU/L)	BILI (μmol/L)	ALB (g/L)
N	143	143	143	143	143	143	73	73	73	73
Mean	36.7	74.4	1.85	25.3	79.4	95.2	17.8	22.9	7.96	44.5
SD	15.9	17.8	0.252	4.71	38.3	50.4	11.6	11.7	5.36	3.27
CV%	43.2	24	13.6	18.6	48.3	53	65.2	51.1	67.4	7.35
Median	35	73.4	1.84	24.8	88.7	99.3	15	20	6.8	44
Min	9	31.8	1.08	14	3.77	6.1	5	9.4	3	38.7
Max	73	132	2.52	38.9	195	317	72	95	36.8	52.8

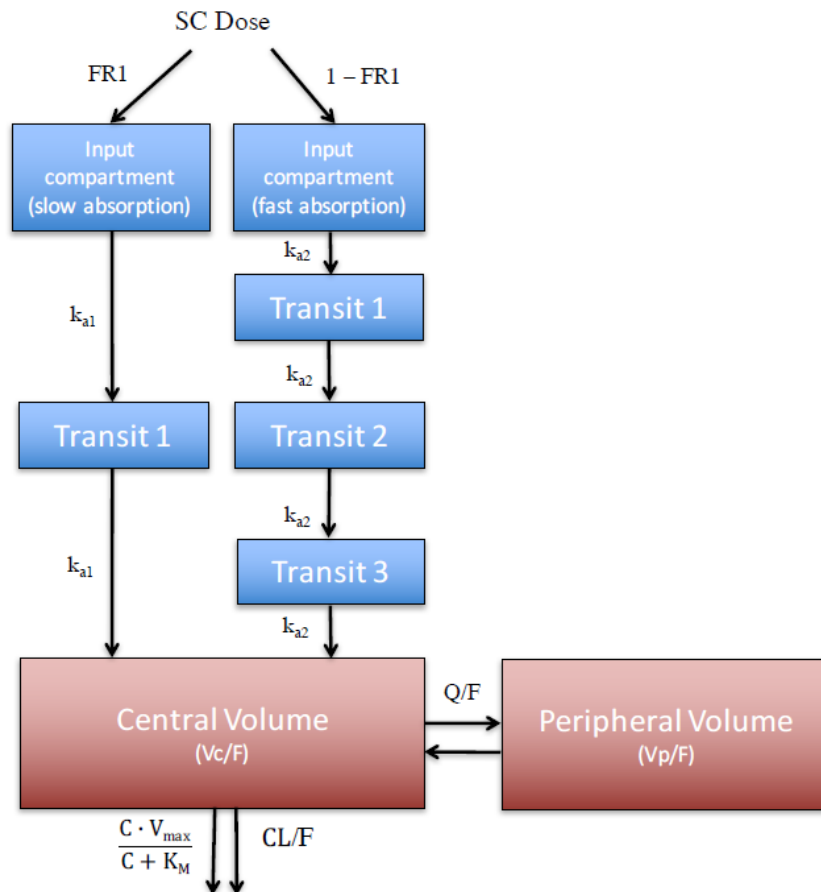
SD = standard deviation; CV% = percent coefficient of variation; eGFR = estimated glomerular filtration rate; CRCL = creatinine clearance; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; ALB = albumin.

Source: dic202005-253335-suppl, Table 5.

Abbreviation: PK, pharmacokinetics

The nedosiran PK can be described by a two-compartment disposition model with a dual-transit absorption model to better describe the biphasic absorption of nedosiran when administered subcutaneously ([Figure 14](#)). A dual linear and nonlinear Michaelis-Menten model was implemented to describe the over proportional increase in PK exposure as dose increased. Between-subject variability was included on apparent central volume of distribution, absorption transit rate constant for the slow pathway, absorption transit rate constant for the fast pathway, maximum metabolic rate, and fraction of the dose absorbed via the slow pathway. The parameter estimates are shown in [Table 74](#).

Figure 14. Schematic of the Population Pharmacokinetics Model



SC = subcutaneous; FR1 = fraction of the dose absorbed via the slow pathway; k_{a1} = absorption transit rate constant for the slow pathway; k_{a2} = absorption transit rate constant for the fast pathway; Q/F = apparent inter-compartmental clearance; V_{max} = maximum metabolic rate; K_M = Michaelis-Menten constant; CL/F = apparent clearance; V_c/F = apparent volume of distribution for the central compartment; V_p/F = apparent volume of distribution for the peripheral compartment.

Source: dic202005-253335, Figure 23.

Table 74. Final Parameter Estimates for the Population PK Model

Parameter Name	Updated Dataset Estimated Value (%RSE)	Previous Dataset Estimated Value (%RSE)	Fold-Change (Proportional)
Apparent Clearance (CL/F, L/h)	5.69 (11.0)	5.72 (11.4)	0.99
Exponent for WT on CL/F and Q/F	0.75 FIX	0.75 FIX	1.00
Exponent for eGFR on CL/F	0.872 (17.5)	0.864 (17.5)	1.01
Maximum Metabolic Rate (V_{max} , mg/h)	3.94 (15.6)	3.97 (16.1)	0.99
Michaelis-Menten Constant (K_M , ng/mL)	293 (15.0)	301 (15.2)	0.97
Apparent Inter-compartmental Clearance (Q/F, L/h)	2.45 (13.1)	2.43 (13.2)	1.01
Apparent Volume of Distribution (V_c /F, L)	147 (3.7)	145 (3.7)	1.01
Exponent for WT on V_c /F and V_p /F	1 FIX	1 FIX	1.00
Exponent for eGFR on V_c /F	0.191 (18.0)	0.19 (19.5)	1.01
Apparent Volume for the Peripheral Compartment (V_p /F, L)	5300 (26.8)	5320 (27.2)	1.00
Percentage of the Dose Absorbed via the Slow Pathway (FR1)	69.8 (1.3)	70.2 (1.3)	0.99
First-order Absorption Rate Constant for the Slow Pathway (k_{a1} , 1/h)	0.219 (4.9)	0.214 (5.0)	1.02
Exponent for WT on k_{a1} and k_{a2}	-0.834 (11.5)	-0.816 (11.8)	1.02
Covariate Effect of PH1 on k_{a1}	1.54 (7.8)	1.56 (7.7)	0.99
First-order Absorption Rate Constant for the Fast Pathway (k_{a2} , 1/h)	16.7 (2.5)	16.6 (2.6)	1.01
Between Subject Variability for V_c /F (% CV)	27.1 (11.1)	27.5 (11.6)	0.99
Between Subject Variability for k_{a1} (% CV)	42.1 (9.5)	42 (9.8)	1.00
Between Subject Variability for k_{a2} (% CV)	27.6 (7.5)	27.5 (7.4)	1.00
Between Subject Variability for V_{max} (% CV)	35.3 (14.8)	35.4 (14.5)	1.00
Between Subject Variability for FR1 (Additive) [§]	0.352 (12.6)	0.335 (12.7)	1.05
Residual Unexplained Variability (Proportional) (%)	27.7 (5.2)	27.7 (5.2)	1.00

Source: dic202005-253335-suppl, Table 9.

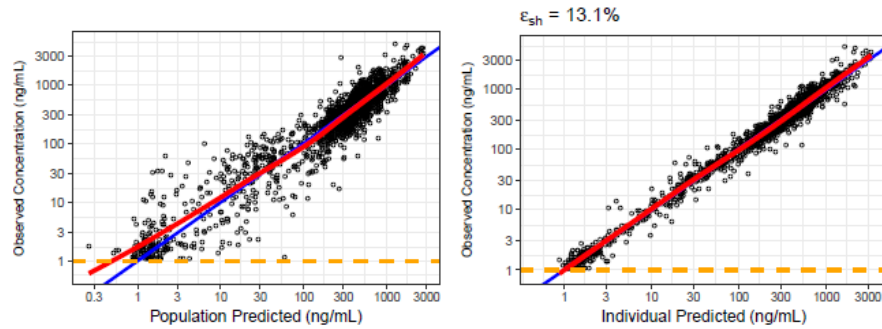
Standard errors obtained by importance sampling.

Abbreviations: CV, coefficient of variation; eGFR, estimated glomerular filtration rate; PH1, primary hyperoxaluria type 1; PK, pharmacokinetics; RSE, relative standard error; WT, weight

Allometric scaling by body weight was included on clearance (including apparent clearance from the central compartment, apparent intercompartmental clearance) and volume terms (including apparent central volume of distribution, apparent volume of distribution for the peripheral compartment) with exponents fixed to 0.75 and 1, respectively. Additionally, eGFR was included as a covariate on apparent clearance from the central compartment and apparent central volume of distribution. Body weight was found to be a significant covariate on absorption transit rate constant for the slow pathway and absorption transit rate constant for the fast pathway. In addition, a diagnosis of PH1 was found to be a significant covariate on absorption transit rate constant for the slow pathway. Vitamin B6 use at study start was tested and was not recognized as a significant covariate.

The evaluation of the population PK model was based on the model described in the main report rather than the model described previously in supplement 1. The PK samples and model structure were identical for the two models with minor change in parameter estimates (fold-change <5%). Plots of observed versus population predicted plasma concentrations and observed versus individual predicted plasma concentrations are presented below in [Figure 15](#). Plots of the observed versus the population predicted concentrations demonstrated acceptable bias, with the majority of data evenly scattered around the line of unity. Plots of the observed concentrations versus the individual predicted concentrations, which account for random effects, were more tightly scattered around the line of unity. There appears to be no obvious bias as demonstrated by the trend line for the data directly overlaying the line of unity. Additional diagnostic plots of conditional weighted residuals are shown in [Figure 16](#), which highlight that the final model fitted the data with relatively good precision and acceptable bias.

Figure 15. Goodness-of-Fit Plots for the Population PK Model

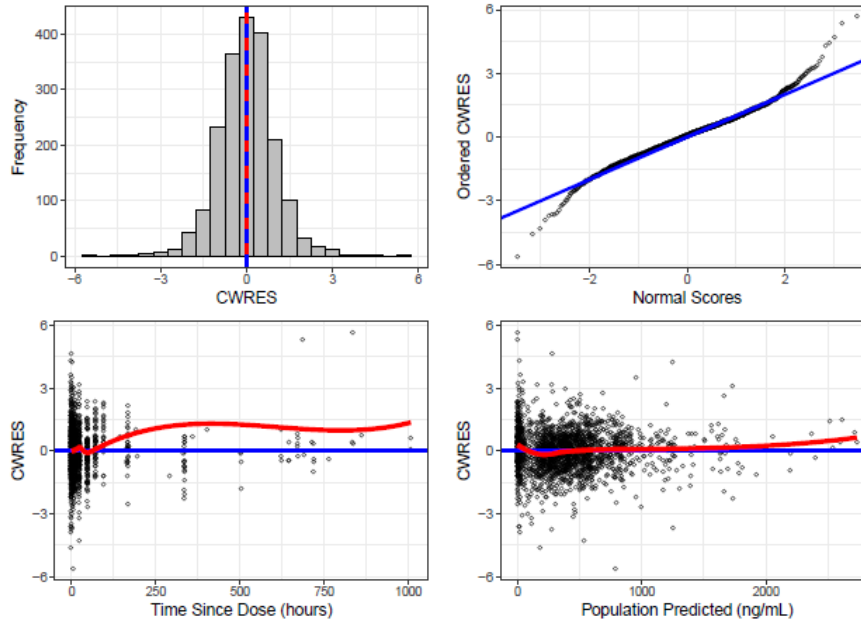


The blue lines represent the line of unity, the red lines show the trend in the data (Loess smooth), the orange dashed line represent the LLOQ at 1.00 ng/mL, and ϵ_{sh} shows shrinkage for the residual variability. Note: x and y-axis on log-scale.

Source: dic202005-253335, Figure 28.

Abbreviations: LLOQ, lower limit of quantification; PK, pharmacokinetics

Figure 16. CWRES Plots for the Population PK Model



The solid blue lines represents the line of identity or zero, the red lines represents the trend in the data (Loess smooth) or the mean.

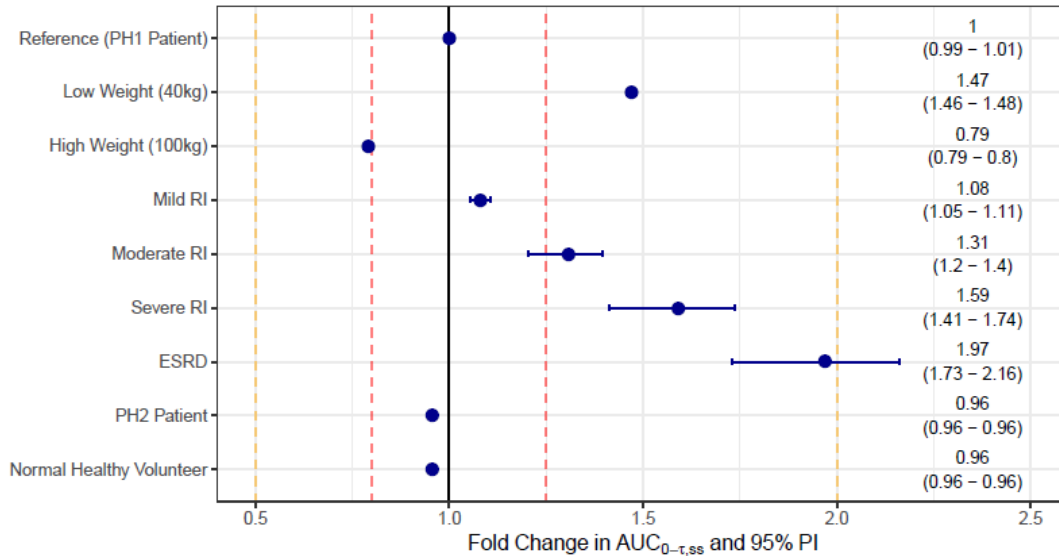
Source: dic202005-253335, Figure 29.

Abbreviations: CWRES, conditional weighted residuals; PK, pharmacokinetics

The magnitude of the effect of the included covariates on nedosiran exposure was evaluated by deriving the fold change in $AUC_{\tau,ss}$ and $C_{max,ss}$ for each covariate relative to a reference subject. The reference subject was defined as a PH1 patient receiving 170 mg nedosiran once monthly (Q1M), with a body weight of 70 kg and normal renal function (eGFR 90 mL/min/1.73 m²). A total of 1000 simulations were conducted for each covariate effect subgroup, with the magnitude of the covariate effect randomly sampled from a normal distribution using the uncertainty in the parameter estimates of each individual covariate effect from the final model, and were used to derive a 95% prediction interval (2.5th to 97.5th percentiles of the simulations) for each covariate group. The impact of covariates on the exposure metrics ($AUC_{\tau,ss}$ and $C_{max,ss}$) are

summarized in [Figure 17](#) and [Figure 18](#). The magnitude of the effect of covariates on PK exposures was minor (less than an approximately 0.25-fold change) for most covariates apart from participants with low and high weight, severe renal impairment, or ESRD, with the 95% prediction interval contained within the 50 to 200% range of the reference subject.

Figure 17. Model-Predicted Effect of Covariates on Fold Change in Nedosiran $AUC_{\tau,ss}$

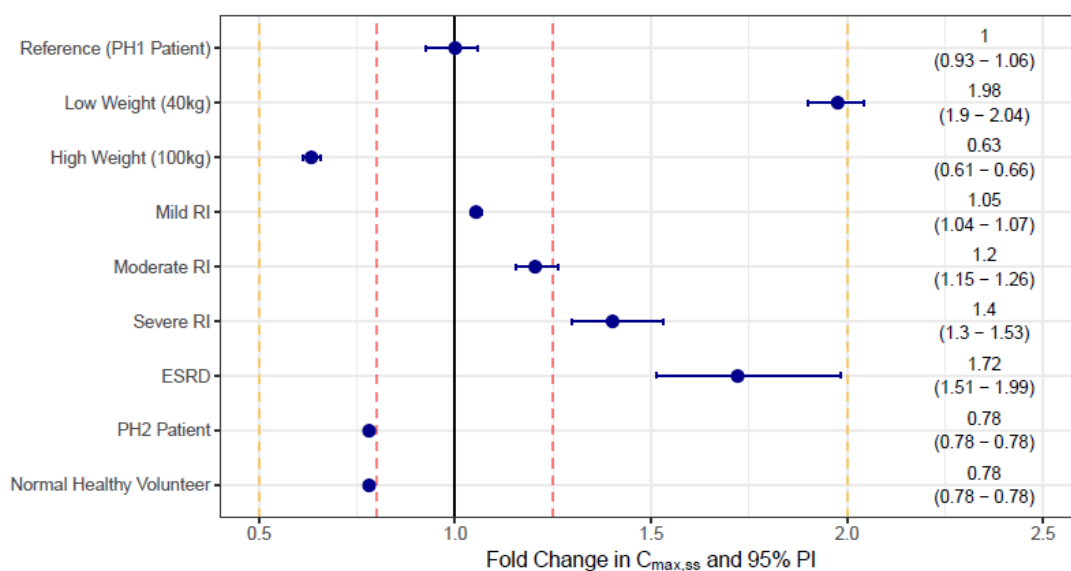


The solid black line represents the median of the reference group, defined as adults (weight 70 kg) with normal renal function (eGFR 90 mL/min/1.73 m²) receiving 170 mg dose of nedosiran Q1M. Dashed red or orange lines represent the 80-125% or 50-200% range of the reference group, respectively. The blue dots and error bars represent the median and 95% (2.5th to 97.5th percentiles of the simulations) prediction intervals (PI) based on 1000 simulated subjects within each group including uncertainty around the estimated covariate effect(s).

Source: dic202005-253335-suppl, Figure 36.

Abbreviations: $AUC_{\tau,ss}$, area under the plasma concentration-time curve over a dosing interval at steady state; eGFR, estimated glomerular filtration rate; PH1, primary hyperoxaluria type 1

Figure 18. Model Predicted Effect of Covariates on Fold Change in Nedosiran $C_{max,ss}$



The solid black line represents the median of the reference group, defined as adults (weight 70 kg) with normal renal function (eGFR 90 mL/min/1.73 m²) receiving 170 mg dose of nedosiran Q1M. Dashed red or orange lines represent the 80-125% or 50-200% range of the reference group, respectively. The blue dots and error bars represent the median and 95% (2.5th to 97.5th percentiles of the simulations) prediction intervals (PI) based on 1000 simulated subjects within each group including uncertainty around the estimated covariate effect(s).

Source: dic202005-253335-suppl, Figure 37.

Abbreviations: $C_{max,ss}$, maximum observed concentration at steady-state; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; PH1/2, primary hyperoxaluria type 1/2; RI, renal impairment

Population PKPD Model

The PKPD model was developed based on 588 24 h urinary oxalate corrected for body surface area observations from 46 PH1 patients (of which 16 were rollover participants from Study DCR-PHXC-301) in Studies DCR-PHXC-101, DCR-PHXC-201, and DCR-PHXC-301. The 46 patients were 9 to 46 years old, with body weight ranging from 35 to 116 kg. A total of 21 males and 25 females were included in the studies. The demographics summary for all studies is provided in [Table 75](#).

