# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 215842Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 132214

**MEETING PRELIMINARY COMMENTS**

Dicerna Pharmaceuticals, Inc.
Attention: Andrew Henderson, MBA
Senior Director, Regulatory Affairs
87 Cambridgepark Drive
Cambridge, MA 02140

Dear Mr. Henderson:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for DCR-PHXC.

We also refer to your correspondence, received and dated December 21, 2021, requesting a meeting to discuss the study data and statistical analyses intended to support approval of DCR-PHXC (nedosiran) for the treatment of primary hyperoxaluria type 1.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, an electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, please call me at (240) 402-3596.

Sincerely,

*{See appended electronic signature page}*

Brian Proctor, MS, RAC
Senior Regulatory Health Project Manager
Cardiology and Nephrology
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, & Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:

- Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

# PRELIMINARY MEETING COMMENTS

**Meeting Type:** A
**Meeting Category:** Resolution

**Meeting Date and Time:** January 28, 2022 from 12-1 pm
**Meeting Location:** Teleconference

**Application Number:** IND 132214
**Product Name:** Nedosiran (DCR-PHXC)
**Indication:** Treatment of primary hyperoxaluria (PH)
**Sponsor Name:** Dicerna Pharmaceuticals, Inc.

## FDA ATTENDEES (tentative)

*Office of Cardiology, Hematology, Endocrinology and Nephrology*

| | |
|---|---|
| Hylton V. Joffe, MD, MMSc | Director |
| Lisa Yanoff, MD | Deputy Director |

*Office of Cardiology, Hematology, Endocrinology and Nephrology, Division of Cardiology and Nephology*

| | |
|---|---|
| Norman Stockbridge, MD, PhD | Director |
| Aliza Thompson, MD, MS | Deputy Director |
| Kirtida Mistry, MBBCh, DCH, MRCPCH | Clinical Reviewer |
| Mary Ross Southworth, PharmD | Deputy Director for Safety |

*Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, & Nephrology*

| | |
|---|---|
| Edward Fromm, RPh, RAC | Chief, Project Management Staff |
| Brian Proctor, MS, RAC | Senior Regulatory Project Manager |

*Office of Clinical Pharmacology, Division of Clinical Pharmacology I*

| | |
|---|---|
| Sudharshan Hariharan, PhD | Clinical Pharmacology Team Leader |
| Harisudhan Thanukrishnan, PhD | Clinical Pharmacology Reviewer |

*Office of Biostatistics, Division of Biometrics II*

| | |
|---|---|
| Jialu Zhang, PhD | Biometrics Team Leader |
| Steve Bai, PhD | Biometrics Reviewer |

## SPONSOR ATTENDEES

| | |
|---|---|
| Aniruddha Amrite, PhD | Director, Clinical Pharmacology |
| Nuno Antunes, PhD | Clinical Scientist, Late-Stage Clinical Development |
| Shreeram Aradhye, MD | Executive Vice President and Chief Medical Officer |

| | |
|---|---|
| Alexandra Haagensen, MD | Senior Medical Director |
| Andrew Henderson, MBA | Executive Director, Regulatory Affairs |
| Steven Kates, PhD | Vice President, Regulatory Affairs |
| James Park, BA | Associate Director, Clinical Operations |
| Jay Russak, MBA | Director, Clinical Operations |
| Kerry Russell, MD, PhD | Vice President, Late Stage Clinical Development |
| Catherine Sullivan, BS | Director, Medical Writing |
| [redacted] (b) (4) | |
| Jing Zhou, MS | Senior Director, Biostatistics |

**Introduction:**
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for January 28, 2022 from 12-1 pm between Dicerna Pharmaceuticals, Inc. and the Division of Cardiology and Nephology. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

## 1.0 BACKGROUND

Nedosiran (DCR-PHXC) is a drug product containing DCR-L1360 drug substance, a small interfering RNA (siRNA) duplex conjugated to N-acetylgalactosamine (GalNAc) sugar residues, in water or saline for subcutaneous injection. DCR-L1360 is designed to bind to and destroy lactate dehydrogenase type A (LDHA) mRNA in the liver to reduce translation to LDHA, an enzyme that catalyzes the final step in the formation of oxalate.

Dicerna is developing nedosiran for the treatment of primary hyperoxaluria (PH). They have completed enrollment of the following studies: (1) DCR-PHXC-101, a phase 1, single-ascending dose study in healthy adults and patients ≥6 years of age with PH1 or PH2; (2) DCR-PHXC-201, a 6-month, randomized, double-blind, placebo-controlled trial in patients ≥6 years of age with PH1 or PH2 and an eGFR ≥30 mL/min/1.73 $m^2$; and (3)

DCR-PHXC-104, a randomized, placebo-controlled, single-dose study in patients ≥6 years of age with PH3 and an eGFR ≥30 mL/min/1.73 $m^2$. They also have several additional ongoing or planned studies in patients with PH:

- DCR-PHXC-203: a 6-month, open-label study in children <6 years of age with PH1 or PH2 and an eGFR ≥30 mL/min/1.73 $m^2$ (n=10)
- DCR-PHXC-204: a 6-month study in patients of any age with PH1 or PH2 and an eGFR <30 mL/min/1.73 $m^2$ including patients on dialysis (n=12)
- DCR-PHXC-301: an open-label extension study for patients previously enrolled in studies of DCR-PHXC and their PH-diagnosed siblings (n~60)

Dicerna was granted Breakthrough Therapy Designation for the treatment of PH1 on July 2, 2019 and an Initial Comprehensive Multidisciplinary Breakthrough Therapy meeting was held on November 4, 2019 to review the proposed clinical, nonclinical, and manufacturing development plans to support the approval of nedosiran.