Table 75. Summary of Demographics for the PKPD Dataset*

	Age (year)	Weight (kg)	Body surface area (m ²)	Body mass index (kg/m ²)	Baseline UO ₂₄ (μmol/24h)	Baseline UO ₂₄ CR ^a (mmol/mmol)	eGFR (mL/min/1.73m ²)	Sex
N	46	46	46	46	46	18	46	Female: 25
Mean	24.1	71.3	1.81	24.5	1440	112	80.5	(54.3%)
SD	8.66	18.2	0.264	4.65	552	61	30.5	Male: 21
CV%	35.9	25.6	14.6	18.9	38.3	54.7	37.9	(45.7%)
Median	22.5	69.2	1.78	24.5	1350	92	80.2	
Min	10	35	1.26	14	722	46	34.8	
Max	46	116	2.36	34.8	2830	281	195	

SD = standard deviation; CV% = percent coefficient of variation; eGFR = estimated glomerular filtration rate; UO₂₄CR = spot urine oxalate: creatinine ratio; UO₂₄ = 24 hour urinary oxalate observations (adjusted per 1.73 m² body surface area (BSA)) in participants aged <18 years).

^a Baseline UO₂₄CR values were available from study DCR-PHXC-201 only.

Source: dic202005-253335-suppl, Table 7.

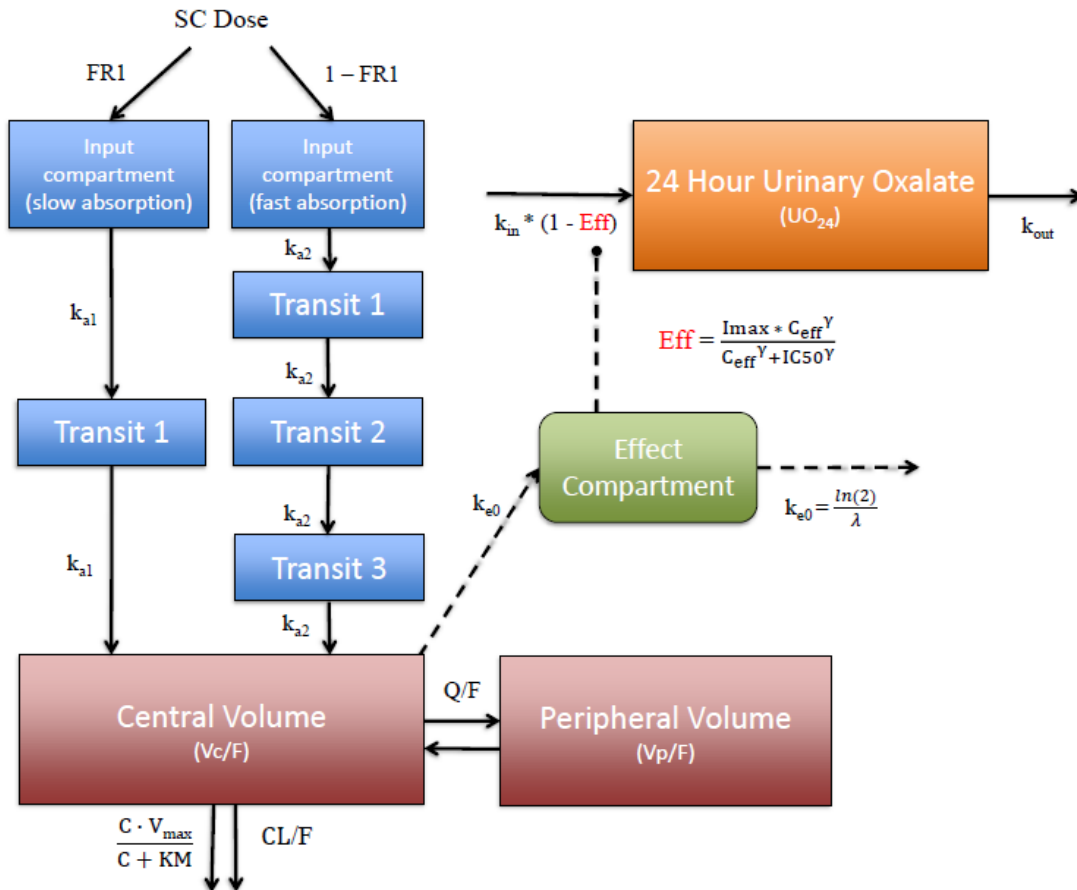
* The minimum age in the Applicant's submitted dataset is 9 years.

Abbreviations: PKPD, pharmacokinetics-pharmacodynamics

An indirect response model with an effect compartment was used to describe the 24 h urinary oxalate (UO₂₄) data. The model used the predicted individual concentrations from the population PK model at the effect compartment to drive the effect on UO₂₄, with the drug effect

of nedosiran modeled as an I_{max} model inhibiting the production of UO_{24} . A Hill coefficient (γ) was estimated to describe the shape of the concentration-effect relationship. Between-subject variability terms were included on baseline UO_{24} , half-maximal inhibitory concentration, and maximum inhibitory concentration (Figure 19). An additive error model was used to describe the residual unexplained variability of UO_{24} . The covariate analysis revealed no statistical evidence for any covariate effects. Parameter estimates from the final population PKPD model of nedosiran are reported in Table 76.

Figure 19. Schematic of the Population PKPD Model



Source: dic202005-253335-suppl, Figure 6.

Abbreviations: C, plasma concentration; C_{eff} , concentration in the effect compartment; CL, plasma clearance; F, bioavailability; IC_{50} , concentration resulting in 50% inhibition; I_{max} , maximum inhibition; k_a , absorption rate constant; k_{in} , zero-order rate constant for input; KM, Michaelis Menten constant; Q, intercompartmental clearance; SC, subcutaneous; PKPD, pharmacokinetics-pharmacodynamics; Q/F, Vc, central volume; VP, peripheral volume; V_{max} , maximum reaction rate

Table 76. Parameter Estimates for the Final Population PKPD Model

Parameter Name	Estimated Value (%RSE)
Baseline 24 hour Urinary Oxalate (UO ₂₄ , $\mu\text{mol}/24\text{h}$)	1420 (4.7)
First-order Elimination Rate of UO ₂₄ (K _{out} , 1/week)	0.338 (12.5)
Maximum Inhibitory Effect (I _{max} , %)	64.5 (3.3)
Half Maximal Inhibitory Concentration in Effect Compartment (IC ₅₀ , ng/mL)	1.04 (24.4)
Hill Coefficient (γ)	2.56 (14.2)
Equilibration Half-life in the Effect Compartment (λ , week)	21.9 (17.3)
Between Subject Variability for Baseline UO ₂₄ (% CV)	31.7 (9.3)
Between Subject Variability for IC ₅₀ (% CV)	86 (15.5)
Between Subject Variability for I _{max} (% CV)	29.4 (61.5)
Residual Unexplained Variability (Additive) (SD, $\mu\text{mol}/24\text{h}$)	205 (8.7)

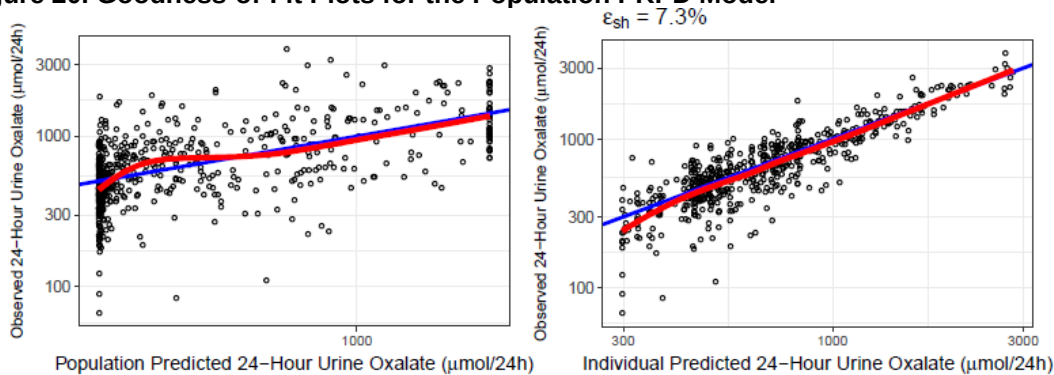
%RSE = percent relative standard error. %CV = approximate coefficient of variation. Standard errors obtained via importance sampling.

Source: dic202005-253335-suppl, Table 10.

Abbreviations: IC₅₀, concentration resulting in 50% inhibition; I_{max}, maximum inhibition; K_{out}, xx;

Goodness-of-fit plots are displayed in [Figure 20](#) and [Figure 21](#). No obvious bias was identified. The prediction and variability corrected visual predictive check plot showed acceptable predictive capability of the PKPD model ([Figure 22](#)).

Figure 20. Goodness-of-Fit Plots for the Population PKPD Model

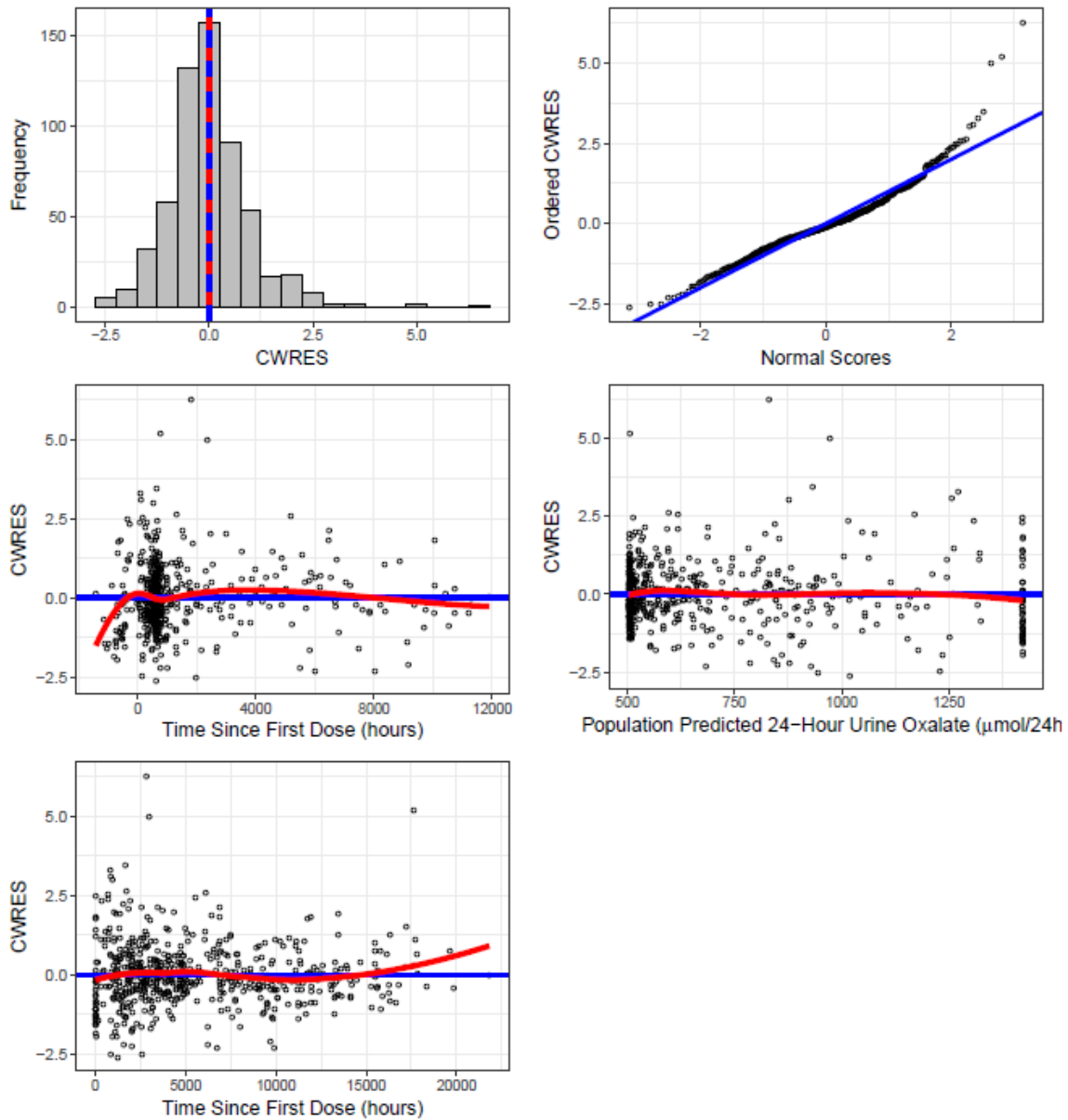


The solid blue lines represent the line of unity, the solid red lines represent the trend in the data (Loess smooth), and ϵ_{sh} shows shrinkage for the residual variability.

Source: dic202005-253335-suppl, Figure 18.

Abbreviation: PKPD, pharmacokinetics-pharmacodynamics

Figure 21. CWRES Plots for the Population PKPD Model

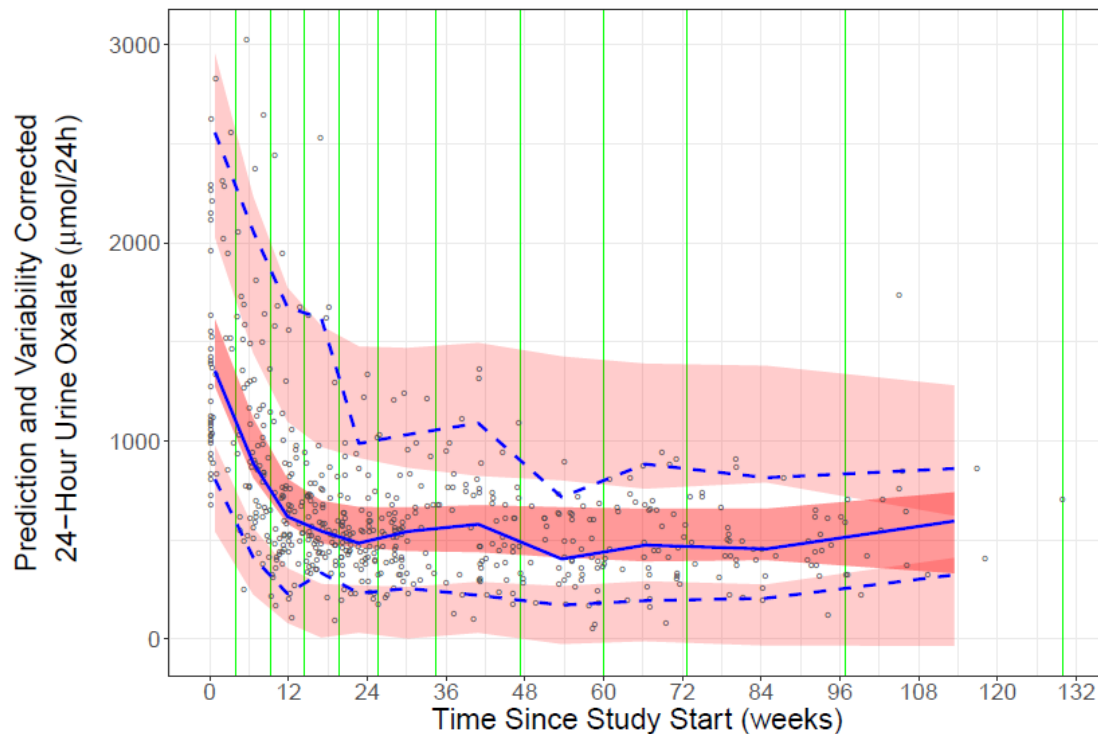


The solid blue lines represents the line of identity or zero, the red lines represents the trend in the data (Loess smooth) or the mean.

Source: dic202005-253335-suppl, Figure 19.

Abbreviations: CWRES, conditional weighted residuals; PKPD, pharmacokinetics-pharmacodynamics

Figure 22. Pvcvpc for the Final Population PKPD Model



Open circles = individual observed, dashed blue lines = observed 5th & 95th percentiles of the observed data, solid blue line = observed median concentration, shaded red areas = 95% prediction interval around the model predicted 5th, 50th, & 95th percentiles, green lines = bin limits.

Source: dic202005-253335-suppl, Figure 10.

Abbreviations: PKPD, pharmacokinetics-pharmacodynamics; pvcVPC, prediction and variability corrected visual predictive check

Reviewer's Comment

The reviewer was able to reproduce the Applicant's proposed population PK model and PKPD model. The proposed models appear to be acceptable. Renal function (normal, mild RI, and moderate RI) was identified as a covariate for the population PK model, whereas eGFR was not identified as significant for the PKPD model. Hepatic function (normal and mild HI), age, sex, and race/ethnicity were not statistically significant covariates in either the population PK model or the PKPD model. Of note, no data from pediatric patients <9 years of age were included in PKPD model development. Hence, the effect of age on the PKPD relationship in pediatric patients below 9 years of age remains uncertain.

Population PK Simulation

To predict nedosiran and 24 h urinary oxalate concentrations corrected for body surface area following administration of nedosiran in pediatric (aged 6 to <12 years), adolescent (aged ≥12 to <18 years) and adult (aged ≥18 to <65 years) patients with PH1, virtual subject databases were created. The pediatric virtual subject database (n=1000) was generated for (virtual) children aged 6 to <12 years. For each participant ≥10 years, body weight was simulated from the appropriate World Health Organization weight-for-age tables according to age and sex using a Z-score sampled from the normal distribution with a mean of zero and SD of 1. For each participant >10 years, body weight was randomly sampled from the Continuous National Health and

Nutrition Examination Survey database for a matching age and sex. Clinical data in adult participants suggests that a significant proportion of nedosiran is eliminated via renal excretion. Therefore, a maturation function that describes the increase in glomerular filtration rate with age was included in the derivation of eGFR used in the pediatric simulations. First, an eGFR was randomly generated for each pediatric participant from a uniform distribution between the ranges specific for the relevant renal function category. Second, a maturation function ([Figure 23](#)) was applied to the randomly generated eGFR which is individualized for the virtual participants' age.

Figure 23. Maturation Function

$$F_{GFR} = \frac{PMA^{3.4}}{47.6^{3.4} + PMA^{3.4}}$$

Source:

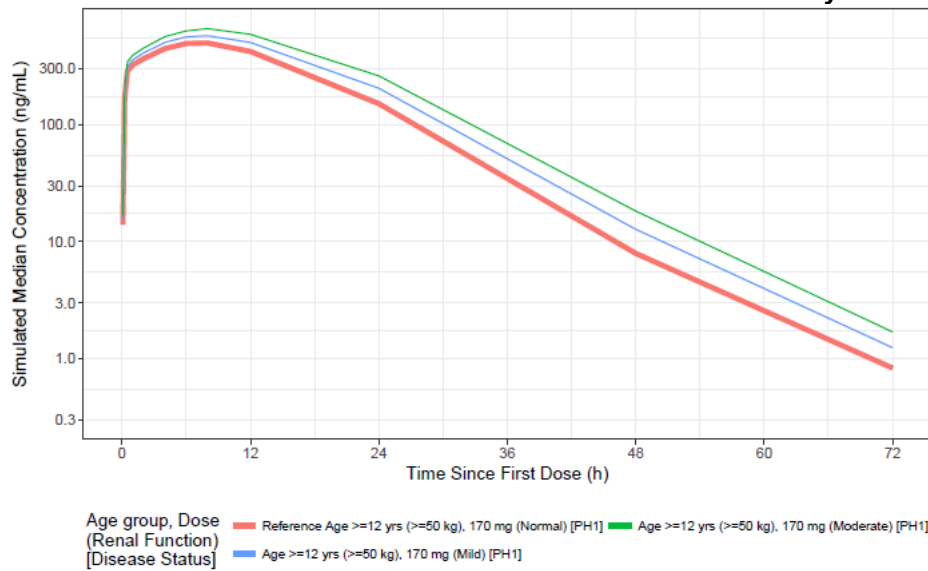
Postmenstrual age in weeks (PMA) is calculated as postnatal age plus 40 weeks as age in the virtual subject database commences at birth (age =0).

The simulations were replicated for participants with the RI categories outlined below:

- Normal renal function: 90 – <150 mL/min/1.73 m²
- Mild renal impairment: 60 – <90 mL/min/1.73 m²
- Moderate renal impairment: 30 – <60 mL/min/1.73 m²

Simulated nedosiran concentration-time profiles for patients with age ≥12 years and body weight ≥50 kg following the first dose stratified by renal function are displayed in [Figure 24](#). The PK exposure metrics (AUC_{tau,ss} and C_{max,ss}) of the simulated dosing regimens in adolescents and adults with PH1 with weight ≥50 kg, stratified by renal function are shown in [Figure 25](#) and [Figure 26](#). The AUC and C_{max} increased with decreasing renal function.

Figure 24. Simulated Nedosiran Concentration-Time Profiles Stratified by Renal Function



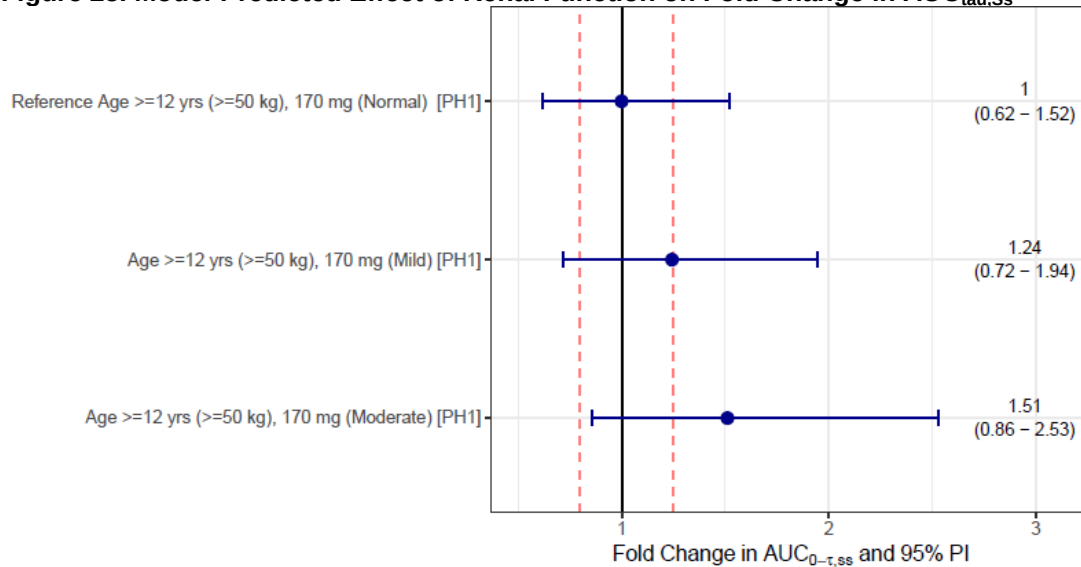
The solid lines show the median of the virtual patients (n=1000) in each dosing regimen simulated using the updated model. Time is truncated to 72 hours postdose.

Source: dic202005-253335, Figure 64.

The dose level in the figure refers to nedosiran sodium weight, e.g. 170 mg, 136 mg, and 3.5 mg nedosiran sodium contain 160 mg, 128 mg, and 3.3 mg free base nedosiran, respectively.

Abbreviation: PH1, primary hyperoxaluria type 1

Figure 25. Model-Predicted Effect of Renal Function on Fold Change in $AUC_{0-\tau,ss}$



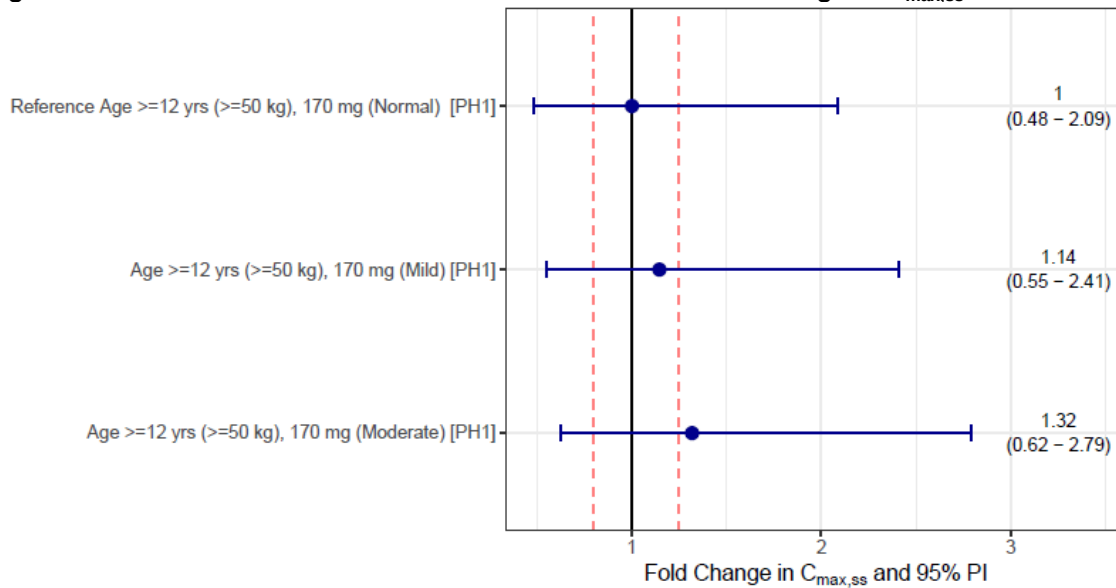
Source: dic202005-253335, Figure 65.

The solid black line represents the median of the reference group, defined as adolescents and adults (weight ≥ 50 kg) diagnosed with PH1 receiving 170 mg dose of nedosiran Q1M. Dashed red lines represent the 80-125% range of the reference group. The blue dots and error bars represent the median and 95% (2.5th to 97.5th percentiles of the simulations) prediction intervals (PI) based on 1000 simulated subjects within each group including between subject variability.

The dose level in the figure refers to nedosiran sodium weight, e.g., 170 mg, 136 mg, and 3.5 mg nedosiran sodium contain 160 mg, 128 mg, and 3.3 mg free base nedosiran, respectively.

Abbreviations: $AUC_{0-\tau,ss}$, area under the plasma concentration-time curve over a dosing interval at steady state; PH1, primary hyperoxaluria type 1; Q1M, monthly

Figure 26. Model-Predicted Effect of Renal Function on Fold Change in $C_{max,ss}$



Source: dic202005-253335, Figure 67.

The solid black line represents the median of the reference group, defined as adolescents and adults (weight ≥ 50 kg) diagnosed with PH1 receiving 170 mg dose of nedosiran Q1M. Dashed red lines represent the 80-125% range of the reference group. The blue dots and error bars represent the median and 95% (2.5th to 97.5th percentiles of the simulations) prediction intervals (PI) based on 1000 simulated subjects within each group including between-subject variability.

The dose level in the figure refers to nedosiran sodium weight, e.g. 170 mg, 136 mg, and 3.5 mg nedosiran sodium contain 160 mg, 128 mg, and 3.3 mg free base nedosiran, respectively.

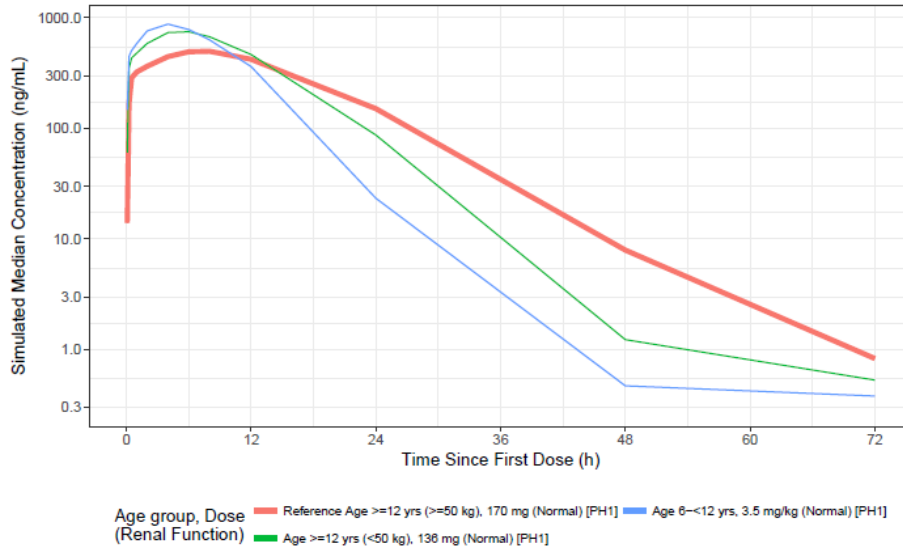
Abbreviations: $C_{max,ss}$, maximum plasma concentration at steady-state; PH1, primary hyperoxaluria type 1; Q1M, monthly

The following proposed nedosiran dosing regimens were evaluated in the simulations:

- 170 mg Q1M: Reference group – adolescents and adults with PH1 (age ≥ 12 to < 65 years and weight ≥ 50 kg) with normal, mild, or moderate RI
- 136 mg Q1M: Adolescents and adults with PH1 (age ≥ 12 to < 65 years and weight < 50 kg) with normal, mild, or moderate RI
- 3.5 mg/kg Q1M: Children (age 6 to < 12 years) with PH1 with normal, mild, or moderate RI

Simulated nedosiran concentration-time profiles following the first dose for the above scenarios are displayed in [Figure 27](#). From the simulations, pediatric patients (age 6 to < 12 years) are expected to have a relatively higher C_{max} and faster elimination compared to adolescents and adults (age ≥ 12 years). The PK exposure metrics ($AUC_{tau,ss}$ and $C_{max,ss}$) of the simulated dosing regimens for adults and adolescents over varying renal function categories (normal, mild RI, and moderate RI) are summarized in [Figure 28](#), [Figure 29](#), [Figure 30](#), [Figure 31](#), [Figure 32](#), and [Figure 33](#). Patients with age ≥ 12 years and body weight ≥ 50 kg receiving 170 mg Q1M nedosiran who were in the corresponding renal function category were used as the reference group.

Figure 27. Simulated Nedosiran Concentration-Time Profiles Stratified by Age (Normal Renal Function)



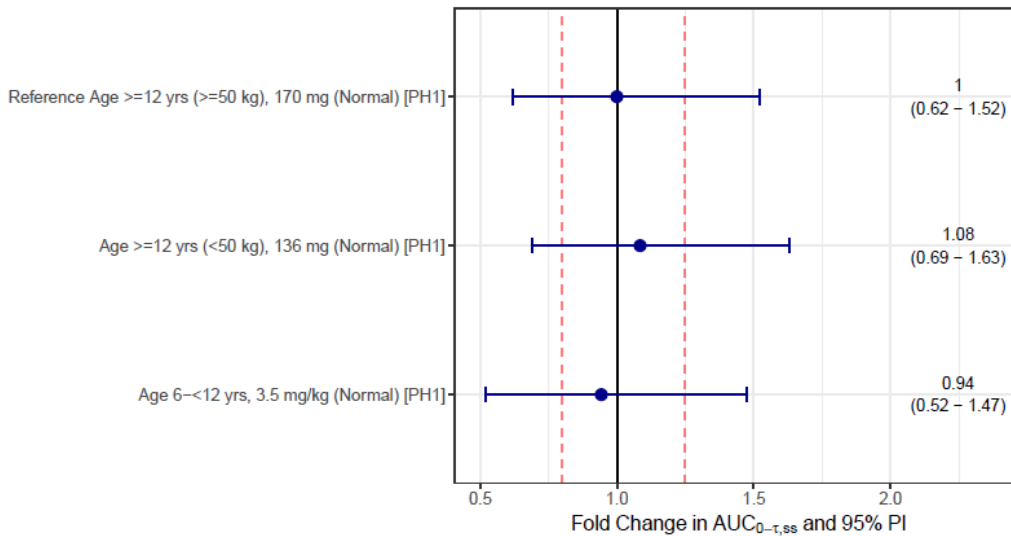
The solid lines show the median of the virtual patients (n=1000) in each dosing regimen simulated using the updated model. Time is truncated to 72 hours postdose.

Source: dic202005-253335, Figure 57.

The dose level in the figure refers to nedosiran sodium weight, e.g. 170 mg, 136 mg, and 3.5 mg nedosiran sodium contain 160 mg, 128 mg, and 3.3 mg free base nedosiran, respectively.

Abbreviations: PH1, primary hyperoxaluria type 1

Figure 28. Model-Predicted Effect of Age on Fold Change in $AUC_{\tau,ss}$ (Normal Renal Function)



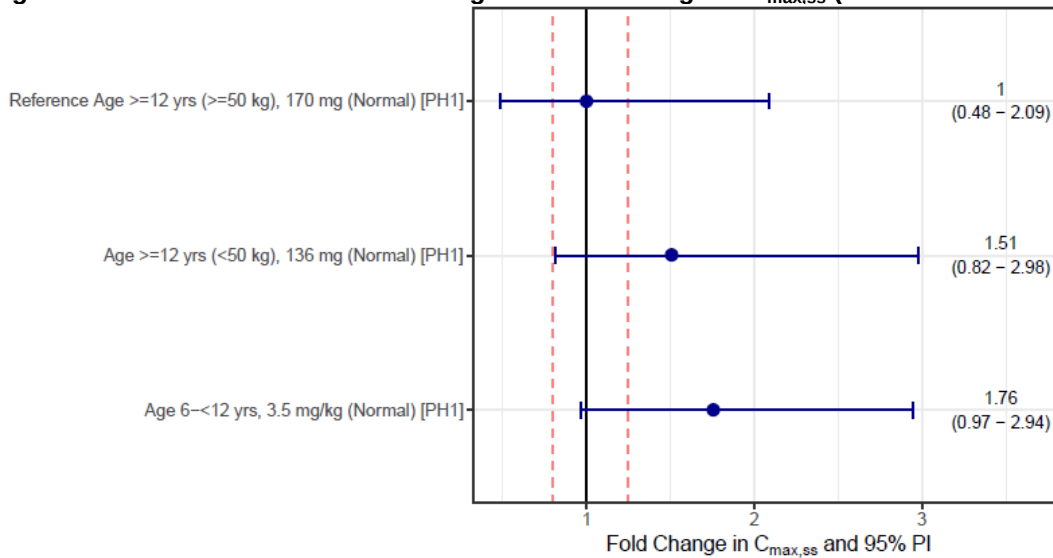
Source: dic202005-253335, Figure 58.

The solid black line represents the median of the reference group, defined as adolescents and adults (weight ≥50 kg) diagnosed with PH1 receiving 170 mg dose of nedosiran Q1M. Dashed red lines represent the 80-125% range of the reference group. The blue dots and error bars represent the median and 95% (2.5th to 97.5th percentiles) prediction intervals (PI) based on 1000 simulated subjects within each group including between subject variability.

The dose level in the figure refers to nedosiran sodium weight, e.g., 170 mg, 136 mg, and 3.5 mg nedosiran sodium contain 160 mg, 128 mg, and 3.3 mg free base nedosiran, respectively.

Abbreviations: $AUC_{\tau,ss}$, area under the plasma concentration-time curve over a dosing interval at steady state; PH1, primary hyperoxaluria type 1; Q1M, monthly

Figure 29. Model-Predicted Effect of Age on Fold Change in $C_{max,ss}$ (Normal Renal Function)



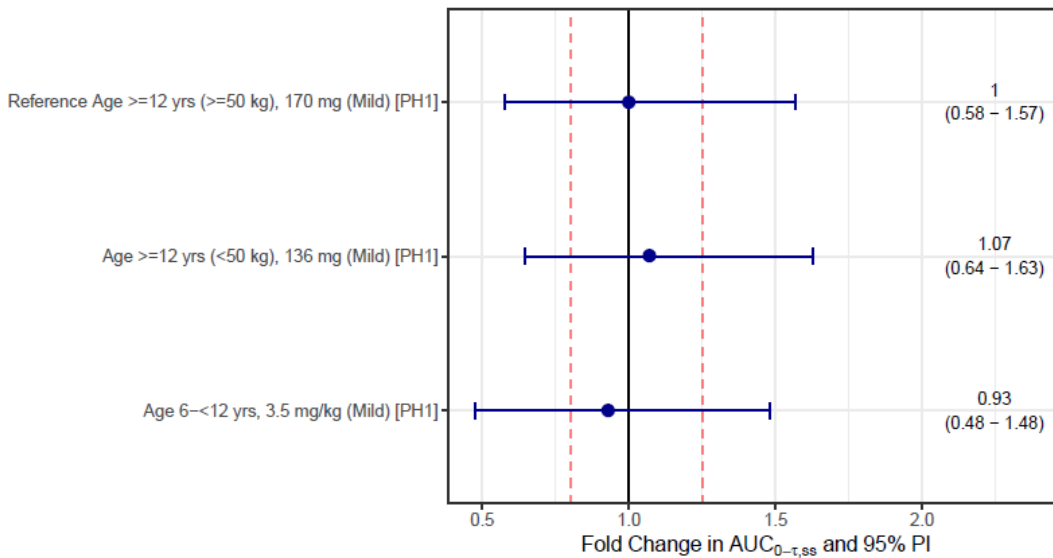
Source: dic202005-253335, Figure 60.