The Agency provided pre-NDA written responses to the Sponsor on November 2, 2020, on a proposed NDA submission for the treatment of PH1, PH2, and PH3 based on the results of studies DCR-PHXC-201 and DCR-PHXC-104. On August 11, 2021, the Sponsor informed the Agency (via email) that they will seek approval only for PH1 based on an effect on urinary oxalate in PH1 but not PH2 during the placebo-controlled period of study DCR-PHXC-201. Given the new information, the Agency requested that Dicerna share the topline results of study DCR-PHXC-201 and request another pre-NDA meeting to discuss further. At a meeting on October 21, 2021, Dicerna presented the topline results of study DCR-PHXC-201 and the Division provided feedback on issues that should be addressed before a marketing application is submitted.

Dicerna requested this meeting to obtain feedback on their plans to address the concerns raised by the Division during the October 21, 2021 meeting.

## 2.0 DISCUSSION

### 2.1. Clinical

***Question 1:*** Does the Agency agree that the proposed plan for analysis of efficacy data from the PH1 subgroup of the DCR-PHXC-201 study is adequate to demonstrate efficacy for the PH1 indication?

***FDA Response to Question 1***: To address the Division's request for additional analyses in patients with PH1 to support efficacy in that population, you propose to conduct all pre-specified efficacy analyses outlined in the statistical analysis plan for Study 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. In addition, you propose to assess the percent change in 24-hour Uox from baseline to Day 180 (averaged from Day 90 to 180) in patients with PH1, and the proportion of patients

with PH1 with normal 24-hour Uox at Day 180. You also indicate that you plan to include the analyses for the subgroup of patients with PH1 as an addendum to the clinical study report for DCR-PHXC-201 and in Module 2.7.3 of the NDA.

Your proposed analyses in patients with PH1 seem reasonable. Please also provide the following analyses for the trial population as a whole: the percent change in 24-hour Uox from baseline to Day 180 (averaged from Day 90 to 180) and the proportion of patients with normal 24-hour Uox at Day 180.

***Question 2:*** The Sponsor has conducted a series of subgroup, sensitivity, and post hoc analyses to address the question of baseline imbalances in 24-hour Uox between the active and placebo arms of the DCR-PHXC-201 study and to demonstrate consistency of the results in the setting of multiple analysis strategies. Does the Agency agree that, with these additional analyses, the Sponsor has adequately addressed the Agency's concern regarding the baseline Uox imbalance in this study?

***FDA Response to Questions 2***: Given the baseline imbalances between the two study arms in 24-hour Uox levels and the proportion of patients with high baseline Uox levels, the Division expressed concerns about the impact of these imbalances on the efficacy findings in Study DCR-PHXC-201. To address these concerns, you have provided the following analyses:

- The primary endpoint analysis with baseline Uox as a covariate in the ANCOVA model (pre-specified primary endpoint analysis).
- The primary endpoint analysis in the subgroup of patients with "high" baseline Uox >1600 µmol/24 hours in the overall population (pre-specified subgroup analysis) and patients with PH1 only.
- A post hoc primary endpoint analysis in the subgroup of patients with baseline Uox <1600 µmol/24 hours 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-hour Uox >2800 µmol/24 hours (>6x the upper limit of normal and "significantly higher" than the mean for the placebo group).
- A post hoc analysis of percent change from baseline in 24-hour Uox in DCR-PHXC-301 for patients with PH1 who were previously in the placebo arm in DCR-PHXC-201.

The proposed analyses appear reasonable. We note that Study DCR-PHXC-201 randomized 11 patients with PH1 to placebo; however, in your briefing document, you have provided data for the change in Uox from baseline for only nine placebo patients from DCR-PHXC-201 who rolled over to DCR-PHXC-301. Please provide the change in Uox from baseline for all placebo patients with Uox data in DCR-PHXC-301; for placebo patients without Uox data in DCR-PHXC-301, please clarify the reason these data are missing or not provided.

***Question 3a:*** Does the Agency agree that data from Study DCR-PHXC-301 would constitute confirmatory evidence in support of the substantial evidence of effectiveness for nedosiran in the treatment of PH1?

***FDA Response to Questions 3a:*** You propose to submit the following data from the open label extension study, DCR-PHXC-301, as confirmatory evidence of effectiveness:

- For 13 patients with PH1 who have rolled over into DCR-PHXC-301 from the single-dose phase 1 study, DCR-PHXC-101, you plan to submit an analysis of the mean maximum percent change in 24-hour Uox from baseline (1) after a single dose of nedosiran in Study DCR-PHXC-101; (2) to the last pre-dose 24-hour Uox in DCR-PHXC-301 (you indicate that the interval between the single dose in DCR-PHXC-101 and the first dose in DCR-PHXC-301 ranged from approximately 10 to 23 months); and (3) to the maximum percent change in 24-hour Uox in DCR-PHXC-301 to demonstrate the changes in 24-hour Uox whilst on treatment, off-treatment, and on-treatment again.
- For nine patients with PH1 previously randomized to placebo in DCR-PHXC-201, you plan to submit an analysis of the percent change in 24-hour Uox from DCR-PHXC-201 baseline to Month 3 (n=9) and Month 6 (n=5) in DCR-PHXC-301, based on the available data at data cutoff (September 28, 2021). You propose to provide 6-month Uox data for the remaining 4 patients at the time of the safety update.