The solid black line represents the median of the reference group, defined as adolescents and adults (weight ≥ 50 kg) diagnosed with PH1 receiving 170 mg dose of nedosiran Q1M. Dashed red lines represent the 80-125% range of the reference group. The blue dots and error bars represent the median and 95% (2.5th to 97.5th percentiles of the simulations) prediction intervals (PI) based on 1000 simulated subjects within each group including between subject variability.

The dose level in the figure refers to nedosiran sodium weight, e.g., 170 mg, 136 mg, and 3.5 mg nedosiran sodium contain 160 mg, 128 mg, and 3.3 mg free base nedosiran, respectively.

Abbreviations: $C_{max,ss}$, maximum plasma concentration at steady-state; PH1, primary hyperoxaluria type 1; Q1M, monthly

Figure 30. Model-Predicted Effect of Age on Fold Change in $AUC_{tau,ss}$ (Mild Renal Function)



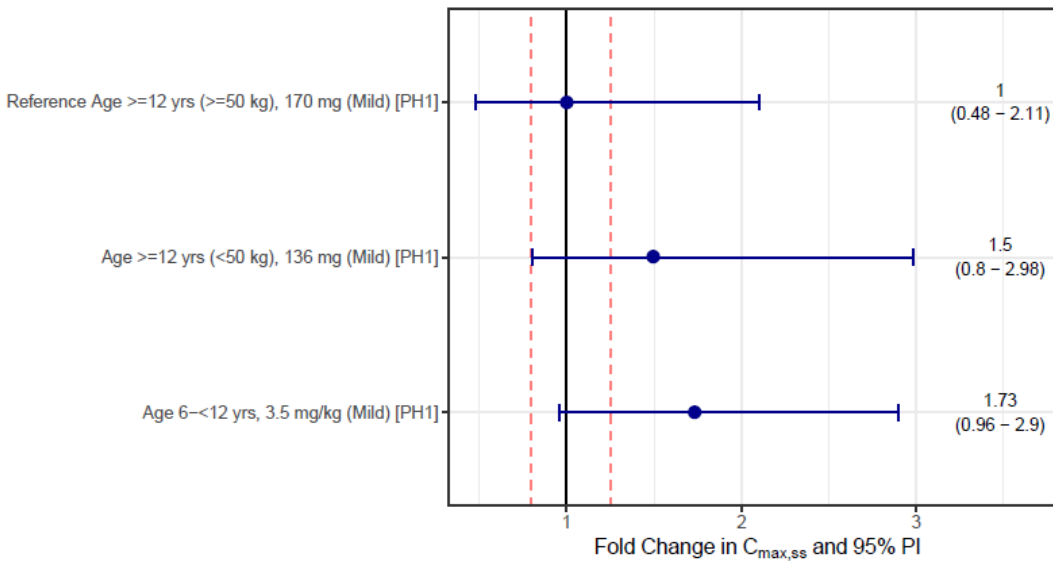
Source: dic202005-253335, Figure 124.

The solid black line represents the median of the reference group, defined as adolescents and adults (weight ≥ 50 kg) diagnosed with PH1 receiving 170 mg dose of nedosiran Q1M. Dashed red lines represent the 80-125% range of the reference group. The blue dots and error bars represent the median and 95% (2.5th to 97.5th percentiles of the simulations) prediction intervals (PI) based on 1000 simulated subjects within each group including between subject variability.

The dose level in the figure refers to nedosiran sodium weight, e.g., 170 mg, 136 mg, and 3.5 mg nedosiran sodium contain 160 mg, 128 mg, and 3.3 mg free base nedosiran, respectively.

Abbreviations: $AUC_{tau,ss}$, area under the plasma concentration-time curve over a dosing interval at steady state; PH1, primary hyperoxaluria type 1; Q1M, monthly

Figure 31. Model-Predicted Effect of Age on Fold Change in $C_{max,ss}$ (Mild Renal Function)



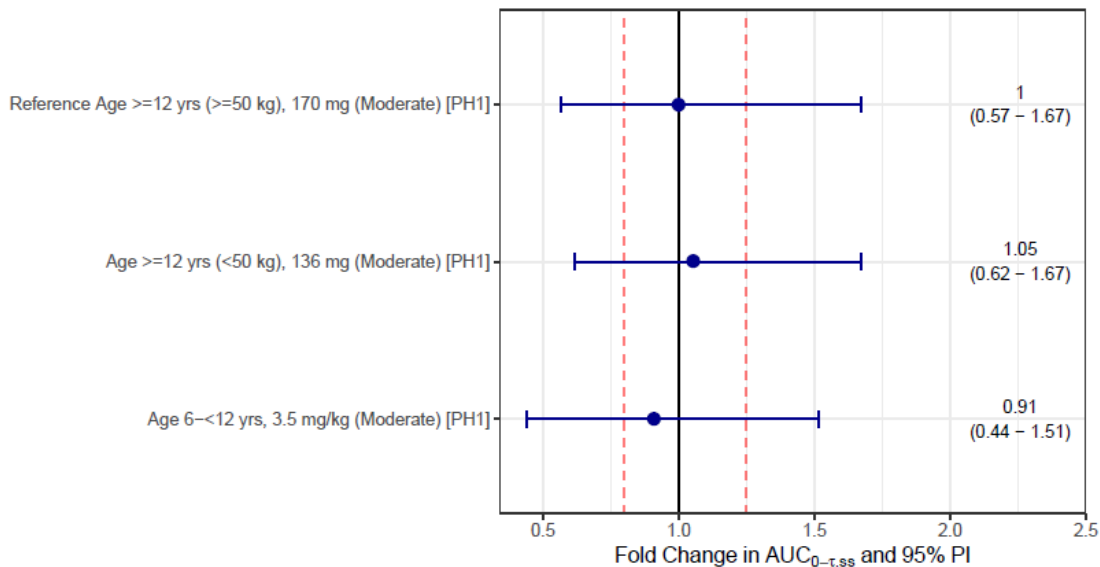
Source: dic202005-253335, Figure 126.

The solid black line represents the median of the reference group, defined as adolescents and adults (weight ≥ 50 kg) diagnosed with PH1 receiving 170 mg dose of nedosiran Q1M. Dashed red lines represent the 80-125% range of the reference group. The blue dots and error bars represent the median and 95% (2.5th to 97.5th percentiles of the simulations) prediction intervals (PI) based on 1000 simulated subjects within each group including between subject variability.

The dose level in the figure refers to nedosiran sodium weight, e.g., 170 mg, 136 mg, and 3.5 mg nedosiran sodium contain 160 mg, 128 mg, and 3.3 mg free base nedosiran, respectively.

Abbreviations: $C_{max,ss}$, maximum plasma concentration at steady-state; PH1, primary hyperoxaluria type 1; Q1M, monthly

Figure 32. Model-Predicted Effect of Age on Fold Change in $AUC_{0-\tau,ss}$ (Moderate Renal Function)



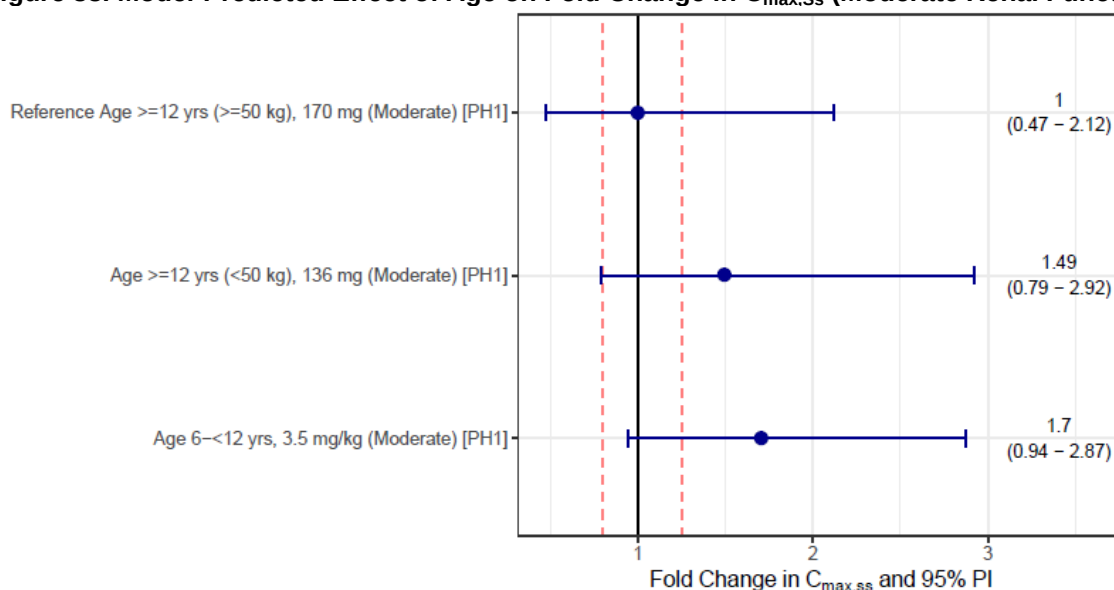
Source: dic202005-253335, Figure 128.

The solid black line represents the median of the reference group, defined as adolescents and adults (weight ≥ 50 kg) diagnosed with PH1 receiving 170 mg dose of nedosiran Q1M. Dashed red lines represent the 80-125% range of the reference group. The blue dots and error bars represent the median and 95% (2.5th to 97.5th percentiles of the simulations) prediction intervals (PI) based on 1000 simulated subjects within each group including between-subject variability.

The dose level in the figure refers to nedosiran sodium weight, e.g. 170 mg, 136 mg, and 3.5 mg nedosiran sodium contain 160 mg, 128 mg, and 3.3 mg free base nedosiran, respectively.

Abbreviations: $AUC_{0-\tau,ss}$, area under the plasma concentration-time curve over a dosing interval at steady state; PH1, primary hyperoxaluria type 1; Q1M, monthly

Figure 33. Model-Predicted Effect of Age on Fold Change in $C_{max,ss}$ (Moderate Renal Function)



Source: dic202005-253335, Figure 130

The solid black line represents the median of the reference group, defined as adolescents and adults (weight ≥ 50 kg) diagnosed with PH1 receiving 170 mg dose of nedosiran Q1M. Dashed red lines represent the 80-125% range of the reference group. The blue dots and error bars represent the median and 95% (2.5th to 97.5th percentiles of the simulations) prediction intervals (PI) based on 1000 simulated subjects within each group including between subject variability.

The dose level in the figure refers to nedosiran sodium weight, e.g., 170 mg, 136 mg, and 3.5 mg nedosiran sodium contain 160 mg, 128 mg, and 3.3 mg free base nedosiran, respectively.

Abbreviations: $C_{max,ss}$, maximum plasma concentration at steady-state; PH1, primary hyperoxaluria type 1; Q1M, monthly

Reviewer's Comment

The minimum age of participants involved in the population PK model development was 9 years. Given that maturation of renal and hepatic function is close to complete by 6 years of age and a maturation function for eGFR was included in the population PK model simulation, the estimated nedosiran PK profile down to 6 years of age is acceptable.

Based on population PK simulations, the C_{max} at steady state is higher for patients 6 to < 12 years of age and patients of age ≥ 12 years and body weight < 50 kg as compared to the reference group of patients of age ≥ 12 years and body weight ≥ 50 kg for each of the corresponding categories of renal function (normal, mild RI, and moderate RI). In contrast, the AUC at steady state for the three age groups is similar. The model further indicates that PK exposures (C_{max} and AUC) increase as renal function (normal, mild RI, and moderate RI) decreases.

The Reviewer summarized the fold-change in C_{max} and AUC at steady state for different age and renal function groups using only patients aged ≥ 12 years with a body weight ≥ 50 kg and normal renal function as reference (Table 77). The steady state C_{max} for the pediatric patients aged 6 to < 12 years with normal, mild RI, and moderate RI increased by 76%, 99%, and 125%, respectively, compared to the reference. For patients with age ≥ 12 years with body weight < 50 kg, the fold-change in C_{max} varied from approximately 1.5 to 2. The steady state AUC had relatively less of an increase compared with C_{max} .

The clinical team has confirmed that the safety profile was acceptable in the three healthy volunteers who received a single dose of 12 mg/kg nedosiran in DCR-PHXC-101, which resulted in a C_{max} of approximately 3000 ng/mL and, according to the clinical team, no major safety

concerns have been identified in the nedosiran clinical development program to date. Hence, the higher PK exposures in pediatric patients 6 to <12 years and patients with body weight <50 kg and RI do not raise a safety concern. Of note, the approved indication will only be for patients 9 years of age and older because of lack of efficacy and safety data in patients younger than 9 years.

Table 77. Model-Predicted Fold Change in $C_{max,ss}$ and $AUC_{tau,ss}$ With Patients Aged ≥ 12 Years With a Body Weight ≥ 50 Kg and Normal Renal Function as Reference

RI	Age, BW, and Dose	$C_{max,ss}$ [ng/mL]	C_{max} vs. Ref	AUC_{ss} [ng*h/mL]	AUC vs. Ref
Normal	$\geq 12y$, $\geq 50kg$, 170 mg	510 (247 - 1605)	1	12266 (7580 - 18649)	1
	$\geq 12y$, <50kg, 138 mg	769 (416 - 1519)	1.51	13301 (8437 - 19975)	1.08
	6-12y, 3.5mg/kg	896 (493 - 1502)	1.76	11564 (6352 - 18061)	0.94
Mild	$\geq 12y$, $\geq 50kg$, 170 mg	584 (282 - 1230)	1.15	15224 (8782 - 23840)	1.24
	$\geq 12y$, <50kg, 138 mg	874 (469 - 1744)	1.71	16287 (9817 - 24750)	1.33
	6-12y, 3.5mg/kg	1013 (558 - 1693)	1.99	14144 (7269 - 22578)	1.15
Moderate	$\geq 12y$, $\geq 50kg$, 170 mg	672 (318 - 1423)	1.32	18529 (10499 - 30983)	1.51
	$\geq 12y$, <50kg, 138 mg	1005 (531 - 1964)	1.97	19531 (11445 - 31030)	1.59
	6-12y, 3.5mg/kg	1145 (633 - 1930)	2.25	16829 (8126 - 28055)	1.37

Source: Reviewer's analysis.

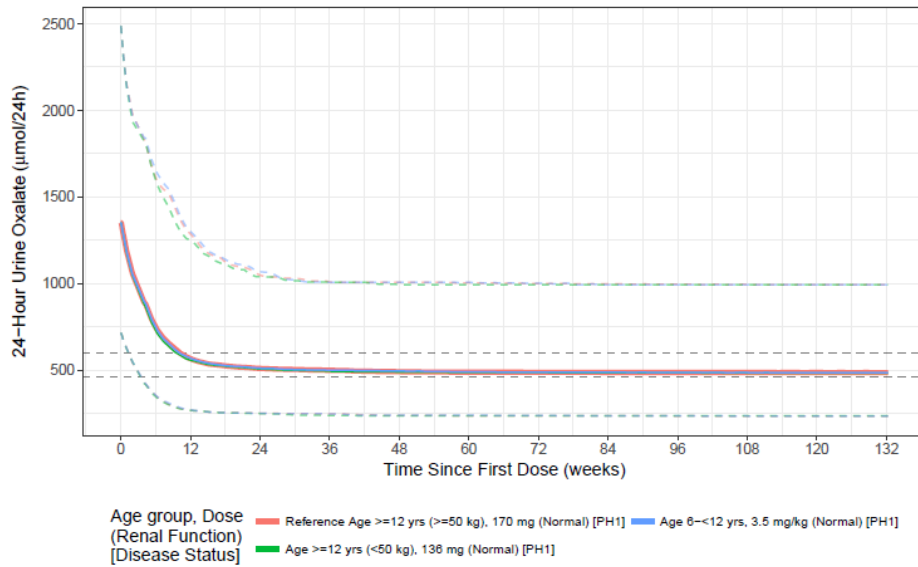
The dose level in the table refers to nedosiran sodium weight, e.g., 170 mg, 136 mg, and 3.5 mg nedosiran sodium contain 160 mg, 128 mg, and 3.3 mg free base nedosiran, respectively.

Abbreviations: $AUC_{tau,ss}$, area under the plasma concentration-time curve over a dosing interval at steady state; $C_{max,ss}$, maximum plasma concentration at steady-state; RI, renal impairment

Population PKPD Simulation

PKPD simulations were performed under scenarios identical to those discussed in the population PK simulation section. The limit of normal and near-normal limit were set to $<460\mu\text{mol}/24\text{ h}$ and $<600\mu\text{mol}/24\text{ h}$, respectively. The time courses of simulated 24 h urine oxalate under the proposed dosing scenarios stratified by age are displayed in [Figure 34](#) for normal renal function, [Figure 35](#) for mild RI, and [Figure 36](#) for moderate RI. The percentages of simulated PH1 patients within the normal and near normal ranges at the end of Weeks 13, 26, 39, 52, and 128 are displayed in [Table 78](#), [Table 79](#), and [Table 80](#). Overall, there were no major differences across the age groups and RI categories.

Figure 34. Simulated 24 h Urinary Oxalate-Time Profiles Stratified by Age (Normal Renal Function)



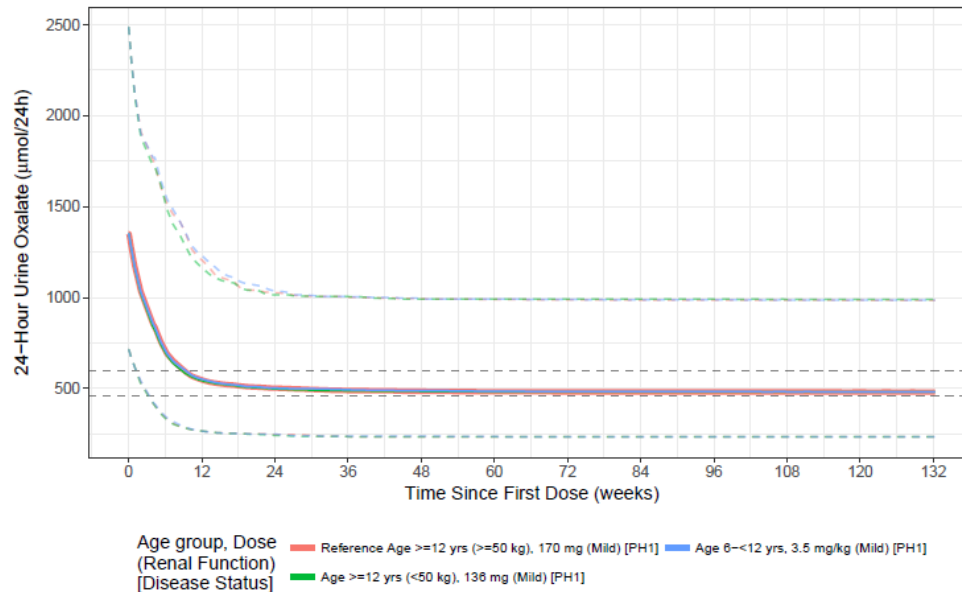
The solid lines show the median of the virtual PH patients (n=1000) in each dosing regimen simulated using the updated model, and the coloured dashed lines show the 97.5th and 2.5th percentiles, comprising the 95% prediction intervals. Horizontal dashed lines represent the limit of normal (<460 μmol/24 hrs) and near-normal ranges (<600 μmol/24 hrs).

Source: dic202005-253335-suppl, Figure 14.

The dose level in the figure refers to nedosiran sodium weight, e.g. 170 mg, 136 mg, and 3.5 mg nedosiran sodium contain 160 mg, 128 mg, and 3.3 mg free base nedosiran, respectively.

Abbreviation: PH1, primary hyperoxaluria type 1

Figure 35. Simulated 24 h Urinary Oxalate-Time Profiles Stratified by Age (Mild Renal Impairment)



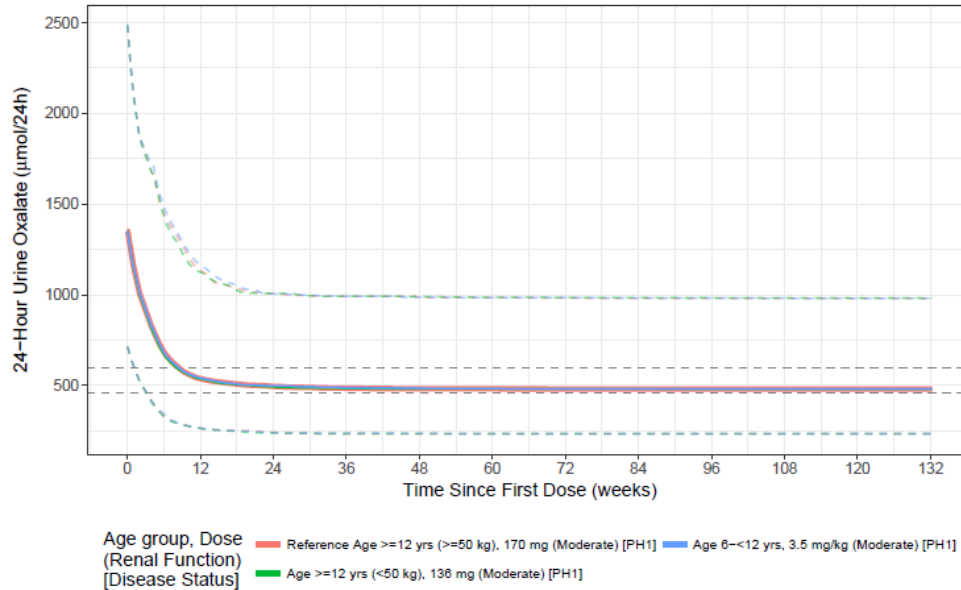
The solid lines show the median of the virtual PH patients (n=1000) in each dosing regimen simulated using the updated model, and the coloured dashed lines show the 97.5th and 2.5th percentiles, comprising the 95% prediction intervals. Horizontal dashed lines represent the limit of normal (<460 μmol/24 hrs) and near-normal ranges (<600 μmol/24 hrs).

Source: dic202005-253335-suppl, Figure 40.

The dose level in the figure refers to nedosiran sodium weight, e.g. 170 mg, 136 mg, and 3.5 mg nedosiran sodium contain 160 mg, 128 mg, and 3.3 mg free base nedosiran, respectively.

Abbreviation: PH1, primary hyperoxaluria type 1

Figure 36. Simulated 24 h Urinary Oxalate-Time Profiles Stratified by Age (Moderate Renal Impairment)



The solid lines show the median of the virtual PH patients (n=1000) in each dosing regimen simulated using the updated model, and the coloured dashed lines show the 97.5th and 2.5th percentiles, comprising the 95% prediction intervals. Horizontal dashed lines represent the limit of normal (<460 μmol/24 hrs) and near-normal ranges (<600 μmol/24 hrs).

Source: dic202005-253335-suppl, Figure 42.

The dose level in the figure refers to nedosiran sodium weight, e.g. 170 mg, 136 mg, and 3.5 mg nedosiran sodium contain 160 mg, 128 mg, and 3.3 mg free base nedosiran, respectively.

Abbreviation: PH1, primary hyperoxaluria type 1

Table 78. Percentage of PH1 Patients in the Normal and Near-Normal Range in Adults, Adolescents, and Pediatrics (Normal Renal Function)

Dose Q1M	Week Number	Percent of PH1 Patients	
		<460 μmol/24h/1.73m ²	<600 μmol/24h/1.73m ²
Reference Age ≥12 yrs (≥50 kg), 170 mg (Normal) [PH1]	13	31.3	57.6
	26	40.0	67.6
	39	42.0	70.4
	52	42.4	71.1
	128	43.7	72.1
Age ≥12 yrs (<50 kg), 136 mg (Normal) [PH1]	13	33.0	59.1
	26	40.5	69.0
	39	42.3	70.9
	52	43.0	71.5
	128	43.7	72.3
Age 6-12 yrs, 3.5 mg/kg (Normal) [PH1]	13	31.2	56.6
	26	39.3	67.4
	39	41.3	70.1
	52	42.4	70.9
	128	43.4	71.9

Source: dic202005-253335-suppl, Table 11

The dose level in the table refers to nedosiran sodium weight, e.g. 170 mg, 136 mg, and 3.5 mg nedosiran sodium contain 160 mg, 128 mg, and 3.3 mg free base nedosiran, respectively.

Abbreviation: PH1, primary hyperoxaluria type 1; Q1M, monthly

Table 79. Percentage of PH1 Patients in the Normal and Near-Normal Range in Adults, Adolescents, and Pediatrics (Mild Renal Impairment)

Dose Q1M	Week Number	Percent of PH1 Patients	
		<460 $\mu\text{mol}/24\text{h}/1.73\text{m}^2$	<600 $\mu\text{mol}/24\text{h}/1.73\text{m}^2$
Reference Age ≥ 12 yrs (≥ 50 kg), 170 mg (Mild) [PH1]	13	34.1	61.5
	26	41.3	69.9
	39	43.1	71.8
	52	43.5	72.3
	128	43.9	72.9
Age ≥ 12 yrs (<50 kg), 136 mg (Mild) [PH1]	13	35.0	62.9
	26	41.9	70.7
	39	43.2	71.7
	52	43.4	72.4
	128	44.0	73.0
Age 6-<12 yrs, 3.5 mg/kg (Mild) [PH1]	13	33.6	60.1
	26	40.7	69.0
	39	42.8	71.1
	52	43.1	71.8
	128	43.5	72.4

Source: dic202005-253335-suppl, Table 19.

The dose level in the table refers to nedosiran sodium weight, e.g. 170 mg, 136 mg, and 3.5 mg nedosiran sodium contain 160 mg, 128 mg, and 3.3 mg free base nedosiran, respectively.

Abbreviation: PH1, primary hyperoxaluria type 1; Q1M, monthly

Table 80. Percentage of PH1 Patients in the Normal and Near-Normal Range in Adults, Adolescents, and Pediatrics (Moderate Renal Impairment)

Dose Q1M	Week Number	Percent of PH1 Patients	
		<460 $\mu\text{mol}/24\text{h}/1.73\text{m}^2$	<600 $\mu\text{mol}/24\text{h}/1.73\text{m}^2$
Reference Age ≥ 12 yrs (≥ 50 kg), 170 mg (Moderate) [PH1]	13	36.0	63.8
	26	42.4	71.0
	39	43.6	72.4
	52	43.8	72.6
	128	44.1	73.1
Age ≥ 12 yrs (<50 kg), 136 mg (Moderate) [PH1]	13	36.6	65.4
	26	42.8	71.2
	39	43.6	72.6
	52	44.0	72.9
	128	44.3	73.0
Age 6-<12 yrs, 3.5 mg/kg (Moderate) [PH1]	13	35.4	62.2
	26	41.5	70.1
	39	43.2	72.0
	52	43.4	72.3
	128	43.7	72.6

Source: dic202005-253335-suppl, Table 20.

Abbreviations: PH1, primary hyperoxaluria type 1; Q1M, monthly

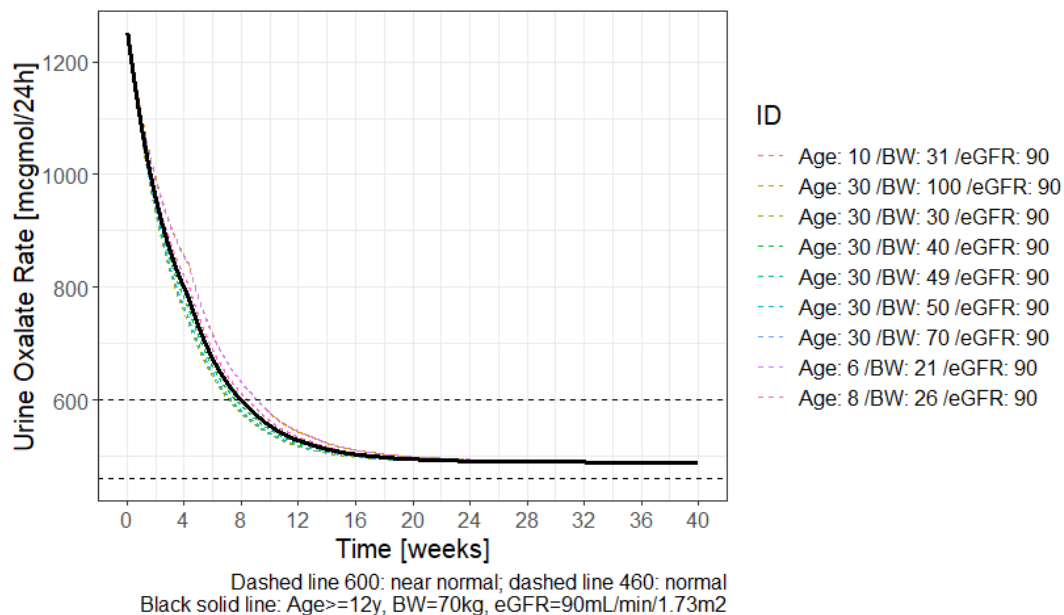
Reviewer's Comment

As discussed elsewhere in this review, following subcutaneous administration, nedosiran is delivered to the hepatocyte, its site of action. Because the plasma concentration of nedosiran does not reflect its concentration in the liver, the efficacy of nedosiran is not directly correlated with plasma concentration and PKPD simulations were used to further evaluate the impact of age, body weight and renal function on efficacy. Based on the Applicant's simulations, the PD response appeared to be similar among the subgroups stratified by age, body weight, and renal function.

The reviewer also performed independent PKPD simulations with representative patients from each subgroup. The simulated body weights for patients ≥ 12 years of age were 30, 40, 49, 50, 70, and 100 kg. For pediatric patients < 12 years of age, the average body weights for boys and girls were based on the Centers for Disease Control growth chart for the corresponding age: 21 kg for a 6-year-old, 26 kg for an 8-year-old, and 31 kg for a 10-year-old. The eGFR values that were used were 30, 45, 60, 75, and 90 mL/min/1.72 m². The representative patients were generated by combining the different values for age, body weight, and eGFR. The reference patient was a patient with age of 30-year-old, body weight of 70 kg, and eGFR of 90 mL/min/1.72 m². The simulation results were consistent with the Applicant's, i.e., showed a similar PD response among the subgroups. ([Figure 37](#), [Figure 38](#), [Figure 39](#), [Figure 40](#), and [Figure 41](#)).

Because only one pediatric patient < 12 years of age (a 9-year-old patient) was included in the PKPD model development, the effect of age on the PKPD relationship in pediatric patients 6 to 9 years of age remains uncertain.

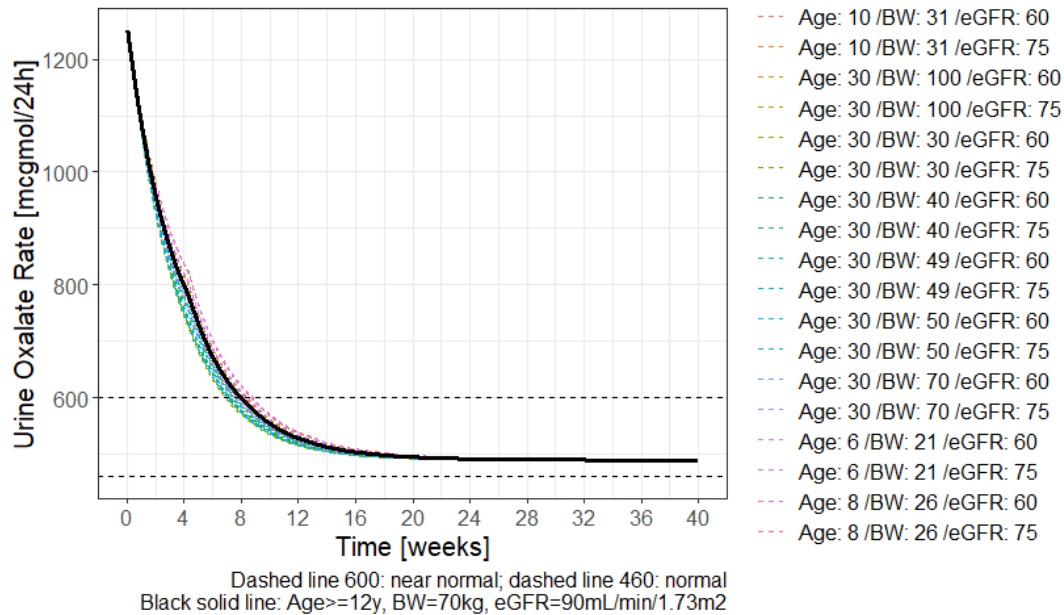
Figure 37. PKPD Simulation for Representative Patients With Normal Renal Function



Source: Reviewer's analysis.

Abbreviations: BW, body weight; eGFR, estimated glomerular filtration rate; ID, identity; PKPD, pharmacokinetics-pharmacodynamics

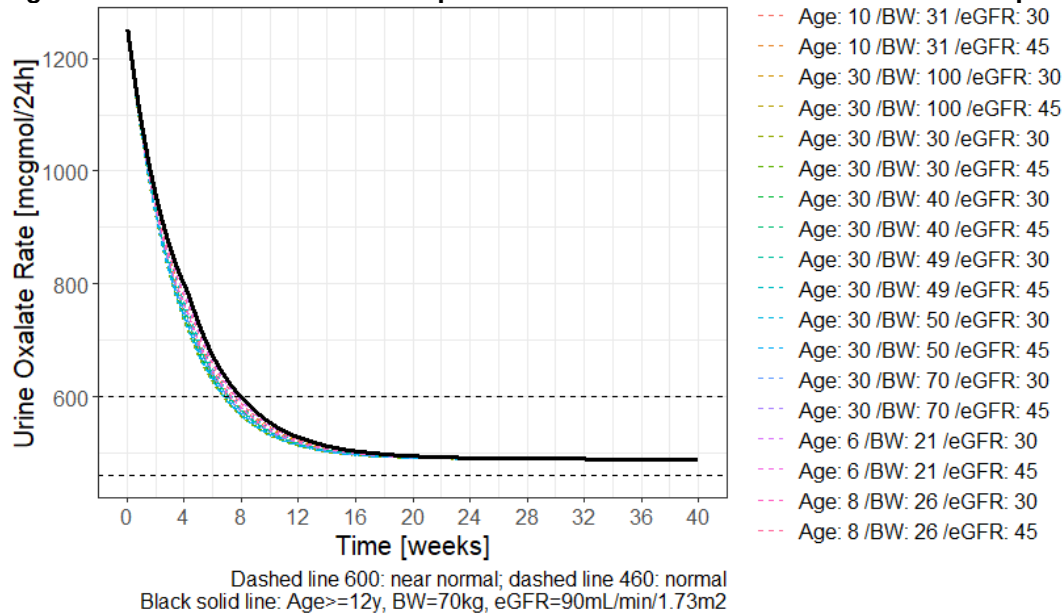
Figure 38. PKPD Simulation for Representative Patients With Mild Renal Impairment



Source: Reviewer's analysis.

Abbreviations: BW, body weight; eGFR, estimated glomerular filtration rate; ID, identity; PKPD, pharmacokinetics-pharmacodynamics

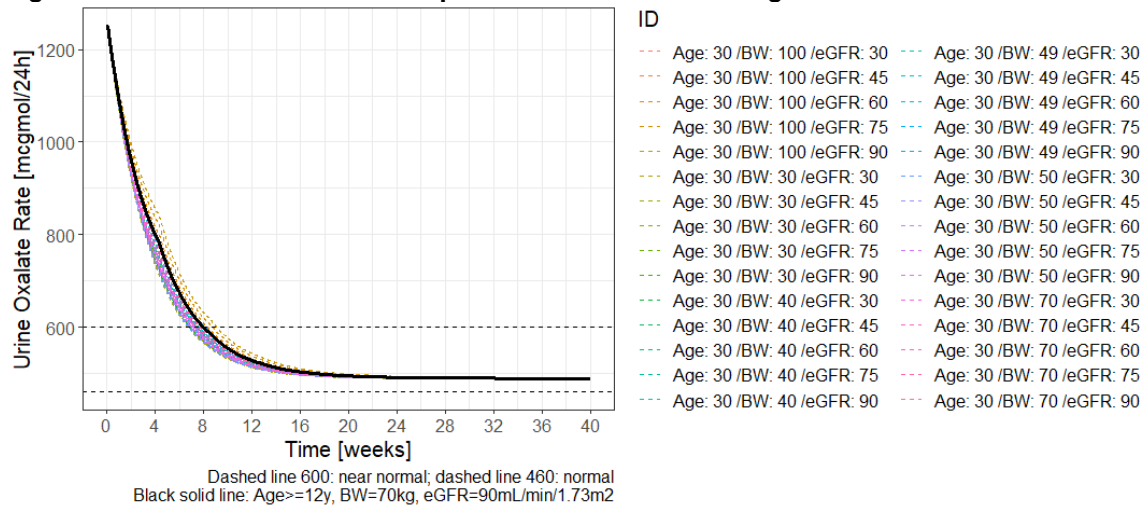
Figure 39. PKPD Simulation for Representative Patients With Moderate Renal Impairment



Source: Reviewer's analysis.