In principle, the proposed analyses of Study DCR-PHXC-301 could serve as confirmatory evidence of effectiveness. See also our response to Question 4.

***Question 3b:*** In response to the Agency's request, the Sponsor has conducted a series of analyses to address the question of how durable the effects of nedosiran are in lowering 24-hour Uox. Does the Agency agree that these additional analyses adequately address the question of durability of response?

***FDA Response to Questions 3b:*** To support the durability of the treatment's effect, you propose to submit the following:

- For the 13 patients with PH1 from the single-dose study DCR-PHXC-101 who have rolled over to DCR-PHXC-301, you plan to provide data on the percent change in 24-hour Uox from DCR-PHXC-101 baseline to Months 3, 6, 12, and 18 in DCR-PHXC-301 (all 13 patients have 24-hour Uox data to Month 15 and 12 patients have data to Month 18 at data cutoff), and the proportion of patients achieving 24-hour Uox ≤ULN or ≤1.3×ULN at Months 3, 6, 12, and 18 in DCR-PHXC-301.
- For 13 patients who were randomized to nedosiran in DCR-PHXC-201 and rolled over to DCR-PHXC-301, you plan to provide data on the percent change in 24-hour Uox from DCR-PHXC-201 baseline over time (in addition to the 6-month treatment period of DCR-PHXC-201, 13 patients have an

additional 3 months of Uox data from DCR-PHXC-301, 8 patients an additional 6 months, and 3 patients an additional 12 months at data cutoff).

The proposed analyses seem reasonable. We have the following additional comments:

a. You indicate that the interval between the single dose in DCR-PHXC-101 and the first dose in DCR-PHXC-301 ranged from approximately 10 to 23 months. Please clarify why you used the 24-hour Uox from DCR-PHXC-101 as the baseline for your analyses (as opposed to the pre-specified baseline according to the SAP for Study DCR-PHXC-301, i.e., "the baseline is an average of the two 24-hour Uox Screening results for the 301 study for participants rolling over from DCR-PHXC-101").
b. We note that Study DCR-PHXC-201 randomized 18 patients to nedosiran. Please clarify why you plan to provide data for only 13 of those patients.

***Question 4:*** The Sponsor proposes to include 24-hour Uox data at Month 3 of DCR-PHXC-301 for all 9 DCR-PHXC-201 placebo-rollover participants and at Month 6 for 5 of the 9 in the NDA. Month 6 data for the remaining 4 participants will be provided at the time of the safety update after filing. See Table 3. Does the Agency agree with the Sponsor's proposal?

***FDA Response to Questions 4***: No, we do not agree. You should submit at least 6 months of Uox data for all placebo patients with PH1 from Study DCR-PHXC-201 who have rolled over to receive nedosiran in DCR-PHXC-301 and submit all available Uox data beyond 6 months until data cutoff. Based on our preliminary evaluation of the clinical data, we believe your product qualifies for a rolling review. As such, we recommend that you submit the completed portions of your NDA as planned in Q1 of 2022; the review clock will begin once the complete NDA has been submitted. Please refer to the guidance on Expedited Programs for Serious Conditions – Drugs and Biologics for additional information.

***Question 5:*** Does the Agency agree that the studies presented in Table 4 and the data analysis plans of these studies described above meet the substantial evidence of effectiveness standard based on one adequate and well controlled clinical investigation plus confirmatory evidence and are adequate to demonstrate safety in support of an NDA for nedosiran in the treatment of PH1?

***FDA Response to Questions 5***: See response to Question 3a regarding meeting the substantial evidence of effectiveness requirement. For safety, you propose to submit an Integrated Summary of Safety (Studies DCR-PHXC-101, DCR-PHXC-102, DCR-PHXC-103, DCR-PHXC-104, DCR-PHXC-201, and DCR-PHXC-301) with a data cutoff of September 28, 2021, and antidrug antibody reports for Studies DCR-PHXC-104, DCR-PHXC-201, and DCR-PHXC-301. Your proposal seems reasonable.

## 3.0 OTHER IMPORTANT MEETING INFORMATION

### PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

### DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

## LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

## SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017,** the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD

Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

**SECURE EMAIL COMMUNICATIONS**

Secure email is required for all email communications from FDA to sponsors when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), sponsors must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

**ABUSE POTENTIAL ASSESSMENT**

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

**PATIENT-FOCUSED ENDPOINTS**

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

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/s/

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BRIAN L PROCTOR
01/26/2022 10:23:21 AM

IND 132214

**MEETING REQUEST-**
**WRITTEN RESPONSES**

Dicerna Pharmaceuticals, Inc.
Attention: Andrew Henderson, MBA
Senior Director, Regulatory Affairs
33 Hayden Avenue
Lexington, MA 02421

Dear Mr. Henderson:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for DCR-PHXC.

We also refer to your submission dated September 3, 2020, containing a meeting request. The purpose of the requested meeting was to obtain feedback on your proposed NDA submission.

Further reference is made to our Meeting Granted letter dated September 8, 2020, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your October 2, 2020 background package.

If you have any questions, please call Brian Proctor, Regulatory Project Manager, at (240) 402-3596.