Abbreviations: BW, body weight; eGFR, estimated glomerular filtration rate; ID, identity; PKPD, pharmacokinetics-pharmacodynamics

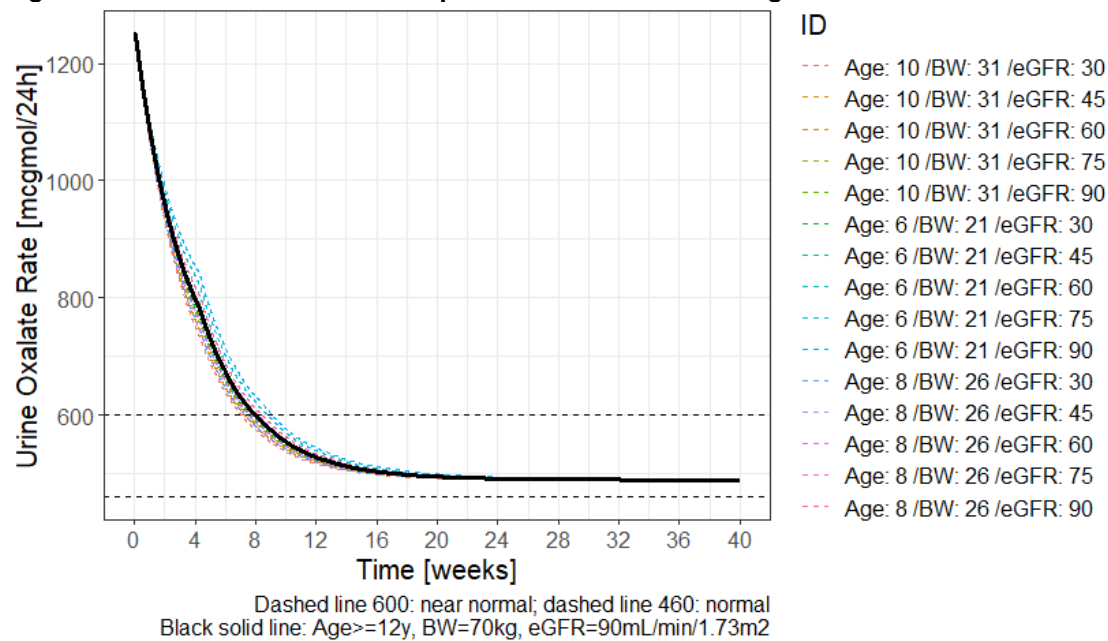
Figure 40. PKPD Simulation for Representative Patients of Age ≥ 12 Years



Source: Reviewer's analysis.

Abbreviations: BW, body weight; eGFR, estimated glomerular filtration rate; ID, identity; PKPD, pharmacokinetics-pharmacodynamics

Figure 41. PKPD Simulation for Representative Patients of Age 6 to <12 Years



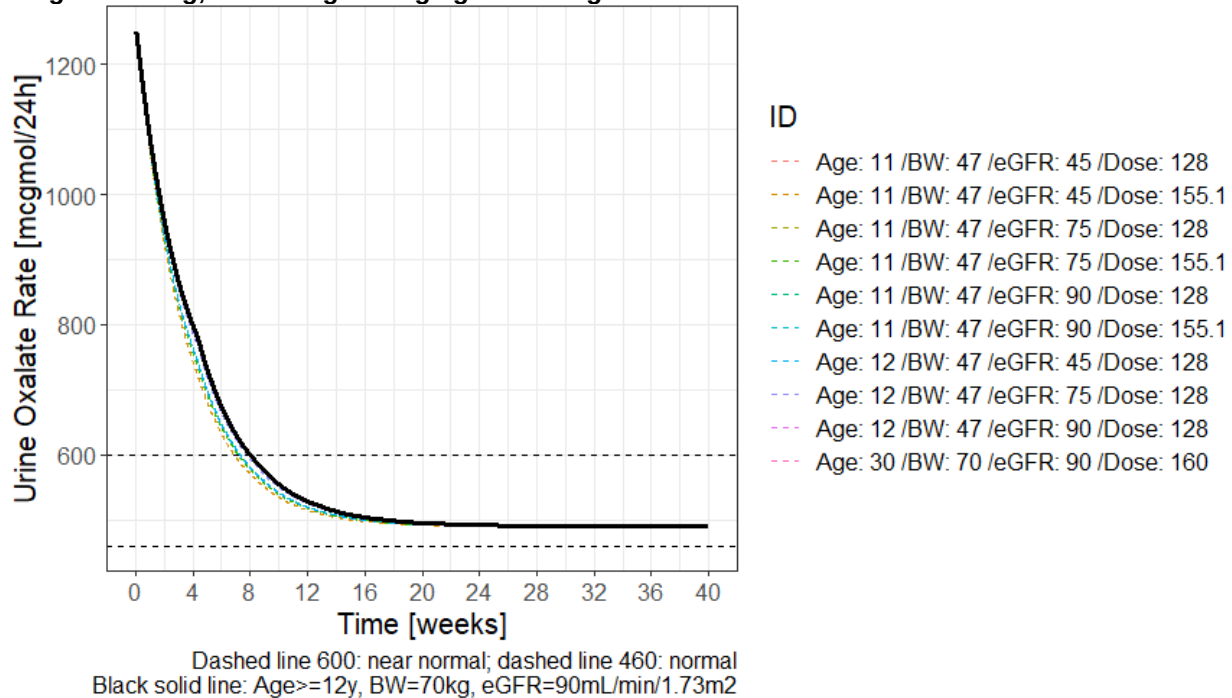
Source: Reviewer's analysis.

Abbreviations: BW, body weight; eGFR, estimated glomerular filtration rate; ID, identity; PKPD, pharmacokinetics-pharmacodynamics

To confirm the appropriateness of the dosing cap of 128 mg for pediatric patients 9 to <12 years of age and body weight <50 kg, independent PKPD simulation was performed for a representative pediatric patient with body weight of 47 kg, aged 11 years, and with varying degrees of eGFR. The simulation result showed comparable urine oxalate response for the representative pediatric patients receiving either 3.3 mg/kg (155.1 mg) or 128 mg (Figure 42). The urine oxalate response reached comparable steady state level as the reference (aged

≥ 12 years, body weight of 70 kg, with normal renal function, receiving 160 mg nedosiran)
([Figure 42](#)).

Figure 42. PKPD Simulation for a Representative Pediatric Patient Aged 11 Years With Body Weight of 47 kg, Receiving 3.3 mg/kg or 128 mg Nedosiran



Source: Reviewer's analysis.

Abbreviations: BW, body weight; eGFR, estimated glomerular filtration rate; ID, identity; PKPD, pharmacokinetics-pharmacodynamics

In summary, the Applicant's population PK and PKPD models appear to be acceptable. Based on model simulations, the proposed dosing regimens for patients ≥ 9 years of age with varying levels of renal function (normal, mild RI, or moderate RI), and with an additional dosing cap of 128 mg for pediatric patients 9 to <12 years of age and body weight <50 kg (see [Section 6.1](#)), appear to be acceptable. The following labeling statement, which was proposed by the Applicant, is also acceptable:

"No clinically significant differences in the pharmacokinetics or pharmacodynamics of nedosiran were observed based on age (9 to 73 years old), sex, race/ethnicity, mild-to-moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m²) or mild hepatic impairment (total bilirubin $\leq$ ULN and AST $>$ ULN; or total bilirubin >1 to $1.5\times$ ULN and any AST)."

14.6. Pharmacogenetics

Not applicable.

15. Study / Trial Design

Not applicable.

16. Efficacy

16.1. Random Highs and Lows From Use of AUC to Calculate Mean Percentage Change in Uox

Use of AUC to calculate mean change at steady-state will generate noise that is noninformative to clinical outcome. In the analyses shown in [Table 81](#), the last three measurements from participant (b) (6) were used to provide a case study of the statistical properties of AUC to calculate percentage change from baseline urinary oxalate (Uox). The rows in [Table 81](#) differ only in the order in which measurements were taken. Although the mean percentage change in Uox is exactly the same for each row, equal to -4%, the magnitudes and directions of the AUC vary. For a sufficiently large trial, the AUCs will average out to provide a useful point estimate of percentage change – this can be seen by taking the average of the six AUCs in [Table 81](#) and dividing by 60, the number of days over which AUC was calculated; the result is the -4% seen as the average AUC in each row. However, for small sample sizes, such “averaging out” will be less likely to occur, and the use of AUC as a measure of percent change may increase uncertainty in the calculated mean Uox and, as shown in the last row of [Table 81](#), AUC may not even reflect the sign of percentage change.

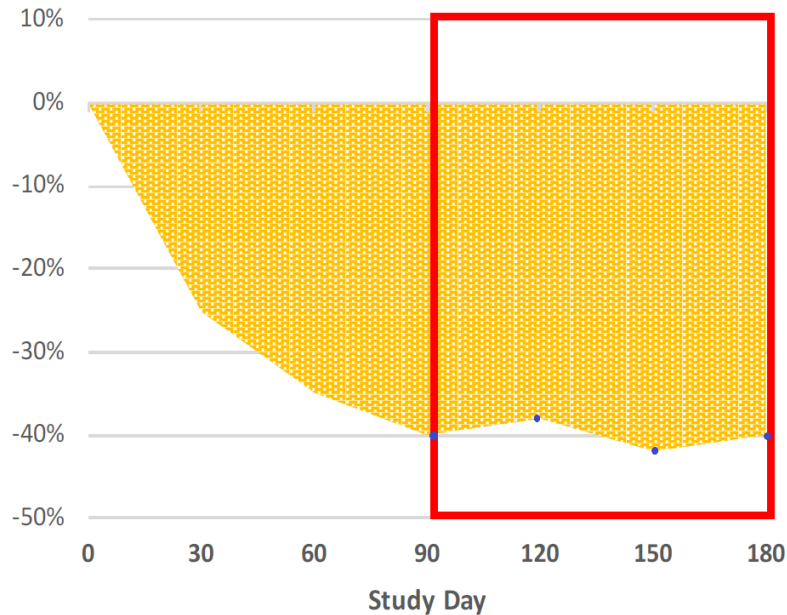
Table 81. Dependence of AUC on Time Sequence of Collected Data

AUC Replicate	Timepoint			AUC
	Percentage Change Uox			
	Day 120	Day 150	Day 180	
Replicate 1	45%	-30%	-27%	-630.00
Replicate 2	45%	-27%	-30%	-585.00
Replicate 3	-27%	45%	-30%	495.00
Replicate 4	-27%	-30%	45%	-630.00
Replicate 5	-30%	-27%	45%	-585.00
Replicate 6	-30%	45%	-27%	495.00

Source: Reviewer program endpoints and auc.xls, data from participant (b) (6).
Abbreviations: AUC, area under the concentration-time curve; Uox, urinary oxalate

The Applicant’s use of AUC implicitly uses single-imputation of missing data to measure percent change in urinary oxalate. The Applicant’s use of such imputation contradicts recommendations by the National Academy of Sciences. [Figure 43](#) illustrates this point (i.e., that such single imputation is implicit in the Applicant’s calculation of AUC). In [Figure 43](#), AUC from Days 90 to 180 is calculated as an area from four actual data points (in blue) observed on Days 90, 120, 150, and 180, and with values for the 87 other days after Day 90 (within red box) imputed to lie on line-segments connecting the two nearest measured endpoints.

Figure 43. Applicant's Calculation of AUC Using Single Imputation. Measured Data Points in Blue



Source: Adapted from Figure 5 of the protocol.
Abbreviation: AUC, area under the concentration-time-curve

The imputed data point for data missing on each day is then calculated as a single imputation using linear interpolation between the values of the adjacent two data points actually observed. However, as discussed below, such single imputation fails to take into account variability inherent in the imputation and, if the mean of the imputed values is not equal to the mean of the interpolated data point, the calculated value of AUC may not reflect the actual mean percentage change in UO_{24} experienced by each patient over the specified time period.

To examine the validity of the Applicant's single imputation method, one can make use of actual data from UO_{24} collected by the Applicant. Data were collected at first screening and 30 days after randomization. Data were also collected at intermediate time points, between first screening and 30 days and, for such intermediate timepoints, one can examine the correspondence between singly-imputed and actual values – if single linear imputation between data collected between the first and the 30-day measurement is correct, the measured and imputed data will be the same.

However, measured and imputed data are not the same. In particular, all of the single imputations used in the Applicant's calculation of AUC inappropriately reduced the magnitude of the percent change in urinary oxalate concentration for each participant ([Table 82](#)). A linear regression on the data in [Table 82](#) indicates a nominally significant relationship between observed data as a function of singly imputed data for the calculation of AUC ($p=0.04$); however the slope is only 0.06, with only 20% of the variance in the observed data explained by the Applicant's imputation.

Table 82. Single Imputation for AUC vs. Observed Values of 24 h Urinary Oxalate for Data Collected Between First Screening and Day 30

Participant	N	24-hour Urinary Oxalate	
		Single Imputation for AUC	Observed
(b) (6)	1	0.3	4.8
	1	2.1	-18.9
	1	-0.3	14.8
	1	0.0	-21.8
	1	-0.2	-0.6

Source: Reviewer program auc imputation urinary oxalate.sas.

Abbreviations: AUC, area under the concentration-time curve; N, number of participants

The single linear-interpolation-based imputations used by the Applicant altered the mean and standard deviation of percentage change. As an example, [Table 83](#) shows observed data from subject (b) (6) collected on Days 120, 150, and 180 and, like AUC, applies interpolation to the intermediate points. The calculated mean and standard deviation of percentage change from Baseline is altered according to the number of imputations conducted. According to the original data (top row of [Table 83](#)), the mean percentage change in UO_{24} is -4.00 and the standard deviation is 42.46. Adding a single linear interpolation imputation halfway between each observed data point (second row), the mean change in UO_{24} is reduced from -4.00 to -6.60 and the standard deviation is reduced from 42.46 to 32.81. Adding yet another imputation (third row) further decreases the calculated mean and standard deviation. AUC calculations by the Applicant over 90 days may be considered as involving even more such imputations, adding 87 data points to the 4 originally observed.

Table 83. Impact of Single Linear Imputation on Mean and Variance of Percentage Change in 24 h Uox Given the Same AUC*

Box Given the Same Age												
Imputation	Observed and Imputed Values for Percentage Change in Uox									Mean	St Dev	
Original data	45									-27	-4.00	42.46
One midpoint	45		7.5							-27	-6.60	32.81
Two midpoints	45	26.25	7.5	-11.25						-27	-8.33	28.15

Source: Reviewer program endpoints and auc.xls.

* Calculated AUC=-630.00 for all three rows.

Abbreviations: AUC, area under the concentration-time curve; St Dev, standard deviation

To summarize, the statistical properties of AUC of percentage change and its relationship to mean percentage change have not yet been established. Unlike mean percentage change, the value of AUC may vary according to the temporal sequence in which the underlying values of percent change are recorded and, as a consequence, in small trials, such as the present one, AUC is more likely to generate random highs and lows in mean outcome that are not clinically relevant. Further, as shown in [Table 83](#), in which the AUC values for all rows are the same, equal to 630, a single value of AUC may map to several values of mean percentage change, i.e., there is no one-to-one correspondence between AUC and mean percentage change. The Applicant's calculation of AUC also involves single imputation of missing values, in direct violation of recommendations by the National Academy of Sciences, and the imputation method used, linear interpolation, produces results that do not match collected data ([Table 82](#)). For these reasons, AUC is not an ideal endpoint to use in clinical trials when the clinical question of interest aligns with mean percentage change.

16.2. Adaptive Randomization and Assessment of Statistical Significance

For the adaptive randomization, each enrolling patient was first identified according to one of the six strata defined by stratum elements age (two categories) and eGFR (three categories). Next, the hypothetical observed (if that participant were assigned to a particular treatment) and expected (according to the planned 2:1 randomization ratio) number of participants in each stratum element were compared, with the difference recorded for each treatment. The difference for each stratification factor was then weighted by 0.33 (placebo goal of 2:1 randomization) given hypothetical assignment to placebo or by 0.67 given hypothetical assignment to nedosiran, and then the weighted differences were summed for each treatment over both stratum elements to form an imbalance score, with the enrolled participant assigned with an 80% probability to the treatment which resulted in the lowest imbalance score. For the first participant, or for participants in which the imbalance scores were equal, treatments were randomly assigned according to the nominal 2:1 randomization ratio.

Given the adaptive randomization, rerandomization tests are preferable when testing for statistical significance. To conduct such tests, 50 new randomizations were first conducted with randomized arm assigned to each individual according to the Applicant's adaptive randomization scheme. Then, as in the current submission, multiple imputation of missing data was used to create 50 datasets for each rerandomized trial, with each dataset analyzed using the original mixed model repeated measures. The results for each rerandomized trial were then combined using Rubin's rule to obtain confidence limits and p-values.

Rerandomization tests performed in this manner confirmed the statistical significance of the primary endpoint results. To provide adequate precision in the estimated p-values, at least 10,000 rerandomizations were needed. The analysis documented here was based on 13,500 trial rerandomizations and yielded a p-value of 0.001 when participants with PH1 or PH2 were analyzed, and a p-value of <0.001 when participants with PH1 were analyzed.

Treatment with nedosiran also reduced absolute Uox excretion ([Table 84](#)).

Table 84. Change in 24 h Urinary Oxalate Excretion, Imputation on Days 90 to 180 Only

Population	Placebo (μmol/day)	Nedosiran (μmol/day)	Difference* (95% CI) p-Value
PH1 and PH2	298 (N=12)	-547 (N=23)	-845 (-1179, -500) <0.0001
PH1	282 (N=11)	-653 (N=18)	-935 (-1285, -585) <0.001

Source: Reviewer program primary efficacy urinary oxalate 2023 03 28.sas.

* Statistical significance and confidence intervals nominal only – endpoint selected post hoc without multiplicity adjustment.

Calculated using mixed model repeated measures combined using Rubin's rule.

Abbreviations: CI, confidence interval; PH1/2, primary hyperoxaluria type 1/2

16.3. Potential Impact of Randomization Imbalances According to Race

All Asian participants in this trial were assigned to the nedosiran arm. Although there is no reason to believe that participants who were Asian might have a larger response than other groups, analyses were conducted excluding Asian participants. When the data were reanalyzed with Asian participants excluded, the least square estimated magnitude of treatment effect and (nominal) statistical significance were retained ([Table 85](#)).

Table 85. Primary Endpoint, 24 h Uox AUC Δ% Days 90 to 180, Asian Participants Excluded

Population	Placebo	Nedosiran	Difference* (95% CI) p-Value
PH1 and PH2	1960 (N=12)	-3369 (N=17)	-5328 (-7790, -2867) <0.0001
PH1	1250 (N=11)	-4460 (N=13)	-5710 (-8210, -3210) <0.0001

Source: Reviewer program primary efficacy AUC urinary oxalate mi itt.sas.

* Statistical significance and confidence intervals nominal only – endpoint selected post hoc without multiplicity adjustment.

Calculated using mixed model repeated measures combined using Rubin's rule.

Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; PH1/2, primary hyperoxaluria type 1/2; Uox, urinary oxalate

16.4. Potential Impact of Randomization to Larger Than Labeled Adult Doses

As mentioned in the footnote to [Table 84](#), dosing for adults weighing <50 kg was changed during the trial; in Version 4 of the protocol released on April 20, 2019, dosing for this group of adults was changed from 170 mg monthly to 137 mg monthly. Two such adults received the higher dose before the dosing change, and no such adults were enrolled after the dosing change. Without the two adults weighing less than 50 kg who received a higher dose than that proposed in labeling, the magnitude of the treatment effect and (nominal) statistical significance of the primary endpoint were retained ([Table 86](#)).

Table 86. Primary Endpoint, 24 h Uox AUC Δ% Days 90 to 180, Adults <50 kg Excluded

Population	Placebo	Nedosiran	Difference* (95% CI) p-Value
PH1 and PH2	1433 (N=12)	-3546 (N=21)	-4979 (-7246, -2712) <0.0001
PH1	946 (N=11)	-4645 (N=16)	-5591 (-7849, -3333) <0.0001

Source: Reviewer program primary efficacy AUC urinary oxalate mi itt.sas.

* Statistical significance and confidence intervals nominal only – endpoint selected post hoc without multiplicity adjustment.

Calculated using mixed model repeated measures combined using Rubin's rule.

Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; PH1/2, primary hyperoxaluria type 1/2; Uox, urinary oxalate

16.5. Potential Impact of Missing Data on Analysis Results

Sensitivity analysis to account for potential inaccuracies in the imputation of missing data should address a broad range of 'extreme' scenarios in which the investigational treatment has no or even negative effects on outcome among participants missing data. The Applicant did not provide extensive sensitivity analyses and so these analyses were conducted by the review team.

Tipping point sensitivity analyses were conducted by the review team using multiple imputation, with 50 datasets in which missing data (Table 11) were imputed for Uox normalized by body surface area for participants ≤ 18 years of age, as in the primary analysis, at Days 90, 120, 150, or 180. Imputations were conducted using multiple regression with the following independent variables: treatment, age category, eGFR category, and day. For each of these datasets, specified shifts were applied to the imputed values for each treatment arm, and these shifted values were used to calculate for each trial participant a new value for UO_{24} AUC $\Delta\%$ Days 90 to 180. These AUC values were then analyzed for each imputed dataset, with results combined for each set of shifts using Rubin's method.

The tipping point analyses confirmed the robustness of the results to assumptions on missing data for the combined PH1 and PH2 participants (Table 87) and for the PH1 only participants (Table 88), with statistical significance retained for all plausible shifts in urinary oxalate excretion in missing data. The results provided in these tables show the impact on the treatment effect of shifts in the treatment arm ranging from 0 to an additional 1000 $\mu\text{mol/day}$, in which outcomes in missed assessments reflect increases rather than decreased urinary oxalate excretion in the nedosiran arm, and concurrently assess shifts in the placebo arm ranging from 0 to -1000 $\mu\text{mol/day}$, in which outcomes in missed assessments reflect decreases rather than lack of change for urinary oxalate excretion in the placebo arm.

Table 87. Tipping Point Analysis, PH1 and PH2 Participants

Placebo Arm		Nedosiran Arm				
Shift in Urinary Oxalate ($\mu\text{mol/day}$)	0	200	400	600	800	1000
AUC Treatment Effect (p-Value)						
-1000	-3951	-3724	-3496	-3269	-3041	-2814
	<0.001	0.001	0.003	0.007	0.01	0.03
-800	-4156	-3929	-3701	-3474	-3247	-3019
	<0.001	<0.001	0.001	0.004	0.008	0.02
-600	-4361	-4134	-3906	-3679	-3452	-3224
	<0.001	<0.001	<0.001	0.002	0.004	0.01
-400	-4566	-4339	-4111	-3884	-3657	-3429
	<0.0001	<0.001	<0.001	<0.001	0.002	0.006
-200	-4771	-4544	-4316	-4089	-3862	-3634
	<0.0001	<0.0001	<0.001	<0.001	0.001	0.003
0	-4976	-4749	-4521	-4294	-4067	-3839
	<0.0001	<0.0001	<0.0001	<0.001	<0.001	0.002

Source: Reviewer program fda tipping aucd90n.sas.

Abbreviations: AUC, area under the concentration-time curve; PH1/2, primary hyperoxaluria type 1/2

Table 88. Tipping Point Analysis, PH1 Participants

Placebo Arm Shift in Urinary Oxalate (μmol/day)	Nedosiran Arm					
	0	200	400	600	800	1000
	AUC Treatment Effect (p-Value)					
-1000	-4624 <0.0001	-4439 <0.001	-4253 <0.001	-4068 0.001	-3882 0.003	-3697 0.006
-800	-4807 <0.0001	-4621 <0.0001	-4436 <0.001	-4250 <0.001	-4065 0.001	-3879 0.004
-600	-4989 <0.0001	-4804 <0.0001	-4618 <0.0001	-4433 <0.001	-4247 <0.001	-4062 0.002
-400	-5172 <0.0001	-4986 <0.0001	-4801 <0.0001	-4615 <0.001	-4430 <0.001	-4244 0.001
-200	-5354 <0.0001	-5169 <0.0001	-4983 <0.0001	-4798 <0.0001	-4612 <0.001	-4427 <0.001
0	-5537 <0.0001	-5351 <0.0001	-5166 <0.0001	-4980 <0.0001	-4795 <0.0001	-4609 <0.001

Source: Reviewer program fda tipping aucd90n.sas.

Abbreviations: AUC, area under the concentration-time curve; PH1/2, primary hyperoxaluria type 1/2

16.6. Discrepant Results From Various Methodologies to Evaluate Uox Percentage Change From Baseline

The Applicant proposed to include information in Section 14 of the label on the percent change from baseline in urinary oxalate; however the Applicant used various methods of calculation which produced conflicting results. Results shown in the first row of [Table 89](#) (b) (4), in which estimates of 24 h Uox AUC change from Baseline over Days 90 to 180 were divided by 90 days to obtain a percent change in AUC at steady-state. However, the 14.6% increase in the placebo arm is inconsistent with the trend graph (b) (4) (Figure 44), which indicates a decrease from Baseline among placebo patients from Days 90 to 180 rather than an increase. Further, both of these estimates conflict with the results shown in Table A4 of the Applicant's clinical study report, which are included in the second row of [Table 89](#). In this analysis, the increase in urinary oxalate in the placebo arm is less than that obtained using the AUC-based method (b) (4), but is still inconsistent with what is seen in the trend graph.

Table 89. Alternative Methods for Percentage Change in 24 h Urinary Oxalate Concentration, Days 90 to 180, PH1 mITT

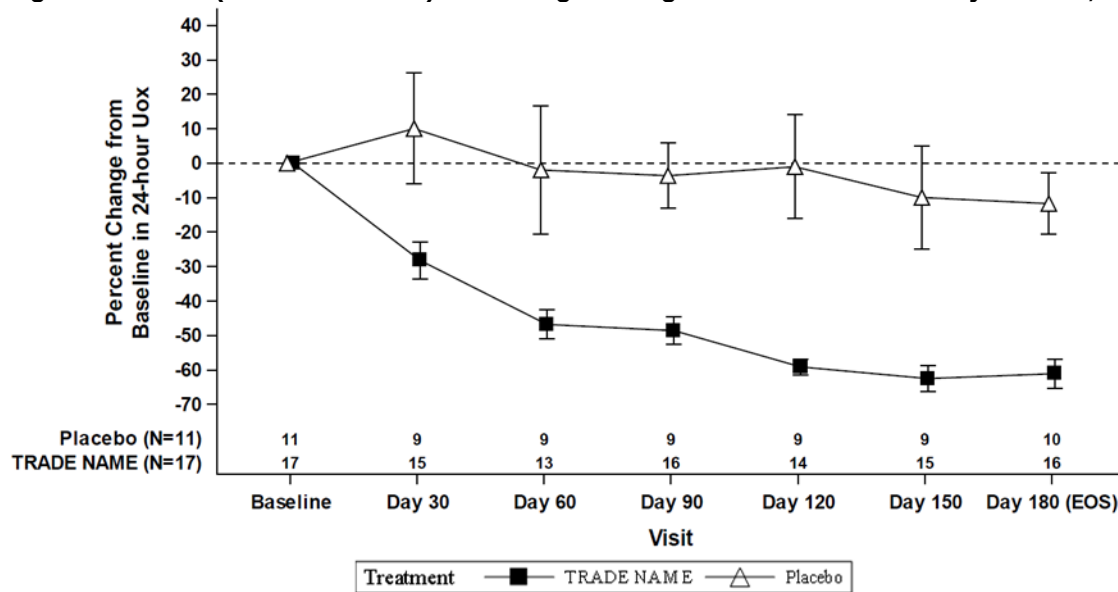
Source	Placebo	Nedosiran	Difference ^a (95% CI) p-Value
(b) (4) =AUC÷90	1317/90=14.6%	-4575/90=-50.8%	-65% (-41%, -90%) <0.0001
Adapted from analysis from Table A4 in the CSR	6.5%	-52.5%	-59% (-81%, -37%) <0.0001

Source: Primary efficacy urinary oxalate itt last 4 visits 2023 03 28.sas.

^a Nominal confidence limits and p-value – endpoint selected post hoc without multiplicity adjustment.

Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; CSR, clinical study report; mITT, modified intent-to-treat; PH1, primary hyperoxaluria type 1

Figure 44. Mean ($\pm$ Standard Error) Percentage Change From Baseline Urinary Oxalate, PH1 mITT



Source: (b) (4), adapted from analysis for CSR Figure 14.4.4a.
Abbreviations: CSR, clinical study report; mITT, modified intent-to-treat; PH1, primary hyperoxaluria type 1

Given the aforementioned discrepancies, it is worthwhile to consider the various approaches used by the Applicant. The estimate shown in the first row of [Table 89](#) was obtained by dividing the change from baseline AUC by the number of days over which the AUC was calculated, a method that has not yet been studied in the statistical literature and that has undesirable statistical properties in small studies (see discussion of random highs and lows in [Section 16.1](#) of this review). The mixed model repeated measures analysis shown in Table A4 in the clinical study report is shown in the last row of [Table 89](#). This analysis included the following independent factors: treatment, baseline urinary oxalate concentration, age group, eGFR group, and study day (90, 120, 150, or 180), but the results conflict with the data used to generate [Figure 44](#) which, in turn, failed to include imputation for missing data and calculated point estimates using simple averages, without any adjustments for covariates.

To address these issues with the approaches used by the Applicant, the review team implemented a single comprehensive intent-to-treat analysis which imputed 50 datasets for 24 h Uox measurements at Days 0, 30, 60, 90, 120, 150, and 180 and then evaluated the mean change from baseline in 24 h urinary oxalate over Days 90, 120, 150, and 180 for each imputed dataset using mixed model repeated measures with independent factors of treatment, eGFR group, age group, Baseline 24 h Uox concentration, and visit by treatment interaction, with a compound symmetric covariance matrix, with the results subsequently combined using Rubin's rule.

17. Clinical Safety

Table 90. Participants With Treatment-Emergent Adverse Events by Preferred Term, Safety Population, Trials DCR-PHXC-201

Preferred Term	Nedosiran N=23 n (%)	Placebo N=12 n (%)	Nedosiran vs. Placebo Risk Difference (%) (95% CI)
Any AE	19 (82.6)	10 (83.3)	-0.7 (-26.9, 25.4)
Injection site erythema	5 (21.7)	0	21.7 (4.9, 38.6) *
Nausea	4 (17.4)	1 (8.3)	9.1 (-13.0, 31.1)
Abdominal pain	2 (8.7)	0	8.7 (-2.8, 20.2)
Dysmenorrhea	2 (8.7)	0	8.7 (-2.8, 20.2)
Injection site pain	2 (8.7)	0	8.7 (-2.8, 20.2)
Neutrophil count decreased	2 (8.7)	0	8.7 (-2.8, 20.2)
Oropharyngeal pain	2 (8.7)	0	8.7 (-2.8, 20.2)
Abdominal discomfort	1 (4.3)	0	4.3 (-4.0, 12.7)
Acne	1 (4.3)	0	4.3 (-4.0, 12.7)
Alopecia	1 (4.3)	0	4.3 (-4.0, 12.7)
Anxiety	1 (4.3)	0	4.3 (-4.0, 12.7)
Calculus urinary	1 (4.3)	0	4.3 (-4.0, 12.7)
Dizziness	1 (4.3)	0	4.3 (-4.0, 12.7)
Dysgeusia	1 (4.3)	0	4.3 (-4.0, 12.7)
Dyspnea exertional	1 (4.3)	0	4.3 (-4.0, 12.7)
Gastroenteritis	1 (4.3)	0	4.3 (-4.0, 12.7)
Genital pain	1 (4.3)	0	4.3 (-4.0, 12.7)
Gingivitis	1 (4.3)	0	4.3 (-4.0, 12.7)
Gout	1 (4.3)	0	4.3 (-4.0, 12.7)
Hematuria	1 (4.3)	0	4.3 (-4.0, 12.7)
Influenza-like illness	1 (4.3)	0	4.3 (-4.0, 12.7)
Injection site bruising	1 (4.3)	0	4.3 (-4.0, 12.7)
Injection site rash	1 (4.3)	0	4.3 (-4.0, 12.7)
Irritable bowel syndrome	1 (4.3)	0	4.3 (-4.0, 12.7)
Ligament sprain	1 (4.3)	0	4.3 (-4.0, 12.7)
Lymphocyte percentage increased	1 (4.3)	0	4.3 (-4.0, 12.7)
Metrorrhagia	1 (4.3)	0	4.3 (-4.0, 12.7)
Migraine with aura	1 (4.3)	0	4.3 (-4.0, 12.7)

Preferred Term	Nedosiran N=23 n (%)	Placebo N=12 n (%)	Nedosiran vs. Placebo Risk Difference (%) (95% CI)
Muscle spasms	1 (4.3)	0	4.3 (-4.0, 12.7)
Nasopharyngitis	1 (4.3)	0	4.3 (-4.0, 12.7)
Neutrophil percentage decreased	1 (4.3)	0	4.3 (-4.0, 12.7)
Non-cardiac chest pain	1 (4.3)	0	4.3 (-4.0, 12.7)
Renal pain	1 (4.3)	0	4.3 (-4.0, 12.7)
SARS-CoV-2 test positive	1 (4.3)	0	4.3 (-4.0, 12.7)
Tachycardia	1 (4.3)	0	4.3 (-4.0, 12.7)
Testicular injury	1 (4.3)	0	4.3 (-4.0, 12.7)
Thermal burn	1 (4.3)	0	4.3 (-4.0, 12.7)
Tinea capitis	1 (4.3)	0	4.3 (-4.0, 12.7)
Tooth abscess	1 (4.3)	0	4.3 (-4.0, 12.7)
Toothache	1 (4.3)	0	4.3 (-4.0, 12.7)
Urethral discharge	1 (4.3)	0	4.3 (-4.0, 12.7)
Urinary tract infection	1 (4.3)	0	4.3 (-4.0, 12.7)
Vaccination site pain	1 (4.3)	0	4.3 (-4.0, 12.7)
Vision blurred	1 (4.3)	0	4.3 (-4.0, 12.7)
White blood cell count decreased	1 (4.3)	0	4.3 (-4.0, 12.7)
White blood cell count increased	1 (4.3)	0	4.3 (-4.0, 12.7)
Pain in extremity	2 (8.7)	1 (8.3)	0.4 (-19.1, 19.8)
Arthralgia	1 (4.3)	1 (8.3)	-4.0 (-21.7, 13.7)
Blood creatine phosphokinase increased	1 (4.3)	1 (8.3)	-4.0 (-21.7, 13.7)
Blood creatinine increased	1 (4.3)	1 (8.3)	-4.0 (-21.7, 13.7)
Neck pain	1 (4.3)	1 (8.3)	-4.0 (-21.7, 13.7)
Upper respiratory tract infection	1 (4.3)	1 (8.3)	-4.0 (-21.7, 13.7)
Headache	4 (17.4)	3 (25.0)	-7.6 (-36.6, 21.4)
Adverse event following immunization	0	1 (8.3)	-8.3 (-24.0, 7.3)
Alanine aminotransferase increased	0	1 (8.3)	-8.3 (-24.0, 7.3)
Arthritis	0	1 (8.3)	-8.3 (-24.0, 7.3)
Aspartate aminotransferase increased	0	1 (8.3)	-8.3 (-24.0, 7.3)
Chronic gastritis	0	1 (8.3)	-8.3 (-24.0, 7.3)
Cough	0	1 (8.3)	-8.3 (-24.0, 7.3)
COVID-19	0	1 (8.3)	-8.3 (-24.0, 7.3)
Decreased appetite	0	1 (8.3)	-8.3 (-24.0, 7.3)
Depression	0	1 (8.3)	-8.3 (-24.0, 7.3)
Dermatitis acneiform	0	1 (8.3)	-8.3 (-24.0, 7.3)
Diarrhea	0	1 (8.3)	-8.3 (-24.0, 7.3)
Dyspepsia	0	1 (8.3)	-8.3 (-24.0, 7.3)
Flank pain	0	1 (8.3)	-8.3 (-24.0, 7.3)
Gastroesophageal reflux disease	0	1 (8.3)	-8.3 (-24.0, 7.3)
Glutamate dehydrogenase increased	0	1 (8.3)	-8.3 (-24.0, 7.3)
Hydronephrosis	0	1 (8.3)	-8.3 (-24.0, 7.3)
Hypercholesterolemia	0	1 (8.3)	-8.3 (-24.0, 7.3)
Intervertebral disc protrusion	0	1 (8.3)	-8.3 (-24.0, 7.3)
Meniscus injury	0	1 (8.3)	-8.3 (-24.0, 7.3)
Menstrual disorder	0	1 (8.3)	-8.3 (-24.0, 7.3)
Osteoarthritis	0	1 (8.3)	-8.3 (-24.0, 7.3)
Rhinitis	0	1 (8.3)	-8.3 (-24.0, 7.3)

	Nedosiran N=23 n (%)	Placebo N=12 n (%)	Nedosiran vs. Placebo Risk Difference (%) (95% CI)
Preferred Term			
Sensory disturbance	0	1 (8.3)	-8.3 (-24.0, 7.3)
Vitamin D deficiency	0	1 (8.3)	-8.3 (-24.0, 7.3)
Fatigue	1 (4.3)	2 (16.7)	-12.3 (-35.0, 10.4)
Renal colic	1 (4.3)	2 (16.7)	-12.3 (-35.0, 10.4)
Nephrolithiasis	2 (8.7)	3 (25.0)	-16.3 (-43.4, 10.8)
Abdominal pain upper	0	2 (16.7)	-16.7 (-37.8, 4.4)
Back pain	0	2 (16.7)	-16.7 (-37.8, 4.4)

Source: adae.xpt; software: R.

Treatment-emergent adverse events defined as any AE with an onset date/time on or after administration (including any partial administration) of the first dose of study intervention and through the study completion date from the end of study case report form. Duration is the 6-month treatment period.