Sincerely,

*{See appended electronic signature page}*

Aliza Thompson, MD, MS
Deputy Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology and Nephrology
Center for Drug Evaluation and Research

Enclosure:

- Written Responses

U.S. FOOD & DRUG ADMINISTRATION

# WRITTEN RESPONSES

**Meeting Type:** B
**Meeting Category:** Pre-NDA
**Application Number:** IND 132214

**Product Name:** Nedosiran (DCR-PHXC)
**Indication:** Treatment of primary hyperoxaluria (PH)
**Sponsor Name:** Dicerna Pharmaceuticals, Inc.

**Regulatory Pathway:** 505(b)(1)

## 1.0 BACKGROUND

Nedosiran (DCR-PHXC) is a drug product containing DCR-L1360 drug substance, a small interfering RNA (siRNA) duplex conjugated to N-acetylgalactosamine (GalNAc) sugar residues, in water for subcutaneous injection. DCR-L1360 is designed to bind to and reduce the amount of lactate dehydrogenase type A (LDHA) mRNA in the liver to reduce translation to LDHA, an enzyme that catalyzes the final step in the formation of oxalate.

Dicerna is developing nedosiran for the treatment of primary hyperoxaluria (PH). They have completed enrollment of a phase 1, single-ascending dose study in healthy adults and patients ≥6 years of age with PH1 or PH2 (DCR-PHXC-101) and have several additional ongoing or planned studies in patients with PH:

- DCR-PHXC-201: a 6-month, randomized, double-blind, placebo-controlled trial in patients ≥6 years of age with PH1 or PH2 and an eGFR ≥30 mL/min/1.73 $m^2$ (n=36).
- DCR-PHXC-203: a 6-month, single-arm study in children <6 years of age with PH1 or PH2 and an eGFR ≥30 mL/min/1.73 $m^2$ (n=10).
- DCR-PHXC-204: a 6-month study in patients of any age with PH1 or PH2 and an eGFR <30 mL/min/1.73 $m^2$ including patients on dialysis (n=12).
- DCR-PHXC-104: a randomized, placebo-controlled, single-dose study in patients ≥6 years of age with PH3 and an eGFR ≥30 mL/min/1.73 $m^2$ (n=6; 4 DCR-PHXC and 2 placebo).
- DCR-PHXC-301: an open-label extension study for patients previously enrolled in studies of DCR-PHXC and their PH-diagnosed siblings (n~60).
- DCR-PHXC-102: a single 170-mg-fixed-dose PK, safety, and tolerability study of DCR-PHXC in volunteers with end stage renal disease (who do not have PH), including participants on hemodialysis.

Dicerna was granted Breakthrough Therapy Designation for the treatment of PH1 on July 2, 2019 and an Initial Comprehensive Multidisciplinary Breakthrough Therapy meeting was held on November 4, 2019 to review the proposed clinical, nonclinical, and manufacturing development plans to support the approval of nedosiran.

Dicerna requested this meeting to obtain feedback on a proposed NDA submission for the treatment of PH based on the results of studies DCR-PHXC-201, DCR-PHXC-203, and DCR-PHXC-104.

## 2.0 QUESTIONS AND RESPONSES

### 2.1. Clinical

***Question 1:*** Does the Agency agree with the Safety Data Integration strategy for the ISS and pooling approach from the individual studies' ADaM datasets?

***FDA Response to Question 1:*** In brief, you propose to include data from your phase 1 (DCR-PHXC-101, -102, -103, and -104) and phase 2 (DCR-PHXC-201, -203, and -204) studies, as well as the open-label extension study DCR-PHXC-301 in the Integrated Summary of Safety. You propose to pool data from studies according to number of doses administered (single or multiple), study population (healthy volunteers, patients with PH, and patients with "impaired renal function"), and data from the first 30 days in patients with PH. You will submit integrated ADaM datasets and study-level SDTM and ADaM datasets. We agree that the proposed approach is acceptable.

***Question 2:*** If the Sponsor can provide supporting evidence to characterize the relationship between urinary oxalate levels and new stone formation (b) (4)

***FDA Response to Question 2:*** Study DCR-PHXC-104 will randomize patients ≥6 years of age (b) (4) Efficacy will be assessed by 24-hour urinary oxalate. (b) (4) We recommend further discussion of this issue when the results of your natural history study are available.

***Question 3:*** Does the Agency agree that, for support of efficacy of DCR-PHXC, no ISE is needed and that Study DCR-PHXC-201 and DCR-PHXC-104 will be sufficient to support the proposed indication?

***FDA Response to Question 3:*** We agree that no ISE is needed and that study DCR-PHXC-201 could support an indication for PH1 and PH2. Your indication will reflect the population in which there are adequate data to support efficacy and safety. See the response to Question 2 regarding Study DCR-PHXC-104.

***Question 4:*** Does the Agency agree with the definition of Treatment-Emergent Adverse Event (TEAE) for the ISS?

***FDA Response to Question 4:*** Yes, we agree. You propose to define TEAEs as "Adverse events that start on or after the administration of study drug during the treatment period, or if they occur prior to the administration of study drug and worsen in severity/grade or relationship to investigational medication after the administration of study drug during the treatment period. Treatment period is defined as first dose date through study completion date."

***Question 5:*** Does the Agency have any comments on the proposed TPP for nedosiran?

***FDA Response to Question 5:*** Per USP Salt Policy: a) when an active ingredient in a drug product is a salt, the drug product title will contain the name of the active moiety (or neutral form), and not the name of the salt, and b) the strength should also be expressed in terms of the active moiety rather than the salt strength equivalent. Products that use the active moiety in the name and strength should include an equivalency statement to indicate the amount of active moiety related to the amount of active ingredient (salt). This equivalency statement should appear on the container label, carton labeling, and other labeling. For additional information, refer to *Naming of Drug Products Containing Salt Drug Substances Guidance for Industry, 2015*.

## 2.2. Nonclinical/Clinical

***Question 6:*** Does the Agency agree with the Sponsor's plan to submit the NDA whether or not a validated ADA assay is available at the time of filing?

***FDA Response to Question 6:*** No, we do not agree. DCR-L1360 is a synthetic high molecular weight compound that may pose immunogenicity risks to patients. As previously conveyed, ADA responses to DCR-L1360 should be monitored using appropriately validated ADA assays during pivotal clinical studies to ensure the validity of ADA assay measurements. The assays should demonstrate specificity, sensitivity, reproducibility, precision, accuracy, linearity, and robustness. Complete ADA assay validation reports are expected at the time of NDA submission.

## 2.3. Regulatory

***Question 7:*** Does the Agency agree with the overall clinical and nonclinical organization of the NDA?

***FDA Response to Question 7:*** Yes, the overall data organization appears reasonable. In the meeting package, you outline the reproductive and developmental toxicology studies using DCR-PHXC; because DCR-PHXC is inactive in mice, studies using DCR-

PHXC in mice assess off-target effects but not the risk of silencing LDHA mRNA expression. According to the Investigator's Brochure, you tested the mouse surrogate DCR-m355a at only one dose (10 mg/kg) in the mouse embryo-fetal development (EFD) study. We question whether the proposed single dose arm of DCR-m355a at 10 mg/kg is adequate to assess the risk of silencing LDHA mRNA expression on embryo-fetal development. Provide justification for this approach along with supportive data. We encourage you to submit the mouse EFD study report as soon as it is available.

***Question 8:*** Does the Agency agree with the Sponsor's plan for a rolling NDA submission?

***FDA Response to Question 8:*** Yes, we agree. You propose to submit information to the NDA in three "waves" over three consecutive months (Month 1: non-clinical study reports; Month 2: non-clinical summaries and most CMC data; Month 3: CMC summaries and stability data, clinical sections, and draft labeling).

***Question 9:*** Does the Agency agree that, based on the seriousness of PH and the lack of approved pharmacological treatments for all types of genetically defined PH, this NDA will qualify for a priority review?

***FDA Response to Question 9:*** This decision will be made after NDA submission.

***Question 10:*** Does the Agency plan to involve an Advisory Committee in the review of critical questions of this NDA?

***FDA Response to Question 10:*** The need for an Advisory Committee meeting will be determined after NDA submission.

**Additional Requests from the Agency**

1. Please submit to the IND an encrypted SAS dataset of the randomization list for study DCR-PHXC-201, including the randomization number, treatment arm, and stratification factors (if any). Please include an unencrypted define file describing the randomization list variables.
2. Sample clinical trial kits, from both treatment arms, identical to those used during Study DCR-PHXC-201. Ship them to Brian Proctor's desk address in the same packaging as used for shipping to investigative sites. Notify him when the packages have shipped.

Please submit the following information at the time of NDA submission:
*Randomization:*

3. The encryption key for the randomization list in #1 and a dataset that links the subject's randomization number and unique subject ID to the allocated medication kit/box number, medication name, and associated define file.

*Protocol and SAP*

4. All versions of the protocol and SAP for key studies, the date when changes were implemented, and the number of subjects enrolled in the trial at the time changes were made. Include a Summary of Changes for each version.

*Trial Materials*

5. Case report forms (CRFs) and narratives for all subjects who died, dropped out, discontinued study drug for any reason, or experienced a serious adverse event (SAE). CRFs must include all clinical documents collected regardless of whether you label them as "CRFs" (Medwatch forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.).
6. A description of the responsibilities of each academic research organization (ARO) or clinical research organization (CRO) used in key studies.
7. All charters for committees involved in conducting key studies (Data Safety Monitoring Board [DSMB], Steering Committee, etc.)
8. All meeting minutes of all groups with any responsibility for the management of the trial, e.g., Executive Committee, Clinical Endpoint Committee, Steering Committee and DSMB. Include agendas and all data/slides presented to the Committee. Indicate whether the meeting was opened or closed. Ensure that these packages include a table of contents and are bookmarked by date.

*General Data and Analyses*

9. All code and datasets used to create analyses found in the main sections of key clinical documents (clinical summaries, study reports) and code that was used to create or clean up your analysis datasets. Footnote tables and figures with the name of the script used to create the table or figure.
10. Subject ID variable for any open label extension study datasets that links the subject to the ID used in the pivotal trial datasets.
11. Dataset that contains all subjects that were unblinded. Include the unique subject ID, the treatment received, who requested unblinding, date of unblinding, and the reason for unblinding.
12. Table that includes the following information for key studies:
    i. Dates of first patient and last patient visits
    ii. Date of data lock
    iii. Dates for each interim analysis
    iv. Dates of all versions of the SAP (with a hyperlink to each SAP)
    v. Dates of the initial protocol and all revisions (with a hyperlink to the protocol and each revision).

*Other*

13. Statement of Good Clinical Practice confirming that all clinical studies were conducted under the supervision of an Institutional Review Board and with adequate

informed consent procedures. If you were granted an IRB Waiver during this trial because a specific site or country operated under a Central Ethics Committee (CEC) and/or Local Ethics Committees (EC), please reference the waiver and include the date.