Coded as Medical Dictionary for Regulatory Activities preferred terms.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: AE, adverse event; CI, confidence interval; COVID-19, coronavirus disease 2019; N, number of patients in treatment arm; n, number of patients with adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Table 91. Participants With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, DCR-PHXC-201, PH1 Only

System Organ Class Preferred Term	Nedosiran N=18 n (%)	Placebo N=11 n (%)
Any SAE	1 (5.6)	2 (18.2)
Cardiac disorders (SOC)	1 (5.6)	0
Tachycardia	1 (5.6)	0
Investigations (SOC)	0	1 (9.1)
Blood creatinine increased	0	1 (9.1)
Renal and urinary disorders (SOC)	0	1 (9.1)
Nephrolithiasis	0	1 (9.1)
Renal colic	0	1 (9.1)

Source: adae.xpt; software: R.

Treatment-emergent adverse events defined as any adverse event with an onset date/time on or after administration (including any partial administration) of the first dose of study intervention and through the study completion date from the end of study case report form.

Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Duration is the 6-month treatment period.

Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event; PH1, primary hyperoxaluria 1; SAE, serious adverse event; SOC, system organ class

Table 92. Participants With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, DCR-PHXC-201, PH1 Only

System Organ Class Preferred Term	Nedosiran N=18 n (%)	Placebo N=11 n (%)
Any AE leading to discontinuation	1 (5.6)	1 (9.1)
Cardiac disorders (SOC)	1 (5.6)	0
Tachycardia	1 (5.6)	0
Investigations (SOC)	0	1 (9.1)
Blood creatinine increased	0	1 (9.1)

Source: adae.xpt; software: R.

Treatment-emergent adverse events defined as any adverse event with an onset date/time on or after administration (including any partial administration) of the first dose of study intervention and through the study completion date from the end of study case report form.

Duration is the 6-month treatment period.

Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event; PH1, primary hyperoxaluria 1; SOC, system organ class

Table 93. Participants With Treatment Emergent Adverse Events, DCR-PHXC-201, PH1 Only

Preferred Term	Nedosiran N=18 n (%)	Placebo N=11 n (%)
Any AE	16 (88.9)	9 (81.8)
Injection site erythema	5 (27.8)	0
Abdominal pain	2 (11.1)	0
Injection site pain	2 (11.1)	0
Nausea	2 (11.1)	0
Neutrophil count decreased	2 (11.1)	0
Abdominal discomfort	1 (5.6)	0
Acne	1 (5.6)	0
Alopecia	1 (5.6)	0
Anxiety	1 (5.6)	0
Calculus urinary	1 (5.6)	0
Dysgeusia	1 (5.6)	0
Dysmenorrhea	1 (5.6)	0
Dyspnea exertional	1 (5.6)	0
Gastroenteritis	1 (5.6)	0
Genital pain	1 (5.6)	0
Gingivitis	1 (5.6)	0
Gout	1 (5.6)	0
Hematuria	1 (5.6)	0
Injection site bruising	1 (5.6)	0
Injection site rash	1 (5.6)	0
Irritable bowel syndrome	1 (5.6)	0
Lymphocyte percentage increased	1 (5.6)	0
Metrorrhagia	1 (5.6)	0
Muscle spasms	1 (5.6)	0
Nasopharyngitis	1 (5.6)	0
Neck pain	1 (5.6)	0
Neutrophil percentage decreased	1 (5.6)	0
Non-cardiac chest pain	1 (5.6)	0
Oropharyngeal pain	1 (5.6)	0
Renal pain	1 (5.6)	0
SARS-CoV-2 test positive	1 (5.6)	0
Tachycardia	1 (5.6)	0
Testicular injury	1 (5.6)	0

Preferred Term	Nedosiran N=18 n (%)	Placebo N=11 n (%)
Thermal burn	1 (5.6)	0
Tinea capitis	1 (5.6)	0
Tooth abscess	1 (5.6)	0
Toothache	1 (5.6)	0
Urethral discharge	1 (5.6)	0
Urinary tract infection	1 (5.6)	0
White blood cell count decreased	1 (5.6)	0
White blood cell count increased	1 (5.6)	0
Pain in extremity	2 (11.1)	1 (9.1)
Arthralgia	1 (5.6)	1 (9.1)
Blood creatine phosphokinase increased	1 (5.6)	1 (9.1)
Blood creatinine increased	1 (5.6)	1 (9.1)
Upper respiratory tract infection	1 (5.6)	1 (9.1)
Nephrolithiasis	2 (11.1)	2 (18.2)
Adverse event following immunization	0	1 (9.1)
Alanine aminotransferase increased	0	1 (9.1)
Arthritis	0	1 (9.1)
Aspartate aminotransferase increased	0	1 (9.1)
Chronic gastritis	0	1 (9.1)
Cough	0	1 (9.1)
COVID-19	0	1 (9.1)
Decreased appetite	0	1 (9.1)
Depression	0	1 (9.1)
Dermatitis acneiform	0	1 (9.1)
Diarrhea	0	1 (9.1)
Dyspepsia	0	1 (9.1)
Flank pain	0	1 (9.1)
Gastroesophageal reflux disease	0	1 (9.1)
Glutamate dehydrogenase increased	0	1 (9.1)
Hydronephrosis	0	1 (9.1)
Hypercholesterolemia	0	1 (9.1)
Intervertebral disc protrusion	0	1 (9.1)
Meniscus injury	0	1 (9.1)
Menstrual disorder	0	1 (9.1)
Osteoarthritis	0	1 (9.1)
Rhinitis	0	1 (9.1)
Sensory disturbance	0	1 (9.1)
Vitamin D deficiency	0	1 (9.1)
Headache	3 (16.7)	3 (27.3)
Fatigue	1 (5.6)	2 (18.2)
Renal colic	1 (5.6)	2 (18.2)
Abdominal pain upper	0	2 (18.2)
Back pain	0	2 (18.2)

Source: adae.xpt; software: R.

Treatment-emergent adverse events defined as any AE with an onset date/time on or after administration (including any partial administration) of the first dose of study intervention and through the study completion date from the end of study case report form. Duration is the 6-month treatment period.

Coded as Medical Dictionary for Regulatory Activities preferred terms.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; N, number of patients in treatment arm; n, number of patients with adverse event; PH1, primary hyperoxaluria 1; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Table 94. Participants With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, DCR-PHXC-201, PH1 Only

System Organ Class FMQ (Narrow)	Nedosiran N=18 n (%)	Placebo N=11 n (%)
Blood and lymphatic system disorders (SOC)		
Leukopenia	1 (5.6)	0
Cardiac disorders (SOC)		
Arrhythmia	1 (5.6)	0
Tachycardia	1 (5.6)	0
Gastrointestinal disorders (SOC)		
Nausea	2 (11.1)	0
Abdominal pain	3 (16.7)	2 (18.2)
Diarrhea	0	1 (9.1)
Dyspepsia	0	3 (27.3)
General disorders and administration site conditions (SOC)		
Local administration reaction	7 (38.9)	0
Decreased appetite	0	1 (9.1)
Fatigue	1 (5.6)	2 (18.2)
Hepatobiliary disorders (SOC)		
Hepatic Injury	0	1 (9.1)
Infections and infestations (SOC)		
Bacterial infection	2 (11.1)	0
Fungal infection	1 (5.6)	0
Purulent material	1 (5.6)	0
Viral infection	1 (5.6)	1 (9.1)
Nasopharyngitis	2 (11.1)	2 (18.2)
Metabolism and nutrition disorders (SOC)		
Lipid disorder	0	1 (9.1)
Musculoskeletal and connective tissue disorders (SOC)		
Gout	1 (5.6)	0
Arthralgia	1 (5.6)	1 (9.1)
Arthritis	1 (5.6)	1 (9.1)
Back pain	0	3 (27.3)
Nervous system disorders (SOC)		
Dysgeusia	1 (5.6)	0
Headache	3 (16.7)	3 (27.3)
Psychiatric disorders (SOC)		
Anxiety	1 (5.6)	0
Depression	0	1 (9.1)

System Organ Class FMQ (Narrow)	Nedosiran N=18 n (%)	Placebo N=11 n (%)
Renal and urinary disorders (SOC)		
Renal and urinary tract infection	1 (5.6)	0
Reproductive system and breast disorders (SOC)		
Abnormal uterine bleeding	1 (5.6)	0
Respiratory, thoracic and mediastinal disorders (SOC)		
Dyspnea	1 (5.6)	0
Cough	0	1 (9.1)
Skin and subcutaneous tissue disorders (SOC)		
Erythema	5 (27.8)	0
Alopecia	1 (5.6)	0
Rash	2 (11.1)	1 (9.1)
Vascular disorders (SOC)		
Hemorrhage	3 (16.7)	0

Source: adae.xpt; software: R.

Treatment-emergent adverse events defined as any AE with an onset date/time on or after administration (including any partial administration) of the first dose of study intervention and through the study completion date from the end of study case report form. Duration is the 6-month treatment period.

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term..."

Abbreviations: FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; PH1, primary hyperoxaluria 1; SOC, system organ class

Table 95. Participants With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, DCR-PHXC-201, PH1 Only

Laboratory Parameter	Nedosiran N=18 n/N_w (%)	Placebo N=11 n/N_w (%)
Creatinine, high (mg/dL)		
Level 1 ($\geq 1.5\times$ baseline)	1/18 (5.6)	1/11 (9.1)
Level 2 ($\geq 2\times$ baseline)	0/18 (0)	1/11 (9.1)
Level 3 ($\geq 3\times$ baseline)	0/18 (0)	0/11 (0)
eGFR, low (mL/min/1.73 m ²)		
Level 1 ($\geq 25\%$ decrease)	0/16 (0)	2/9 (22.2)
Level 2 ($\geq 50\%$ decrease)	0/16 (0)	1/9 (11.1)
Level 3 ($\geq 75\%$ decrease)	0/16 (0)	0/9 (0)
CPK, high (U/L)		
Level 1 ($> 3\times$ ULN)	4/18 (22.2)	0/11 (0)
Level 2 ($> 5\times$ ULN)	2/18 (11.1)	0/11 (0)
Level 3 ($> 10\times$ ULN)	1/18 (5.6)	0/11 (0)

Source: ad b.xpt; software: R.

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is the 6-month treatment period.

Abbreviations: eGFR, estimated glomerular filtration rate; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; PH1, primary hyperoxaluria 1

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action / Drug Resistance

Not applicable.

21. Other Drug Development Considerations

None.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

One clinical site inspection (Dr. John Lieske; Site 101) was completed by the Office of Scientific Investigations. The clinical site was chosen using a risk-based approach primarily based on the number of enrolled participants (7 of 35 enrolled participants), large treatment effect on the primary endpoint, and prior inspectional history. Based on the results of this inspection, the study (Protocol DCR-PHXC-201) appears to have been conducted adequately, and the clinical data generated by this site appears to be reliable in support of this NDA. See the Office of Scientific Investigations memorandum for further details.

23. Labeling: Key Changes and Considerations

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft PI ([Table 96](#)). The PI was reviewed to ensure that it meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- Prescribing Information
- Patient Information
- Instructions for Use – Vial
- Instructions for Use – Prefilled Syringe

24. Postmarketing Requirements and Commitments

These are the postmarketing requirements:

- Complete a 26-week GLP carcinogenicity study of nedosiran and murine surrogate (DCR-m355) by subcutaneous injection in TgRasH2 mice.
- Complete a long-term (2-year) GLP carcinogenicity study of nedosiran by subcutaneous injection in one rodent species.

25. Financial Disclosure

Table 97. Covered Clinical Studies: DCR-PHXC-101, DCR-PHXC-104, DCR-PHXC-201, and DCR-PHXC-301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: DCR-PHXC-101: 32; DCR-PHXC-104: 81; DCR-PHXC-201: 118; DCR-PHXC-301: 94		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 (an investigator-initiated grant for (b) (6)) Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

26. References

Literature and Websites

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- Proschan, MA and LE Dodd, 2019, Re-randomization tests in clinical trials, *Stat Med*, 38(12):2292-2302.

Guidances for Industry

- FDA, 2022, Guidance for Industry; M10 Bioanalytical Method Validation and Study Sample Analysis, <https://www.fda.gov/media/162903/download>.

Review Team

Table 98. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Brian Proctor, MS
Nonclinical reviewer	Belay Tesfamariam, PhD
Nonclinical team leader	Jean Wu, PhD
OCP reviewer	Harisudhan Thanukrishnan, PhD
OCP team leader	Doanh Tran, PhD
Pharmacometrics reviewer	Ye Yuan, PhD
Pharmacometrics team leader	Hao Zhu, PhD
Clinical reviewer	Kirtida Mistry, MBBCh, DCH, MRCPCH
Clinical team leader	Aliza Thompson, MD, MS
Biometrics reviewer	Robert Abugov, PhD
Biometrics team leader	Jialu Zhang, PhD
Cross-disciplinary team leader	Aliza Thompson, MD, MS
Division director (pharm/tox)	Calvin Elmore
Division director (OCP)	Shirley Seo
Division director (OB)	Mark Rothmann
Deputy Division director (clinical)	Aliza Thompson, MD, MS
Office director (or designated signatory authority)	Hylton V. Joffe, MD, MMSc

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

Table 99. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	SPQA: Ted Carver; Drug Substance: Dan Jansen, Zhengfu Wang; Drug Product: Dan Berger; Facilities: Allison Aldridge/Rose Xu
Microbiology	BreOnna DeLaine-Elias, Neal Sweeney
OBP	Faruk Sheikh, Harold Dickensheets, Fred Mills, Mayumi Takahashi
OPDP	Charuni Shah
OSI	Tina Suyoung Chang
OSE/DEPI	Mingfeng Zhang, Margie Goulding
OSE/DMEPA	Ebony Whaley, Colleen Little, Hina Mehta
OSE/DRISK	Cristen Lambert, Yasmeen Abou-Sayed
DPMH	Katherine Kratz, Miriam Dinatale
Acknowledgements	Norman Stockbridge, MD, PhD

Abbreviations: OPQ, Office of Pharmaceutical Quality; OBP, Office of Biotechnology Products; OPDP, Office of Prescription Drug Promotion; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; DPMH, Division of Pediatrics and Maternal Health

26.1. Reviewer Signatures

Table 0-100 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Aliza Thompson OCHEN DCN	Sections: 1-4, 6-7, 10-12, 15, 17, 22-25	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Aliza Thompson			Digitally signed by Aliza Thompson Date: 9/29/2023 6:51 AM EDT GUID: 2023929105114	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Risk Management Reviewer Discipline Secondary Reviewer	Yasmeen Abou-Sayed OMEPRM DRM	Sections: Risk Management	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	
Signature: Yasmeen Abou-Sayed			Digitally signed by Yasmeen Abou-Sayed Date: 9/29/2023 7:42 AM EDT GUID: 2023929114215	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Kirtida Mistry OCHEN DCN	Sections: 1 to 4, 6.2.1.4, 7, 8.3, 8.4, 10 to 12, 17, 22, and 25	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Kirtida Mistry			Digitally signed by Kirtida Mistry Date: 9/29/2023 7:45 AM EDT GUID: 2023929114522	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Robert Abugov OB DBII	Sections: 6.2.2.3, 6.2.2.4, 16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Robert Abugov			Digitally signed by Robert Abugov Date: 9/29/2023 7:48 AM EDT GUID: 202392911484	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Harisudhan Thanukrishnan OCP DCEP	Sections: 5.2, 8.1, 8.2, 14.1, 14.2, 14.3, 14.4	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Harisudhan Thanukrishnan Digitally signed by Harisudhan Thanukrishnan Date: 9/29/2023 8:04 AM EDT GUID: 202392912423				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Jialu Zhang OB DBII	Sections: 6.2.2.3, 6.2.2.4, 16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jialu Zhang Digitally signed by Jialu Zhang Date: 9/29/2023 8:08 AM EDT GUID: 202392912837				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Risk Management Reviewer Discipline Tertiary Reviewer	Laura Zendel OMEPRM DRM	Sections: N/A	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	DRM did not contribute to the IAMA, however, we note no risk mitigation or REMS issues for this application.
Signature: Laura Zendel Digitally signed by Laura Zendel Date: 9/29/2023 8:36 AM EDT GUID: 2023929123617				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Secondary Reviewer	Michael Monteleone OCHEN DCN	Sections: 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Michael Monteleone Digitally signed by Michael Monteleone Date: 9/29/2023 8:41 AM EDT GUID: 2023929124145				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Primary Reviewer	Michael Monteleone OCHEN DCN	Sections: 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Michael Monteleone

Digitally signed by Michael Monteleone

Date: 9/29/2023 8:42 AM EDT
GUID: 2023929124241

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non- clinical Discipline Tertiary Reviewer	Calvin Elmore OCHEN DPTCHEN	Sections: 5.1, 7.1, 8.4, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Calvin Elmore

Digitally signed by Calvin Elmore

Date: 9/29/2023 8:45 AM EDT
GUID: 2023929124535

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Tertiary Reviewer	Mark Rothmann OB DBII	Sections: 6.2.2.3, 6.2.2.4, 16	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	
Signature: Mark Rothmann			Digitally signed by Mark Rothmann Date: 9/29/2023 8:47 AM EDT GUID: 2023929124711	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Risk Management Reviewer Discipline Primary Reviewer	Cristen Lambert OMEPRM DRM	Sections: risk management	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	
Signature: Cristen Lambert			Digitally signed by Cristen Lambert Date: 9/29/2023 8:48 AM EDT GUID: 2023929124820	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Doanh Tran OCP DCEP	Sections: 5.2, 6.1, 8.1, 8.2, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Doanh Tran			Digitally signed by Doanh Tran Date: 9/29/2023 9:07 AM EDT GUID: 202392913723	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non- clinical Discipline Secondary Reviewer	Jean Wu OCHEN DPTCHEN	Sections: 5.1, 5.2 (partial), 7.1, 8.4, 13, 24	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jean Wu			Digitally signed by Jean Wu Date: 9/29/2023 9:12 AM EDT GUID: 2023929131221	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	Belay Tesfamariam OCHEN DPTCHEN	Sections: 5, 7, 8, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Belay Tesfamariam Digitally signed by Belay Tesfamariam Date: 9/29/2023 9:14 AM EDT GUID: 202392913140				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Ye Yuan OCP DPM	Sections: 6.1, 8.1, 8.2, 14.4	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Ye Yuan Digitally signed by Ye Yuan Date: 9/29/2023 9:24 AM EDT GUID: 2023929132434				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Hao Zhu OCP DPM	Sections: 5.2, 6.1, 8.1, 8.2, 14.1, 14.2, 14.3, 14.4	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Hao Zhu		Digitally signed by Hao Zhu Date: 9/29/2023 9:40 AM EDT GUID: 202392913403		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Tertiary Reviewer	Shirley Seo OCP DCEP	Sections: 5.2, 6.1, 8.1, 8.2, 14.1, 14.2, 14.3, 14.4	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Shirley Seo		Digitally signed by Shirley Seo Date: 9/29/2023 9:56 AM EDT GUID: 202392913560		

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ALIZA M THOMPSON
09/29/2023 12:57:36 PM

HYLTON V JOFFE
09/29/2023 02:08:25 PM