14. Rationale for assuring the applicability of foreign data to U.S. population/practice of medicine in the submission for phase 3 trials conducted primarily outside of the United States. This should include whether the patients are the same and whether the medical systems treat the disease the same way with respect to interventions.
15. An annotated version of these pre-NDA meeting minutes that include a hyperlink, when applicable, to the analysis and/or documents requested. This document is usually placed in Module 1.

See also LABORATORY TEST UNITS FOR CLINICAL TRIALS below regarding reporting laboratory values in U.S. conventional units and SI units.

## 3.0 OTHER IMPORTANT MEETING INFORMATION

### PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

### DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data*

(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

**LABORATORY TEST UNITS FOR CLINICAL TRIALS**

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and

product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

**SUBMISSION FORMAT REQUIREMENTS**

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017,** the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

**SECURE EMAIL COMMUNICATIONS**

Secure email is required for all email communications from FDA to sponsors when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), sponsors must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

**ABUSE POTENTIAL ASSESSMENT**

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

**PATIENT-FOCUSED ENDPOINTS**

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product

development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

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**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.**

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/s/

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ALIZA M THOMPSON
11/02/2020 11:21:31 AM

# CDER Breakthrough Therapy Designation Determination Review Template

| | |
|---|---|
| **IND/NDA/BLA #** | 132214 |
| **Request Receipt Date** | May 7, 2019 |
| **Product** | DCR-PHXC |
| **Indication** | Treatment of Primary Hyperoxaluria |
| **Drug Class/Mechanism of Action** | siRNA targeting mRNA for lactate dehydrogenase type A (LDHA) |
| **Sponsor** | Dicerna Pharmaceuticals |
| **ODE/Division** | ODEI/Division of Cardiovascular and Renal Products |
| **Breakthrough Therapy Request(BTDR) Goal Date (within 60 days of receipt)** | July 7, 2019 |

*Note: This document must be uploaded into CDER's electronic document archival system as a* ***clinical review: REV-CLINICAL-24 (Breakthough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes,*** *and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

**Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.**

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

   The treatment of Primary Hyperoxaluria (PH).

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

***If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:***

3. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

***If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:***

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequeate and sufficiently complete to permit a substantive review?
      - ☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
      - ☐ Undetermined
      - ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

**4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:**

***If 3b is checked "No", BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If MPC review is not required, email Miranda Raggio and Sandy Benton as soon as this determination is made so that the BTDR can be removed from the MPC calendar.***

***If 3b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.***

**5. Clearance and Sign-Off (no MPC review)**

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

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**Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.**

**6. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.**

DCR-PHXC is a drug product containing DCR-L1360 drug substance, a small interfering RNA (siRNA) duplex conjugated to N-acetylgalactosamine (GalNAc) sugar residues, in water or saline for subcutaneous injection. DCR-L1360 is designed to bind to and destroy lactate dehydrogenase type A (LDHA) mRNA in the liver to reduce translation to LDHA, an enzyme that catalyzes the final step in the formation of oxalate. Dicerna is developing DCR-PHXC for the treatment of primary hyperoxaluria types 1, 2, and 3 (PH1, PH2, and PH3), rare diseases caused by autosomal-recessive defects in enzymes that result in overproduction of oxalate in the liver and deposition of calcium-oxalate in tissues, particularly the kidneys.

PH1 is the most common (estimated prevalence of 1 to 3 cases per million) and severe form of PH. In PH1, calcium oxalate deposition initially leads to nephrolithiasis, nephrocalcinosis, and progressive loss of renal function. As glomerular filtration rate (GFR) declines, reduced oxalate excretion by the kidney leads to higher oxalate levels and

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

systemic oxalosis. Non-renal manifestations that occur after the loss of renal function include bone fractures, cutaneous ulcers, anemia, retinal deposits, peripheral neuropathy, synovitis, cardiomyopathy, and arrhythmias. The age at symptom onset for PH1 ranges from infancy to adulthood with a median age at diagnosis of 5 to 6 years. The clinical phenotype and disease severity is heterogeneous, even within a single family, and can range from severe oxalosis in an infant to occasional nephrolithiasis in an adult. The median age at diagnosis of end-stage renal disease (ESRD) is 24 years.

PH2 and PH3 are less common (~10% and 5% of patients with PH, respectively) and generally have less severe clinical manifestations, although the natural history is not well-described/understood.

On December 19, 2018, Dicerna requested Preliminary Breakthrough Therapy Designation Request Advice. During a teleconference on January 24, 2019, the Division requested additional information, which the sponsor has included in the current request.

**7. Information related to endpoints used in the available clinical data:**

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The sponsor has provided data on 24-hour urinary oxylate excretion, one of several secondary PD markers evaluated in their study.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease.

No drug has been approved for the treatment of PH. We have indicated to sponsors that we would be willing to accept a substantial change in urinary oxalate in patients with high baseline levels as a surrogate endpoint in patients with PH1. (b) (4)

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

Plasma oxalate concentrations remain relatively normal in patients with preserved kidney function because oxalate is rapidly cleared by the kidneys; however, there is interest in using plasma oxalate as a surrogate marker in patients with reduced kidney function.

**8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population.**

There are no approved pharmacologic treatments for PH, but some patients with PH1 respond to supraphysiological doses of pyridoxine (vitamin B6). Other treatments include high fluid intake and potassium or sodium citrate. The best available treatment option for patients with advanced chronic kidney disease is a combined liver and kidney transplant.

**9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].**

Lumasiran, an siRNA targeting the mRNA for hydroxyacid oxidase-1, was granted breakthrough therapy designation for the treatment of PH1 on February 23, 2018. The designation was based on marked and sustained reductions in urinary oxalate in seven patients with PH1 treated with lumasiran in an ongoing phase 2 study.

**10. Information related to the preliminary clinical evidence:**

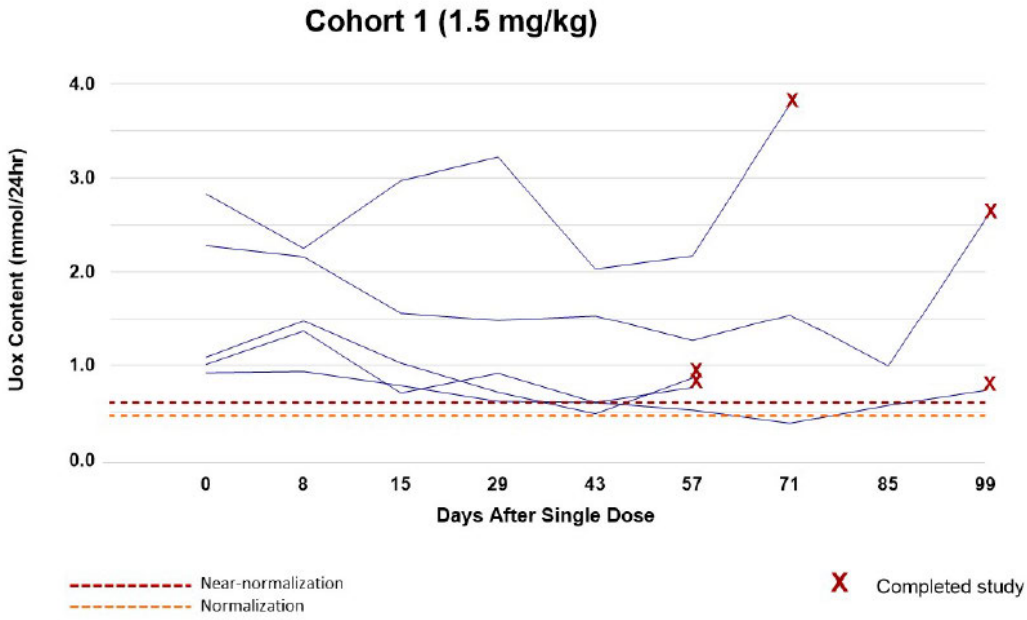
a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

DCR-PHXC-101 is an ongoing, single-ascending dose study in healthy volunteers (Group A) and patients with PH1 or PH2 (Group B, Cohorts 1 to 4). All patients were required to have a baseline urinary oxalate ≥0.7 mmol/24 hours (normal <0.46 mmol/24 hours) and an eGFR ≥30 mL/min/1.73m$^2$. Subjects in Group A received a single 0.3, 1.5, 3.0, 6.0 or 12 mg/kg dose of DCR-PHXC or placebo. Patients with PH1 in Cohorts 1, 2, and 3 received a single open-label DCR-PHXC dose of 1.5 mg/kg, 3.0 mg/kg, or 6.0 mg/kg, respectively. (b) (4) During the study, vitamin B6 is to remain stable, if applicable, and patients are to avoid vitamin C supplements around the time of 24-hour urine collections. Patients are instructed to avoid oxalate-rich foods and to eat moderate amounts of protein and calcium.

The primary objective of the study is to evaluate the safety and tolerability of single doses of DCR-PHXC. Secondary objectives are to characterize PK/PD. One of the PD markers is 24-hour urine oxalate excretion. Two 24-hour urine collections are obtained during screening and additional collections are performed through Day 57 or until urinary oxalate excretion returned to ≥ 80% of baseline, whichever is latest.

To date, the sponsor has enrolled 25 healthy volunteers, 15 patients with PH1, and 3 patients with PH2. All subjects have been dosed, and all but four patients in Group B have reached the Day 57/End of Study visit. The sponsor provided the following figures for 24-hour urinary oxalate excretion over time for the 14 patients who have completed follow-up through Day 57.

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.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Near-normalization
Normalization
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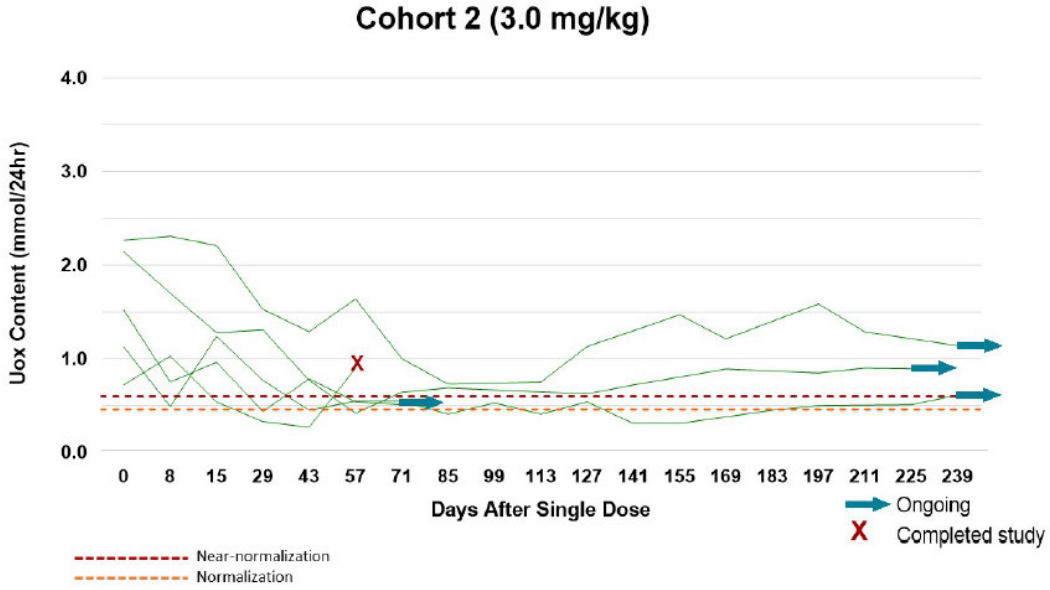
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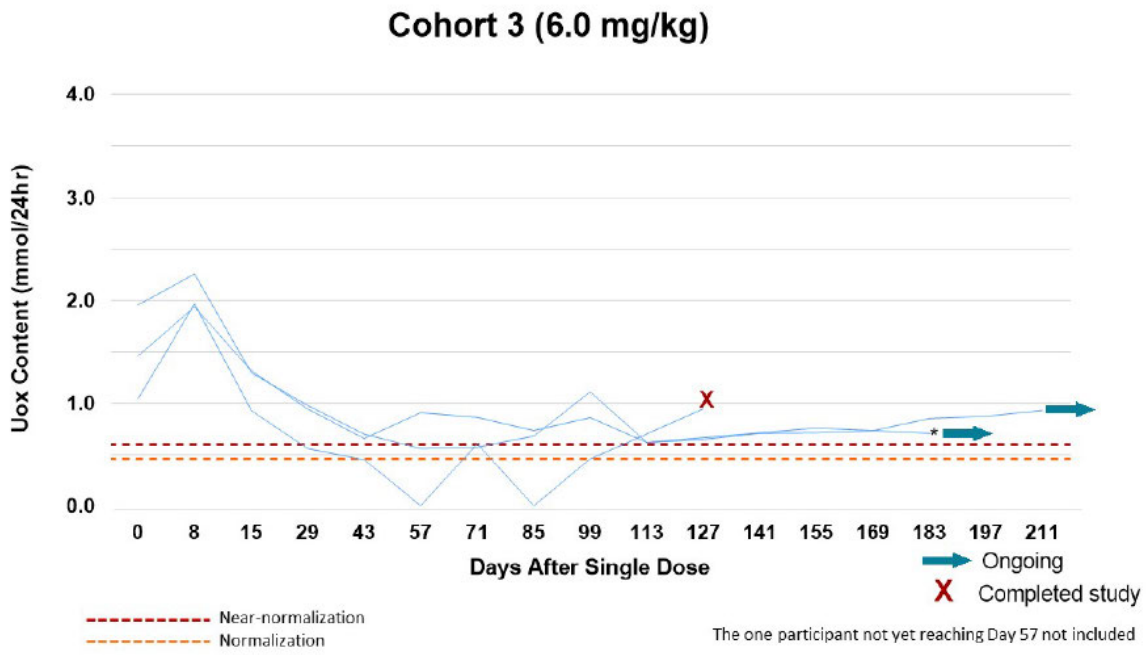


(b) (4)

The Division previously asked the sponsor to address the completeness of 24-hour urine collections during the study. The sponsor believes 20% variability in 24-hour urinary creatinine excretion would exceed biologic variation and raise questions regarding the completeness of the collection. In post hoc analyses, the sponsor excluded 27/124 (22%) post-dose 24-hour urine collections with variability in 24-hour creatinine excretion compared with baseline that exceeded 20%. The sponsor provided figures of percent change in urinary oxalate from screening to maximal reduction based on this new dataset, noting that the figures with and without these values appeared similar.

b. Include any additional relevant information. Consider the following in your response:

The main adverse reaction observed to date has been injection site tenderness. In Group B, there have been four of SAEs (two fever and one each of urolithiasis and appendicitis).

*Reviewer's comment: The event of urolithiasis does not raise concerns regarding efficacy of the product given the lag time in developing/passing stones.*

**11. Division's recommendation and rationale (pre-MPC review):**

☒ GRANT: We recommend granting Breakthrough Therapy Designation for PH1. Patients with PH1 treated with DCR-PHXC in the sponsor's phase 2 study had marked and sustained reductions in levels of urinary oxalate consistent with the mechanism and expected timecourse of action of the drug. We believe this provides sufficient preliminary clinical evidence in this rare disease to support Breakthrough Therapy Designation.

☒ DENY: We do not recommend granting Breakthrough Therapy Designation for PH2 and PH3. (b) (4)

**12. Division's next steps and sponsor's plan for future development:**

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

We will continue ongoing discussions with the sponsor regarding the design of their phase 3 program.

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

**13. List references, if any:** None.

**14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting?** YES ☒ NO ☐

**15. Clearance and Sign-Off (after MPC review):**

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

**Revised 10/17/17/M. Raggio**

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**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.**

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/s/
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KIMBERLY A SMITH
06/17/2019 08:52:14 PM

ALIZA M THOMPSON
06/18/2019 05:59:41 AM

NORMAN L STOCKBRIDGE
06/18/2019 06:27:20 AM